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The article on the facing page is an abridgment of the lecture delivered in Stockholm, Sweden, in December when Professor H. Keffer Hartline received the Nobel Prize. The text, copyright © The Nobel Foundation 1968, is published with the permission of the Foundation.

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VISUAL RECEPTORS AND RETINAL INTERACTION

BY H. KEFFER HARTLINE

Professor H. Keffer Hartline received the Nobel Prize in Physiology and Medicine for 1967 at ceremonies in Stockholm on 18 November. Sharing the award with Dr. Hartline were Ragnar Granit, Visiting Professor of the Rockefeller, and George Wald of Harvard. This is the second successive year that members of The Rockefeller University faculty have been thus honored: Peyton Rous received the award in 1966.

At a dinner given in honor of Dr. Hartline by his undergraduate alma mater, Lafayette College, President Bronk spoke of their long association that led to Dr. Hartline's move to the Rockefeller from The Johns Hopkins University with Dr. Bronk in 1953: "During 38 years as friend and colleague at the Johnson Foundation of the University of Pennsylvania, The Johns Hopkins, and The Rockefeller University, I have known Keffer Hartline to be always ready to sacrifice position and prestige in order to have favorable opportunities for research ... In remarkable degree, he is indifferent to material rewards ... Because he is enthusiastic, selfless, and considerate, he is a natural teacher who is greatly admired by scores of his graduate students who now hold academic positions of distinction.... The wide significance of Hartline's research, the diversity of scientific disciplines and techniques that he employs, the elegance and versatility of his experiments attest the value of broad training in both the physical and biological sciences."

NEUROPHYSIOLOGY received an impetus of far-reaching effect in the 1920's, when Adrian and his colleagues developed and exploited methods for recording the activity of single neurons and sensory receptors. These studies laid the foundations for the unitary analysis of nervous function.

My early interest in vision was spurred by another contribution of Adrian's—his study, with R. Matthews, of the massed discharge of nerve impulses in the eel's optic nerve. I aspired to the obvious extension of this study: application of unitary analysis to the receptors and neurons of the visual system.

Oscillograms of the action potentials in a single nerve fiber are now commonplace. The two oscillo-

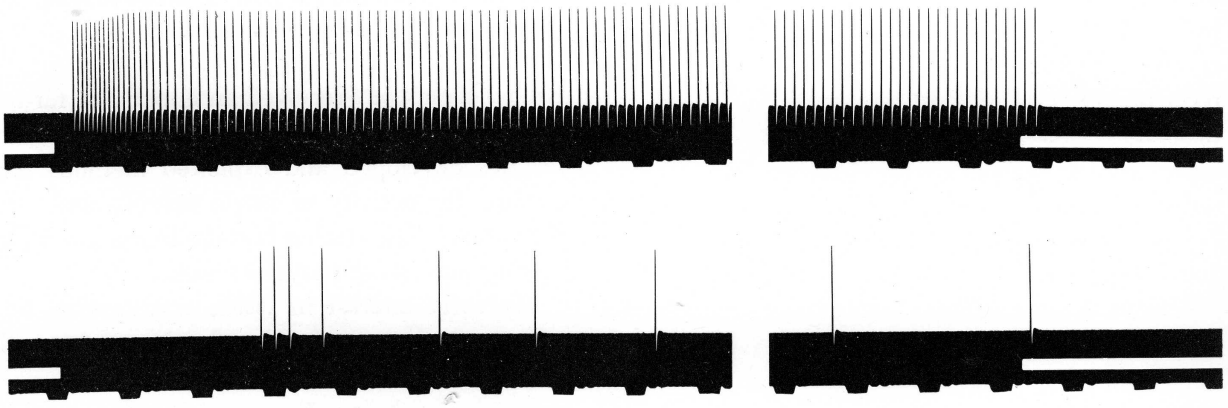
grams shown below are from an optic nerve fiber whose retinal receptor was stimulated by light. For the top record a bright light was used; for the bottom record a dim one, 1/10,000th as bright. As is now well known, higher intensities of stimulation are signaled by higher frequencies of discharge of uniform nerve impulses.

In 1931, when C. H. Graham and I sought to apply to an optic nerve the technique developed by Adrian and Bronk for isolating a single fiber, we made a fortunate choice of experimental animal. The xiphosuran arachnoid, *Limulus polyphemus,* commonly called "horseshoe crab," abounds on the eastern coast of North America. These "living fossils" have lateral compound eyes that are coarsely faceted and connected to the brain by long optic nerves. The optic nerve in the adults can be frayed into thin bundles which are easy to split until just one active fiber remains; the records in the illustration shown below were obtained from such a preparation.

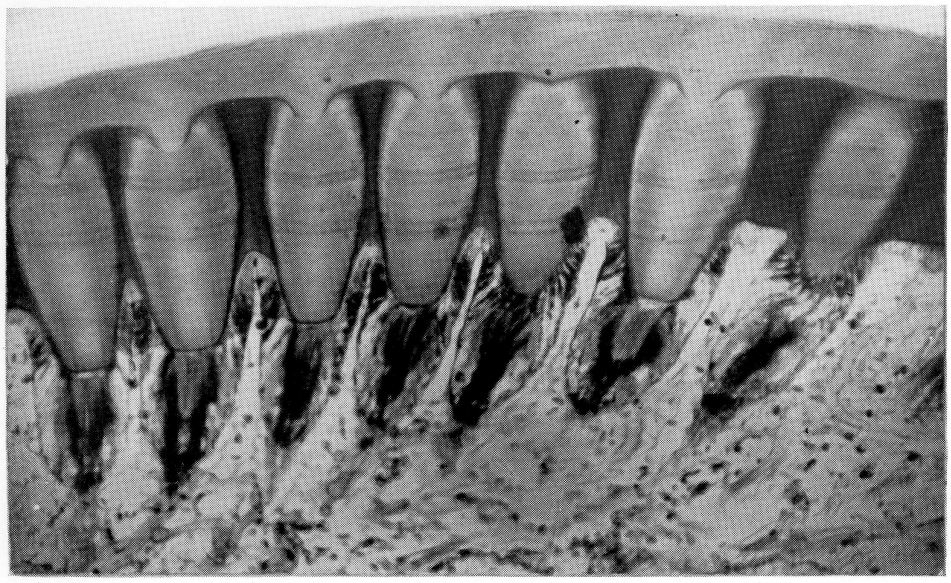
The sensory structures in the eye of *Limulus* – shown in the micrograph at right – are clusters of retinular cells, arranged radially around the dendritic process of a bipolar neuron (eccentric cell). Each cluster lies behind its corneal facet and crystalline cone, which give it its own small visual field. Each such ommatidium, although not as simple as I once thought, seems to act as a functional receptor unit. Restriction of the stimulating light to just one facet elicits discharge in just one fiber – the axon of the bipolar neuron whose dendritic process is in intimate contact with the light-sensitive rhabdom that is borne by the encircling retinular cells.

The study of the responses of single optic nerve fibers from the *Limulus* eye has shown that many familiar properties of visual mechanisms may reasonably be ascribed to properties of the visual receptor. An example is seen in the high-frequency transients that accent the onset of illumination in the records reproduced below and the sensory adaptation that quickly ensues in each. These patterns of activity parallel well-known attributes of vision: the ability to respond vigorously to sudden changes – even small ones – while retaining the ability to function over the wide range of ambient light intensity to which animals are exposed.

The response patterns shown on this page are not faithful representations of the light stimuli, which were simple exposures of constant intensity. To some extent, the receptor mechanism distorted the sensory information. This illustrates a broad principle established by the earliest studies of single sensory endings: receptors, by virtue of their inherent properties, operate upon the information they collect from their surroundings to favor certain features of it. The



Oscillograms of the electrical activity (discharge of nerve impulses) in a single optic nerve fiber from the compound eye of Limulus, *stimulated by illumination of the facet associated with its receptor. Upper record, response to light of high intensity; lower record, response to light 1/10,000th as intense. Time marked in 1/5 sec. in trace at bottom of each record. Signal marking onset of steady illumination blackens white band just above time marks.*



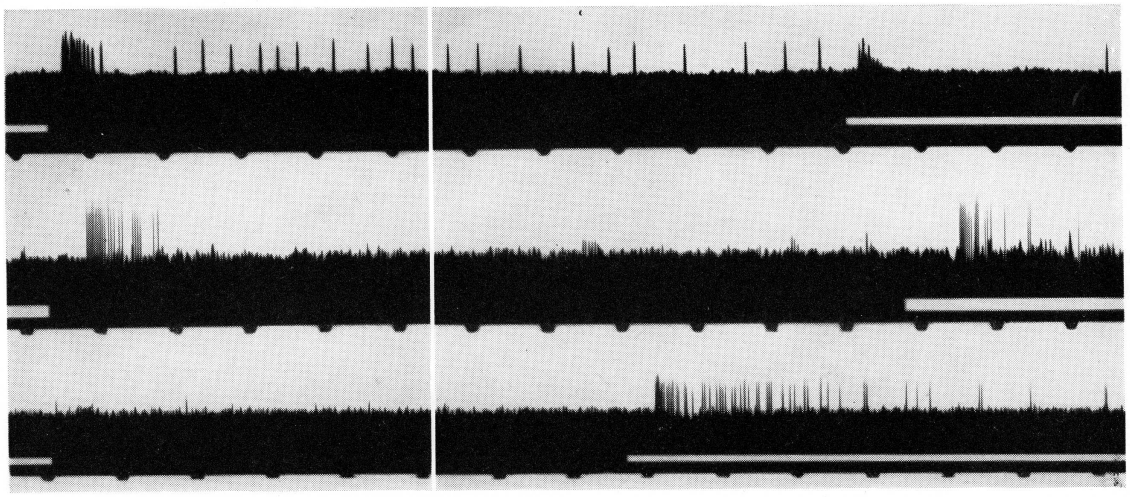
Section perpendicular to cornea through a portion (approx. 1½ mm.) of the compound eye of Limulus, *showing seven ommatidia. The cornea is above; the crystalline cones project downward to sensory portions of the ommatidia, which have been partially bleached to reveal the retinulae. Fibers of optic nerve and plexus show faintly below. Micrograph by William H. Miller.*

processing of sensory data begins in the receptors.

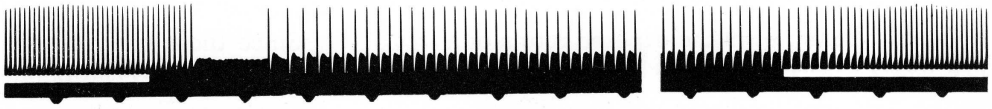
Successful recording from single fibers in the optic nerve of *Limulus* emboldened me to apply the same methods to the vertebrate eye. The optic nerve of a vertebrate is very different from that of *Limulus;* dissection of bundles of fibers from it seemed a hopeless task. Moreover, this was before Granit and his colleagues developed microelectrodes for retinal recording. But Nature has provided a ready-made dissection of the optic nerve, spreading it in a thin layer over the vitreous surface of the retina. Picking up small bundles from the exposed retina of a frog's eye was easy; splitting one of them until a single active fiber remained was not too difficult.

The findings, top figure next page, were unexpected: different optic nerve fibers responded to light in different ways. Some fibers gave discharges much like those in *Limulus;* some responded vigorously at onset and again at cessation of illumination or when slight changes in intensity were made, and were otherwise silent. Still other fibers gave no response during illumination, firing a vigorous and prolonged train of impulses only when light was dimmed. Slight movements of a small spot or shadow elicited responses in some fibers if they were within the square millimeter or so of retinal area that is a fiber's receptive field. Convergence and summation of excitatory and inhibitory influences were found to take place within the receptive fields of fibers. Thus, there is interaction in the retina, as Granit had shown, and as Adrian and Matthews had demonstrated earlier. It is evident that a great deal of elaborate and sophisticated "data processing" takes place in the thin layer of nervous tissue that is the retina.

Since those early observations, a wealth of new knowledge has been obtained by workers in many laboratories. From studies of the retinas of mammals as well as of cold-blooded vertebrates, from recordings of units, for example, in the ganglionic layers in the eyes of crustaceans and insects, and by the use of various patterns of light, moving and stationary and of various colors, new and surprising properties of retinal neurons have been and are constantly being discovered. It is now clear that the retina is even more powerful in the integrative tasks it performs than my early experiments had intimated.



Oscillograms of the electrical activity of single optic nerve fibers dissected from the retina of a frog's eye. Three of the response types commonly found are figured. Time marked in 1/5 sec. in trace at bottom of each record. Signal marking onset of steady illumination blackens white band just above time marks.



Inhibition of the activity of a steadily illuminated photoreceptor unit in the eye of Limulus *by illumination of a group of 20-30 neighboring units (signaled by blackening of the white band above the 1/5 sec. time marks).*

Can we understand how these diverse and complex response patterns, highly specialized for specific tasks, are generated in the retina? Broad Sherringtonian principles can guide us – the interplay of excitatory and inhibitory influences in convergent and divergent pathways, with various spatial distributions, thresholds, time courses. But the application of broad principles to specific cases of such complexity is not easy. It is here that comparative physiology can help. The animal world is rich in its variety of visual systems, built in different ways and with different degrees of complexity, although all are governed, we are confident, by the same universal, basic principles.

In this, *Limulus* has again proved to be a valuable experimental animal. It, too, has a retina, although a much simpler one than those of the vertebrates or higher invertebrates. Interaction in the *Limulus* retina is complex enough to be interesting, yet simple enough to be analyzed with relative ease.

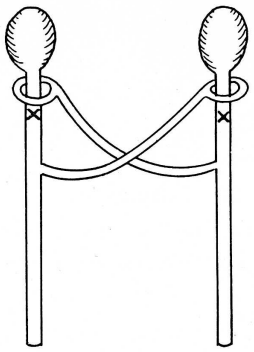
When I first worked with *Limulus,* I thought that the receptor units acted independently of one another. But I soon noticed that extraneous lights in the laboratory, rather than increasing the rate of discharge of impulses from a receptor, often caused a decrease in its activity. Neighboring ommatidia, viewing the extraneous room lights more directly than the receptor on which I was working, could inhibit that receptor quite markedly.

