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Half a Century in the Neurosciences: Personal Comments on Choices and Decisions

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If I were to meet the young man who emerged from the Swedish Normallyceum to matriculate at Helsingfors University in the spring of 1919, I am afraid I would find him a most disappointing companion. "Ripeness is all," and so profound are the changes brought about over the years that one would feel abashed at having to hail that youngster as an alter ego. Also, as a character he would seem to possess all one's faults without the insight and experience by which one cleverly tries to hide them.

The young man was interested in psychology—a widespread weakness in young people—and his gifted teacher, the philosopher Eino Kaila, introduced him to the experimental variety of that science. This was the time in Germany when Gestalt psychology rose to prominence, headed by a clique of talented enthusiasts. The best known were perhaps K. Wertheimer, W. Köhler, K. Koffka, and A. Gelb. The Gestalt school had started a spirited attack on what they held to be a disintegrative and meaningless splitting-up of mental events by most of the experimental approaches of the time. Their leading thesis was that the experienced world consists of formed (*gestaltete*) entities, not further reducible by experimentation, though accessible to experiments properly designed to demonstrate Gestalt qualities or rules.

An example is needed to show how this attitude could be experimentally realized. I shall take an experiment that Gelb and I carried out in 1922 when I worked with him for two months in Frankfurt in a laboratory whose formal head was Professor F. Schumann (Gelb and Granit, 1922). We had a set of Maltese crosses photographically produced so as to make a given nuance and brightness of gray appear either as the cross or as its background. The threshold of a small spot of light was found to be higher when projected on the cross than when projected on the background between two of its arms. Crosses and backgrounds were alternated on separate charts. The experiment was designed on the Gestalt principle to check whether an integrated Gestalt might not create a greater resistance to an added disturbance than a background experience of the same physical qualities. It seemed that it did.

The Gestalt approach, whatever its theoretical value, has to its credit a number of important studies, such as those of Goldstein and Gelb on cases of head wounds from World War I and Köhler's behavioral experiments with chimpanzees. The latter became very well known and rendered him the nickname of "*Affenköhler*." The impending threat of Nazism broke up the school. Some of its most influential members emigrated to the United States, and the young man of whom I have

spoken decided, on the advice of an uncle who was a practicing physician, that it would be necessary to study medicine seriously if he was to do something sensible in psychology. He therefore abandoned the field, and this is where I also quit him now. However, he may have left some trace in my upbringing because now, in my retirement, like a snake biting its tail I have begun to understand that psychological points of view could be used very profitably in the study of voluntary movement as a physiological process.

It is curious to reflect how young physiology is as a science. Those of us who were born at the turn of the century have had personal contact with pupils of the fathers of our science. While still interested in psychology, I listened—I believe in 1920—to lectures by Robert Tigerstedt in a course on the physiology of the special senses, and he was a pupil of Carl Ludwig. Tigerstedt was a true *Gelehrter*, a polyhistor such as our times do not produce. His textbook was read in many countries, but his reputation rests mainly on his large and authoritative monograph on circulation, containing everything published in that field up to the day of its appearance (Tigerstedt, 1921–1923). With Bergman, Tigerstedt discovered renin, a little too early for the physiology and biochemistry of his own time. As a young physiologist he moved from Helsingfors to the Caroline Institute in Stockholm, but in the end he left the chair at the institute and returned to Helsingfors University as professor of physiology. His son Carl succeeded him in this position.

When in 1926 I was made demonstrator (*Assistent*) at the Physiological Institute in Helsingfors, Robert Tigerstedt's creation, I still thought of physiology as something to be studied for the sake of a future career in experimental psychology, but the long-lasting medical course brought about a gradual change of attitude and interest. Clinical work was not without its temptations. However, I became more and more interested in the nervous system and the special senses, vision above all, for their own sake, and started to improve my knowledge in these disciplines.

