5.1 Introduction by Gordon M. Shepherd with Supplemental Comments by Milton Brightman

Rall, W., Shepherd, G. M., Reese, T. S., and Brightman, M. W. (1966). Dendrodendritic synaptic pathway for inhibition in the olfactory bulb. *Exp. Neurol.* 14:44–56.

Rall, W., and Shepherd, G. M. (1968). Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb. *J. Neurophysiol.* 31:884–915.

My part in this study grew out of my work on the physiology of olfactory bulb neurons, carried out under Charles Phillips at Oxford from 1959 to 1962. At that time, the main model for the electrophysiological analysis of neuronal properties and synaptic circuits in the central nervous system was the spinal motoneuron, based on the pioneering work of John Eccles in Canberra and of Kay Frank and Michael Fuortes at NIH. In order to extend this approach, we decided to develop the olfactory bulb as a simple cortical system within the mammalian forebrain, based on several attractive features: its clear separation of afferent and efferent fibers, sharp lamination, near-symmetrical arrangement of layers, and distinct neuron types with well-developed dendritic trees and axonal branching patterns. We found in anesthetized rabbits that the large output cells, the mitral cells, can easily be driven directly by antidromic invasion or synaptically by olfactory nerve volleys, and that the impulse response is followed by profound and long-lasting inhibition (Phillips et al. 1961, 1963; Shepherd 1963a), results that were reported independently by two other laboratories (Green et al. 1962; Yamamoto et al. 1963). We also recorded from the other cell types and worked out one of the early local circuit diagrams in which the mitral cells are subject to feedback and lateral inhibition by the granule cells acting as inhibitory interneurons (Shepherd 1963b). We noted the analogy with Renshaw inhibition in the spinal cord, but with two differences: first, the granule cell lacks an axon, so that the inhibitory output is presumably mediated by its long superficial spine-covered process, and second, impulse firing by the granule cell is limited to brief bursts, so that there must be "sustained transmitter actions outlasting the initial impulse activity."

As the end of my time in Oxford grew near, I wrote to several investigators back in the United States about postdoctoral positions. Among them, because of his early papers on dendrites, was Wilfrid Rall. He wrote back that he was interested not only in our evidence about dendrites but also in the large extracellular field potentials we had discovered in the olfactory bulb. He therefore invited me to join him in a theoretical analysis of the generation of the field potentials in the olfactory bulb by the bulbar neurons. Although he had no position to offer himself, he was able to arrange a joint position for me under Wade Marshall and Kay Frank in the Laboratory of Neurophysiology, then in the west wing of Building 10. This was

a result of his close collaboration with Kay and his group on the analysis of dendritic integration in motoneurons.

The prospect of working with Wil was exciting for me for several reasons. Although I had little mathematical background, I had been interested in applying computers to the analysis of neurophysiological data since spending the summer of 1956 running one of the earliest analog computers in Walter Rosenblith's laboratory at MIT. I had also been inspired by the idea of modeling neurons after hearing a talk by Francis Crick at Oxford on the modeling of DNA around 1961. So it seemed like an ideal opportunity to do the kind of multidisciplinary study that people were beginning to talk about as desirable in biology.

Nonetheless, the collaboration was a gamble for both of us. The idea of interrupting my experimental career by taking off two years from the laboratory to do a theoretical study was met with skepticism by most of my colleagues. There was no clear precedent for that kind of career path in the neurophysiology of the central nervous system. On Wil's part, he was obviously taking a risk on someone he had never met, and who lacked any obvious mathematical qualifications to be in NIH's Office of Mathematical Research. Moreover, Wil's work on the motoneuron had encountered stiff opposition from his former mentor, Eccles, and there was deeply rooted disbelief among nearly all neuroanatomists and neurophysiologists (there were not yet "neuroscientists") that theoretical studies had any relevance whatsoever to the complexities of central neurons. However, Wil and I hit it off from the start, and we never had any doubts that we were doing a potentially important project that required our close collaboration.

By the time I arrived in Bethesda, Wil had already settled on the basic approach to the problem. With regard to the field potentials, the key idea was that they are generated by synchronous action of the active cells, and that because of the near radial symmetry of the bulb, the potentials result from a potential divider effect of the recording electrodes along the external current pathway. This reduced the three-dimensional field-potential distribution to a one-dimensional problem, which in turn enabled the active populations to be represented by single representative neurons, so that we could draw on his previous work on field potentials around single neurons.

