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The rise of neuron sciences in the 20th century

Part 2: From the new neuron sciences to neuroscience (1940-1980)

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ABSTRACT

In the field of study of the nervous system, a great revolution starting in the 1940s takes place after the Second World War. Before the war, fundamental questions at stake dealt with the nature of neurotransmission, chemical or electrical. The first turning point was made in the distinguished field of neurophysiology where a better understanding of neuronal electrogenesis and fine dissections of nervous networks followed the introduction of the new intracellular recording technique. This technique is associated with biophysics, electron microscopy and ultracentrifugation. Consequently, the chemical theory of neurotransmission is uniformly adopted with the appearance of the quantal theory and the vesicular theory. The new path of the discovery of neurotransmitters is open with the help of biochemical methods. Noradrenergic and aminergic paths are described with novel histological techniques, whereas electrophysiology is used to find their functions. All disciplines work together in the study of the synaptic organisations of nerve centers and local inhibition phenomena.

Neuronal sciences adopt neuropharmacology to create a novel neurochemistry. New dissection procedures, morphological network tracing tools and surgical techniques offer novel ways of intervening and manipulating. These innovations of the 1950s and 1960s are central in building a new international community unified by the American neuroscience movement.

Key words: *neuroscience, microelectrode, histofluorescence, chemical theory of neurotransmission, quantal theory of neurotransmission, synaptic vesicles.*

INTRODUCTION

The 1930s saw the emergence of the new discipline of *neurophysiology*, whose new tools were the cathode-ray oscillograph, electroencephalography and associated recording devices [1]. This new field, essentially British in origin, had received a boost in 1932 from the Nobel Prize in Physiology or Medicine awarded to

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Charles Sherrington and Edgar Adrian. A large international community was formed through exchanges between laboratories and participation in international congresses, such as that of psychologists held in Paris in 1937, to which Hans Berger, the discoverer of electroencephalography, had been invited.

The 1940s were a period of subterranean maturation for numerous research projects in cellular neurophysiology, as the central controversy over the nature of neurotransmission – chemical or electrical – reached its climax. In the field of morphological and biochemical studies, despite René Couteaux's discovery of the synaptic gutter of the neuromuscular junction, revealed by the Janus green, and the development of certain histochemical procedures such as Koelle's staining of cholinesterase activities, it was electron microscopy, biophysics, biochemistry and pharmacology that paved the way for the adoption of the new tools of the 1950s: electron microscopy, ultracentrifugation, radioisotopes, microelectrodes and histofluorescence.

From the early 1950s, these techniques led to an explosion of new observations and a complete reconfiguration of the theoretical field of neurophysiology in all fields. Neurobiology took off, combining biochemistry and morphology with electrophysiology studies in the discovery of neurotransmitters, such as Steve Kuffler's discovery of GABA in invertebrates. By this decade, the project of a neuroscience was taking shape, combining neurobiology and biophysics. In the 1960s, the neuroscience community was reorganized through a new institutionalization process that led to the creation of a neuroscience society, not only in the United States, but in many other countries, including France in 1988.

THE NEW CELLULAR NEUROPHYSIOLOGY

Understanding neuronal electrogenesis

One of the key problems of neurophysiology in the 1930s concerned the model for explaining the genesis of supra-liminal electrical activity in nerves and neurons – the action potential – and its relationship to infra-liminal activity, i.e. variations in the basal potential of nerve elements [2]. As early as 1907, Louis Lapicque, professor of physiology at the Sorbonne, Paris, France, devised a simple and correct model of the action potential generated when the basal potential exceeds a certain threshold. The use of extracellular microelectrodes to study infra-liminal slow activity was developed to understand its role in overall bioelectrical phenomena, both on isolated nerves and on the cell bodies of giant neurons (of the order of a millimeter), such as those in the nerve ganglia of the aplysia.