At the time Helsingfors University, like other Scandinavian universities, was dominated by the German academic tradition, and most of the textbooks were in the German language. Alongside the course I read, first and foremost, Ewald Hering, then Helmholtz, Mach, König, von Kries, the special articles in the great German *Handbücher*, and some psychologists such as Ebbinghaus, Wundt, and G. E. Müller. I even read through Freud's *Vorlesungen über Psychoanalyse*, but apparently too late in the day relative to my own development, because I found them utterly unscientific, though highly entertaining as products of an original mind. Another quite original mind and great writer was William James, whose *Psychology* I studied at an early date with much admiration. Like Freud, James had had a medical education. But, though in published correspondence James made some very caustic remarks about the narrow-mindedness and bigotry of scientists, including experimental psychologists (naming Hugo Münsterberg), he himself stayed within the boundaries of scientific criticism when writing psychology.

I departed from the pattern of my own generation in feeling much attracted by the English language and civilization. For my first visit to a foreign country, in 1920 (thanks to the generosity of my father), I chose to go to a holiday course at London University in order to study English. This left me with a permanent feeling for Dr. Johnson's remark that the man who is tired of London is tired of life.

It is well known among physiologists that the decisive breakthrough of electronics in physiology took place within the English-speaking world with papers by Adrian, Erlanger, Forbes, and Gasser, whose achievements are too familiar to need recapitulating. In spite of my academic background in German physiology, I was well prepared for drifting over into a slow Anglo-Saxon reeducation at a time when we, who had advanced to the Einthoven string galvanometer and the capillary electrometer, had to be reeducated anyway in preparation for the electronic era of neurophysiology. In point of fact, my personal reorientation toward physiology as a final career was the outcome of that process. It involved relearning physiology in a second language and, I felt, also with a change of emphasis.

Psychophysics of vision was my best subject and leading interest, but for a medical man it seems natural to start with the retina and think of some sensible, fresh approach reaching beyond pure stimulus-response relationships of a more elementary character. The study of Ramón y Cajal's work made me realize that it would be profitable to regard the retina as a nervous center. It impressed me a great deal to find him saying that the retina was his first love and that the study of its structure served as an introduction to his later work on other parts of the central nervous system. I still believe that this roundabout route to the brain is as good in physiology as its histological counterpart. For me the main question was, of course, how and where to begin. I made an effort with a study of interaction between the center and the periphery in the afterimage of movement (1927), but soon understood, on reading Sherrington's *Integrative Action of the Nervous System*, that I knew too little about the central nervous system to realize fully my general idea of translating psychophysical observations into what John Fulton was later to term "neurophysiology."

Sherrington at the time (1928) was surrounded by a lively group of well-trained young people engaged in teaching and experimenting, and it was my great fortune to be kindly received by him and the others—Sybil Cooper, R. S. Creed, Derek Denny-Brown, J. C. Eccles, and E. G. T. Liddell. Struggling alone for so long in order to reach a sensible attitude about the science of the eye, I felt happy when Sherrington immediately said that I had hit upon the right track and added that he had always wanted someone interested in the eye to work in his laboratory. Creed and I had many interests in common, including the eye; Eccles and I worked on the spinal cord, at times with Sherrington. What a pleasure not to be alone, to work for a change within a school where definite things had to be known and whose head was a wise and kindly old man of wide reading and culture, familiar with physiology virtually from its beginning. However, I have written about him elsewhere, in the first chapter of my appraisal of Sherrington's contributions to our field (Granit, 1966).

Sherrington wrote me a letter of introduction to Adrian, whom I visited for a day in Cambridge in 1928. At that time Adrian had carried out his pioneer work with Rachel Matthews on the optic nerve of the conger eel. Then, as on many later occasions, he gave me much of his time, though I never worked in his laboratory.

In the autumn of 1928, or it may have been in the spring of 1929, Alan Gregg of the Rockefeller Foundation visited Helsingfors and asked me to serve as his in-

terpreter for visits to the university professors. His subsequent support and that of Sherrington sufficed to make D. W. Bronk appoint me a Fellow of the Eldridge R. Johnson Foundation of the University of Pennsylvania. Bronk had returned from a sojourn with Adrian at Cambridge and been offered the leadership of that brand-new institution. My wife and I came over in the autumn of 1929—our wedding trip—to a still virtually empty house; but this deficiency was soon remedied, and it became a place where everything one wanted could be obtained and where one could do what one wanted. This was my wife's and my introduction to the United States, another permanent association offering us new friends, new opportunities for work, a new way of living, and at the time also a country blazing in the brilliant coloring of October.