With regard to simulating the action potentials and synaptic potentials that give rise to the field potentials, the timing was propitious because Wil was just finishing the first stage of developing the compartmental method for neuronal modeling. During the fall after I arrived, he was preparing to deliver his seminal paper launching these methods at the Ojai Symposium on Neural Modeling, held in November of 1962 (Rall 1964). In that paper

(see part 4 of this book) he adapted the compartmental program (SAAM) developed by his colleague Mones Berman for kinetic analysis and applied it to the analysis of synaptic integration in an extended dendritic tree.

In our study we extended these methods from the motoneuron to olfactory bulb neurons. We determined early that the field potentials generated by an antidromic volley in the mitral cell axons were likely to be associated with a sequence of antidromic invasion of the mitral cells followed by synaptic excitation of the granule cells, so that simulating these potentials would require representative models of each type of neuron. Since no one had modeled whole neurons before, incorporating the structural diversity of axon, soma, and dendrite as well as the functional properties of synaptic potentials and action potentials, we had to make some hard decisions about the amount of detail to include. Hence the rather long Methods section in the ultimate paper (Rall and Shepherd 1968), explaining at some length the rationale for representing the critical components of each type of neuron. The action-potential model was a particular challenge in this regard. Our first choice was to use the Hodgkin-Huxley model of the impulse in the squid axon, but the parameter values had not yet been determined for mammalian neurons, and given the already considerable computational load imposed by the multicompartmental representation of the neurons and their synaptic properties, the additional load of the full Hodgkin-Huxley equations would have made the models too cumbersome. Wil therefore wrote a Fortran program for the compartmental simulation that included a simplified impulse model as well as the field-potential calculations using the potential divider concept. The impulse model consisted of a pair of nonlinear differential equations representing an activating conductance followed by a quenching conductance. We carried out several voltage clamp simulations showing that these equations behaved in general agreement with the equations describing the sodium and potassium conductances of the Hodgkin-Huxley impulse model. We mention in the paper that a more detailed exploration of this model was in preparation; although this was never realized, the model was used further in Goldstein and Rall 1974.

Modeling the mitral cells required more accurate estimates of the sizes of mitral cell somas and dendrites, and modeling the relation between intracellular and extracellular potentials required estimates of the packing densities of mitral and granule cells. Paul Maclean made his laboratory in Building 10 available so that I could prepare some histological material of the rabbit olfactory bulb for this purpose. Tom Powell had driven home to me the importance of good quality perfusion and fixation and attention to tissue shrinkage, so I used a balanced fixative (Bouin's fluid) and took extra care with these steps. Grant Rasmussen generously gave me some

space in Building 9 to work with this material. There I became acquainted with Jan Cammermeyer, who had made it his life's work to battle the infamous "dark neurons," which he showed were caused by too early removal of perfused brain tissue. Because these would interfere with our measurements, I religiously waited several hours after perfusion before starting cautiously to remove the bulbs. Sections were made in all three planes in the bulb, and with the excellent fixation and cresyl violet staining I was able to carry out the cell measurements.

An even more fortunate result of working in Building 9 was that I met Tom Reese and Milton Brightman, who were working down the hall. Tom was finishing his electron-microscopical study of the cellular organization of the olfactory epithelium, and by early 1964 he and Milton started their study of the olfactory bulb. Up to that time there had been no study of the fine structure or synaptic organization of the olfactory bulb. It soon became apparent to us that we had the opportunity for a collaborative study combining electrophysiology, electron microscopy, and biophysical modeling, which must have been the first to involve all three approaches (the combined structural and functional studies of the cerebellum by Eccles, Ito, and Szentagothai and of the retina by Dowling, Boycott, and Werblin were also getting under way about this time). The perfusions for the electron microscopy were difficult, so the study went slowly (at least it seemed to me).

Meanwhile there was plenty to do with Wil. When I arrived, he was working on some camera lucida drawings of Golgi-impregnated motoneurons of cats that had been obtained by Aitken and Bridger as a part of a larger study of motoneuron morphology. Wil was interested in seeing whether the equivalent cylinders for the dendritic trees were different for different size trees. We spent many months on that data but in the end gave it up because we were unsure about how many dendritic branches were hidden or cut off. During this time the mathematical research office moved from Building 10 to Building 31. As an experimentalist I enjoyed the rare privilege of rubbing elbows with mathematicians on a daily basis, and I came quickly to appreciate the unique role the office was playing in bringing theory to bear on modern experimental biology. I also made many new colleagues through Wade Marshall's neurophysiology laboratory and the active Friday noon seminars there in his conference room in Building 10.