According to Bernstein's ionic hypothesis, the action potential results from the supra-liminal opening of ion-permeable pores, when basal electrical activity exceeds a threshold. At the time, cellular electrophysiology was dominated by researchers adopting plant models, such as giant, easily manipulated unicellular algae. This science demonstrated that the action potential is associated with a sharp increase in the electrical conductivity of cell membranes (Blinks). The Americans, Cole and Curtis, followed by the British Hodgkin and Huxley, demonstrated this fact on giant squid axons. Then, in 1939, the British succeeded in implanting an electrode in a giant axon to measure the polarity and the value of the transmembrane potential: the action potential develops from the negative resting potential (hyperpolarized, -50 mV) to very positive values (+50 mV). This result suggested that the action potential resulted from the opening of selective ionic permeabilities to certain ions far from their equilibrium potential,

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such as Na⁺ ions. During the 1940s, these studies were reproduced on muscle fibers, then, in the early 1950s, on neurons (Eccles, then Philipps, Albe-Fessard, Buser, Woodbury, Patton).

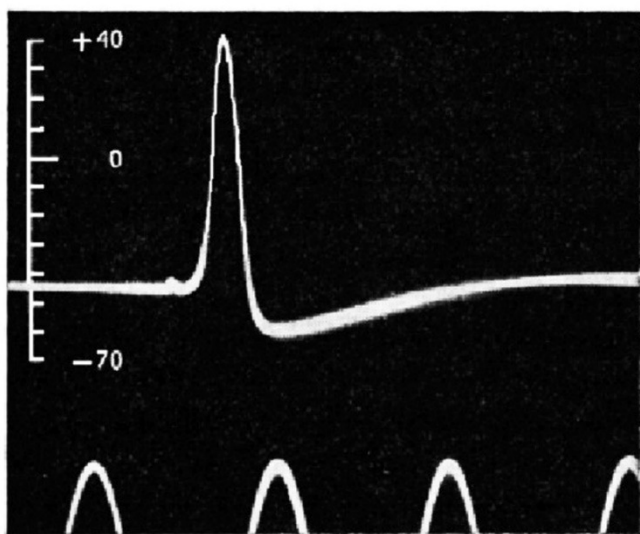


Figure 1: Recording of an intracellular action potential in a giant squid axon. After Hodgkin and Huxley, 1945. Courtesy of Nature Publishing Group.

Ion selectivity is fundamental not only to the generation of the action potential, but also to the maintenance of the resting potential (K⁺ ions), inhibitory potentials (Cl⁻ ions), and slow potentials following the action potential. This research led not only to the concept of the selective ion channel, but also to the refutation of the electrical hypothesis of neurotransmission. His most famous proponent, John Eccles, immediately adopted the chemical theory when he recorded certain highly hyperpolarized inhibitory synaptic potentials (1952), incompatible with his electrical hypothesis due to remote field effects.

This research culminated in a synthesis presented by Eccles himself at the *Cold Spring Harbor Laboratory* colloquium in 1952, in the

form of a quantitative model of action potential and synaptic potential electrogenesis, based on direct neuronal measurements and analogies between the membrane properties of the giant squid axon and those of neurons. This laid the foundations for cellular electrophysiology, and enabled studies into the microphysiology of excitable elements to take pride of place at the major CNRS international symposium held at Gif-sur-Yvette in 1955.

Electrical activity of dendrites

The first models of the new cell physiology involved well-defined cellular compartments, such as a single-cell alga, a giant squid axon segment or the globular soma of a giant aplysia neuron. Wilfrid Rall's first models were of neurons with very simple compartments, comprising a soma and an axon. But what about dendrites? The 1955 meeting of the American Society of Electroencephalography was devoted entirely to these structures. The theme was an old one, but it had not yet undergone any great upheaval since Ramón y Cajal's speculations and his abandonment of Golgi's idea of the nourishing role of dendrites, located close to blood capillaries to extract nutrients. The French neurophysiologist Pierre Buser remembers a visit to Paris by his *Rockefeller Institute* colleague Lorento de Nó, during which the latter, one of Cajal's last students, during a presentation, caught his American colleague McCulloch representing a neuron in spherical form in a cybernetics diagram. "No, McCulloch, a neuron is like this", said Lorento de Nó, as he drew a point which thus schematized the neuronal soma and from which emanated an axon, but above all an immense complex dendritic tree¹.

¹ Personal communication to the author.