At the Johnson Foundation I met W. A. H. Rushton from Cambridge, initiating his experimental attack on the theory of isochronism, and a year later H. K. Hartline turned up from a long stay in Munich and started to build apparatus for his elegant studies of the retinae of *Limulus*, *Pecten*, and the frog. These two, and J. C. Eccles with whom I actually worked, are the friends of my own age group who have played the greatest role in my scientific development. A second period at Oxford, this time as a Rockefeller Fellow (1932–1933), completed my orientation toward the physiology of the nervous system.

I have made a long story short, believing that a person's start in science is nearly always of some interest but that readers must not be overdosed with individual fripperies. Looking back, I realize that these ripening years in neurobiology took a long time, where by "ripening" I mean arriving at a world of ideas broad and independent enough to sustain a durable interest in their development by experimentation. I have always believed that biological work presupposes a desire to advance understanding within a field, rather than a desire to express one's experimental cleverness. At the Johnson Foundation I made a systematic attempt at translating psychophysical observations into retinal neurophysiology, using the fusion of a flickering light as an index of excitability. My best coworker was the late C. H. Graham, finally professor of psychology at Columbia University. The most interesting results demonstrated varieties of spatial interaction (excitatory as well as inhibitory) by that index; and some of the findings were a close replication of results obtained by Adrian with the optic nerve of the conger eel (Granit, 1930; Granit and Harper, 1930; Graham and Granit, 1931).

From 1932 onwards I turned to electrophysiological methods. The results brought me invitations in 1940 to Harvard and to Stockholm, where in the end I settled down and founded an institute of my own as part of the Medical Nobel Institute (which belongs to the Royal Caroline Institute, Stockholm's medical university). The generous support of the Wallenberg Stiftelsen in Stockholm and of the Rockefeller Foundation made the move possible, and in 1946 the government created a chair in neurophysiology attached to the institute.

In the late forties I began to feel that I had been in the field of vision too long and needed a change. To this end I spent a term in my own laboratory repeating, for practice, most of the physiological experiments (on the cat) that others had done on the spinal cord after my time in Sherrington's laboratory fifteen years

earlier. I concluded that a profitable opening would be the unduly neglected field of muscular reception in relation to spinal cord, muscular activity, and gamma control. Leksell had published his thesis on the gamma system in 1945, but I could not persuade him to follow it up; nor did the subject attract others to whom I offered it. From Leksell's point of view his attitude was sensible; he was a neurosurgeon, basically interested in his own discipline, and the spinal-cord aspect by itself required full-time laboratory work. At about that time (1948) Rushton turned up for a year of sabbatical leave in my laboratory, feeling, like myself, that he needed a change from his old interest in peripheral nerve. Rushton took up the subject of vision and both of us started a new scientific enterprise. Neither of us has regretted that decision.

An attractive aspect of motor work is that movement serves as an interpreter of what has been put in, whether an artificial electrical stimulus, an afferent message for a reflex, or a voluntary command. The completed integration is handed out to the observer or experimenter, and his role, apart from discovering general principles, is to investigate the mechanisms—their site, nature, and interaction—in order to reach a functional and structural interpretation of them. By “general principles” I mean statements of basic facts with some finality to themselves, such as that the pyramidal path increases in size from rat to man, that movement rather than conscious perception is disturbed by cerebellar lesions, and that muscle contractions are graded by firing and/or recruitment of fresh motoneurons.

This seems a suitable occasion for adding to the list of such principles two generalizations referring to the relation between the brain and its environment that most obviously are valid for higher organisms. One is that the greater the elaboration required for a percept or a motor act, the greater the number of cells engaged in it. “Elaboration” may not be the best possible term, but what I mean can be well illustrated by citing examples: delicate manipulation of objects, a high degree of sensory discrimination or generalization, and high levels of consciousness. I include in the last category acts and percepts that originally required a high degree of consciousness but which by practice have become automatized. Examples on the motor side are the large cortical areas devoted to thumb and finger movements (see the well-known figurines of Penfield and Rasmussen and of Woolsey); on the sensory side one could mention the great cortical expansion of the small fovea relative to the rest of the retina (Marshall and Talbot, Whitteridge).

