XIX. NEUROPHYSIOLOGY*

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RESEARCH OBJECTIVES

The Neurophysiology laboratory is concerned with a variety of dissimilar problems in nervous activity.

P. D. Wall is measuring repetitive responses from single interneurons in the spinal cord with a view to discovering whether the repetition is endogenous to the cell itself or reflects activity in multiple chains of neurons. He is also concerned with how the individual internuncials each code several modalities of sensation. A graduate student, A. R. Johnson, is engaged in making a servo-analysis of human voluntary muscle movement.

J. Y. Lettvin examines membrane properties in single units, i.e., nodes of Ranvier and cell bodies. He is also involved in measurements in the visual system of the frog, as described in Section XIX-A, and in this has the help of a graduate student, E. M. Duchane; an as yet unofficial visitor, U. Maturana; and W. S. McCulloch.

W. H. Pitts is re-examining the theoretical properties of nerve membrane à la Hodgkin and Huxley in the light of recent findings from voltage-clamp studies in this and other laboratories. He is also involved in the physical chemical theory of the behavior of our electrodes.

W. S. McCulloch is developing his system for ultrastable nerve nets, as discussed in the Quarterly Progress Report of October 15, 1957, page 129, and is part of the group that is investigating vision. A graduate student, R. C. Gesteland, has invented an extremely clever way of examining the order of liquids at phase boundaries, and will be developing the experimental apparatus upon his return in March 1958.

A. VISION IN THE FROG

1. Introduction

For this report we discuss a problem in vision in some detail in order to acquaint our friends more clearly with our present aims and to tell how we interpret observations that have already been made. From the discussion it will be apparent what our next experiments are to be. The problems are: How does a frog code visual data; and can we show that the code that we have found is sufficient to account for its behavior?

A. M. Andrew has found a set of neurons, fed by optic nerve, whose individual activity is of such a character that simple homogeneous operations on this group can abstract position, velocity, and direction of movement in the visual field. Emma M. Duchane has noted a similar but more limited activity in optic nerve. We give the background for going beyond these data, some of which are testable guesses. None of the comments should be taken as applying to any other sensory system than the system that is discussed. In particular, they do not apply to audition, in which the eighth nerve has a much more direct connection with receptors than does the optic nerve.

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We chose to study Rana pipiens because of its anatomy. Its retina has no pronounced fovea which is radically different from the surrounding parts of the retina; there is only a gradual increase in the density of receptors from noseward tailward. From each eye it has only one major visual path, which runs from the retina to the superior colliculus on the other side of the mid-brain. The colliculus itself contains a complicated scheme of vertical connections, but this scheme does not vary systematically along the surface.

The detailed anatomy of the visual pathway can be described as follows: The primary light receptors of the retina consist of a single layer of independent elements that are connected in many-many fashion to one layer of neurons, the bipolar cells, which, in turn, synapse in many-many relation to a layer of ganglion cells, whence issue the axons that form the bulk of the optic nerve. The two latter layers are further interconnected by a variety of neurons lying parallel to the surface of the retina and across the chains of bipolar and ganglion cells. Moreover, all of these kinds of cells are further innervated by fibers coming from the brain by way of the optic nerve. The optic nerve itself crosses the base of the skull and turns tailward to run on top of the colliculus, where the fibers pass through several layers and split into terminal branches at about a quarter of a millimeter below the surface. At this depth there lies a layer of large neurons and just beneath it a layer of smaller ones; each of the latter sends dendrites into as much as one-third of the surface of the colliculus. This brief summary will be enough to enable the reader to follow our discussion.

Most of what we know about the function of the nervous elements in retina consists of observations on the response of ganglion cells to varying illumination of the receptors. Hartline, Kuffler, Barlow, and Granit are particularly noted for such studies; Hartline and Barlow have given us most of our information on the frog. This is a synopsis of their results: There are approximately a million receptors in each frog eye (over an area of approximately 60 mm^2) and approximately half a million optic-nerve fibers (of which nine-tenths are less than 1 micron across and thus escaped count until the recent work of Maturana). Each fiber has a "receptive field," which is a region wherein illumination of receptors can produce impulses in the fibers. There are three sorts of fibers: the on, the on-off, and the off. The first kind shows activity when a light strikes the center of the receptive field; usually it fires at a rate that slowly increases until it reaches a steady frequency, and stops when the light is turned off. The second kind exhibits a short train of impulses whenever a light goes on or off at the center of its receptive field. The third responds with a longer train of impulses but only when the light at the center of the field is switched off.