Through most of 1964 Wil and I developed a rhythm for doing the work. In the morning we would collect the printout at the computer center of the results of the overnight run of the model. We would spend the morning pouring over the results and the afternoon determining which parameters to add or change. Then it was punching them into the IBM

cards and leaving them at the computer center where the Honeywell 800 would grind away overnight. When you only get one or two runs per night, it puts great pressure on your intuition to sense what are the constraining variables and which parameter change will give the most insight into how the model is functioning. That economy is behind the strong feelings Wil and those of us who have worked with him have about the importance of constructing models that are adequately constrained.

By the summer of 1964 we had the models for antidromic impulse invasion of the mitral cells and synaptic excitation of the granule cells pretty well worked out. That left just a couple of months in the fall to wrap up the study before I had to leave for a visiting position at the Karolinska Institute in Stockholm. Our writing mode was to sit together with Wil writing things down in a bound protocol book as we arrived at an interpretation and conclusion. Things seemed to be coming together except for one unsolved problem. After mitral cell antidromic invasion, how are the granule cells excited so that they can then inhibit the mitral cells? The assumption in our Oxford circuit diagram was that this excitation came by way of axon collaterals of the mitral cells. However, the localization of the field potentials in our computational model showed that there was an intense depolarization of the peripheral process of the granule cells in a relatively thin layer at the level of the mitral cell secondary dendrites, which was difficult to reconcile with the different distributions of axon collaterals. The more we struggled with this problem, the more the constraints of the model indicated that the excitation of the granule cell processes must occur at the same narrow level as the subsequent inhibition of the mitral cell dendrites. But how? In a moment, one afternoon, the idea hit us that the excitation of the granule cells must come from the same dendrites that the granule cells then inhibit; in other words, synaptic excitation in one direction and synaptic inhibition in the other must occur between the same two processes. I knew from the classical literature that there was no precedent for this kind of interaction between dendrites, and Wil knew from his knowledge of synaptic mechanisms that there was no precedent for this in the physiological literature. However, the model indicated strongly that some kind of two-way synaptic mechanism must be present.

When I left NIH in November 1964, the project fell into limbo. Most of the analysis was complete, but there were still figures to finalize and much of the text to write. Anyone who knows Wil knows that writing does not come easily for him. Furthermore, the work on the olfactory bulb had taken time away from the major study of synaptic integration in motoneurons that he was continuing to pursue with Kay Frank and his colleagues, and he felt, quite rightly, that that study had the highest priority

in order to establish the credibility of the model for dendritic integration. We also needed to know from Tom and Milton whether there was any electron-microscopical evidence for the kind of bidirectional synaptic interactions we were postulating.

Fortunately, the evidence was not long in coming. In a few months Wil wrote me in Stockholm that Tom and Milton had indeed found synapses between mitral and granule cell dendrites. When he heard that these were ordinary synaptic contacts situated side by side with opposite polarities, Wil immediately told them that these were precisely the kinds of connections to mediate the interactions we had postulated. Soon we heard that synapses between dendrites in the olfactory bulb had also been seen by Hirata (1964), who referred to them as the "atypical configuration," and by Andres (1965), but the identification of the synaptic processes was not clear, and without the physiology and model it was difficult to infer a function for the synapses because they seemed to be opposing each other. The convergence of our prediction with the identified synapses was not only an exciting result but Tom's and Milton's electron micrographs and serial reconstructions were stunningly clear, so we agreed to write a short paper together on the dendrodendritic synapses and their interactions and send it to *Science*. The result? Rejection, with the comment by the referee "not of general interest."

This setback occurred while there was continuing skepticism toward Wil's studies of the motoneuron. That period was the low point in Wil's fight for the functional importance of the dendrites, and for the place of theory in the study of neuronal function. I think it was only his stubborn belief in himself that carried him through those difficult years between 1959 and 1966. I was too naive to have any doubts myself. The support of Kay Frank, Bob Burke, Phil Nelson, Tom Smith, and their colleagues was especially important in seeing Wil through this period. I mention these things to give the reader an appreciation of how much opposition Wil had to overcome, and how far things have progressed between then and now. Fortunately, it was the dark before the dawn.