The second generalization might be regarded as a corollary of the first, inasmuch as it is based on the common idea that the reason for a cortical expansion is the need for more contact points to facilitate the extensive combinations of data required for evaluation and anticipation. Hence the second generalization maintains that the greater the elaboration in the sense defined, the greater the number of sites in the brain engaged in the particular act or percept concerned. This is well illustrated by the large number of widely separated sites that are engaged in a motor act as defined by anatomical and clinical evidence and recently by Evarts's well-known physiological studies of wrist movement in the trained monkey. Another example is the steadily expanding number of visual areas, a minimum of nine at the moment (Cowan, Powell, Zeki).

These two generalizations are characteristically biological; they are as independent of physics or chemistry as the notion of evolution formulated by Darwin and Wallace. They deal with purposive responses of the organism to the environment and hence belong to the teleological aspects of physiology. I have been more explicit on teleological explanations elsewhere (Granit, 1972).

It must now be common knowledge that the organ of highest control, our brain, cannot be discussed as if it were a question of localization versus general representation. The whole problem is obsolete. It created a long-lasting dispute once upon a time, but this did not end in complete victory for either side. "We now realize that there are highly localized functions, even tricks—if I may say so—that only certain aggregates of cells can perform, as well as functions that require coactivation of several cortical areas widely apart. As we penetrate problems of localization, we tend to end up with problems of organization." (I quote myself from an unpublished essay on the nature of biological explanations.)

I have emphasized all these points in order to prepare a final confrontation with the question of whether this well-documented multicellular character of organized brain activity really can be understood by the single-cell techniques that in so many respects have been so rewarding. Having been one of the early birds in recording from single cells (retina), I have now been at the game long enough to have seen the whole field develop during my own active era of single-cell experimentation. The gain in understanding has been impressive, not only in terms of fundamental mechanisms at synapses and cell membranes but also from functional points of view in an integrative context. One might mention, for instance, the columnar organization of tactile specification in the cortex (Mountcastle), the processing of information within the retina (Barlow, Tomita, Dowling, and others), cells in the visual striate area responding to orientation (Hubel and Wiesel), the gamma system, the colony concept of pyramidal motor cells (Phillips), the different organizations for phasic and tonic motoneurons, much work on invertebrates, etc. These mechanisms form but a small selection from an overwhelming multitude of triggers, "detectors," "mandatory neurons" of different kinds, etc., discovered by the single-cell technique as used in an integrative context. And there is more to come, while, of course, this technique is and always will be indispensable for the analysis of specific synaptic events at cell membranes in chemical or physical terms. But this is another story.

Returning to the question of whether unicellular studies provide good enough insight into multicellular organizations, I do not think their importance in that regard should be exaggerated. In the first instance, one cannot but suspect that many aspects of coding intrinsically depend upon a combination of cells, which remains un-get-at-able by the single-cell approach, even if it is favored by an input extended in a plane (skin, retina). By the refined histological techniques of today many connections from primary projections to an ever-increasing number of sites in the brain have been discovered, as well as interconnections between them. At such levels of polysynaptic complication unicellular signals tend to degenerate into mere "spikes," detecting, to be sure, combinations of excitation and inhibition but not the relevance of the signal being transmitted. It is well known that in the

primary afferent projections the discharge of a single cell often can be meaningfully interpreted as a "cue" or "detector." Similarly, on the motor side, its message can be evaluated as being significant for the regulation of movement in some way or other. In both these examples it is likewise possible to use the spike to analyze the organization of which it is an indicator. It is from these points of view that the unicellular response within a distant site loses its specific connotation, even though it is still capable of supporting lengthy papers on uninterpretable interactions. And when it comes to functions such as speech, understanding the significance of a sentence or a visual pattern, or deficiencies of motor control, few people would think of approaching them by the single-cell technique except in order to procure a useful hint or two.

This is where the "ablationists" come in with their behavioral tests and histological checks. As histology goes on improving, so does "ablationism," which can be regarded as its offshoot into the physiology and pathology of the nervous system. Ablation has always been regarded by physiologists as an equivocal technique because of compensatory processes, the risk for destruction of unwanted parts, and the fact that in many cases it merely tells us what the organism can do without the piece ablated, instead of telling us what the latter did *in situ*. But today my definite impression is that methods based on ablations have undergone great improvement, partly, as I said, because of the improved histology, but partly also because of improvement in the critical evaluation of behavioral tests. This is actually more of a difficulty than is histological verification. At its best a good ablation experiment becomes a salubrious antidote against overinterpretation of single-cell data. Of this, the field of vision provides excellent examples (see reviews by Doty, 1973, and Weiskrantz, 1972). It is truly surprising what an animal can do after ablation of the striate area.