The diameter of a receptive field in the frog is of approximately 1 mm, and it is surrounded by another zone whose own illumination prevents the characteristic response of the fiber to lights within its receptive field. Thus each fiber is affected by somewhat

more than a hundredth of all receptors. The exact number depends greatly upon the brightness of the testing light and the brightness of the background; the size of the receptive field tends to shrink after it becomes adapted to the dark, and the inhibitory zone vanishes.

2. Relevant Observations on Other Animals

In cats, the relation of receptive field to fiber has been most systematically expressed by Kuffler and his co-workers. In an on fiber a spot of light excites an on response from the center of the field, an on-off response from a concentric intermediate zone, an off response at the periphery, and inhibits all of these responses from the area immediately outside the field. The reverse order occurs (except for outer inhibition) in an off fiber. The on and off regions within any receptive field are competitive and mutually inhibitory, with the quality of response given by the region wherein the stimulus is greater. One certain difference between cat and frog retinal activity is that all ganglion cells in the cat are said to be continuously active even in the dark; in the frog very few continuously firing fibers are seen.

As for the colliculus, very little is known. Polyak's massive anatomical work on the visual system mentions it on only two pages. Since 1909, the dictum has been that mammals see just as well without a colliculus. Nobody doubts that it is the only visual center in frogs (and the main one in birds, of which hawks and owls have five times as good eyesight as any mammal), but clinicians do not care about such beasts. What seems to have happened is that a separate and parallel visual system has evolved to serve foveal vision. For example, in the cat the fovea has no direct representation in the colliculus at all – only the periphery of the retina does. The substitute system, formed of the lateral geniculate body and visual cortex, handles information about the whole visual field, and some function is relayed to the colliculus, which has direct information only from the periphery. Thus the cat has at least two visual paths to the colliculus, neither of which serves any function that has been detected by neurologists, which make the internal physiology of the nucleus quite different from that of the frog. Heinrich Klüver decorticated chimpanzees, leaving only the retino-collicular system, and discovered that the animals did not recognize shapes and the like; they could learn to react only to a particular value of total luminous flux but could never tell how it was distributed in space or time. Julia Apter discovered that stimulation of a point on the colliculus in the cat caused the eyes to move so that they centered on that place in the visual field at which a spot of light would have produced greatest response at the stimulated point on the colliculus when the eyes were at rest; the matter is discussed fully in an early paper from this group (W. P. and W. S. McC.).

3. Visual Behavior

Returning to the frog, we now ask what he sees with this apparatus which corresponds to only a small part of what mammals have (although the colliculus of the frog is more elaborate than that of mammals). From his actions we can guess, with Yerkes, that he cares more about movement than scenery and more about size than shape. A frog will starve surrounded by unmoving food. He will not take a mealworm from a densely packed, wriggling mass of them, but he will when they are separated from each other. A hungry frog will strike to eat an object of any shape or color if it is below a certain size and moving within the proper distance from it. His strike is of two sorts. He will either turn and center himself on the prey, then jump, presumably using the small overlap of both visual fields to judge distance, or he will leap at an angle to his long axis without turning, and hence catch his prey on the run. The former pattern is elicited by wriggling objects with little or no translational movement; the latter pattern, by translational motion of prey, with and without wriggling.