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In fact, it was electroencephalographers who restored the importance of dendrites, interpreting evoked cortical potentials as potentials generated in the dendritic territories of neurons. Bronk, Chang and Purpura thus imagined that dendrites, like axons, were excitable elements, places where action potentials were generated and propagated, as was only demonstrated in the 1990s by the *patch-clamp* technique. Throughout his career, Nobel laureate Eccles himself neglected the impact of synaptic activities remote from the cell body on overall neuronal activity. As the CNRS neurophysiologist and Collège de France (Paris, France) professor Alfred Fessard suggested in the 1950s, the low weight of individual distant synapses is in fact a factor in dendritic integration, which depends on the synchronicity of a large number of synapses in limited portions of the dendritic arborization.

During this period, the group of American neurophysiologists who called themselves the "axonologists" were the most vocal in claiming the axon as the only element of neuronal initiation and conduction on a long scale of a true action potential, with a large amplitude and duration of less than a millisecond. It was inconceivable to them that the same could be said of dendrites. This psychological block leads us to believe that the fundamental properties of the neuron were conceivable only at its transmission and output pole, as if this region condensed a kind of virility and power unimaginable for a distant cellular element like a dendrite. This dendrite controversy was one of the battles taken up in the 1960s by the new neuroscience when it opposed the dogmas of the old neurophysiology of the 1930s.

At the other end of the neuron...

Since the 19th century, the major vertebrate neuron model has naturally been the motor neuron of the spinal cord, a large neuron that can be extracted by hand using fine needles after hardening the tissue with chromic acid. In the early 1860s, the German Otto Deiters observed a single, fine filament on these isolated neurons, the *axis cylinder*, the first description of the axon, i.e. a single nerve fiber with a connection to a cell.

In the 1950s, Bernhardt Katz recorded unitary activity at the ends of motor neuron axons using extracellular and intracellular microelectrodes on the muscle surface or inside a muscle fiber. He measured "synaptic potentials", i.e. potentials at the junction between the nerve and the innervated zone, a term first used by British Brian Matthews with Alfred Fessard. Katz also sought to detect unitary activities, notably by lowering the extracellular concentration of calcium ions, and observed the all-or-nothing nature of unitary activities of constant minimum amplitude. This result could be compared with the chemical theory of neurotransmission: invasion of the presynaptic element by the action potential triggered an all-or-nothing phenomenon analogous to the genesis of the action potential, or to the contraction of isolated muscle fibers, but which resulted in the release of a neurotransmitter packet at the end of the nerve fibers, the post-synaptic effect of which was a mini-potential of constant amplitude, a miniature synaptic potential, still called "miniature" today. Large synaptic potentials were then explained by the increased frequency and synchronization of these "miniatures".

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THE DEFINITIVE ADOPTION OF THE DOCTRINE OF CHEMICAL NEUROTRANSMISSION

In the early 1950s, a consensus was reached in favor of the chemical neurotransmission theory, following advances in neurophysiology and new measurements of synaptic potentials [3]. As early as 1950, Alfred Fessard and his Geneva colleague Jean Posternak wrote an important review of the latest developments in this controversy [4]. The

chemical theory, previously supported by pharmacological data to the point of being accepted for nerve ganglion transmission by the electrophysiologists themselves, was then the subject of new and very diverse objectivations, which took advantage of modern post-war techniques, initially including electron microscopy and ultracentrifugation.



Figure 2: Alfred Fessard and Horace Magoun. Thanks to Jean Fessard for reproduction.

The discovery of synaptic vesicles by electron microscopy

The context for the discovery of synaptic vesicles was the early development of electron microscopy in the early 1930s. In the biological

field, Albert Claude used this technology at MIT to isolate the Rous sarcoma virus, then with Christian de Duve and George Palade, to highlight, in conjunction with ultracentrifugation and enzymatic biochemistry, certain cellular compartments such as lysosomes. Francis O. Schmitt used the new instrument, also at MIT, to study nerve and muscle constituents. At the same

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time, De Robertis and Palay independently produced the first electron microscope images of neurons and synapses, in which small vesicles of uniform size and large numbers were visualized. Could these vesicles in synapses be reservoirs for the neurotransmitter? For the most part, the young microscopists specializing in their new technology remained cautious in their descriptions and interpretations.

The quantum theory of neurotransmission

It was at the Gif-sur-Yvette (France) congress in 1955 that neurophysiologist Katz formulated the hypothesis of the quantum theory of neurotransmission, before any of the morphologists had even considered the question, but with full knowledge of their work. This hypothesis was based on a very simple idea. The uniformly sized synaptic vesicles would represent the neurotransmitter packets released by the action potential arriving at the free end of the axon and generating the miniature synaptic currents recorded by Katz at the neuromuscular junction. Katz imagined a mechanism for the exocytosis of these vesicles to the plasma membrane and the generation of an associated post-synaptic current in the muscle.