However, I shall restrict my comments to the motor field, within which my reading and experimentation are of a more recent date. The now-available knowledge that many cells in many different sites take part in motor acts is apt to be discouraging. It suggests an inordinate number of local electrodes and a very optimistic faith in interval recording and correlation statistics. This experiment must be left to the believers in its future. But several electrodes could, indeed, be implanted without too much trouble and without an excess of machinery. The essential problem will then be to introduce constraints to limit the number of possibilities.

An analogy will make my meaning clear without involving technicalities. The central nervous system is capable of combining "anything" with virtually "anything else." As an example, take the word "horse." Sitting down thinking of my associations to "horse" for a while, I found them to be almost limitless. Yet I use the word "horse" only in a limited number of sensible contexts. Only when this is done does it become relevant either for my use of communication by means of the internal logic of language or for thinking about something. A "sensible context" in this example corresponds to a constraint applied to the electrophysiological analysis of a movement.

Introducing constraints into an experiment with a number of local electrodes

takes us back into teleology, as it generally presupposes making use of some *purpose* of the motor act to be analyzed. Study of motor purposes begins with questions that sound conventionally physiological, but it ends high up in psychology with “demands” of a complex nature involving consciousness. Examples of conventionally physiological problems using teleological constraints are provided by a number of experiments trying to understand the role of recurrent inhibition in motor control or the different properties of tonic and phasic motoneurons in relation to fast and slow muscles and their employment in different tasks of motor regulation. A large number of familiar problems belong to this category. Further up in the hierarchy of movements, constraints will in general involve the volitional component that has the character of a “demand.”

In the motor field I believe that far too little has been made of electrical recording of voluntary movement with demand as the leading variable. The experiments require men or monkeys as subjects, and a great asset of this approach is its close contact with the vast reserve of information from clinical neurology. In everyday life an exceedingly large number of motor acts are executed in response to a variation of demand. Surely it must be a relevant question to ask how different sites participate in such acts. Answers are bound to lead to some insight into basic principles of organization of “hardware” within the motor field.

This approach is not wholly untried. As indicated, clinical neurologists and neurosurgeons use demanded movements in their standard tests, and do so also in combination with local destructions, ablations, and case pathology. There are also electrophysiological studies making use of demanded movements. Buchwald and Eldred (1962) have shown that in a learning process the gamma motoneurons can be conditioned to respond to a cue more easily than the alpha motoneurons. Much experimentation by the technique of measuring H-reflexes in man shows that during the preparatory period of a voluntary act these reflexes undergo complex changes varying with demand and taking place also in motoneurons not participating in the final movement (e.g., Requin, 1969; Requin and Paillard, 1969). The preparatory period has also been studied in man and monkeys by electronic summation of potentials recorded electroencephalographically, though so far without sufficient attention devoted to demand as a variable. In the recording of the discharge of muscle-spindle afferents in man, a demand for a greater or lesser force of contraction is clearly reflected in the firing rate of the spindles (Hagbarth and Vallbo, 1969; Vallbo, 1970). Evarts's (1967) technique of recording from cells in the motor cortex of trained monkeys is loaded with possibilities for studying varying demands, and so is the electromyographic technique used by Marsden, Merton, and Morton (1972) for this very purpose. Some comments on these questions will be found in the *Report from the Conference on the Control of Movement and Posture* (Granit and Burke, 1973).

I am, of course, under no illusion that in the long run the electrophysiological approach will be omnipotent in solving all motor-control problems, but these comments are meant to emphasize that it still is capable of conquering new domains of understanding. My active time in neurophysiology has coincided with the electronic era, and so it seemed pertinent to discuss the role of electrophysiology in

an integrative context. Many of the best known results of the microphysiological reductionist aspects of the period have consequently been neglected. These are the ones that have been most in the limelight, having been rewarded with ten Nobel Prizes.

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