The frog enjoys some temporary memory for shape and size. When given ants to eat he will take one but no more; he does not like the taste. But after the distraction of taking a mealworm, he seems to forget his distaste for ants and strikes for one again. If a frog sees anything moving that is as large as a small snake, or larger, nearby, he flees if he can or puffs himself up if cornered, but only if the object does not move too fast, for if it is moving above a certain speed he does not seem to notice it at all. Revolving scenery around a frog, say turning a drum with vertical stripes on the inside around him, makes him turn in the same direction. When he leaps from place to place, it is hard to say whether he means to end at a particular spot, perhaps at the next lilly pad, or on the water around it. That is, for an animal that can move equally well on water or land it should not make much difference where he goes. Yerkes, for example, is sure that the animal uses no visual cues to orientate himself in his surroundings; we think that while this is true on land, it may not be so for the swimming frog. Altogether, it is hard to say how much steady-state perception a frog has, or even how much he needs to act in the way he does.

Several years ago Sperry and Weiss did a remarkable study on regenerated optic nerves in frog (they do not grow back in higher vertebrates). If the nerve was cut but the eyeball left in its normal position, then after regeneration of the fibers to colliculus the frog saw normally with that eye and could use it successfully in taking prey. If, after section of the nerve the eyeball was rotated 180° about the axis through the pupil, then after regrowth the frog saw upside down with that eye. If both right and left nerves were cut and the eyeballs interchanged but not otherwise rotated, the frog referred the image to the proper side of the body but saw inverted about the meridian through each eye. (Remember that his eyes face in opposite directions.) Such experiments were

made by measuring the strike of the frog against the position of a moving target and by finding which way he rotated inside a revolving striped drum.

These findings have been a thorn in the side of nerve physiologists and are improperly neglected in general discussions of sensation and perception. It is almost as if the abhorred doctrine of specific nerve energies had been exhumed: the results seem to imply that a particular position on the retina always governs a particular movement of the frog's body in space with respect to the side on which the retina lies – and that this is a fixed relation because the frogs of Sperry and Weiss' experiments could not learn to correct for the distortion produced.

4. Work in This Laboratory

The experiments of A. M. Andrew on frog colliculus can be summed up as follows: If a small spot of light is flashed off and on at one part of a retina, an area can be found on the surface of the colliculus where gross electrodes record maximum on-off transients, and, using these maxima, we can show a roughly continuous map of the visual field. If a microelectrode is thrust into such a place of maximum response, we find, some 3 mm below the surface, a region in which the slow transients have increased suddenly to a maximum in one polarity. Approximately 0.2 mm deeper, they change polarity, and still deeper they disappear altogether. Now a slow transient generally changes sign when a tract ends; and we know that the optic-nerve fibers do end close to this depth. Embedded in this layer are nerve cells that fire once or twice to an on or off no matter how intense the change. They also have a limited receptive field. Under these neurons and below the electrical signs of the optic tract lies another set of neurons characterized in their behavior by a curious set of laws beside their firing to on and off. For each cell there exists a unique point in the retina at which, whenever a spot of light moves at uniform velocity away from it, the cell responds with a frequency that increases with the velocity of the spot over a certain range and is not greatly affected by its brightness. Furthermore, the movement can begin more than a radian away from the point and provoke the same response, as long as it moves directly away from it. Furthermore, the response changes with duration of movement, and, for the reason just given, this change cannot be attributed simply to the altered position. Again, movement of a spot toward the point produces no response and neither does circumferential movement. No sequence of separate on's and off's produced this kind of response (the ϕ effect – apparent movement) but it appeared even when the spot of light was too dim to produce any on or off response when it was held in one place. Finally, none of these cells showed any degree of response to steady illumination. Out of fifty or so such neurons two were found departing from these laws. One gave maximal response to a vertical movement in one direction, but not in the other, through a particular point. The response was diminished as the angle was increased with respect

to the vertical. Another, less well-defined, gave a similar type of response at some large angle from the horizontal. It is only fair to add that A. M. Andrew would claim that the data are too scanty to justify such explicit laws – yet they are the simplest way of describing his results.

