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CORTICAL NEUROBIOLOGY:
A Slanted Historical Perspective

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I have been asked to compose an essay on the development of ideas in cortical neurophysiology over the past two decades. That, it seems to me, amounts to writing a paper that is all introduction—no methods, no results —perhaps some discussion. Not a task one undertakes lightly, and I make no guarantees as to the outcome.

When asked to reminisce about the good old days, two thoughts occur to me. One: the "good old days" are right now. Competitive and overcrowded and at times almost vicious as the field has become, we have nevertheless to keep pinching ourselves to wake up and appreciate how lucky we are to be in a field of science that is moving and breathlessly exciting. And unlike the situation in those "good old days," it is now at least possible to earn a living at it. We are now where molecular biology was 10 to 15 years ago and where physics was when I was in college. To be in a field of science at just the right time takes, among other things, a lot of luck.

My second thought is a completely different one. A few years ago Torsten Wiesel and I decided to put together a set of reprints with forethoughts and afterthoughts, a book of readings like so many others, except that with characteristic modesty these readings would be restricted to our own papers. (An average of one paper a year seems meager to Medical School Promotions Committees, but if you live long enough it adds up.) Well, we partitioned the work in some fair manner such as me writing two-thirds and Torsten one-third, but when we got to the 1963–1965 visual-deprivation papers, through some misunderstanding we each independently wrote some pages of introduction, describing how and why we started closing cats' eyes.

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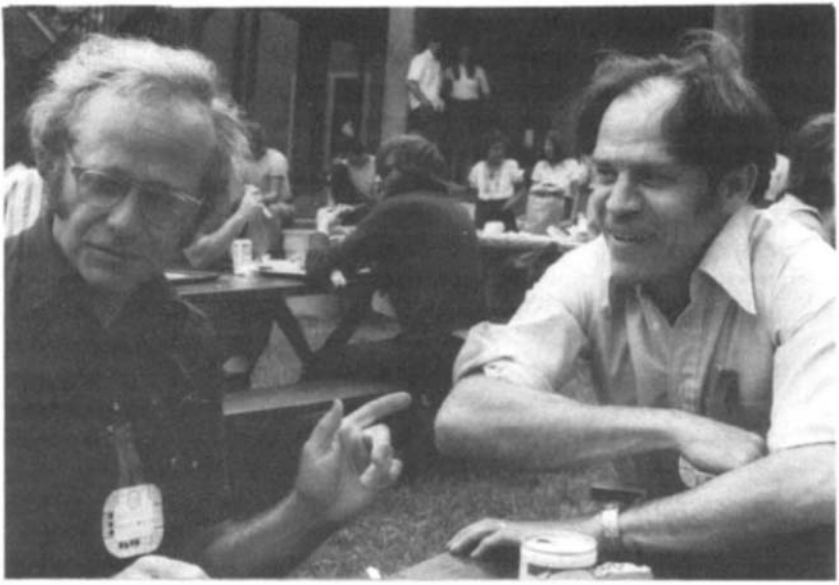
When I saw Torsten's version I was flabbergasted, and even a bit angry. His version was that we had wanted to examine postnatal development of the visual cortex, and so closed one eye to hold up development in that pathway. According to me, we simply wanted to see whether we could produce an amblyopic eye and then look physiologically for the point or points in the pathway at which the failure occurred. These motivations, to be sure, aren't mutually exclusive, but I would have sworn that at the time the work was done our motives, whatever they were, were the same. In any case, if I describe how I think things were in cortical neurophysiology twenty years ago, you have to realize that my memory of things past may be a far cry from the way things really were. As in Akutagawa's story, *Rashomon,* even at a given time no two people have the same assessment of current events.

So much for my introduction to my introduction. I now turn to how things really were in the good old days, and subsequent developments. A glance at Howell's *Textbook of Physiology,* vintage about 1950, will convince anyone that we have come a very long way. Even then, a half-century after Cajal's *Histologie du Système Nerveux,* despite the work of people like Adrian, Woolsey, Jasper, and Penfield, the question of cortical localization was still hotly debated. One of the first scientific papers I ever heard, in 1953, was by Lashley, at the Montreal International Physiological Congress. I have no recollection at all of what Lashley said at that plenary session (one almost as crowded as a Presidential Symposium of the Society for Neuroscience) but he then was one of the strongest antagonists of the concept of precise cortical localization, and I must confess that when I try to detect the difference between Brodmann's areas 18 and 19 in a Nissl section of the cerebral cortex I'm not unsympathetic to Lashley. But in those dark ages it was worse than that. Elsewhere in this volume Eccles has reviewed the medieval problems of electrical vs chemical synapses at nerve-muscle junction and spinal cord; then everyone was at least agreed that the business was done at the synapses. When it came to the cortex, the concepts of nebulous electrical field effects were still taken seriously. It is hard to believe, today, that as recently as 1955 no less a person than Roger Sperry saw fit to dice up the cortex with vertically placed sheets of mica or tantalum wires in order to stop the supposed current flow or short circuit it, and thus quash those concepts. And along with ephaptic mechanisms one had glia and all kinds of ideas as to what *they* might be doing; one had reverberating circuits and suppressor strips. Any sensible person who was well read in the literature, and had physics or biochemistry as options, would surely avoid a field in such a sad state.