In June I was back in the United States to attend a meeting on sensory receptors at Cold Spring Harbor, where John Dowling reported the studies showing similar reciprocal synapses in the retina. After the meeting I came to Bethesda so that we could decide what to do about getting our paper published. Wil contacted William Windle, the editor of *Experimental Neurology*, who invited us to submit it there. We submitted it in July; it was accepted but not published until January 1966 (Rall et al. 1966). The results on reciprocal synapses in the retina came out independently during this same time period.

By the end of 1966 I was back in the United States, and Wil had finished the study of synaptic integration in motoneurons. The publication of the five motoneuron papers in collaboration with Kay Frank's group in 1967 in the *Journal of Neurophysiology* (see chapter 6.2 in this volume) finally brought vindication for Rall's approach to the analysis of dendrites. It also meant that we could turn to writing the full manuscript of our olfactory bulb study. During 1967, while at MIT and finally Yale, I made periodic trips to Bethesda to get the manuscript done. We would sit together and discuss each sentence and often each word as he would write it out in longhand, for later typing by a secretary. It was slow, but it was a marvelous intellectual experience. I have often taken up pencil and paper (or more recently, sat at the computer) and done the same with a student or colleague if the subject is something I really care about. The paper was finally submitted in March 1968 and published in the last issue of the *Journal of Neurophysiology* that year. It was just over six years since I had arrived in Bethesda.

Epilogue

In considering the significance of this work, the 1966 paper emphasizes the fine-structural evidence for the reciprocal synapses. The beautiful electron micrographs of Reese and Brightman showed these clearly, and their serial reconstruction was so definitive that there never was any doubt about the identity of the participating dendrites. This further left no doubt about the presence, identity, and prevalence of dendrodendritic synapses, which was significant at the time in providing a kind of benchmark for others as they encountered less clearly identifiable presynaptic dendrites in other parts of the nervous system. The physiology section describes how successive phases of the field potentials reflect a sequence of mitral cell invasion, granule cell excitation, and mitral cell inhibition that is mediated in the model by the reciprocal dendrodendritic interactions. It was a satisfying case in which a theoretical model predicted anatomical connections, and in addition provided an explanation for how they would constitute a functional circuit.

In Rall and Shepherd 1968 the emphasis was on the independent evidence from the physiology and the biophysical model that led to the postulate of the reciprocal interactions. Several points in the results reflect key steps in constructing the model that, although not often mentioned, occupied much of our effort. These included (1) the potential divider model for the recording of the field potentials; (2) the contrasting ratios of intracellular and extracellular current paths for mitral versus granule cells

(which became crucial in driving us to the postulate of the mitral-to-granule cell connection); (3) the evidence that intracellular conduction velocity cannot in general be inferred from extracellular field potentials; and (4) the exploration of active versus passive dendritic properties (this was the first attempt to combine both into a model of a single neuron, and was the start of our later interest in active properties of dendrites and dendritic spines). All of these points were crucial in putting constraints on the model. Modern-day neuronal models of course bring much more computational power to bear, enabling more extensive simulations of geometry and membrane properties, but few incorporate both extracellular and intracellular data and are as tightly constrained as this original model.

The discussion in the 1968 paper went into some detail regarding the implications of the results. Wil was very much the driving force behind this. The confluence of anatomy, physiology, and biophysical models provided insights into types of neuronal organization not known before, and he wanted to follow these implications to their logical conclusion in order to point out the new principles that were implied. Among these implications were (1) presynaptic dendrites can have either synaptic excitatory or inhibitory outputs; (2) cells without axons, such as the amacrine or granule cell, have synaptic outputs like other neurons; (3) neurons can have local input-output functions not involving the entire neuron; and (4) action potentials are not needed for synaptic activation or neuronal output. There were also implications regarding dendritic spine functions that would be pursued by both Wil and myself in later work. The results specifically supported our previous idea that the granule cells are the general inhibitory interneuron in the olfactory bulb and that they mediate a kind of Renshaw inhibition, but by a different type of local synaptic pathway. I would not have had the temerity myself to stick my neck out in so many directions, but as each point came up in our discussions, Wil assessed it on its merits. We did have the advantage that between us we had a good grasp of the relevant biophysical and physiological literature; my training at Oxford had emphasized the classical antomical literature as well, and Tom and Milton gave us the current coverage of the relevant fine structure. The discussion therefore attempted to place the new findings within a synthesis of these overlapping fields.