5. Discussion

As Sperry and Weiss have said, there seem to be two general ways to account for their results. One is that the amphibian optic-nerve fibers (as well as the cells on which they end) differ from each other, not only by accident of position, but intrinsically, let us say, by sensitivity to chemical gradients so that not only are the original synaptic relations the only allowable ones but they are actually sought out in regrowth, each cell calling to its own, until the original order is established, and it is as if the nerve had not been cut. And since the colliculi are mirror images of each other, the interchange experiment simply means that the nerve has regenerated properly to the mirror homologue. This hypothesis, the most strongly advocated when discussion of these data has arisen, follows strictly from the assumption that since the visual field is mapped in the optic nerve, position in the field is given to the brain by position in the optic nerve of excited fibers, and hence that movement is conveyed by the proper switching of active fibers in the nerve map. But the guess of ordered regrowth requires an extraordinary amount of chemical or of other kinds of discrimination on the part of some half million fibers, and is most bizarre in the case of the right-left interchange, where fibers would have to cross each other systematically to produce a mirror image about the vertical meridian.

The second guess, maintained by us more or less in isolation, is that the output of the retina is already encoded in terms of coordinates and of direction or handedness that are intrinsic to the retina itself. This hypothesis would rest on thin air except for the work of A. M. Andrew. Yet before we argue his results we must digress to the question of continuous maps in nerve physiology, since it represents a bulwark of the argument for an ordering factor in fine, as well as gross, regrowth of a nerve.

During the embryological building of a nervous system, fibers are laid down in parallel; that is, they do not tend to braid or twist about each other, and thus any grouping of primary fibers in a nerve gives a map of the area from which they arose. If these fibers end, even overlapping in their terminal arbors, on another set of nerve cells, and this second set also gives rise to a tract in which no fibers cross each other or do so systematically, then we ought to expect some of the mapping in the primary fibers to be preserved, and so on, through synapse after synapse. And it is a fact that at three or more synapses removed from the primary sense elements, we find in cortex a crude mapping of touch over the body, of the visual field, of frequency of an auditory stimulus, and so on. It is often tacitly supposed, despite Descartes'

warning, that the existence of such a mapping obviates the need for other ways of expressing the relative position of sensory receptors. Especially with respect to vision, such an assumption has become so entrenched that naive surgeons hope to connect an array of photocells with a set of electrodes thrust into the visual cortex and thereby make a blind man see. They cannot really be blamed; for this notion, whatever disclaimer is made in arguments, is embodied in the way physiologists have attacked vision. In a typical experiment, one finds a neuron anywhere from the retina on, then flashes a spot of light on and off in different parts of the visual field until one finds that point from whose stimulation a maximum response is recorded in the neuron. Such an experiment takes for granted that translating a static continuous map is the important function of subsequent cells with respect to receptors. The only exception that comes to mind is the work of Kuffler and Barlow on the competition of two spots of light in one receptive field (as described earlier in this report).

Returning to A. M. Andrew's work: It can be shown that relatively nonlocalized operations in whatever nuclei may succeed his layer of neurons can abstract the position, velocity, and direction of a point moving in a plane. For example, let us generalize by assuming that all of the cells of the first kind (responsive to any radial movement away from a point) have the same dependence of frequency on speed, and that all of the cells of the second kind have similar responses among themselves, but form two groups representing two directions. (The argument is rough because the data are, and we do not want to assume too particular a mechanism.) Let a spot begin moving at point A in the visual field, as shown in Fig. XIX-1, and in the direction marked. Then those cells of the first type (responding to "away" in any direction) which are connected to points above the chord through A drawn perpendicular to the direction of motion will fire because the movement has a radial component with respect to each point and away from each point. Thus, from the number of firing cells, we get a measure of the distance of the normal to the vector from the center of the field. Within the group of excited cells those that are connected to points in line with the vector will show the greatest rate of firing, and that rate will measure the absolute velocity of the spot. The spectrum of firing cells, i.e., how many are firing at each of several frequencies, can be used to measure the distance of the vector from the center. Having defined a circular locus for A with respect to the center of the field and having determined the absolute velocity, we must now find out where A lies on the circle and in which sense it rotates. This information is given by the second group of neurons (directional), qualifying that given by the first group, in this wise: Let there be at least two subgroups, each of which responds to a preferred direction with respect to a uniformly spaced set of points throughout the visual field and let these directions be those shown in Fig. XIX-2. Let each subgroup project to a separate nucleus. Then, by comparing the absolute velocity of the vector with its projections on both subgroups (obtained by

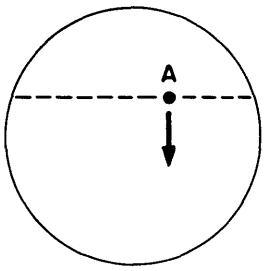

Fig. XIX-1.