An experiment illustrating inhibition in the *Limulus* retina is shown at the foot of page four. Illumination of a small group (20-30) of ommatidia in the neighborhood of an arbitrarily chosen, steadily illuminated test receptor caused a substantial slowing of its discharge. After the light on the neighboring receptors was turned off, there was a prompt recovery, followed by a small but distinct overshoot – a postinhibitory rebound.

The basic properties of the inhibition in the *Limulus* eye are quickly summarized. The brighter the light on neighboring receptors, the greater the slowing of the discharge of a receptor being tested. The greater the number of neighboring receptors illuminated, the greater their effect: thus, there is spatial summation of inhibitory influences. Receptors close to a given receptor inhibit it more strongly, on the average, than do distant ones. Each ommatidium in the eye has its surrounding field of inhibition, and the influences are mutual: each receptor, being a neighbor of its neighbors, inhibits and is inhibited by those neighbors. Interaction in the *Limulus* eye, as far as is yet known, is purely inhibitory. Floyd Ratliff and I, with many colleagues in our laboratory, have been engaged over the past decade and a half in the analysis of this process.

The anatomical basis for the inhibitory influences that are exerted mutually in the *Limulus* eye is a network of nerve fibers – a true retina – lying just behind the layer of ommatidia and interconnecting them. Over this plexus of fiber bundles that run laterally from ommatidium to ommatidium, the inhibitory influences pass: cut these bundles and the inhibition vanishes. Our colleague William H. Miller has shown that fibers in these bundles arise as branches of the axons from the ommatidia that traverse the plexus on their way to become the optic nerve. Scattered profusely through the plexus are clumps of neuropil, rich in synaptic regions and packed with synaptic vesicles.

Electrophysiological evidence confirms the synaptic nature of the inhibitory interaction in the *Limulus* retina. Hyperpolarizing potentials are observed by



Schematic representation of the recurrent nature of the mutual inhibition of two receptor units. Excitation of each generates trains of impulses which originate at or near the point of emergence of the axon from the cell body, marked X. *Influences pass back up the recurrent branches to exert inhibition at synapses at or near the points of emergence (liberal use of artistic [?] license).*

intracellular recording in the eccentric cell of an ommatidium, coincident with inhibition of the receptor; Richard Purple and Frederick A. Dodge, Jr. in our laboratory have shown that these are inhibitory postsynaptic potentials like those met with elsewhere in nervous systems.

Before proceeding to a detailed consideration of inhibitory interaction, we may ask what roles it might play in vision. One role is enhancement of contrast. Strongly excited receptor elements in brightly lighted regions of the retinal image exert a stronger inhibition on receptors in more dimly lighted regions than the latter exert on the former. Thus, the disparity in the actions of the receptors is increased and contrast enhanced. Since inhibition is stronger between close neighbors than between widely separated ones, steep intensity gradients in the retinal image – edges and contours – will be accentuated by contrast.

"Simultaneous contrast," "border contrast," and the like are well known in visual physiology. A century ago Ernst Mach correctly ascribed them to inhibitory interaction in the visual system. Most of us have noted the fluted appearance of uniform steps in intensity, such as those in shadows cast by multiple light sources, as, for example, a cluster of candles. The Mach bands flanking a simple intensity gradient are also familiar "illusions" in which the contrast effect is overemphasized by the use of a special pattern of light. Such "distortions" of sensory information, ordinarily unnoticed, serve a useful function to accent and "crispen" important features of the visual scene and to sharpen spatial resolution. It is possible to demonstrate analogous distortions of spatial patterns of optic nerve activity in *Limulus,* when its eye views patterns of light similar to those just described. These phenomena are all the result of inhibitory interaction in the visual system.

Inhibitory interaction in the retina is a simple neural mechanism that operates on the sensory data supplied by the receptors, modifying spatial features just as the inherent mechanism of the receptors modifies temporal characteristics. Both of these "data processing" operations are integrative functions taking place in the earliest phases of the visual process.

Enhancement of contrast is but one consequence of inhibitory interaction. Inhibition plays a pervading and subtle role in vision as elsewhere in nervous function. To the basic excitation furnished by light, retinal inhibition adds a molding influence, increasing temporal and spatial resolution and supplying a mechanism for increased versatility of response. The opportunity to analyze this process in a retina that is much simpler than the retinas of higher animals should prove helpful in understanding the more complex functions of more complex visual systems.

We begin this analysis with experiments on the interaction of just two ommatidia. Illuminated together, each receptor of an interacting pair discharges impulses at a lower rate than when it is illuminated by itself. Analysis shows that the lowering of frequency of each must be associated quantitatively with the concurrent frequency of the other. It is the output of a receptor unit – its rate of discharge of nerve impulses – that determines how much inhibition it exerts on other units. A receptor that inhibits another receptor affects the very output that in turn inhibits it. Thus, the inhibitory interaction is recurrent in its operation, as may be visualized schemati-

cally for just two elements in the drawing at the left. Mathematically, this interaction of two units can be expressed by a pair of simultaneous equations. Experiments show that, above an abrupt threshold, a linear relation holds between the output of each receptor and the inhibition it exerts on the other. Thus, the simultaneous equations describing the interaction are piecewise linear.

To describe the interaction of n receptor units, a set of n simultaneous equations, piecewise linear, must be written, and in the equation for each unit inhibitory terms must be introduced and summed to express the inhibition on that particular unit by all of the units that act upon it:

$$r_p = e_p - \sum_{j=1}^{n} K_{p,j}(r_j - r^0_{p,j}), \qquad p = 1, 2, \ldots n$$

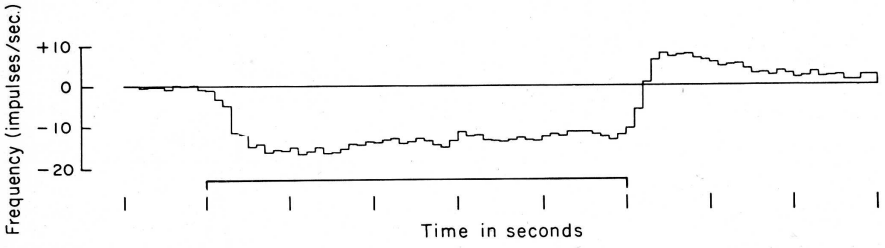
In this set of equations, r_p is the response of the receptor p, which, if illuminated alone, would have discharged impulses at a rate e_p, but which is subjected to the summed inhibitory influences expressed by the linear terms in brackets. In each term, $K_{p,j}$ is the inhibitory coefficient measuring the action of receptor j on p; $r^0_{p,j}$ is the associated threshold of that action.

In the eye, receptors are deployed spatially in a mosaic, and the strength of their interaction, as already noted, depends on their separations. In general, the coefficients K decrease and the thresholds r^0 increase with increasing separation of interacting ommatidia in the eye. Detailed maps of the inhibitory field surrounding small groups of ommatidia have recently been made by our colleague Robert Barlow.

The set of simultaneous equations developed in this analysis provides a succinct and useful formal description of steady-state inhibitory interaction in the retina of *Limulus*. Quantitative measurements of the activity of interacting receptors and groups of receptors in various configurations are satisfactorily accounted for. With measured or inferred inhibitory fields, spatial patterns such as Mach bands are successfully represented. Ratliff's recent book on Mach bands treats this subject in detail. Von Békésy, using mathematically equivalent formulations to represent inhibitory interaction, discusses in his recent book the applications to other sensory systems. Even on the motor side, the Renshaw system in the spinal cord seems to operate according to principles similar to those expressed here, as Granit and his colleagues, and V. Wilson at The Rockefeller University, have recently shown.

Up to this point we have restricted our discussion of the inhibitory interaction to the steady state of receptor activity, after all the mutual interactions have come into balance. Whenever changes occur in the patterns of light and shade on the retinal mosaic, receptor transients occur, new distributions of excitation are established, and readjustments of the inhibitory interactions are mediated over the retinal network. The interplay of excitation and inhibition is a dynamic process.

Vision itself is a dynamic process. There is little in the world that stands still, at least not as imaged on our retinas, for our eyes are always moving. The



Inhibition of a steadily illuminated receptor, produced artificially by electrical shocks applied to optic nerve fibers from neighboring receptors to generate a train of antidromic volleys of constant frequency. Frequency of discharge of impulses during an experimental run of 9 seconds that included the 5-second period of inhibition (signaled by step at bottom) is plotted as ordinate (vs. time as abscissa) after subtracting the frequency of discharge during a "control" run taken over a comparable period with no inhibition. The ordinates are given as impulses per second above or below the control. Experiment by David Lange.

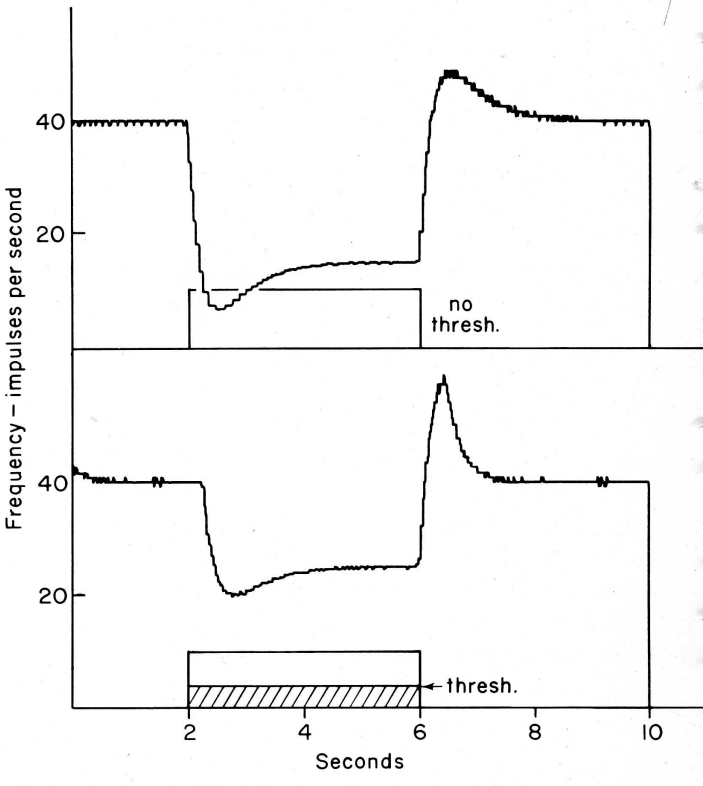
visual system is almost exclusively organized to detect change and motion. How can we explain this? How are we to understand, for example, the exquisite sensitivity of some of the frog's retinal fibers to slight movements of the shadow of a fine wire across their receptive fields? Or what mechanisms can explain the specific responses that are elicited by the movement of small objects, but only if they move with respect to a stationary background, as Lettvin and his colleagues, and others, report? Study of visual dynamics in a retina as simple as that of *Limulus* can hardly solve such problems, but it may suggest principles that can be applied toward their solution.

If responses are recorded from representative receptors in two interacting groups in a *Limulus* eye, and one group subjected to a small increment in intensity, the other, steadily illuminated, will be disturbed only by the inhibitory influences exerted by the first.

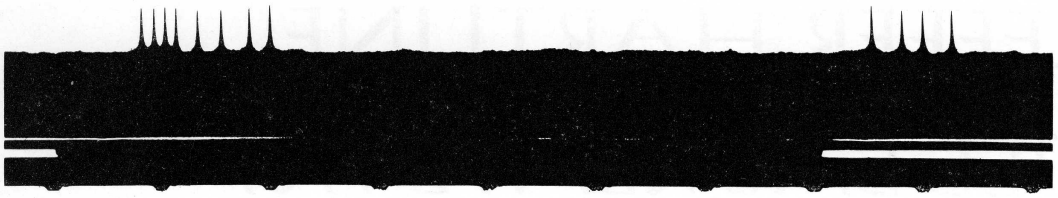
Such an experiment furnishes a good example of dynamic responses in the visual pathway, but the time courses of photoreceptor discharges are difficult to control, and those features that are contributed by the dynamic properties of the inhibitory interaction are hard to distinguish. Fortunately, lateral inhibition of a receptor unit can be produced artificially by electrical stimulation of the optic nerve fibers from the receptor's neighbors, as T. Tomita first showed. This affords an exact control of temporal factors that is not possible when the neighbors are excited naturally by light.

By this method, sinusoidally modulated inhibition can be exerted on a receptor, and if the influences are above all thresholds, linear systems-analysis can be applied. Our colleagues F. Dodge, B. Knight, and J. Toyoda have been engaged in such a study. Alternatively, abrupt stepwise increments of inhibition can be generated artificially to excite the transients of the inhibitory system, as shown on page seven. Since the latencies and transients of the photic mechanism are thereby avoided, the dynamics of the inhibition itself are revealed. Inhibition is then seen to set in after an appreciable delay of its own, and often, although not always, with a transient undershoot at the beginning. After the cessation of inhibition, no matter how it is produced, the postinhibitory rebound always occurs; it is a true "off" response.

Before we can understand fully the dynamics of inhibitory interaction, we must consider a new feature of the inhibitory process in the *Limulus* eye, first analyzed by Charles Stevens and recently studied by Purple and Dodge. This is the inhibition of a receptor unit by its own discharge. By tending to oppose any change in the discharge rate of a receptor



Simulations by means of a computer program of the responses of a steadily excited receptor subjected to a period of constant inhibition from neighboring elements, as in the actual experiment shown on page seven. The decay constants assigned to the self-inhibitory and lateral-inhibitory influences were respectively 1 sec. and 0.5 sec. For the upper tracing, a threshold of zero was assigned; for the lower tracing, an unrealistically large threshold was introduced to illustrate and exaggerate the asymmetries at onset and cessation of the inhibition, especially the "postinhibitory rebound."