There were of course healthy streams, and things had begun to change. Part of the awakening was related to technical progress. Until the late 1950s most work in physiology of the cortex depended on the EEG and evoked



David H. Hubel and Torsten N. Wiesel.

potentials. Not surprisingly the main thrust then was towards understanding the part that the cortex plays in sleep and waking and in attention. (Learning was also mentioned *sotto voce;* Hebb was decades ahead of his time; the idea of memory-and-macro-molecules that later polluted the field was still not yet hatched.) No one could see the changes in the EEG of a person falling asleep and not be fascinated—it is still just as fascinating. Unfortunately as far as our understanding goes, the EEG, and for that matter the problems of sleep and arousal, are now not so much better understood than they were then. For the EEG one can see little progress. For sleep, we indeed now do have REM sleep, the locus ceruleus and the raphé nuclei, and a host of transmitters to think about today, but that only says that we have in 1981 a better grasp of the magnitude of the problem, not that we are one iota nearer to understanding what happens to the cortex in sleep or why it happens. The problem then of course was that the tool available (and I say the tool, because the EEG was about the only one at hand) was completely empirical. Some of the discoveries made with it, such as the recognition of slow-wave sleep stages and REM sleep, were momentous, but the boot-strap operation, of coming to understand the EEG by using the EEG, was not possible. So the subject languished.

The closely related evoked potential method produced more fundamental results because the problem it addressed, a definition of the sensory areas

and a working out of the topography within some of them, were simpler. The stream of work that began with Adrian, Talbot and Marshall, Bard, Woolsey and others has continued right to the present, though microelectrodes have largely replaced the saline wicks and coarse wires that registered the evoked potentials. It's a closely guarded secret that of the two techniques, evoked potentials and single-cell recording, the evoked potential technique is far more difficult to carry out and to interpret: that is what makes Talbot and Marshall's 1941 paper still such a wonder to contemplate.

It was the microelectrode that made the difference, between 1955 and 1965, but it took time and a lot of technical development before it came to be used effectively. Early in that era a number of groups succeeded in inserting micropipettes into cortex, and even in recording spikes. A crucially important technical innovation was the Davies chamber (and its variants), which allowed one to keep the cortex from bouncing around with the heart beat and respiration, long enough to allow one to find what kinds of stimuli, if any, would influence the occurrence of those spikes. Metalic electrodes—indium, gold, platinum, tungsten, which didn't break and didn't plug and had remarkably low resistance at the frequencies that counted for extracellular work—were a great help. Curiously, why they work as well as they do, especially the big dishmop-like platinum-black ones, is still not understood at all. I think that the most important advance was the strategy of making long microelectrode penetrations through the cortex, recording from cell after cell, comparing responses to natural stimuli, with the object not only of finding the optimal stimulus for particular cells, but also of learning what the cells had in common and how they were grouped. This method came, I believe, mainly from the Johns Hopkins Medical School and was the result of combining the talents of physiologists such as Mountcastle with those of neuroanatomists, especially Jerzy Rose. It led to a clear proof of localization of function in the brain stem, thalamus, and cortex, and led directly to Mountcastle's discovery in 1957 of cortical columns. This fusion of the methods and ideas of physiology and anatomy was a new thing. Previously, physiologists had rarely looked to see where their electrodes were. I'm not sure why, unless perhaps they were convinced that histology was a next-to-impossible art. Conversely, anatomists have been slow to use physiology to monitor placement of their instruments of injection or destruction, doubtless also because of terror over the idea of using an amplifier or oscilloscope. It took physiologists some time to realize that you can't study function without studying form. Physiologists also had to get over their love affairs with electronic gadgetry, and learn that if you want to study pain a good start is to pinch the animal's tail and see if cells respond.