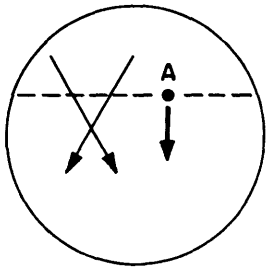

Fig. XIX-2.

finding the maximum firing frequency in each subgroup), we determine the angle at which A is traveling with respect to each of them. And finally, as with the first kind of neurons, the populations of both groups behind the chord normal to the vector and passing through A (as computed for the two separate nuclei) tell us whether the spot is moving clockwise at A or counterclockwise at the point diametrically opposite A on the locus.

This very clumsy example, confected out of hand, only suffices to show that such a method is possible, even with the very incomplete picture of collicular action that we still have. Yet, simply by computing sums, measuring spectra, and taking maxima, we can, in fact, define a moving spot in the visual field in terms of absolute velocity and position with respect to an arbitrary set of coordinates intrinsic in the visual system, without contradicting the data.

At this point three questions can be posed. First: While we have labored a mechanism for a set of collicular cells in a region where everyone admits this sort of abstraction occurs, how is the matter relevant to retinal function? If we refer to the description of the receptive field given earlier in this paper, remembering that it has been described mainly for the cat and assuming tentatively that it holds for the frog, then one additional, and not unreasonable, factor, given movement of a spot through the field, will generate in single optic-nerve fibers an output that is remarkably like that described by Andrew for the collicular cells. That is, suppose there exists a gradient of mutual inhibition that is greatest at the periphery of the field and least at the center. Then movement of a spot of light across a diameter through the field passes through successively inhibited zones from the outermost inhibitory area to the center, and no response occurs. As soon as it passes the center, it generates a response that continues until the spot intersects the inhibitory area again. Curiously enough, with this scheme it should make no difference for either type of receptive field whether it is a bright spot on a dark background or the reverse. This suggestion is not unsupported. Last summer, Emma M. Duchane, of our group, observed exactly this sort of behavior in 3 or 4 optic-nerve fibers inquisitively impaled during an intermission in collicular

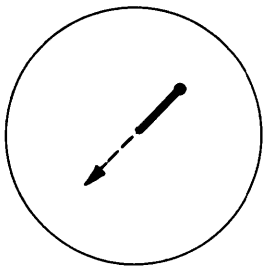

Fig. XIX-3.

experiments. The response of the fibers seemed very much like that seen in individual cells of colliculus but defined a much smaller region, roughly the size of a receptive field.

Second, we ask, If the output of the retina is so coded, what could be the function of the receptive fields with opposed polarity, in view of what was just said? Barlow thinks they are not uniformly intermixed – that the off's are in the region of best resolution. If they were mixed, however, one answer is that it would be a measure of size. If the two kinds of receptive fields occur with equal frequency, consider what happens when a short line of light is translated along itself in the visual field. (See Fig. XIX-3.) The front end of the line will generate a determination of position for the central "on" fibers considered as a group, which will be different from that for the central "off" group. If the velocity and direction are of equal magnitude in the two groups, but position is not, the difference in the two computed positions becomes the measure of the size of a single moving object.

Third, and most interesting, If it takes (and it does!) about a tenth of a second after movement begins for a response to appear in colliculus, how does a frog ever succeed in catching a fly? Well, a fly (and, in fact, many insects) moves in straight lines, stops, and turns sharp corners. In the kind of scheme that we have suggested prediction of a linear path can be achieved by seeing how fast the various sums are changing. Behavioristically, this is palatable, for it seems that a frog cannot extrapolate a curved path; he errs as if he were striking along a tangent or secant to the curve drawn significantly before the strike. He will also not strike if the prey is moved in a path with a certain radius of curvature. An alternative mechanism, suggested by Barlow, is that the maximum excitation from moving a dark spot lies ahead of the center of gravity of the spot, along the line of motion but still within the glebe of the spot. With the observed delays and the known velocities of insects, this prediction would seem inadequate.