Response of a receptor in the eye of Limulus *imitating the "on-off" discharges of vertebrate optic nerve fibers. Obtained by Ratliff and C. Mueller, using a special pattern of stimulation under special conditions of adaptation that suppressed the steady discharge but retained the transients at "on" and "off" – the latter the consequence of postinhibitory rebound.*

unit, this "self-inhibition" has a strong influence on the dynamics of receptor action and interaction.

The rise of inhibition, as successive impulses contribute their additive effects, and its decay – resulting presumably from removal or inactivation of inhibitory transmitter – determine the form of the transients exhibited by the interacting system as it adjusts to changing influences. When lateral inhibition is suddenly applied and builds up on a receptor unit, so that its discharge rate drops, its self-inhibition subsides to a new equilibrium, opposing the full effects of the lateral influence. Lateral inhibition has an inherently shorter time-constant than self-inhibition, hence the transient in the discharge of a receptor usually is an undershoot when lateral inhibition increases, and a postinhibitory rebound when it decreases. Nonlinearities introduced by the thresholds of lateral inhibition, it has been found, increase the delay in the onset of the inhibition, diminish the undershoot, and augment the rebound. This latter effect is significant in suggesting how the vigorous "off" responses may arise in more complex systems. The two cases, linear and nonlinear, are illustrated on page eight by means of a computer simulation like one devised by our colleague David Lange.

For all of the modifications introduced by inhibitory interaction, patterns of optic nerve activity in *Limulus* remain representations of the patterns of light and shade on the receptor mosaic that have not been too grossly distorted. Although significant integration of sensory data is prominent, the effects are mild compared to what takes place in more complex retinas. Even in *Limulus*, however, the potentiality for more extreme modifications of optic patterns can be demonstrated. Ratliff and Conrad Mueller, by careful adjustments of patterns of light, were able to elicit the responses shown above, from a perfectly normal receptor in the *Limulus* eye. They also produced pure "off" responses. In these experiments, by a contrived interplay of excitation (by light on the receptor) and inhibition (by light on its neighbors), taking advantage of time delays and postinhibitory rebound, response patterns simulating some of those observed in the vertebrate retina were "synthesized." What was contrived more or less artificially resembles the dynamic interplay which we believe takes place naturally as a result of the complex neural organization in more highly developed retinas and higher visual centers.

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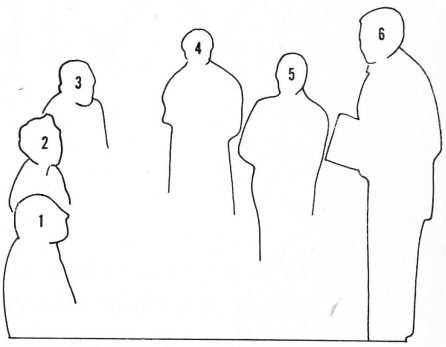
H. KEFFER HARTLINE
NOBEL LAUREATE 1967

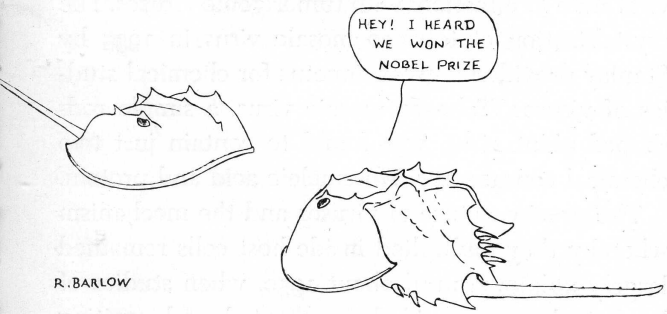
RIGHT, *King Gustav VI Adolph has just presented the Nobel diploma and gold medal to Professor Hartline, and leads the assemblage of 2,000 in applause at the Grand Auditorium of the Concert Hall in Stockholm on December 10.*

BELOW, *Lord Adrian of Cambridge, Trustee Emeritus of The Rockefeller University, left, with Dr. Hartline, at a reception given by the Director of the Nobel Foundation at the Nobel Library of the Swedish Academy; Professor Carl Gustaf Bernhard of the Kungliga Karolinska Institutet is next to Lord Adrian.*

LOWER RIGHT, *Dr. Hartline sighting a sextant while cruising on Dr. Bronk's schooner in 1950. The drawing of the horseshoe crabs is by a former student of Dr. Hartline, Robert B. Barlow, Jr.,* PH.D. *1967.*



1) King Gustav VI Adolph 2) Princess Margaretha 3) Prince Bertil 4) Mrs. H. Keffer Hartline 5) Dr. George Wald, who shares the Prize in physiology or medicine with Dr. Hartline and Dr. Granit 6) Dr. Hartline.



THE REPLICATION OF VIRUSES

BY IGOR TAMM

In 1892 Iwanowski was the first to transmit the mosaic disease of tobacco plants by means of bacteria-free filtrates of tissues from sick plants.[1] He did not realize the significance of this finding and did not investigate the matter further for some years to come. However, in 1898 Beijerinck reported evidence that the causative agent of tobacco mosaic was a new type of infectious agent. This conclusion was based on extensive studies of the properties of the agent. Besides unsuccessful cultivation attempts on bacteriological media and successful serial propagation in plants, Beijerinck also studied its diffusion properties, and demonstrated that it could be recovered in active form following precipitation with alcohol. He found that the agent was inactivated by formalin and boiling. Beijerinck reasoned that tobacco mosaic virus had life because it reproduced in its host organism, but that its state of dispersion was clearly different from that of bacteria. Beijerinck's view of viruses as subcellular infectious agents was not accepted by his contemporaries. Indeed, in 1903 Iwanowski thought that he had successfully cultivated the agent on artificial media.

The same year Beijerinck reported his findings, Loeffler and Frosch succeeded in transmitting the foot-and-mouth disease in cattle by bacteria-free filtrates of infected material. Foot-and-mouth disease virus causes degeneration and sloughing of cells of the mucous membrane and skin of cattle. This results in great reluctance to eat and move about, and causes the death of many stricken animals. Ellerman and Bang discovered the virus of chicken leukemia only ten years later. In 1911 Rous first discovered a virus capable of causing solid tumors in animals. The Rous sarcoma virus induces rapidly growing and spreading tumors in the chicken. The discovery in 1915 of viruses which infect bacteria established the practically universal distribution of viruses in nature.

In the years that followed, many different viruses of animals, plants, and bacteria were isolated, and it was found that, without question, viruses require living cells. It was also demonstrated that viruses consist of discrete particles, which are the infectious units capable of inducing viral diseases. Evidence was obtained that bacterial viruses, called bacteriophages, sometimes did not fully reproduce themselves in infected bacteria, but existed in some kind of subviral form – later known as the prophage. In 1933 Shope discovered that a tumor virus of animals could assume a "masked," noninfective form in the cells of the tumor. At the time, this was a puzzling observation, but it proved to be of the greatest importance, as it was the first demonstration of a subviral state in infections with tumorigenic viruses. The crystallization of tobacco mosaic virus in 1935 by Stanley provided a great impetus for chemical studies of viruses. Tobacco mosaic virus, a simple rod-shaped plant virus, was found to contain just two chemical components: ribonucleic acid and protein.

The precise nature of viruses and the mechanism whereby they multiplied inside host cells remained largely unknown until about 1950, when studies of bacteriophages provided unexpected and exciting new insights. On the basis of results of genetic recombination experiments, Doermann and Dissosway suggested in 1949 that bacteriophages multiply in

This article is adapted from the Alfred Benzon Lecture, which Dr. Tamm delivered in Copenhagen last November. See page 26.

a noninfective form inside bacteria. Three years later Hershey and Chase showed that when a bacteriophage infects a bacterium, the genetic material (DNA) of the bacteriophage particle is injected into the bacterial host cell and initiates viral multiplication without assistance from the protein coat of the virus. This discovery established the central function of viral nucleic acid in virus synthesis. A new era in understanding the nature of viruses had begun. Much evidence that has subsequently accumulated has shown that all viruses lose their protein coats when they infect the cell, and thereby cease to be virus particles. The protein coat is either discarded and left outside the host, as in the case of the bacteriophage, or is digested inside the host cell, as in animal virus infections. With the removal of the protein coat, the viral nucleic acid is set free in the host cell. Viral multiplication then takes place in essentially three steps: first, there is synthesis of new virus-directed enzymes; second, new viral materials, nucleic acid, and protein are synthesized; third, new viral precursor materials assemble into virus particles. Temporally, the three phases overlap to a greater or lesser extent.

In the bacterial cell that becomes nonproductively infected, an entirely different series of events takes place; the viral DNA becomes attached to the bacterial chromosome and replicates in synchrony with the bacterial DNA. The viral DNA is called prophage in this situation. The prophage-carrying bacterium does not produce virus particles unless provoked to do so by ultraviolet light or other means.

Intracellular parasitism is not unique with viruses. Some bacteria, fungi, protozoa, and mycoplasmas also are intracellular parasites, but it was the intimate nature of viral parasitism that led Luria to refer to it as parasitism at the genetic level. All the manifestations of a viral infection result from the functioning of the viral genetic material in a cell. What does this mean in molecular terms? A fundamental characteristic of all viruses is that they contain only one kind of nucleic acid – DNA or RNA – but not both. All cells and microörganisms possess both DNA and RNA. To understand the nature of viral parasitism, it is necessary to probe into questions that bear on the gene function and replication of the viral nucleic acid. 1) How does the viral DNA or RNA express the genetic information coded in it? 2) By what enzymatic mechanism is viral DNA or RNA replicated in the infected cell? 3) Are viral nucleic acids structurally similar to cellular nucleic acids or do they possess unique features?

Since my primary interest has been in viruses that infect man or animals, I will focus attention on certain animal cell-virus systems. Before considering the relationship of viral to cellular biosynthesis, it is useful first to consider the biosynthesis of macromolecules in the normal, uninfected cell. DNA is the basic genetic material in cells. Gene action in a cell consists essentially of the transcription of a specific sequence of bases in DNA into a complementary sequence of bases in an RNA molecule. This messenger RNA then serves as a template in the synthesis of proteins from amino acids. In this translation step, the sequence of bases in messenger RNA is translated into a specific sequence of amino acids in the protein. Besides messenger RNA, two other kinds are transcribed from the cellular DNA: the ribosomal and the transfer RNAs. Ribosomal RNAs are structural components of the cellular organelle on which protein synthesis takes place – the ribosome. Messenger RNA associates with ribosomes to form polyribosomes. Transfer RNAs, one for each amino acid, serve as adapters for activated amino acids. The transfer RNAs carry specified amino acids to growing peptide chains on polyribosomes.

The great bulk of DNA is located in the cell nucleus, and there it is transcribed into the three kinds of RNA. DNA of the cell is double-stranded, whereas the messenger, ribosomal, and transfer RNAs are single-stranded. During cell division and gene replication, DNA is replicated by an enzyme – DNA polymerase – which assembles deoxyribonucleotides into new DNA chains on the DNA template. Another cellular enzyme – RNA polymerase – catalyzes the synthesis of cellular ribonucleic acids from ribonucleotides on the DNA template. In the synthesis of proteins, amino acid-activating enzymes attach amino acids to transfer RNAs, and link amino acids into peptide chains.

The structural organization of animal cells presents an intricate pattern of distribution of cell membranes, which delimit two main compartments – the nucleus and the cytoplasm. In addition, an extensive network of folded membranes delimits systems of canaliculi and cisternae, which constitute the endoplasmic reticulum and the Golgi apparatus of the

cell. Cellular DNA and RNA synthesis is largely localized in the cell nucleus, whereas cellular protein synthesis takes place mainly in the cytoplasm. The polyribosomes are either free in the cytoplasm or attached to the membranes of the endoplasmic reticulum.

Viral biosynthesis takes place in the cytoplasmic or nucleoplasmic matrix proper, and not within some special membrane-bounded space. However, membraneous structures play an active role in viral reproduction. Virus particles are taken into cells in phagocytic vesicles, which are invaginations of the cell membrane. The synthesis of viral proteins takes place on membrane-bound or free ribosomes. Numerous viruses derive an outer envelope from the cell membrane.

I would first like to consider the replication of the simplest kind of animal virus, which consists of a rather small amount of viral RNA enclosed in a protein coat with icosahedral symmetry.

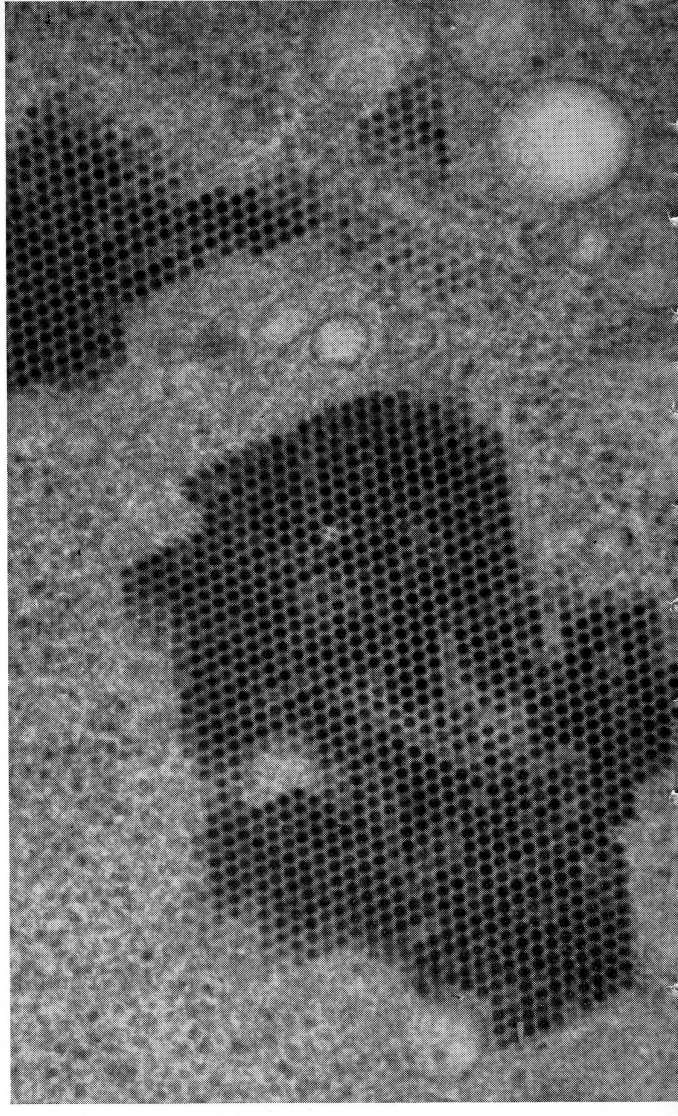
Replication of Polioviruses

Polioviruses are among the smallest of the animal viruses.[2] The individual particles of poliovirus measure 27 mμ in diameter and have a mass of 7 million molecular weight units. The protein shell of the virus consists of repeating structural units. Four protein components in poliovirus have been recognized chemically. Just how they are arranged into the repeating structural units is not as yet known.