It is fair to say that the two papers had a mixed reception. Eccles, despite his opposition to the Rall model of the motoneuron, was characteristically enthusiastic about new data, and he organized a symposium for the 1968 FASEB meeting in Atlantic City on the new evidence regarding synaptic organization, at which Dowling and I spoke. Frank Schmitt included talks by both Wil and myself at the NRP meeting in Boulder in

1969. Roger Nicoll's paper in 1969 on the electrophysiology of the olfactory bulb provided important early support for the model. But physiologists have generally been slow to assimilate the results because of the difficulties of analyzing dendritic properties; for example, after almost 30 years there is not yet clear evidence regarding the functions of the reciprocal synapses in the retina.

Wil and I had intended to pursue further studies together to test the reciprocal model, but the problem with his cataracts made this impossible. In the middle 1970s I therefore began a collaboration with Robert Brayton, a mathematician then at the IBM Watson Research Center, that resulted in a more detailed simulation of the reciprocal dendrodendritic synaptic circuit (Shepherd and Brayton 1979). The significance of this work for subsequent studies of active properties of dendrites and dendritic spines is discussed later in this volume. In 1978 we introduced the isolated turtle brain preparation and applied it to analysis of the synaptic circuits in the olfactory bulb (Nowycky et al. 1978; Mori and Shepherd 1979). This led to direct physiological testing for the reciprocal circuit (Mori et al. 1981); the results of Jahr and Nicoll (1982) were especially convincing in providing evidence from intracellular recordings and pharmacological manipulations for both reciprocal and lateral inhibition.

It was the anatomists who were most immediately influenced by the work. The anatomical findings gave a clear image of the new type of dendritic synaptic organization and served as the model, along with the similar findings in the retina, for the studies just opening up on the synaptic organization of many brain regions. Famiglietti and Peters (1971), Morest (1971), and Ralston (1971) were among the pioneers who showed that presynaptic dendrites are not peculiar to the olfactory bulb and retina but are components of normal circuits in different thalamic relay nuclei. The generality of the findings and interpretations here and in other regions of the nervous system stimulated me to gather the new evidence into a book on the new field of synaptic organization (Shepherd 1974). The term *local circuit* was introduced by Pasko Rakic (1976) to apply to neural organization at this regional level, and the dendrodendritic connections and interactions were the prototype covered by the term *microcircuit*, which was introduced to apply to the most confined and specific of the local circuits (Shepherd 1978).

Although the confirmation of our findings and the general acceptance of the interpretation were gratifying, there is a sense in which Wil, as senior author on this work, has never received the credit that was due. It was a pioneering study, using methods largely developed by him, that, together with the work on the motoneuron, laid the foundations for the field of computational neuroscience. It led to the discovery of a new type of

function of neuronal dendrites. And the findings required revision in fundamental concepts, dating from Cajal, of how neurons are organized. The lack of recognition may be due in part to the fact that the new findings introduced new complexities into understanding the rules of neuronal organization, and the time was simply not yet ripe for a new synthesis that could be readily grasped by experimental neuroscientists. It may also reflect the general tendency of theoretical neuroscientists to ignore the importance of dendritic functions. And it may be because Wil Rall is a modest person who feels the evidence should speak for itself.

References

Andres, K. H. (1965). Der Feinbau des Bulbus Olfactorius der Ratte unter besonderer Berucksichtigung der synaptischen Verbindungen. *Z. Zellforsch.* 65:530–561.

Famiglietti, E. V. Jr., and Peters, A. (1971). The synaptic glomerulus and the intrinsic neuron in the dorsal lateral geniculate nucleus of the cat. *J. Comp. Neurol.* 144:285–334.

Goldstein, S. S., and Rall, W. (1974). Changes of action potential shape and velocity for changing core conductor geometry. *Biophys. J.* 14: 731–757.

Green, J. D., Mancia, M., and Baumgarten, R. (1962). Recurrent inhibition in the olfactory bulb. 1. Effects of antidromic stimulation of the lateral olfactory tract. *J. Neurophysiol.* 25:467–488.