In summary: We have presented some speculations about ranine vision which are based on remarkably few facts. Our apology for presenting them now is that they show why we mean to devote a large part of our effort to retinal physiology. In particular, we have tried to present the difficulty of the problems involved in such a way that it will be clear that the questions are not trivial, and that our alternative view to the popular physiological dicta on vision is justified. We are fortunate in that we shall soon have the collaboration of Umberto Maturana, some of whose anatomical and psychological work on this system has already been embodied in this text. Equally fortunate is the interest and help given this work by O. G. Selfridge and other

friends at Lincoln Laboratory.

B. MEMBRANE PROPERTIES IN NERVE

Some novel methods of measuring membrane properties have arisen and some new observations have been made since our last report. First, it has become possible to use testing currents through the same electrode that is used for recording and to cancel out, without guessing, which part of the measured potential comes from the electrode itself. This has resulted in a lovely series of data from undissected nodes of Ranvier and motor neurons.

Second, resistivity measurements on the medium immediately around the tip of a microelectrode have suggested that the axoplasm is not homogeneous inside a cell, but rather that the core is more resistive than the fluid directly under the membrane and that there is a sharp boundary between the two zones. This datum, although it is tentative, explains the finding by Cole of an anisotropy in radial-versus-longitudinal resistance measurements on axoplasm in the squid.

Third, and perhaps too involved to explain beyond a mere statement, the turn-off of inward current during a depolarizing clamp on frog nodal membrane appears to be coupled to the total amount of inward current, and occurs with a significant delay. This finding makes nodal membrane markedly different from that found in the squid, particularly if, as Tasaki also found, it is possible to get the inward current and its turn-off to occur with no sign of subsequent outward current.

Fourth, a new hypothesis for explaining the dorsal root potential (DRV) and dorsal root reflex has occurred to us. If the fibers of group II are densely packed in their terminal branches at the dorsum of the cord and these are the only fibers participating in both phenomena, then, with packing that is sufficiently dense and the knowledge that the fibers not only liberate potassium into the external space when they are excited but also generate an appropriate current field, we can assume that a chain reaction of excitement may occur, once the density of excited fibers reaches a critical level. Early experiments seem to show this to be true, at least for the dorsal root reflex in very active preparations.

These sundry points will be the basis for a future report.

C. A NEW CATHODE FOLLOWER

If a triode, V_{1B}, were maintained under constant operating conditions by a group of bootstrap circuits, its grid current ought to remain constant and be subject thereby to cancellation, and the input impedance should be increased. Such a circuit is shown in Fig. XIX-4. The cathode load current of V_{1B} is constant if the plate of V_2 shows a gain of 2 with respect to the cathode of V_{1B}, and a resistance, equal to that between