The nucleic acid of the virus is located in the interior of the particle. Poliovirus contains 25 per cent RNA, which is in one molecule with a molecular weight of 2 million. This RNA is single-stranded, and the amount in the virus is thought to be sufficient to code for about 10 proteins.

Specific attachment of poliovirus to the cell involves receptors on the cell surface and combining sites on the viral protein coat. Only primate cells possess a suitable receptor for poliovirus. Following attachment, the infecting virus particles are taken up into the cells by a process of phagocytosis. After the protein coat of the virus particles has been removed in some manner, the genetic material of the virus – the viral RNA – is ready to function.

Some years ago, Levintow and his co-workers[3] discovered that viral RNA is unable to replicate unless synthesis of some new protein first takes place in the infected cell. That is, if the synthesis of proteins in the infected cell is inhibited by a drug such as puromycin no new viral RNA is made. We may conclude that cellular enzymes which are present in the cell at the time of infection are unable to catalyze the synthesis of poliovirus RNA. Cellular RNA polymerase, which makes single-stranded RNA on a DNA template, either cannot read the viral RNA or is simply not available to the virus.

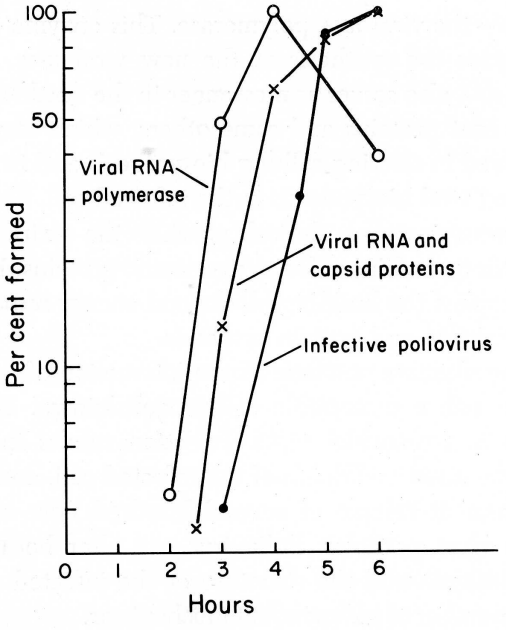


Crystals of poliovirus in the cytoplasm of an infected cell.[2] Sample was taken 7 hours after infection of human cells in continuous culture (HeLa line of cells). Magnification x 72,000.

We know from the work of Darnell and his associates[4] that the genetic material of poliovirus – its single-stranded viral ribonucleic acid – is able to associate with cellular ribosomes and serve directly as a template in the synthesis of new virus-specific proteins.

Thus it appears that the first function the viral RNA performs in the infected cell is to serve as a messenger RNA and make new proteins, among which is a virus-specific RNA polymerase, the enzyme capable of synthesizing viral RNA. A viral RNA polymerase was first found in cells infected with Mengovirus,[5] which, like poliovirus, is a member of the large group of small lipid-free RNA viruses (picornaviruses). Shortly thereafter, a viral RNA polymerase was also demonstrated in poliovirus-infected cells.[6] The viral RNA polymerase can be readily assayed in vitro. The viral RNA polymerase activity is associated with the cytoplasmic fraction of infected cells; the cytoplasmic fraction from uninfected cells shows no significant activity. All four ribonucleoside triphosphates (ATP, GTP, UTP, and CTP) are required for synthesis of RNA by the enzyme. Manganese ions, which stimulate the activity of cellular RNA polymerase, inhibit the activity of viral RNA polymerase. Actinomycin D, which inhibits the synthesis of RNA on a DNA template, has no effect on the synthesis of viral RNA.

The time course of appearance of the viral RNA polymerase activity in infected cells can be seen below. The formation of the enzyme precedes the synthesis of viral RNA and coat proteins and the assembly of infective virus particles. It is clear that maximal amounts of viral RNA polymerase are made before the full yields of viral RNA and virus particles are produced. After reaching maximal levels, the viral RNA polymerase activity in the infected cells decreases sharply, as if the synthesis of the enzyme were turned off by some control mechanism. We know, from experiments with such chemical inhibitors of protein synthesis as puromycin, that cessation of enzyme synthesis rapidly leads to reduced levels of active enzyme in cells and to inhibition of RNA synthesis. This indicates that the enzyme has a short life in the infected cells, and that continued enzyme synthesis is necessary for continued synthesis of viral RNA.

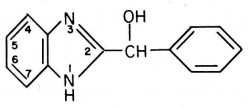


Kinetics of formation of viral RNA polymerase, viral RNA and coat proteins, and poliovirus particles in HeLa cells in culture (adapted from references 4 and 6).

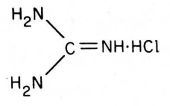
All the ribonucleotide precursors required in poliovirus RNA synthesis are present in the cell at the time of infection. The cells contain the full complement of precursors required for the synthesis of both viral RNA and viral proteins.

The only mechanism by which nucleic acids — either cellular or viral — are known to replicate is by pairing of complementary bases, as proposed by Watson and Crick. In agreement with this principle, when poliovirus RNA replicates, a complementary RNA strand is first made on the parental viral RNA as the template.[7] This complementary strand then acts as template and is transcribed to yield molecules identical to the original parental viral RNA. It is possible that this double copying process requires more than one enzyme, but this has not been established as yet.

Chemical compounds that have a specific effect on



2-(α-Hydroxybenzyl)-benzimidazole (HBB)



Guanidine hydrochloride

Structures of two specific inhibitors of poliovirus replication.

the replication of poliovirus RNA have been found.[8] The hydroxybenzyl derivative of benzimidazole (HBB) and guanidine hydrochloride both selectively inhibit the multiplication of many small RNA viruses, including poliovirus. These compounds have no significant effects on the multiplication of viruses which

belong to other major groups. HBB and guanidine have no effect on cellular RNA synthesis at concentrations sufficient to inhibit significantly the multiplication of sensitive viruses.

Studies of the mechanism of HBB and guanidine action provide an approach to a highly specific step in viral RNA synthesis. Results which we obtained some time ago indicated that these chemical compounds do not interfere with the growth of new viral RNA chains once their synthesis had started. Dr. Lawrence A. Caliguiri and I have recently obtained evidence that guanidine blocks the initiation of new viral RNA chains. Guanidine rapidly inhibits virus-specific RNA synthesis in cells infected with drug-sensitive virus. The slight effect on virus-directed protein synthesis is probably secondary to this inhibition. Analyses of extracts of infected guanidine-treated cells have shown a marked reduction in enzyme-template complexes and in newly-formed and nascent viral RNA strands. Our results indicate that the small amount of viral RNA that is completed in the presence of guanidine is able to associate with ribosomes and be incorporated into mature virus particles in spite of the presence of the chemical.

We can ask if the new RNA polymerase that appears after infection is, in fact, coded by the viral genome, or if the virus merely induces the cell to make a protein which it ordinarily does not make, but for which the information is stored in the cellular genome.

To date, the strongest evidence bearing on this question comes from studies of virus mutants that differ in their sensitivity to the virus-specific inhibitors. The primary action site of the virus-specific drugs hydroxybenzyl-benzimidazole and guanidine clearly involves the mechanism for viral RNA synthesis. The step affected is under the genetic control of the virus, because mutants of the sensitive, wild-type virus have been isolated, and have been found to be either drug-resistant or drug-dependent. While guanidine inhibits the synthesis of the RNA of the wild-type drug-sensitive viruses, guanidine-resistant mutants are able to replicate their RNA in the presence of the inhibitor. Quite unexpectedly, guanidine-dependent mutants have been found which require the drug to synthesize viral RNA. Available evidence suggests that dependence and sensitivity involve opposite drug effects at the same site of action. Further work is needed to substantiate the present hypothesis that these virus-specific chemical compounds affect the initiation of the synthesis of viral RNA chains. If the hypothesis proves correct, it will be attractive to consider the possibility that poliovirus RNA undergoes mutations that express themselves by a change in structure of the viral RNA polymerase, and that this change affects the reactivity of the enzyme toward specific drugs.

TABLE I

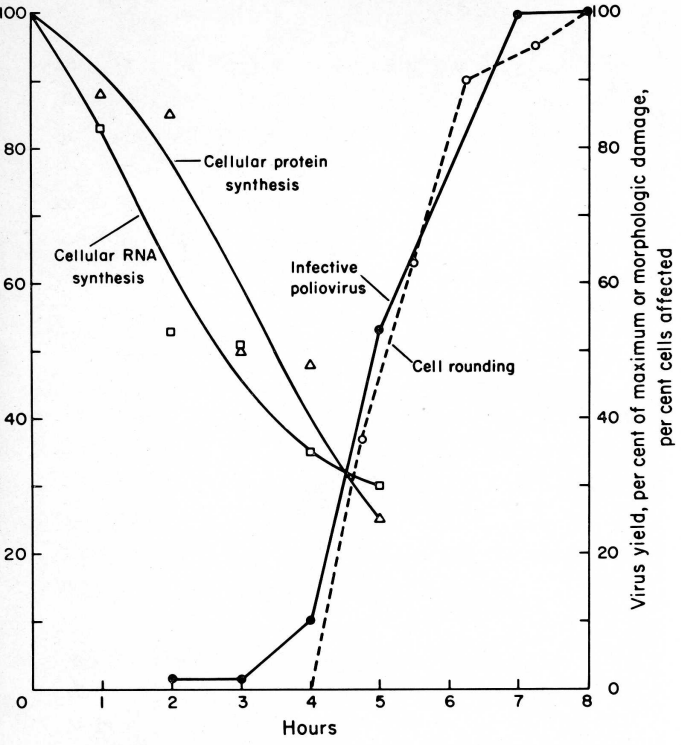
Effects of Guanidine on the Synthesis of Poliovirus RNA

Virus	*Guanidine*	*Synthesis of viral RNA*
Sensitive (wild type)	Absent	+
Sensitive (wild type)	Present	−
Resistant mutant	Absent	+
Resistant mutant	Present	+
Dependent mutant	Absent	−
Dependent mutant	Present	+

To summarize the cardinal features of the virus-cell interaction between poliovirus and susceptible host cells: the cell plays a vital role in the penetration of the viral genetic material into the cytoplasmic matrix, where viral multiplication takes place. However, replication of the viral genetic material cannot occur unless the viral RNA first functions as a messenger RNA in the synthesis of a new virus-specific enzyme – the viral RNA polymerase. This enzyme then catalyzes the synthesis of the new viral RNA. The viral RNA also serves as messenger in the synthesis of viral coat proteins and some others, which may be involved in altering cellular biosynthesis and in regulating viral biosynthesis in the infected cell. Except for messenger RNA, the cell provides the entire synthesizing machinery for virus-specific proteins. It also supplies the building blocks and energy required in viral RNA and protein synthesis.

The ultimate outcome of the interaction of poliovirus with a susceptible cell is well known. Poliovirus is a cytocidal virus. Infection results in the degeneration and death of the infected cell, and the subsequent release of several hundred new infectious virus particles. Poliovirus can alter both the biosynthesis and the structure of the infected cells by a number of independent mechanisms.

Poliovirus quite rapidly depresses the synthesis of cellular RNA and of protein.[9] Many of the cellular polyribosomes that were synthesizing cellular pro-



Effects of poliovirus infection on synthesis cellular RNA *and protein and on cell structure (adapted from reference 9).*

teins at the time of infection are rapidly dispersed after infection, and, as a consequence, cellular protein synthesis becomes inhibited. New polyribosomes that will make viral protein are then constituted. Also, the cellular RNA polymerase becomes inactive and cellular RNA synthesis declines. These effects occur early in the infected cells, prior to the formation of significant quantities of new virus. What causes these inhibitions in cellular protein and RNA synthesis is not known, but it appears that they may be caused by some as-yet-unidentified virus-directed proteins that are synthesized very soon after infection, before the viral coat proteins are synthesized.