A decade later, Victor Whittaker attempted to isolate these vesicles by ultracentrifugation, measuring their acetylcholine concentration to reinforce the theoretical scheme. But he also isolated larger elements, in fact detached synaptic elements – "synaptosomes" – later identified by electron microscopy. This research led to the hypothesis of vesicular release of the neurotransmitter, directly linked to Katz's theory. However, both theories were the subject of controversy until the 1990s, although they are now universally accepted.

The quest for neurotransmitters

For a long time, the model neurotransmitter in neurophysiology was essentially acetylcholine, following Otto Loewi and Dale's discovery of this neurotransmitter's role in controlling heart rate and voluntary muscle contraction. Pharmacology of the cholinergic synapse made it possible to block the receptor with acetylcholine receptor antagonists (curare), inhibit its reuptake or synaptic degradation (eserine). The three associated effects were required to demonstrate that a substance could be considered a neurotransmitter: blocking of the synaptic response, prolongation of the kinetics of the synaptic potential, and exhaustion of the response by strong stimulation. In fact, these exacting standards became an obstacle to recognizing the neurotransmitter function of substances such as glutamate and GABA. The ubiquitous effects of these substances indicated non-specific actions in the nervous system, even though they are the two most general neurotransmitters.

The recognition of GABA as a neurotransmitter by Steve Kuffler's team was an exemplary adventure, combining regional biochemistry and electrophysiology on an invertebrate model to chemically isolate the substance stored at the termination of inhibitory fibers. This new research established an interdisciplinary approach similar to that of Alfred Fessard, David Nachmansohn and Wilhelm Feldberg at the Arcachon Biological Station (France, 1939), which had demonstrated the cholinergic transmission of the torpedo's electrical organ. But all these researchs on neurotransmitters were fraught with pitfalls, as the substances tested also exhibited slow neuromodulatory effects that obscured the results and explained the considerable delay in attributing neurotransmitter function to, for example, glutamate.

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A new neurochemical world

In the 1950s, a new continent of exploration opened up for the new neuronal sciences. The hegemony of classical neurophysiology had been shattered by the success of the chemical theory of neurotransmission. Just as the last bastions of reticularism had been particularly resistant until the advent of electron microscopy, Eccles had insisted on his model of electrical transmission by field effects even before his impromptu adherence to chemical theory. This new neurochemical continent was emerging from research combining biochemistry, pharmacology and electrophysiology in a more integrated way, centered on the concept of synaptic transmission. Its three most significant representatives, Ulf von Euler, Julius Axelrod and Bernard Katz, were awarded the Nobel Prize in Physiology or Medicine in 1970. All three, each in their own way, elucidated certain mechanisms of neurotransmitter synthesis, storage and release.

This new world was also taking shape in a new way in the parallel field of clinical pharmacology and psychiatry, when French physician Henri Laborit tested chlorpromazine and discovered its sedative effect, successfully tested as a neuroleptic at the Hôpital Sainte-Anne (Paris). In the field of nervous system development, the Italian Rita Levi-Montalcini discovered nerve fiber growth factor at the same time, whose effects were not unrelated to Cajal's chemotaxis hypothesis.

In the emerging world of cellular and molecular biochemistry, the sequencing of insulin in the early 1950s marked a turning point in the discovery and study of small peptides, like neurohormones a few years later.

However, despite the integrative role of the theory of chemical neurotransmission, which combined biochemical (neurotransmitter synthesis, degradation and reuptake), cellular (exocytosis), pharmacological (receptor *binding*) and electrophysiological (opening of a receptor-ion channel) mechanisms into a single model, all these new general data were only exploited following the development of new specific tools to discover neuronal pathways characterized by a particular neurotransmitter and functions.