Until the late 1950s neurobiology suffered seriously from the separation of its main component parts, anatomy, physiology, and chemistry. To earn

a living neurophysiologists often had to be competent in renal and cardiac physiology, and neuroanatomists in gross anatomy, with little chance or time to learn the other person's field. I count myself blessed to have been trained first in Montreal at the Montreal Neurological Institute and then at Walter Reed, where Fuortes, Galambos, and Nauta all worked on the same corridor. It took universities and medical schools years to learn that these three components of neurobiology are closely intertwined, and that they all suffer when separated.

The sedulous anatomical-physiological business of studying exhaustively not just one cell but many, in marathon penetrations, had its epitome in Vernon Mountcastle, already a famous person when I first got into the field. I went once to visit him in Baltimore from Walter Reed (where I was lucky enough to be drafted in 1955) to discuss plans for possible postdoctoral training. I arrived around 3 P.M. Vernon was doing an experiment, by himself, and looking reasonably fresh, or perhaps just slightly weary. I said, "Is this the first penetration?" He said, "Yes, I started yesterday morning."

Some months later, around the time that Torsten and I started working together at Hopkins, Vernon gave a paper reporting results from, I think it was, 900 cells, for those days an astronomic number. We knew we could never catch up with that, so we did the next best thing and called our first cell No. 3000 and numbered them from there. When Vernon visited our lab we made sure that we mentioned several times the i.d. number of any cell we described to him. Vernon was most encouraging and suitably excited about our first results. I remember his comment: "What a wonderful system! It will give you enough work to last a good five years."

But to return to the quantitative propensities of neurophysiologists, I remember a momentous occasion when at Walter Reed, in 1957, or so, I felt pleased enough at finding directionally selective cells in area 17 of a purring cat to drag Bob Galambos down to my lab for a demonstration. Bob was suitably impressed—he always gave wonderful positive feedback and was very tolerant of a stubborn and moody postdoc—but said, "David, this is fine, but what is the latency of this cell?" Well, I did feel a bit sheepish, to be preoccupied with postgraduate stuff like movement and not to have even established the latency, so I found a strobe light, and quickly found that this cell's latency was 83 msec. That was odd, considering a myelinated pathway a few inches long, and allowing for a delay of about 1 msec per synapse. I took the lesson to heart: that was the first latency I ever measured, and also the last.

The leading neurophysiologists—those who worked in the periphery and spinal cord—had rather firm ideas about what neurophysiology was. They tried to be quantitative; they expressed results in milliseconds and used graphs. Once around 1962 Jack Eccles came to visit Stephen Kuffler, and Torsten and I got to show him some oriented receptive fields. Again we were

quizzed about latency, and the virtues of intracellular methods and electrical stimulation were pointed out to us. In leaving Jack said, "You know, sooner or later you have to start doing neurophysiology." Jack's attitude was of course correct; we all know the success story that came out of Eccles's work on the cerebellum a few years later. But for better or worse the course of events has been quite different in cerebral and cerebellar cortex. In cerebellum we now know the physiology of the circuit better than anywhere except possibly the retina (or the aplysia abdominal ganglion, to do justice to our host at the Presidential Symposium!), but without the faintest idea of overall information processing. In contrast, for the striate cortex we do know, at least in rough outline, the difference between the meaning of a spike discharge in the input as opposed to the output: the information processing is in some sense understood. But the circuit, in terms of excitation and inhibition and transmitters, is still like midnight in central Africa. The emphasis has been in studying responses of cells in terms of the optimal natural sensory stimuli. In vision this trend began with Stephen Kuffler; Torsten and I simply extended his approach further centrally.

That one still has not got around to doing neurophysiology in the cortex, in Eccles's sense of the word neurophysiology, is of course partly because the anatomy of the cerebral cortex is still far from worked out. The cerebellum, though not exactly childishly simple, does have (and has had since Cajal) a pellucid quality to its anatomy—its cortex has five or six kinds of cells, whose connections have been rather well known for a long time. In the cerebral cortex, Cajal and Lorente de Nó's work had made it clear that the major intrinsic connections run vertically. But until the work of Jennifer Lund, no one had ever taken one cortical area in one animal species and looked long and hard at the Golgi anatomy, an amazing thing given that the Golgi method has been around for more than a century. Lund's recent Golgi work makes it clear how little was really known. Moreover, the half dozen or so major advances in neuroanatomical methods that have been developed in the past ten years or so, especially methods based on axonal transport, and the techniques just appearing for identifying enzymes immunohistochemically, are all accelerating the pace of progress in cortical anatomy, but again making it clear how much there still is to do. It does seem probable that the cerebral cortex will turn out to have stereotyped sets of connections, intricate yet repetitive like a crystal, but an order of magnitude (I'm never sure if that expression just means "ten times") more complex than the cerebellum.