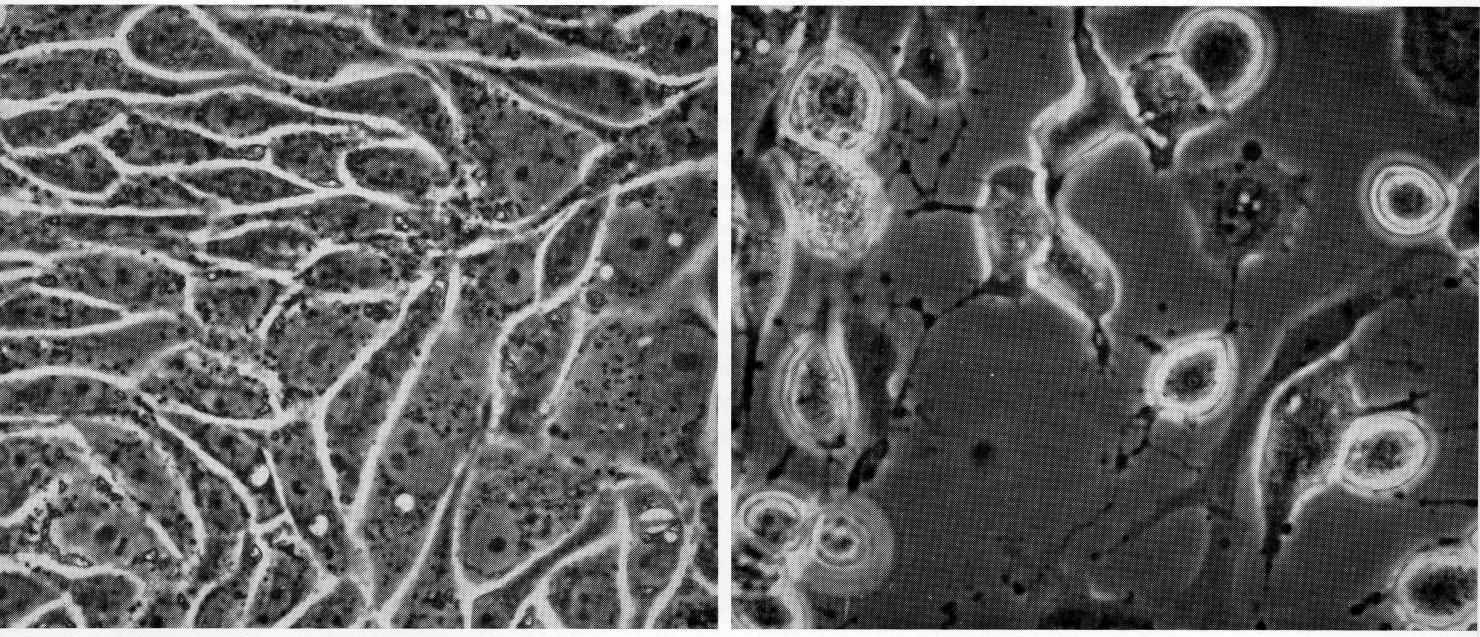
When the synthesis of viral RNA polymerase, viral RNA, and coat proteins gets underway in infected cells, morphological changes become apparent. These involve the membraneous structures of the cells. The most striking of these is the rounding of cells, as shown below. This morphological change, which is a prelude to disruption and degeneration of the infected cell, is caused by newly-synthesized viral proteins that are probably the coat proteins of the virus.[9] There is some evidence that this morphological change may be mediated through the release of lysosomal hydrolytic enzymes.

Another striking change is the appearance in the cytoplasm of numerous small membrane-enclosed bodies, some of which contain virus particles, seen on page 18.[2] These changes may be viewed as an attempt on the part of the cell to segregate the foreign protein that is synthesized in it, but in spite of this, the infected cell eventually succumbs.

Replication of Poxviruses

Polioviruses are among the smallest and simplest animal viruses. At the other end of the spectrum of animal viruses are poxviruses, which contain about

Changes in cell shape caused by poliovirus in monkey kidney cells in culture. LEFT, *uninfected culture;* RIGHT, *infected culture. Magnification* x *600. (Phase contrast photomicrograph taken by Dr. R. Bablanian.)*

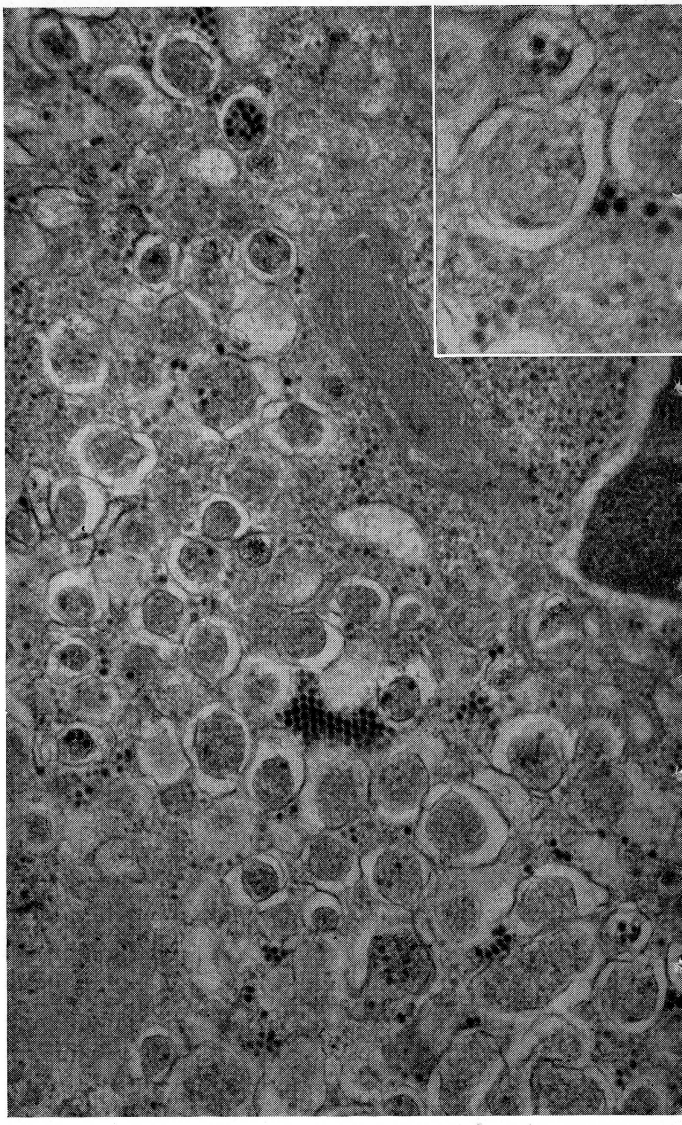


160 million molecular weight units of double-stranded DNA. Poxviruses are the largest and most complex animal viruses known. One member of this group is vaccinia virus, which measures 260 mμ in its longest dimension. The mass of vaccinia virus is nearly 100 times greater than the mass of poliovirus. The molecular weight of the nucleic acid of vaccinia virus is also almost 100 times greater than that of poliovirus RNA. Theoretically, the DNA in vaccinia virus can code for several hundred proteins, but fewer than 20 have so far been recognized. The DNA is double-stranded, and thus has the secondary structure of the cell DNA.

A number of years ago, we were interested in determining the metabolic requirements for the multiplication of this large DNA virus. We found that the synthesis of RNA was an essential requirement. When we chemically inhibited the synthesis of RNA or caused its degradation with ribonuclease, vaccinia virus was unable to multiply.[10] Recent work in several laboratories has demonstrated that from the viral DNA are transcribed a whole series of messenger ribonucleic acids that function as templates in the synthesis of numerous viral proteins.[11] The vaccinia messenger RNAs, made early in the growth cycle of the virus, are smaller than messenger RNAs made later. Similarly, the proteins synthesized early are of lower molecular weight than those synthesized later.

The question has been whether vaccinia virus used cellular RNA polymerase to make its messenger RNAs for the synthesis of virus-specific proteins. A double-stranded DNA cannot itself function as messenger in protein synthesis. Unlike poliovirus RNA, vaccinia virus DNA cannot associate with ribosomes and serve directly as a template in the synthesis of enzyme proteins or viral structural proteins. Therefore, it seemed that vaccinia DNA was obliged to use cellular RNA polymerase to make the messenger RNAs required in protein synthesis. Recently, however, it has been discovered that the virus particle itself contains an RNA polymerase which is capable of transcribing ribonucleic acids from the viral genome.[12]

Among the proteins manufactured in vaccinia-infected cells, there is a DNA polymerase which is immunologically distinct from the DNA polymerase of the host cell. It is highly probable that this is the



Membrane-enclosed bodies in the cytoplasm of a poliovirus-infected HeLa cell.[2] Virus particles, either singly or in groups, are lodged in the cytoplasmic matrix. Magnification x 39,000; insert x 59,000.

enzyme that catalyzes the synthesis of the viral DNA. In addition to the DNA polymerase, a number of other enzymes that function in the pathway of nucleic acid synthesis have been detected. Thus, as with poliovirus, the host cell does not provide the entire metabolic machinery required for viral replication. The replication of vaccinia virus has features of great interest, because both the viral messenger RNA and the virus-specified proteins are made sequentially, and there appear to be effective control mechanisms for turning off at the appropriate time the synthesis of the enzyme proteins made early in the replicative cycle. The essential features of the

TABLE II

Genetic Function and Replication of Viral Nucleic Acids

	Poliovirus	*Vaccinia virus*
Genetic material	Single-stranded RNA (m.w. 2 x 10^6)	Double-stranded DNA (m.w. 160 x 10^6)
Messenger RNA	Viral RNA	Virus-specific RNAs
Enzymes for synthesis of RNA	Made during the viral growth cycle	One enzyme carried into cells in virus particles
Enzymes for synthesis of DNA		Made during the viral growth cycle

multiplication of polio and vaccinia viruses are summarized and compared in the table above.

Like polioviruses, poxviruses also have marked effects on cellular biosynthesis and structure. The synthesis of cellular RNA and proteins becomes inhibited and the cells degenerate and die.

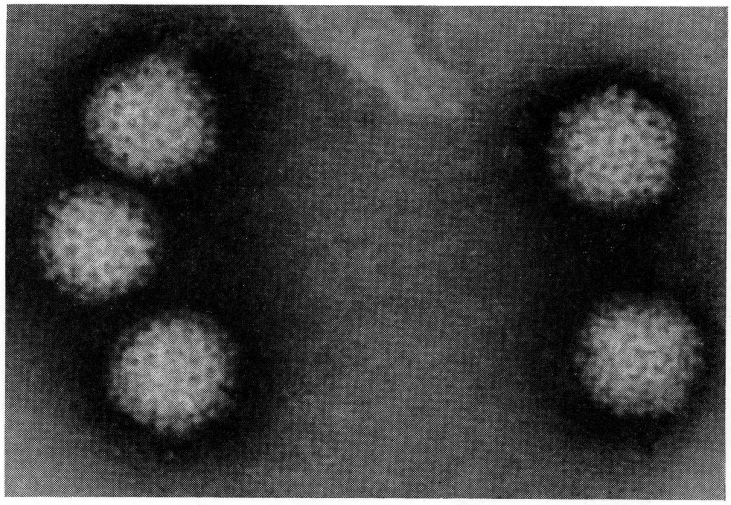
So far, we have discussed a virus – the poliovirus – whose genetic material is single-stranded RNA, and one – the vaccinia virus – whose genome consists of double-helical DNA. In the first, the structure of the viral nucleic acid is similar to that of cellular messenger RNA; in the second, the viral nucleic acid resembles cellular DNA.

Replication of Reoviruses

In 1963, Dr. Peter J. Gomatos and I found that the genetic material in reovirus is a double-stranded ribonucleic acid of considerable size, a type of nucleic acid not previously known to occur either in viruses or in cells.[13] Reoviruses occur widely in the respiratory and enteric tracts of man and animals, but as yet little is known about their relation to disease. Reovirus is of medium size.[14] The diameter of the virus particle is 70 mμ. The outer protein shell of the virus possesses icosahedral symmetry.

We became interested in reovirus because of its behavior in cultured cells. We observed that the time course of multiplication of reovirus was more similar to that of DNA than that of RNA viruses, as the latent period of 7 hours was relatively long and the rate of virus production was relatively slow.[15] Reovirus-infected cells showed accumulations of granular material in the perinuclear area. These inclusions, known to contain virus particles, stained pale green with acridine orange as if they contained double-stranded DNA, but examination with the Feulgen stain showed that they did not. The staining characteristics raised the possibility that the viral RNA might be double-helical.

We isolated the RNA from reovirus and determined a number of its physical and chemical properties.[13] The properties of reovirus RNA, summarized in the table, shown below, provide strong evidence that it is indeed a double-helical structure. An examination of the base composition of reovirus shows that in mole per cents guanine equals cytosine and adenine equals uracil. Purines to pyrimidines are at a one-to-one ratio. Such complementarity in base ratios is



Reovirus.[4] *Magnification* x *250,000*

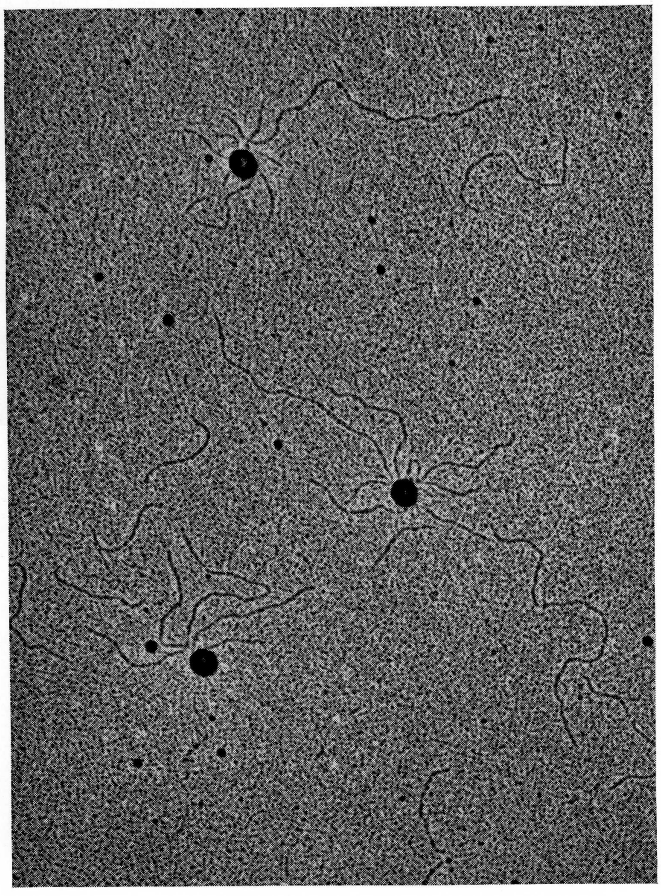
TABLE III

Properties of Reovirus Ribonucleic Acid

Molecular weight	>10.2 x 10^6
Base composition	
Guanine	22%
Cytosine	22%
Adenine	28%
Uracil	28%
Thermal denaturation curve	Sharp
Tm	93°C
Reactivity with formaldehyde	Low
Sensitivity to ribonuclease	Slight

characteristic of base-paired double-stranded nucleic acids. The sharp thermal denaturation, or melting curve, of reovirus RNA is also characteristic of a double-stranded structure. The melting temperature is high: 93°C. On slow cooling the RNA almost completely regains its original double-helical configuration. Reovirus RNA in its native state shows low reactivity with formaldehyde, as would be expected of an internally hydrogen-bonded double-helical structure. Finally, reovirus RNA is resistant to pancreatic ribonuclease. The conclusion that reovirus RNA is a double-stranded structure has been confirmed by x-ray diffraction studies and electron microscopic examination.