NEW BRAIN PATHWAYS

The new theoretical framework of neuroscience that took shape in the early 1950s led to a reconfiguration of the theoretical concepts and central dogmas of neurophysiology, but above all of what is known as *neurobiology* [5]. This is a research project in which discoveries are thought as more likely to occur if new objectivations using the most modern instruments and techniques are carried out on a cellular scale. Within the old schools of neurophysiology, there were sometimes sharp divisions between those in favor of these cellular (and not reductionist) approaches, and those who wished to maintain a more global and integrated approach, taking intermediate scales (nerve circuits, cerebral areas). However, the new tools developed in the 1950s and 1960s by the formers gradually enabled to characterize nerve circuits and their local functioning (the forms of their synaptic plasticity), while coming closer to explaining their possible functions.

Histofluorescence scintillation of nerve tracts

The histofluorescence technique was the first fluorescence visualization technique to detect a neurotransmitter in micrometric axon varicosities and to follow the nervous pathways of adrenergic

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pathways under the microscope. It was a revelation for the whole world to be able to finely map the brain pathways specific to a neurotransmitter, and to imagine its functions according to their connectivity to the various known brain structures.

The discovery of this technique is part of the revolution described above, and more specifically of the adrenergic transmission research program. The aim was to detect the presence of adrenalin in certain vesicles or granules (such as those of the cells of the adrenal medulla) by a reaction converting tryptamine into a fluorescent compound.

This technique then enabled Dahlström and Fuxe to map aminergic pathways. The histochemical constitution of neuronal circuits revealed assemblies of neurons synthesizing the same neurotransmitter, and opened the way to new correlations between the activity of networks and their functional study by electrophysiology.

The discovery of the Renshaw cell

The discovery of the Renshaw cell is one of the finest examples of a rapprochement between certain results acquired by extracellular recording techniques characterizing rather crudely the activities of populations of neurons and the new techniques of the 1950s. As early as 1941,

Birdsey Renshaw performed certain decompositions of electrical activity in the spinal cord according to standards that enabled synaptic

arcs to be distinguished. However, the signal from interneurons interfered with these activities. Renshaw sought to avoid these parasitic interneuron potentials and gathered information on their topography. In 1946, he identified interneuron activity in the ventral roots of the spinal cord, close to the motor neuron bodies. These interneurons exert recurrent inhibition, since they are stimulated by a collateral of the motor neuron (negative feedback).

In 1954, Eccles, Fatt and Koketsu took up Renshaw's studies using the intracellular technique, seeking to demonstrate cholinergic transmission in the central nervous system. They established by new standards that the activities described by Renshaw originate from interneurons inhibiting motor neurons. To discover the cholinergic synapse between motor neuron collaterals and inhibitory interneurons, Paul Fatt applied Dale's principle to the motor neuron, according to which a neuron can only act through a single neurotransmitter. According to this principle, if the motor neuron activates the muscle via acetylcholine, this neurotransmitter must also be involved at the synapse with the interneuron. This correct hypothesis led to the discovery of "Renshaw cells" by the group led by Eccles. This represents a direct application of the new intracellular possibilities for measuring inhibitory synaptic potentials. Eccles discovered a central cholinergic synapse. The effects of the cholinergic repertoire – curare and dihydro- β -erythroidine for blockers, eserine and TEPP for acetylcholinesterase inhibitors, and acetylcholine – confirmed the hypothesis.

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Figure 3: John Eccles (left) and Pierre Buser (right) at Quai Saint Bernard, Pierre and Marie Curie University. Thanks to Pierre Buser.

Thus, a convergence of ancient extracellular data with the possibilities of intracellular recording, interwoven with modern neuropharmacology of cholinergic synapses and a topographical approach using deep penetration of microelectrodes along an oblique gradient through a certain neuronal population, enabled a new characterization of a certain type of neuron and above all of the specific circuit to which it contributed.

Even today, new data are analysing in ever greater details, including in humans, the multiple functions of Renshaw cells in the coordination of movements such as walking, by adjusting the agonist and antagonist muscles of both legs.

Synaptic organizations

Unit recordings using extracellular or intracellular microelectrodes were one of the great adventures of the 1950s and 1960s. Each laboratory tested a variety of protocols to develop its own very fine electrodes, some of which were permanently and chronically implanted in animals for long, continuous recordings. Adrian's dream of unitary measurements in any region of the nervous system became a reality, even if results in the cortex, for example, were disappointing for a long time.