Hirata, Y. (1964). Some observations on the fine structure of the synapses in the olfactory bulb of the mouse, with particular reference to the atypical configuration. *Arch. Histol. Japan* 24:293–162.

Jahr, C. E., and Nicoll, R. A. (1982). An intracellular analysis of dendrodendritic inhibition in the turtle in vitro olfactory bulb. *J. Physiol. (London)* 326:213–234.

Morest, D. K. (1971). Dendrodendritic synapses of cells that have axons: The fine structure of the Golgi type II cell in the medial geniculate body of the cat. *Z. Anat. Entwickl.-Gesch.* 133:216–246.

Mori, K., Nowycky, M. C., and Shepherd, G. M. (1981). Analysis of synaptic potentials in mitral cells in the isolated turtle olfactory bulb. *J. Physiol.* 314:295–309.

Mori, K., and Shepherd, G. M. (1979). Synaptic excitation and long-lasting inhibition of mitral cells in the *in vitro* turtle olfactory bulb. *Brain Res.* 172:155–159.

Nicoll, R. A. (1969). Inhibitory mechanisms in the rabbit olfactory bulb: Dendrodendritic mechanisms. *Brain Res.* 14:157–172.

Nowycky, M. C., Waldow, U., and Shepherd, G. M. (1978). Electrophysiological studies in the isolated turtle brain. *Soc. Neurosci. Absts.* 4:583.

Phillips, C. G., Powell, T. P. S., and Shepherd, G. M. (1961). The mitral cells of the rabbit's olfactory bulb. *J. Physiol.* 156:26–27.

Phillips, C. C., Powell, T. S., and Shepherd, G. M. (1963). Response of mitral cells to stimulation of the lateral olfactory tract in the rabbit. *J. Physiol.* 168:65–88.

Rakic, P. (1976). *Local Circuit Neurons.* Cambridge, Mass: MIT Press.

Rall, W. (1964). Theoretical significance of dendritic trees for neuronal input-output relations. In *Neural Theory and Modeling* ed. R. F. Reiss. Palo Alto: Stanford University Press.

Rall, W., and Shepherd, G. M. (1968). Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb. *J. Neurophysiol.* 31:884–915.

Rall, W., Shepherd, G. M., Reese, T. S., and Brightman, M. W. (1966). Dendrodendritic synaptic pathway for inhibition in the olfactory bulb. *Exp. Neurol.* 14:44–56.

Ralston, H. J. III (1971). Evidence for presynaptic dendrites and a proposal for their mechanisms of action. *Nature* 230:585–587.

Shepherd, G. M. (1963a). Responses of mitral cells to olfactory nerve volleys in the rabbit. *J. Physiol.* 168:89–100.

Shepherd, G. M. (1963b). Neuronal systems controlling mitral cell excitability. *J. Physiol.* 168:101–117.

Shepherd, G. M. (1974). *The Synaptic Organization of the Brain.* Oxford: Oxford University Press.

Shepherd, G. M. (1978). Microcircuits in the nervous system. *Scientific American.* 238:92–103.

Shepherd, G. M., and Brayton, R. K. (1979). Computer simulation of a dendrodendritic synaptic circuit for self- and lateral inhibition in the olfactory bulb. *Brain Res.* 175:377–382.

Yamamoto, C., Yamamoto, T., and Iwama, K. (1963). The inhibitory system in the olfactory bulb studied by intracellular recording. *J. Neurophysiol.* 26:403–415.

Supplemental Comments by Milton Brightman

Our first meeting with Wil, about 30 years ago, here at the NIH, was prompted by Tom Reese's superb electron micrographs of the rat olfactory bulb. The microscopy lab was situated in the basement of Building 9 in what had originally been a plumbing shop. The light was not always adequate and the micrographs were still being rinsed, but I was struck by the image of a single neuronal process that, according to the location of synaptic vesicles, was postsynaptic at one point and presynaptic at another. We were both excited about this unique arrangement.

A short time later, Tom told me that we were to meet with two physiologists who were keenly interested in the finding. It was then that I first met Wil Rall and Gordon Shepherd. Their enthusiasm about what we had seen was very evident as they explained the functional significance of these peculiarly arranged synaptic contacts and how they could account for lateral inhibition in the olfactory cortex. It was the joy with which Wil told us of the implications, as much as anything, that encouraged us to look further.