The electron micrograph on this page shows reovirus RNA released from virus particles.[16] The strands of RNA are of uniform width and have a diameter expected of a double-helical structure. All strands are linear and unbranched. The variable length indicates breakage of strands during preparation.

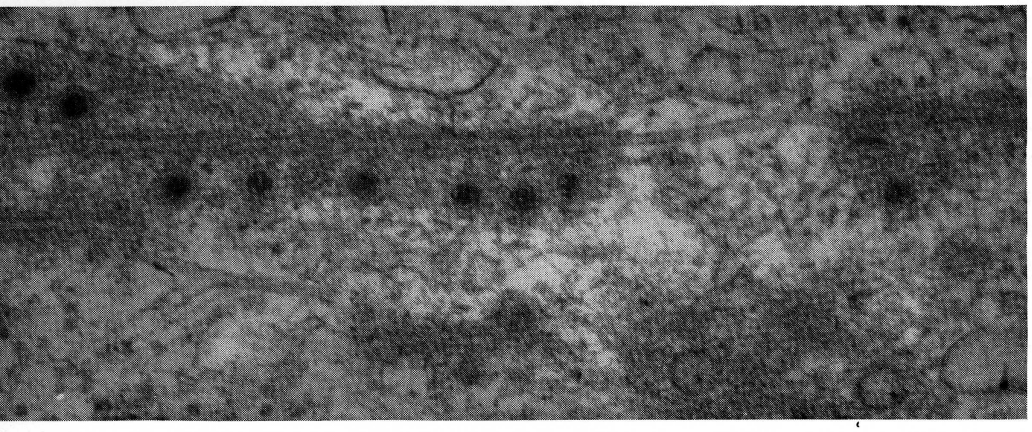


Reovirus RNA *released from virus particles. Magnification x 41,000. (Courtesy Dr. W. Stoeckenius)*

The RNA of reovirus makes up 15 per cent of the mass of the virus particle. On a mass basis, each virus particle contains in excess of 10 million molecular-weight units of RNA. Hence, reovirus contains more RNA per particle than does any other RNA virus. A molecule of reovirus RNA can theoretically code for over 20 different proteins.

Under cell culture conditions, infection with reovirus has little effect on cellular RNA and protein synthesis. This is in sharp contrast to inhibition of cellular RNA and protein synthesis by virulent viruses such as polio and vaccinia viruses. However, reovirus does affect cellular DNA synthesis, which gradually becomes inhibited as the virus multiplies in mouse cells in culture.[17] Furthermore, reovirus preferentially multiplies in association with the microtubules of the mitotic spindle, which is illustrated at right.[18] The thought has been expressed that reovirus might therefore cause abnormalities in the distribution of chromosomes during cell division.

As has already been mentioned, reoviruses — of which there are three immunological types — occur widely in man and in many animal species. Most infections are not associated with apparent disease. However, observations concerning the pathogenicity of two structurally-related plant viruses have provided a strong stimulus for the investigation of possible pathogenic properties of reoviruses. While working on the characterization of reovirus RNA, we became aware that two plant viruses are quite similar to reovirus in size and shape. The wound-tumor virus grows in many different plants and is transmitted by an insect vector, the leaf hopper, in which the virus also multiplies. The wound-tumor virus causes tumors in sweet clover and other plants. It is of great interest that while a plant may be systemically infected with wound-tumor virus, tumors are produced only at sites at which the plant cells are triggered to divide in response to local stress or injury. Our studies of wound-tumor virus RNA have shown that it, too, is double-stranded.[13] Subsequently, it has been demonstrated that the rice dwarf virus also contains double-stranded RNA. As the name indicates, this virus causes dwarfing in rice plants. Thus, double-helical RNA appears to be a unique constituent of certain structurally-related viruses which are widely distributed among animal, insect, and



Microtubules of the mitotic spindle with several reovirus particles embedded within a dense material.[18] Uncoated segments of microtubules are also seen. Magnification x 94,000. (Courtesy Dr. S. Dales)

plant species, So far, double-helical RNA has not been found in normal cells.

The similarity of the structures of reo-, wound-tumor, and rice dwarf viruses and of their nucleic acids raises the question of a possible evolutionary relationship among these viruses that have such diverse hosts. We have not found any evidence of an immunologic relationship between reovirus and wound-tumor virus. Thus, it does not seem likely that one has arisen from the other, at least not in recent times.

Recently, type 3 reoviruses have been isolated from tumor cells from cases of human lymphoma in Africa.[19] In the mouse, reovirus type 3 induces an acute, usually fatal, neonatal infection.[20] However, in some survivors the acute infection is followed by a stunting of growth. When the spleen cells from these stunted mice are given to isogenic new-born mice, many develop an acute and fatal runting syndrome. Surviving mice may develop a lymphoma or may develop normally. The significance of the isolation of reovirus from human lymphoma and of the findings in the mice is not yet clear, but more work along these lines is certainly indicated.

Recent studies by Dr. Gomatos and other investigators[21] have brought to light additional striking characteristics of reovirus RNA and of the mechanism by which the virus replicates.

Commonly, reovirus RNA extracted from virus particles is not in the form of molecules of uniform size representing the whole genome of the virus; rather, it is in three pieces, with respective molecular weights of approximately 800 thousand, 1.4 million, and 2.4 million. This might seem to be fortuitous and merely an artifact of the extraction procedure. However, virus-specific, single-stranded RNAs of three different size groups are made in cells that have been infected with reovirus. These ribonucleic acids are produced in relative amounts that are constant through the exponential growth of virus.

Hybridization experiments between these single-stranded RNAs and the pieces of double-stranded reovirus RNA obtained from the virus have given evidence that the largest single-stranded RNA is complementary to the largest piece of double-stranded viral RNA, and is probably transcribed from it. Similar correspondence exists for the intermediate and the small single-stranded RNAs and the respective intermediate and small pieces of double-stranded viral RNA. These single-stranded RNAs are at least in part messenger RNAs, as they can be found associated with polyribosomes in the infected cells, where they presumably function as templates in virus-specific protein synthesis. Taken together, the evidence indicates that the genome of reovirus consists of three distinct segments.

The question of what enzymes function in the synthesis of the single-stranded messenger RNA and the double-stranded viral RNA cannot be answered today. There is evidence that synthesis of the single-stranded RNAs, as well as the double-stranded viral RNA, requires prior synthesis of proteins.[22] The proteins required may well be virus-specific RNA polymerases. If so, the question is: What serves as the

single-stranded messenger RNA in the synthesis of the enzyme proteins that are required for synthesis of virus-specific RNAs? There appear to be at least two possibilities: 1) reovirus may contain not only double-stranded viral RNA but also some single-stranded messenger RNA; 2) the double-stranded RNA of reovirus may separate into single strands in the cell. Future work should provide answers to these questions.

General Conclusions

I have discussed the replication and virus-cell interaction of only certain selected viruses. There are other very interesting problems which concern the replication of viruses, of which I should particularly like to mention two: the nonproductive infection of cells with tumorigenic DNA-containing viruses, and the steady-state virus-cell relationship in infections with a number of RNA viruses possessing helical nucleocapsids.

Drawing on all the information now at hand, certain conclusions can be stated. Each virus multiplies from its nucleic acid. Single-stranded viral RNA can itself serve as messenger RNA in virus-directed protein synthesis, but double-stranded DNA or RNA cannot. In the latter case, viral messenger RNA is made on the double-stranded viral nucleic acid template. In the replication of a single-stranded viral RNA a complementary strand is made which serves as a template for new viral RNA. The precise mode of replication of double-stranded viral nucleic acids has not yet been demonstrated. The nucleic acids of animal viruses are made of the same constituents as the nucleic acids of host cells. However, they possess virus-specific features.

Although parasitic in most regards, viruses perform the vital reaction of replicating their nucleic acid with enzymes of their own, and not with enzymes of the host. Chemical inhibitors of small RNA viruses have been found that selectively inhibit the replication of viral nucleic acid.

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WALTER A. JACOBS

1883-1967

DR. WALTER A. JACOBS, a distinguished early Member of The Rockefeller Institute, died at his home in Los Angeles July 12. He had become Emeritus in 1949 but continued active work until ten years ago when ill health kept him from his beloved laboratory. His fundamental studies in chemotherapy and later on the cardiac drugs and the alkaloids of ergot contributed much to the early reputation of The Rockefeller Institute and to the establishment of its role in chemical and medical research.

Dr. Jacobs was born in New York City near the site of the present Pennsylvania Station. He received all his earlier education in New York. His father, a tailor, was much interested in science – particularly astronomy – and spent much time with the young boy building a telescope. It was in reading books about the stars that Walter first became interested in the spectrum and then in chemistry and geology. In order to encourage this interest his father built a shack for him in the back yard of their Brooklyn home to serve as a laboratory so that Walter could experiment to his heart's content. His father also provided books which led the boy to satisfy his curiosity by reading and study as well as by experimentation, and thus developed the proper balance which was so fruitful for him throughout his long and outstandingly successful scientific career.

Dr. Jacobs graduated with the B.A. degree from Columbia University in 1904. He stayed an additional year to study with Professor Marston Bogert, an eminent organic chemist of his time, and then went to Berlin to study with Emil Fischer. At that time it was an honor to be accepted in Fischer's laboratory. This young American proved himself without delay. By the end of two years he had published two papers on the synthesis of the optically active forms of serine, isoserine, and diaminopropionic acid, had written his thesis, and had passed the examination for his Ph.D.

In 1907 research positions were few in this country even for a young man with the excellent record Jacobs had made. It was natural for him to seek the advice of Dr. P. A. Levene at the newly established Rockefeller Institute for Medical Research. Dr. Levene, unfortunately, had recently filled his staff and had no further positions available, but when he reviewed Jacobs' research record with Fischer he asked Dr. Flexner, the Director of the Institute, for special permission to accept yet another staff member. Dr. Flexner and the Board of Directors were impressed with the applicant's ability and gave him an appointment as a Fellow at a salary of $1200 per year. This policy of making a place, if at all possible, for a man of outstanding talent who wants more than anything else to work at The Rockefeller Institute, has thus been a policy from the very beginning.

Jacobs was immediately productive in Levene's pioneering studies in the field of the nucleic acids. For example, they were the first to show that the sugar moiety in the ribonucleic acids was D-ribose. A series of papers on inosinic and guanylic acid was

published. He was soon promoted to Assistant and then to Associate.

At that time Dr. Flexner's chief research interest was poliomyelitis. It had been reported that hexamethylenetetramine preparations were capable of delaying the death of monkeys inoculated intracerebrally with active polio virus. Dr. Flexner wanted to follow this lead and test a series of quaternary hexamethylenetetraminium salts as chemotherapeutic agents. Dr. Jacobs was asked initially to make some of these compounds to be tested in Dr. Flexner's laboratory and soon was invited to establish a laboratory of chemotherapy independent of Dr. Levene's laboratory. He was promoted to Associate Member and was soon joined by Dr. Michael Heidelberger who had just returned from a year's study with Willstätter in Zurich. Dr. Heidelberger was a collaborator for the next nine and a half years.

Dr. Flexner's interest in chemotherapy was greatly stimulated by Paul Ehrlich's ideas about chemotherapy and his success in the development of Salvarsan, a synthetic arsenical drug announced in 1910, which was the first effective agent against syphilis. The Rockefeller Institute had in fact assisted in Ehrlich's discovery through a substantial grant. While some of the numerous hexamethylene derivatives synthesized showed bactericidal properties and were also tested against H *influenzae*, none of them came into extensive use.

In contrast, Salvarsan came quickly into wide use, but with the onset of World War I supplies from Germany were cut off. Attempts in other laboratories to synthesize it from the directions given in the patent were unsuccessful. Jacobs and Heidelberger were asked to take up this problem and soon had confirmed the methods for its synthesis. More importantly, the experience stimulated Dr. Jacobs to think of structures which would be more stable and less toxic. He reasoned that pentavalent arsenic would be more stable and that the derivative, in order to be less irritant, should be an amide rather than one with a free carboxyl group. A program for biological testing was set up, with Doctors Wade Brown and Louise Pearce in charge of the testing. Almost the first derivative tested proved to be of great effectiveness against sleeping sickness but not against the primary syphilis infection. With further study, however, it was found to be effective against the later stage of syphilis. As time passed this drug, named Tryparsamide, became of the greatest importance in the treatment of the sleeping sickness scourge in vast sections of Africa. Its discovery made Jacobs world-famous in chemotherapy but he received no formal recognition until 1953, almost forty years later, when he was highly honored by the Belgian government with a monetary award and made an Officer of the Order of Leopold II. Doctors Heidelberger, Brown, and Pearce were also honored.