Through targeted measurement, in a well-chosen neuron, the neurobiological approach hoped to understand the synaptic organization around the recorded neuron and the connectivity of the surrounding network. The underlying rationale was that of Adrian when, in the 1930s, he

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interpreted the receptive fields of retinal units, i.e. the portion of retina likely to activate after illumination a given neuron which axon took part in the optic nerve. Adrian had demonstrated a diffusion of excitation: a very focused retinal illumination, half a millimeter away from the recorded retinal neuron, still managed to activate it. There were millimetre-long circuits in the retina converging on each retinal neuron (ganglion cells).

In 1953, when Kuffler resumed these studies using unitary microelectrodes, he was able to record the receptive fields of ganglion cells in the cat's retina. For some neurons, these recordings revealed an excitatory field center, while its periphery was inhibitory. In other words, neurobiology had won its bet of being able to discover precise properties of nerve circuits by recording a single neuron. This approach led to Hubel and Wiesel being awarded the Nobel Prize in Physiology or Medicine (1981), having begun their studies together at Kuffler a few years after this discovery.

New anatomies, stereotaxis, neurophysiology and psychosurgery

The new brain science methods on which the neuroscience movement is based are even more diversified. They incorporate methodological acquisitions in anatomy, notably through new animal preparations and surgical techniques in humans.

In the field of pure anatomy, John Young isolates the squid's giant axon and proposes it as a neurophysiological model to Cole, Curtis, Hodgkin and Huxley, with the success we all know. Walle Nauta revived the techniques of silver impregnation of degenerated nerve fibers to follow their course after induction of degeneration resulting from severing of the nerve center. His technique met with immense success, earning him the F.O. Schmitt Medal from the *Neuroscience Research Program*.

The modern neuroanatomy of the Ranson school also met with success, with Magoun and Moruzzi's discovery of the ascending activator system of the reticular formation, which opened up numerous possibilities for interpreting sleep and consciousness. Other ingenious dissections led to original preparations such as the "isolated brain" or the "medio-pontine pre-trigeminal" preparation. In addition, the revival of stereotaxy was an essential factor in the destruction and sectioning of deep, targeted areas of the brain, using a coordinate positioning system based on the cranial surface of animals or humans (stereotaxic apparatus).

In the field of neurosurgery, these techniques have given rise to numerous clinical trials in new surgical treatments for epilepsy, but also to abuses in the field of psychosurgery in the 1960s inherited from the 1930s.

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Colloquium in honor of Sir Edgar Adrian, Cambridge 1964. Edgar Adrian can be recognized in the center front row, and also at least Herbert Jasper, Ragnar Granit, Hallowell Davis, Denise Albe-Fessard, Steve Kuffler, Richard Jung, Yves Laporte, Bernard Katz, Alfred Fessard, John Eccles, Alan Hodgkin.

CONCLUSION

We have considered the general context in which the new disciplines behind the rise of the new "American neuroscience" movement developed. The first intensive course in F.O. Schmitt's *Study Program* took advantage of all these innovative new trends. It systematically focuses on the originality and quality of new researches. The tone of the volume, published in 1967 following the course, takes some distance from the classical disciplines of the nervous system sciences, first and foremost neurophysiology, hegemonic since the Nobel Prizes of 1932, 1944, 1961, 1963 and 1967.

Schmitt explicitly states that neurophysiology alone is sterile, just as electrophysiology is still today for some.

The new neuroscience was based on two new pillars: biophysics and neurobiology. Schmitt himself exploited the wealth of X-ray analysis and electron microscopy, but ultimately achieved few discoveries. His own structural analyses were relatively static and descriptive, as in his studies of collagens, whereas other microscopists studied synaptic structures from a dynamic physiological perspective worthy of the early work of Ranvier and Couteaux.

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Neuroscience also based its ambitious program on the consideration of cellular mechanisms such as axonal flow, and the neuronal approach to the study of nerve circuits. The circuit is no longer dissected electrophysiologically from the outside, as in anatomy, but from the inside, through the activity recorded in a single neuron, certain potentials of which testify to specific network activities.

F.O. Schmitt's movement took advantage of the technological and conceptual revolution of the new neural sciences, and succeeded in gathering around him an elite of innovative researchers whose individual successes placed them at the head of a new international community. This community became truly institutionalized with the creation of the American Neuroscience Society (1969), followed by the creation of neuroscience societies in various countries, including France almost twenty years later.

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