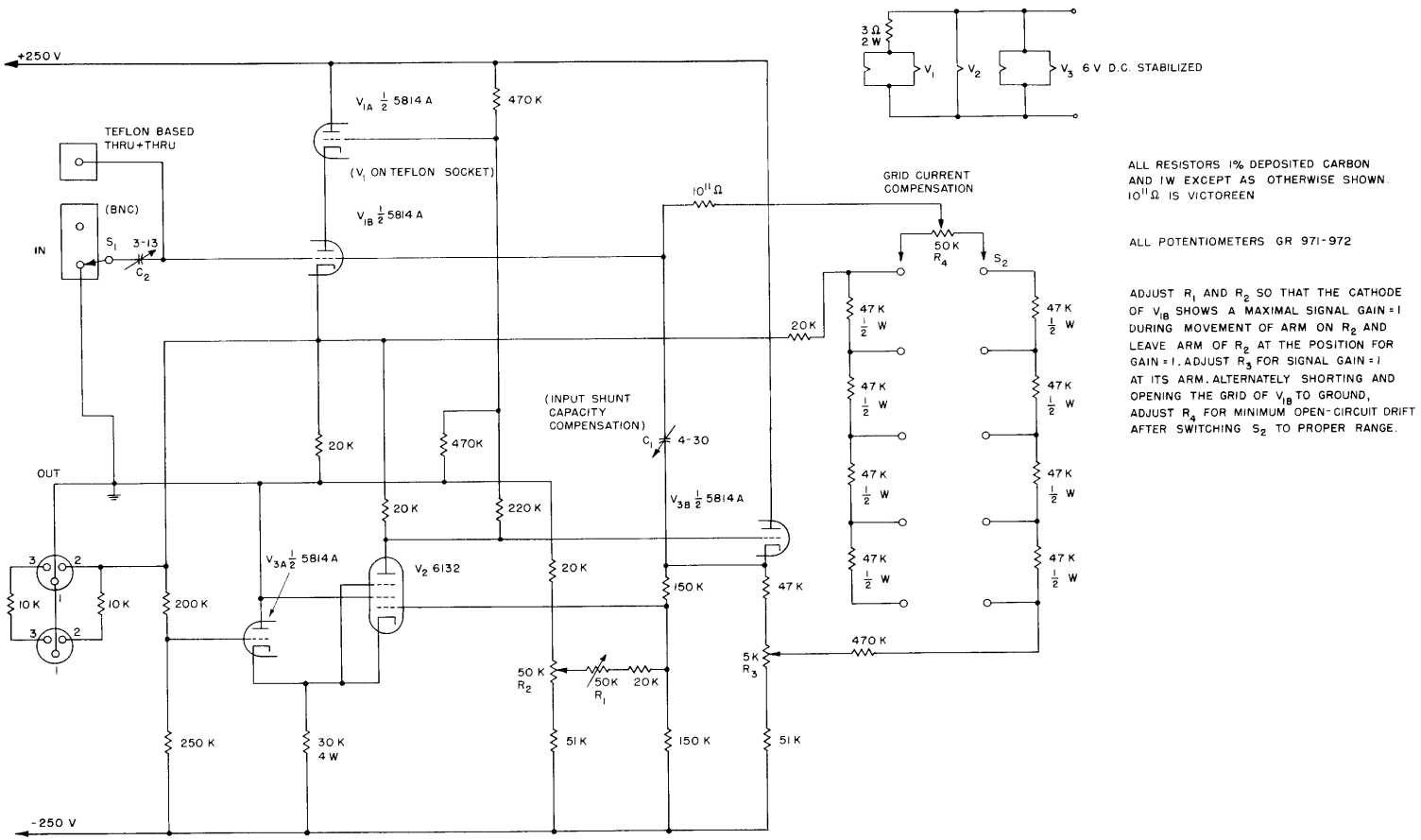

Fig. XIX-4. A new cathode follower.

those two points, is led from the cathode of V_{1B} to ground. The gain of 2 is used to compensate the stray capacitance around the grid of V_{1B}, through C_1 from V_{3B}; and V_2 is adjusted to exactly a gain of 2 by R_1 and R_2. V_{1A} keeps the plate of V_{1B} at unity gain with respect to the cathode of V_{1B}. The two resistive nets, one from the cathode of V_{1B} to the grid of V_{3A} and the other from the plate of V_2 to the grid of V_{1A}, are almost equal so as not to violate the symmetry that is responsible for the constant plate current through V_{1B}. Thus, with constant plate current through V_{1B} and constant plate voltage with respect to the cathode, V_{1B} acts as a cathode follower of unity gain. Tapping off on the cathode load of V_{3B}, we find another point of unity gain at a much lower dc potential. Connecting the two unity-gain points by a resistance, and tapping off through the 10^{11}-ohm resistor to feed back to the grid permits us to cancel grid current down to its own noise level.

The circuit works beautifully. It has an input dc resistance greater than 1×10^{13} ohms, a grid current adjustable to less (and much less with selected tubes) than 1×10^{-13} amp. It is a good device for use with microelectrodes, for its input impedance can be adjusted to $> 1 \times 10^{8}$ ohms up to 50 kc.