Later work involving the synthesis of numerous other arsenicals, resulted in a few with promise but none as effective as Tryparsamide, the one first envisioned. As time passed Dr. Jacobs' interest shifted to bacterial infections, with Dr. Lloyd Felton doing the biological testing on Pneumococcus. Soon large numbers of bactericidal compounds, including interesting derivatives of the cinchona alkaloids, were tested, but none proved practical because of toxicity or side effects.

Some of the derivatives synthesized were azo dyes made by coupling various benzene derivatives to the alkaloids. One of these derivatives was made from sulfanilamide. Jacobs and Heidelberger even suggested that such dyes would break down to sulfanilamide in the tissues and that this could be the active agent, but the suggestion was never followed. About fifteen years later an azo dye "Prontosil" made from sulfanilamide was patented as a bactericide, and Domagk received the Nobel Prize in 1939 for the discovery of the chemotherapeutic action of the sulfanilamides. Jacobs, Heidelberger, and Felton unfortunately had not tested sulfanilamide against susceptible bacteria in their work.

At about this time Dr. Jacobs had become discouraged with the endless synthetic approach to chemotherapy and turned toward the structural investigation of naturally occurring drugs of unknown constitution. His first choice centered around a large group of poisonous substances including digitalis, strophanthus, squill, and convallatoxin used in the treatment of heart disease. He changed the name of his laboratory to "Chemical Pharmacology." He and his collaborators established the major features of the chemical nature and relationships of this complicated group of important drugs during the ensuing fifteen years. In the end they all proved to be sterol derivatives, but it was not until 1933 that the correct ring

structure, the perhydrocyclopentenophenanthrene ring structure, was established for the sterols. At this time all the careful work of Jacobs' laboratory for the preceding fifteen years could be correlated. The poisons all proved to be modified sterol derivatives attached to various plant sugars. Dr. R. C. Elderfield was his main collaborator in this final correlation. His other collaborators had been Doctors A. M. Collins, A. Hoffmann, E. L. Gustus, A. B. Scott, E. E. Fleck. T. B. Grave, E. W. Wignall, and N. M. Bigelow. In work in a closely related field, the triterpenes, he was assisted by Doctors J. C. E. Simpson and O. Isler.

These studies quite naturally established Jacobs as a leading authority in the sterol field, along with Professors Windaus and Wieland in Germany who were awarded the Nobel Prize in 1932 for their structural work in this area. It is of interest that their ring structure proved to be incorrect. Jacobs had at that time a rich field for continued study but decided to abandon it because he felt that the nearly endless detail would be taken up by other chemists with less of the pioneering spirit. He wished to work undisturbed in a new field if at all possible.

In 1932 he began to investigate another class of poisonous drugs with great pharmacological interest, the alkaloids of ergot, whose chemical nature was completely unknown at that time. They had long been used for postpartum hemorrhage in child birth and more recently for migraine headaches. He was soon joined in this study by the writer. In 1934 they isolated a hydrolysis product from the alkaloids to which they gave the name "Lysergic Acid" and showed it to be present in each member of the large family of alkaloids. The diethylamide of this lysergic acid was later synthesized from lysergic acid at the Sandoz laboratories in Switzerland. This derivative is the now famous "mind expanding" drug whose popular name is LSD. The structure of lysergic acid and the major features of the structures of the known alkaloids were established in Jacobs' laboratory. During the next four years Jacobs' work in this field, assisted by Doctors G. Gould and F. C. Uhle, was concluded with the synthesis of dihydrolysergic acid.

When the study of the nature of the alkaloids of ergot was well-advanced, Jacobs' interest again turned to two other large classes of toxic plant alkaloids of unknown structure, the alkaloids of aconite and of veratrine. His collaborators in these studies were Doctors Elderfield, Craig, Uhle, C. Huebner, and W. Pelletier. The veratrine alkaloids proved to be sterol derivatives while the aconite group was found to belong to the diterpenes. In both these large classes the real pioneering work was accomplished in Jacobs' laboratory, but the intricate details could only be established with the coming of infrared spectroscopy, nuclear magnetic resonance, and x-ray diffraction which became available after Jacobs' retirement. Dr. William Pelletier contributed importantly to these later refinements.

It is approximately ten years since Jacobs left his laboratory, during which time the technical approach to the elucidation of the structure of natural products has undergone unprecedented advances. By comparison with the methods of today, the work of Jacobs' laboratory was all accomplished with almost primitive tools. Purifications were followed by painstaking distillations, recrystallizations, and microanalysis. During all this time the laboratory was extremely fortunate in having the services of a master microanalyst, Mr. D. Rigakos, and a superb technician, Mr. Otto Post, who built many clever pieces of equipment for special purposes.

Dr. Jacobs was a highly respected and active member of The Rockefeller Institute for fifty years. He was a very modest and retiring man with an extraordinary judgment of the correctness and reliability of a chemical procedure. His selection of important problems was part of the basis for his outstanding and consistent success. He insisted on complete and repeated experimental verification before publication of any result, a conservatism which in certain cases resulted in a loss of priority.

An account of such a successful research career would scarcely be complete without speaking of the contribution of his wife, Laura Dreyfoos, whom he married in 1907. She was the ideal wife of a dedicated scientist, sharing his interest in geology and music, particularly the Wagnerian operas and the works of Beethoven. He in turn shared her interest in art and in botany. Their two-month summer vacations were spent usually in camping, hiking in the mountains, and in photography. The artistic side of his nature was revealed by the many beautiful slides he would sometimes show when entertaining friends in his home.

LYMAN C. CRAIG

CONSTRUCTION OF NEW BUILDING

Ground breaking begins on October 26 for the foundation of the new building on the south campus, as President Bronk and Paul R. Penndorf, Superintendent of Buildings and Grounds, discuss plans for the seventeen-story structure.

CONSTRUCTION of the largest building to be erected on The Rockefeller University campus was begun in October 1967. The towering structure for which foundations are now being completed south of Gasser Hall, will comprise 139,000 square feet of floor space on 17 floors.

Entrance to the building will be from a terrace a few steps below the entrance to Gasser Hall with which the terrace will connect. This will lead to a spacious lobby on the north. Also on this level will be a large dining area on the east and south with kitchens on the west. On the floor above there will be two lecture rooms, each of which will seat 75, with special acoustic and electronic devices for visual and oral presentations. Also, there will be four conference rooms that will seat as many as 40 in each. Above there will be 13 floors for general research and academic uses. Below the entrance level will be one floor for general building services and a basement.

Because the building will be carried by four corner towers, the interior of each floor will be entirely free of columns excepting at the center where four elevators and stairwells will be located. The absence of interior supporting columns will make possible maximum flexibility in the design of laboratories and the placement of partition walls between rooms. The massive supporting towers also carry major services such as ducts for air conditioning the building and exhausts from chemical hoods.

Plans for the building began to be developed in 1965 by President Bronk, Bernard Lupinek, Superin-

tendent of Buildings and Grounds, and Paul Penndorf, then Associate Superintendent. With the approval of the Trustees, Nelson Aldrich and his firm, Campbell, Aldrich and Nulty, were employed in January 1966 to prepare architectural plans. Their first concept was a three-phase scheme in a "finger" arrangement. Each finger would have been a self-supporting element so that the ultimate building could be built in three separate stages. Further consideration of the most effective use of land area available for future development of the University and recognition of the fact that annual escalation of building costs would increase the ultimate cost of a completed building led to the decision to develop the scheme that would give the University at once as much basic "raw space" as would be needed for ultimate development in the foreseeable future.

An important factor in the furtherance of the building program has been the support of The Population Council. Since 1956, the Bio-Medical Division of the Council has been domiciled at the Rockefeller in laboratories constructed by the Council in Flexner Hall. With the rapid development of the Council's activities and their growing importance, the need for more space became obvious to agencies and individuals supporting the Council. In 1965, the Ford Foundation made a grant of $6,000,000 for the Bio-Medical Division with the provision that $750,000 could be used for the construction of physical facilities provided an additional $750,000 was secured from other sources; that has been done. Subsequently, the Ford Foundation provided an additional $500,000 for construction of a primate research facility. Accordingly, The Population Council will contribute approximately $2 million to the cost of the building in which they will have an appropriate share of space.

Throughout the development of designs for the building, and negotiations with architects and contractors, President Bronk has been aided and counseled by Dr. Lindsley F. Kimball, Chairman of the Trustees' Building Committee that includes William O. Baker, Donald K. David, and Eli Whitney Debevoise. As representatives of the faculty, Dr. Bronk appointed a committee comprising Lyman C. Craig, H. Keffer Hartline, Edward Reich, A. Pais, and Sheldon J. Segal.

The Thomas Crimmins Contracting Company has been awarded the contract for excavation and foundations. It is expected that the work will be completed by early March after which the major structural work will begin under a general contract still to be awarded.

Bernard Lupinek Retires

BERNARD LUPINEK came to The Rockefeller University as an office boy in 1911. His duties – less specialized than his title might indicate – included serving as oiler in the Power House. Working there with the boilers and other equipment, under the guidance of the engineers, stimulated an interest in mechanical engineering which grew steadily in the years ahead.

Barney's headquarters in those early years were in the general location of the present Founder's Hall reception desk. One of the qualities which distinguished him from the start was his expectation that everyone, from the faculty to the stokers in the coal bin, would maintain the high standards of the University in their appearance and behavior. As Mr. Campo, the University Superintendent of Purchases, recalls his first days here in 1917:

> Barney met me in the corridor one morning and noticed that my tie was missing and my shoes were not polished. He remarked, "If you want to remain in the good graces of the Director, Dr. Flexner, you should always wear a tie and keep those shoes polished."

For some 15 years Mr. Lupinek took evening courses ranging from stenography and commercial law to physics, engineering, and architecture. Mr. Lupinek's growing technical knowledge of the University's physical plant, as prodigious as it was, was equaled by his warm and understanding associations with all faculty and personnel. In 1927 he was appointed Superintendent of Maintenance. However, maintenance and alterations of existing facilities were only a portion of his duties. Construction of Welch Hall began at this time, and Theobald Smith and the North Animal House soon followed.

The outmoded condition of many of the existing laboratories and the necessity of constructing laboratories in Theobald Smith Hall gave Barney Lupinek the opportunity of designing and laying out new facilities in keeping with the needs of the Faculty.

His knowledge and understanding of the many facets – ranging from lighting, ventilation, bench

services, and new materials – enabled him to complete laboratories which were bright, functional, attractive, tailored to the individual's needs, and laid out within the confines of the space allotted. No two laboratories at the University were alike, but all unmistakably bore the "Lupinek touch." Since he was a perfectionist, Barney's designs were never static, and he constantly strove to improve each succeeding laboratory.

For his work in these fields he is not only respected and admired by our own faculty, but by architects and laboratory heads from many parts of the world who have sought his advice.

During World War II, The Rockefeller Foundation Virus Laboratories, located at the University, were requested to produce all the yellow-fever vaccine which was urgently needed by the Armed Forces. This meant that facilities for the manufacture of the vaccine had to be set up as rapidly as possible on the fifth floor of Theobald Smith Hall. Barney was called upon to lay out and supervise the necessary alterations, and he succeeded in completing this task in the remarkably short time of three weeks!

My first acquaintance with The Rockefeller University and Mr. Lupinek was early in 1949, when I was directed to establish lines and grades for the greenhouses located north of 64th Street and also on the roof of Flexner Extension.

Mr. Eugene Cotter, a project manager for the Vermilya-Brown Company Inc., introduced me to Mr. Lupinek. His natural warmth, his courtesy, and the complete grasp he had of construction work impressed me. After our first meeting I worked with Barney Lupinek on various construction projects, such as the addition to the Hospital, and Dr. Shope's piggery.

In February of 1955 Mr. Lupinek asked me to join his group and I had the pleasure of working with him on the expansion program which had already started under Dr. Bronk's direction.

Dr. Bronk had become President in 1953 and the program of expansion which he began is still in progress. Every step of the way, Barney has supervised the construction and the multitude of problems and details with his characteristic vigor and enthusiasm. President Bronk and the Board of Trustees changed Mr. Lupinek's title to "Superintendent of Buildings and Grounds" in 1956, and Buildings and Grounds became a separate office.

Mr. Lupinek, left, with Mr. David Rockefeller at the 1964 Convocation.

Construction of Caspary Auditorium, Caspary Hall, and Abby Aldrich Rockefeller Hall began in 1955, and, while they were still in progress, work started on the President's House and the northern portion of the Graduate Students Residence Hall.

Shortly after completion of these additions to the campus, work commenced on the southern portion of the Graduate Students Residence Hall and on the new South Laboratory. Construction of these buildings was completed in 1959, and Mr. Lupinek proceeded with their interior design and construction, including the new laboratories in the South Laboratory for graduate student use and for Professors Lipmann, Dubos, Hirsch, Porter, and Palade.

Additional housing for students and faculty was provided by the construction of Sophie Fricke Hall. The construction of Gasser Hall over the Power House added much-needed laboratory space.

In 1966 Dr. Bronk and the Board of Trustees commissioned Campbell, Aldrich and Nulty to proceed with the design of a new multi-story laboratory building on our south campus at 64th Street. This will be the University's largest building. Again, Barney's talents and experience have been invaluable in working out the many details.

Mr. Lupinek's association with the University has spanned fifty-seven years, interrupted only by a short stint in a stockbroker's office and by service to his country in World War I. President Bronk had prevailed on Mr. Lupinek to serve beyond the usual retirement, but last spring they agreed that his retirement as Superintendent of Buildings and Grounds could become effective on 30 June 1967, with the provision that he continue in the position of Consultant to the President. So we shall still have the pleasure of seeing that friendly, smiling person with the sparkling eyes, the big cigar, and the colorful bow tie. Our esteem for Barney's accomplishments and our delight in his continued presence are going right on.