If in the 1950s there were doubts about the existence of specificity and topography in the cortex, there seemed also to be a profound lack of ideas about what the structure could possibly be doing. About the only thing one could say was that it "analyzed," but no one had any clear thoughts as to

what kind of things the analysis might entail. I suppose that perhaps the main contribution of work over the past decades on the visual cortex has been the demonstration that something does indeed happen between the input and output of area 17. This kind of information, as opposed to mapping, has been harder to obtain in other cortical areas, probably for a variety of reasons. In the auditory system it is harder to imagine what the appropriate biological stimulus should be in a cat that hears so well up to 50 kilocycles; the pathway leading to the cortex is more complex; the response properties of medial geniculate cells are less thoroughly understood than those of lateral geniculate cells. Lately considerable progress is being made in mapping the auditory cortex, and this knowledge may be necessary before one can get at the problem of comparing input and output.

In the 1950s when at Walter Reed I decided once to take advantage of Galambos' laboratory full of audio stimulators and soundproof rooms, and set about to record from the auditory cortex of cats. I remember vividly how one could turn every dial of the stimulator, with sine waves, white noise and clicks, with no effects at all on cortical cells. Then on going into the chamber to check on the cat, I would find that the cell would fire like a machine gun when I rattled the doorknob. Shaking keys was also often very effective. But I never got anywhere in trying to pin down what was so good about these stimuli. I suspect that among other things they were simply interesting to the cat.

An important advance that has come out of work on visual cortex is the realization, first from the physiological work of Toyama, and then anatomical studies by a number of groups, that different layers send their outputs to different places. Meanwhile receptive field mapping has made it possible to compare the properties and the information transmitted by the cells in these layers. While cells in the different layers do things in common, they exhibit marked differences that are presumably tailored to the functions of the structures to which they project. For example the large field motion-sensitive cells of layer V presumably provide just what the superior colliculus needs. The common properties, like responding to oriented lines or favoring one eye, define the several column systems. It is this intricate Chinese puzzle aspect that one finds so challenging and aesthetically pleasing. One can only guess (and there are already many hints) at what kinds of beauty lie in the fifty or more still unexplored cortical areas.

In case anyone thinks I'm at all complacent about area 17 being well in hand, let me reassure you; there are still problems enough even to keep all 5000 (or whatever the number is) area-17 physiologists busy. One has only to think of apical dendrites and that crowning mystery, layer 1. Or if that leaves you cold, there are those reciprocal connections—18 to 17, 17 to the lateral geniculate—which, along with every other reciprocal connection in

the nervous system, except for the gamma efferents, are utterly ununderstood.

It seems to me that another quite different development that I have alluded to earlier is the snowballing or mushrooming of a number of areas in a number of different systems—the Talbot-Marshall-Woolsey-Kaas-Allman school of anatomy-physiology. Grossly it looks as if, far from a Lashleyian subdivision into just a few major functional areas, the cortex is made up of areas whose total number may yet put Brodmann to shame. We really don't know quite what to think about the multiplicity of these areas. In recent years neurobiologists have had their hands full just mapping them out; there has not yet been time to address the physiology except in a preliminary way. Certainly a possibility is that each area will deal with a submodality, one for movement, one for stereopsis, one for color. The idea is not without some experimental support and may turn out to be correct, but it nevertheless to me has a kind of naivete, like the notion that stripped of our cortex—a kind of double scalping—we became alligators, or the notion that our right hemisphere is for art and music and other nice things and our left is rational and analytic and propositional, in short a bore. In the studies that have been done outside of area 17 in monkeys, it must be freely admitted that the avalanching increase in optimal-stimulus complexity which one might have predicted from an extrapolation of the increase that occurs in going from geniculate to cortex has simply not been evident. The first disappointment came when we found nothing very interesting by way of higher order complexity in the Clare-Bishop area in the cat, or the superior temporal sulcus in the macaque. It is too early to guess whether this is just a temporary setback that will pass when one sets about to study these prestriate areas with adequate momentum and determination and patience. At the moment—and I would never have guessed this twenty years ago—we still have our hands full working in area 17.

In an essay that is supposed to have been dealing with the development of ideas about the cortex in general, you may have detected how little I've said about the huge no-person's land beyond the occipital lobe: the speech areas, motor areas, parietal, temporal, and frontal lobes. For most of these I suspect there is first a huge job of blocking out to do, analogous to the job the evoked potentials and long electrode tracks did and are still doing for the main sensory areas. We're full of hope—I think justifiably—that methods like deoxyglucose and the PET scan may begin a revolution here; that will presumably have to take place before any cell-level approach will be possible. One has the feeling of being only in the foothills of some gigantic mountain range. I can only say that the foothills aren't especially boring!