PAUL R. PENNDORF

THE ROCKEFELLER UNIVERSITY NEWS

Gairdner Foundation Awards

THE RIGHT HONORABLE ROLAND MICHENER, Governor General of Canada, conferred the Gairdner Foundation International Special Awards of Merit on Professor Christian de Duve and Professor George E. Palade at The National Club in Toronto on November 17.

Dr. de Duve was selected for the honor in recognition of his "discovery of lysosomes. . . . He isolated and characterized lysosomes chemically and ultrastructurally. These subcellular particles play an important role in physiological and pathological processes. Their discovery has led to a better understanding of many disease processes and has opened innumerable new avenues of research."

Dr. Palade was cited for "his many contributions to the development of methods of preparing cells and tissues so that subcellular components could be adequately preserved and visualized in the electron microscope, and to his pioneering use of these methods to develop knowledge about structure and function of cellular components."

With each award, the Governor General presented a certificate and the sum of $20,000.

Alfred Benzon Prize

ON NOVEMBER 15, 1967, Professor Igor Tamm was awarded the $3,600 Alfred Benzon Prize in Copenhagen, Denmark, "in recognition of his outstanding research on the replication of viruses." This is the third year the honor has been given, and Dr. Tamm is the first American recipient.

Professor J. Hess Thaysen of the University of Copenhagen made the presentation at a ceremony attended by Dr. Bϕje Benzon, Chairman of the Alfred Benzon Foundation. Dr. Tamm then delivered the Alfred Benzon Lecture (page 12) to an audience of chemists, microbiologists, pharmacologists and other scientists, and physicians.

Dr. Tamm began medical studies in his native Estonia, continued them in Sweden, and finished at Yale University, receiving the degree of Doctor of Medicine in 1947. He served as Assistant in Medicine at the Yale University School of Medicine until 1949, when he joined the faculty of The Rockefeller University. He became Professor in 1964.

Dr. Tamm's early studies, begun at Yale, concerned the interaction of influenza viruses with receptor substances. In 1950 he discovered and characterized, with Dr. Frank L. Horsfall, Jr., a mucoprotein which was the first pure substrate for influenza virus neuraminidase. In more recent years, Dr. Tamm has been concerned with the biochemistry and virus-cell relationship of a number of animal viruses.

Distinguished New Yorker Medal

THE CITY CLUB of New York awarded the Distinguished New Yorker Medal to President Bronk at its 75th Anniversary Dinner on October 16. The citation reads, "Detlev W. Bronk personifies the unity of all science. He achieved distinction as a physicist, biophysicist, and physiologist. He has served as the director and coordinator of efforts in all scientific fields. In his distinguished career he has been Chairman of

the National Research Council, President of the National Academy of Sciences, and President of The Johns Hopkins University. Since 1953 he has graced our city again as President of The Rockefeller University. We salute him as New York's man of science."

Science in Human Affairs

THE NEW INSTITUTE for the Study of Science in Human Affairs at Columbia University invited Professor René Dubos to deliver a series of four lectures on the occasion of the 200th Anniversary of the College of Physicians and Surgeons, November 7-10. The titles of the lectures were: The New Pessimism, Science as Social Response, Technology and the Direction of Science, and Science as Knowledge of Consequences. At the end of November Dr. Dubos was Chairman of a two-day symposium in Oklahoma City marking the 20th Anniversary of the Oklahoma Medical Research Foundation, and he was widely quoted in press editorials and news columns across the nation.

Lord Adrian Elected Chancellor

LORD ADRIAN — who is Trustee Emeritus of The Rockefeller, Past President of The Royal Society of London, Nobel Laureate, and formerly Master of Trinity College — has been elected Chancellor of Cambridge University by the University Senate.

The Chancellor is the head of Cambridge University, which was founded in the twelfth century. It is significant of the esteem in which Lord Adrian is held by his colleagues, that he comes to this highest office from the post of Master of Trinity College, as generally the Chancellor is a nonresident.

"...the cage of form"

ARCHIBALD MACLEISH delivered the third Ellery Sedgwick Memorial Lecture in Caspary Auditorium in November. Of his theme — "Heaven and Earth and the Cage of Form" — Mr. MacLeish remarked, "It is a bit mysterious, but when you are a poet and you plan to talk about criticism you had *better* be mysterious." The statesman-scholar then proceeded, with mystery-dispelling incisiveness and charm, to deal with the present state of the practice of literary criticism, particularly the averting of its eyes from the struggle of art to contain life. "The essence of the literary task according to the Chinese sage Lu Chi," Mr. MacLeish said, "is the capture of heaven and earth in the cage of form. Yet our critics are concerned with names not things, the window not the view, writing not what is written — in brief, literature not life. We must observe not only the cage of form and its content, but heaven and earth itself and the relation between the two." Mr. MacLeish concluded with the reading of a number of his new poems, afterwards joining with faculty and students in lively discussions at a reception in the Abby.

AAAS Annual Meeting

DURING CHRISTMAS WEEK, the spirit of Michael Faraday reached out across time into the contemporary life of the University. The Centennial Anniversary of the death of that great natural philosopher was observed at the Rockefeller in conjunction with the Annual Meeting of the American Association for the Advancement of Science. There was an exhibit of replicas of his apparatus and original manuscripts in the Abby, a symposium on his contributions to science, a demonstration lecture by one of Faraday's successors at The Royal Institution, such as Faraday often gave at the Institution.

Although headquarters for the Annual Meeting of the AAAS were held at the Americana and Hilton Hotels, many of the lectures and symposia were held at The Rockefeller University, including two that were televised for broad coverage through educational TV Channel 13 under a grant from the Ford Foundation. This was a precedent-setting feature. Also for the first time the Association arranged visits to universities and scientific institutions under the direction of Dr. Walter G. Berl, Meetings Editor for the Association. President Bronk, a Past President of the Association, served as General Chairman for the 1967 meetings.

Alumni

◖ Recently published books by graduates of the University are the following:

THOMAS P. BENNETT PH.D. 1965 *Modern Topics in Biochemistry: Structure and Function of Biological*

Molecules. T. P. Bennett and E. Frieden. 186 pages New York: The Macmillan Co.; London: Collier-Macmillan; 1966.

——*Graphic Biochemistry. Volume I: The Chemistry of Biological Molecules,* 160 pages. *Volume II: The Metabolism of Biological Molecules,* 128 pages. New York: The Macmillan Co., 1967.

MARY A. BONNEVILLE PH.D. 1961 *An Introduction to the Fine Structure of Cells and Tissues.* Keith Roberts Porter and M. A. Bonneville. 112 pages. Philadelphia: Lea & Febiger, 1963.

SANFORD A. LACKS PH.D. 1960 *Twenty-six Afternoons of Biology: An Introductory Laboratory Manual* (First Edition). George Wald, Peter Albersheim, John Dowling, Johns Hopkins III, and Sanford Lacks. 159 pages. Reading, Massachusetts: Addison-Wesley Publishing Co., Inc., 1962.

PETER G. SATIR PH.D. 1961 *Protoplasmatologia III E* "Structure and Function of Cilia and Flagella," 57 pages. Vienna: Springer Verlag, 1965.

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——*Microbes and Men,* hard-cover edition. 160 pages. New York: McGraw-Hill Book Company, 1963.

——*Microbes and Men,* soft-cover edition. 160 pages. New York: Scholastic Book Services, 1963.

CHARLES F. STEVENS PH.D. 1964 *Neurophysiology: A Primer.* 182 pages. New York: John Wiley & Sons, Inc., 1966.

◧ Alumni who have new appointments this fall include:

DAVID BALTIMORE PH.D. 1964 has left The Salk Institute to become Associate Professor of Biology in Massachusetts Institute of Technology.

THOMAS P. BENNETT PH.D. 1965 has been appointed Assistant Professor of Biology in Harvard University.

MARY A. BONNEVILLE PH.D. 1961 formerly at Massachusetts General Hospital, is now Lecturer in Biology in Harvard University.

PAUL R. BURGESS PH.D. 1965 is now an Instructor at the University of Utah School of Medicine.

ROBERT D. CAMPO PH.D. 1963 has been promoted to Research Associate Professor of Medicine in Temple University School of Medicine where he continues as Assistant Professor of Biochemistry.

BRIAN A. CURTIS PH.D. 1963 is now Assistant Professor and Secretary of the Curriculum Committee in Tufts University School of Medicine, and last summer he was elected Secretary of the Society of General Physiologists.

ALAN FINKELSTEIN PH.D. 1963 has just been promoted from Assistant Professor to Associate Professor of Physiology, Albert Einstein College of Medicine.

LEWIS J. GREENE PH.D. 1962 has just been promoted from Assistant Biochemist to Associate Biochemist in the Biology Department, Brookhaven National Laboratory.

JOHN W. B. HERSHEY PH.D. 1963 is now Research Fellow in Chemistry, Howard University.

SANFORD A. LACKS PH.D. 1960 formerly Associate Geneticist in the Brookhaven National Laboratory, was this fall promoted to Geneticist.

GARLAND R. MARSHALL PH.D. 1966 is now Assistant Professor in the Department of Physiology and Biophysics and the Department of Biological Chemistry of the Washington University School of Medicine.

PETER G. SATIR PH.D. 1961, formerly of the University of Chicago, is now Associate Professor of Anatomy, Department of Physiology and Anatomy, University of California at Berkeley.

LEONARD A. SAUER PH.D. 1966 has returned from Germany where he was a USPHS Special Fellow, and is now Instructor in Medicine and Biochemistry in Yale University School of Medicine.

THOMAS W. SCHLEICH PH.D. 1966 is Research Associate in Chemistry, University of Oregon.

JAMES H. SCHWARTZ PH.D. 1964 has been appointed Associate Professor of Microbiology in the New York University School of Medicine, where he had served as Assistant Professor since 1964.

PHILIP SEEMAN PH.D. 1966 has returned from the University of Cambridge and is now Assistant Professor, Department of Pharmacology, University of Toronto.

CAROLYN W. SLAYMAN PH.D. 1963 and CLIFFORD L. SLAYMAN PH.D. 1963 — recently Assistant Professors in Western Reserve University, School of Medicine — have been appointed respectively Assistant Professor of Microbiology and Physiology and Assistant Professor of Physiology in Yale University School of Medicine.

DANIEL W. STROOCK PH.D. 1966 is now Assistant Professor in Washington Square College of New York

University where he continues as Visiting Member of the Courant Institute of Mathematical Sciences.

WILLIAM H. TALBOT PH.D. 1964 formerly Instructor in Physiology, The Johns Hopkins University School of Medicine, was promoted to Assistant Professor of Physiology.

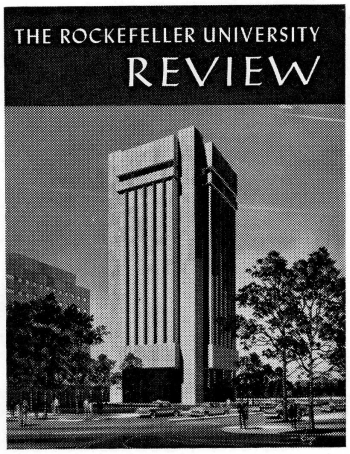
ROGER E. THIES PH.D. 1961 has left his Lectureship at Makerere University College, Uganda, to become Associate Professor of Physiology in the University of Oklahoma Medical Center.

ROBERT R. TRAUT PH.D. 1962 has been appointed an Established Investigator of the American Heart Association in the Institute of Molecular Biology, University of Geneva.

CECIL C. YIP PH.D. 1963 has been appointed Medical Research Scholar of the Medical Research Council of Canada.

Christmas Festivities

THE CHRISTMAS SEASON opened at Rockefeller on December 16, the night of the Winter Ball, which was arranged by the first-year Graduate Fellows for the faculty, students, and administration. Welch Hall was decorated with ten resplendent flags, and 500 hosts and guests danced past 2 a.m. The Children's Christmas Party on December 19 was attended by more than 225 exuberant children accompanied by their parents. The next day, at the invitation of President and Mrs. Bronk, members of the University gathered for the traditional Carol Sing at which tea and punch were served. On January 1, the University's celebrations were informally brought to a close by an eggnog party given by President and Mrs. Bronk at their home to welcome in the New Year.



Architect's rendering of the new seventeen-story building on the south campus between 63rd and 64th streets. The architect is Nelson W. Aldrich of Campbell, Aldrich and Nulty of Boston, Massachusetts. For article see page 26.

ILLUSTRATION ACKNOWLEDGMENTS: Pages 2, *top* 4, and 8 courtesy of H. Keffer Hartline. Pages 3 and *bottom* 4 courtesy of H. K. Hartline, H. G. Wagner, and E. F. MacNichol, Jr., *Cold Spring Harbor Symposia on Quantitative Biology*. Vol. XVII, pp. 125-141 (1952). Page 6 courtesy of Floyd Ratliff, H. K. Hartline, and William H. Miller, *Journal of the Optical Society of America*, Vol. 53, No. 1, pp. 110-120 (1963). Page 7 courtesy of David Lange, *Dynamics of Inhibitory Interaction in the Eye of* Limulus: *Experimental and Theoretical Studies* (thesis), p. 32B. New York: The Rockefeller University (1965). Page 9 after Floyd Ratliff and Conrad G. Mueller, courtesy of *Science*. Vol. 126, pp. 840, 841 (October 25, 1957). Pages 10 and 11 photographs, pages 10 and *top* 11, copyright © The Nobel Foundation 1968; drawing courtesy of Robert B. Barlow, Jr. Page 14 © Academic Press. Page 17 *bottom* courtesy of R. Bablanian. Page 19 courtesy of B. Stewart. Page 20 courtesy of W. Stoeckenius. Page 21 courtesy of S. Dales. Pages 23, 26 and 28 photographs by The Rockefeller University Illustration Service.