RAMÓN Y CAJAL AND THE PHYSIOLOGY OF THE NERVOUS SYSTEM*

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From his school days Ramón y Cajal's training was very largely directed toward anatomy. His father and master, a man of great energy and will, was Anatomical Preparator at the University of Zaragoza, a fact which strongly influenced the son's career. Ramón y Cajal spent many hours in dissection, in studying anatomy and teaching it to students, and for many years this was one of his chief sources of income.

Later on (1880-1884) he tried several times to get a professorship in anatomy, his third attempt being successful. He himself describes the cause of his first failure: "The exercises revealed, as I well presumed, that in classical descriptive anatomy and dissection I was on a level with the best, but impartiality compels me to admit that in certain lights I also showed deplorable deficiencies. I was ignorant of many biological aspects of a philosophical order; I despised many interpretative laws extracted from comparative anatomy, ontogenics and philogenics." He mentions afterwards other motives of a social or personal nature.

One might surmise on reading this paragraph that his preparation was cold and cadaverous. This lack of vital impulse and biological orientation was characteristic of Spanish anatomists of recent years, and not even such an exceptional man as Ramón y Cajal could completely detach himself from the surrounding atmosphere. His preparation, intense, but dry, was misplaced in Madrid of 1880 with his incomplete and lateral view of biology, and it is interesting to see how quickly he convinced his morphological opponents, and how long and sharp were his discussions with physiologists. This was due to the fact that they spoke two different languages, they had two different avenues of thought, which made mutual understanding difficult. Many are familiar with the incidents of his trip to Berlin in 1889 to take part in the yearly

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meeting of the German Anatomical Society, and how he led Kölliker to examine his own preparations, by pulling him by the sleeve. When Kölliker told him: "The results you have obtained are so beautiful that I shall immediately start a series of experiments using your technique. I have discovered you and I wish to announce my discovery to Germany", Ramón y Cajal's renown as a histologist was made. Under the patronage of Kölliker, who was at that time the highest authority on

Fig. 1—Ramón y Cajal, in the years of his professorship in Barcelona.

histology in Germany, Ramón y Cajal's name immediately carried weight. His was a sudden success, based on the interest he aroused in a great man toward his work. This bears an extraordinary resemblance to the success of another professor in Barcelona, Gimbernat, with John Hunter.

This sudden acceptance of Ramón y Cajal's techniques and preparations, as well as the morphological facts he had revealed, is in strong contrast with the lengthy discussions aroused by his most important doctrines: the neuronal theory and the law of dynamical polarization. These discussions were principally by physiologists, the arguments being of an experimental character. Had Ramón y Cajal during the years 1900-1905 headed a School of Physiology in Madrid, it is possible that many of the functional discoveries based on his ideas—which may now be mainly attributed to English physiologists, Langley, Sherrington—might have been reached under his own eye.

A rapid review of Ramón y Cajal's physiological ideas and the results to which they led, without any pretense of exhausting this interesting theme, may constitute better homage to his memory than a dithyrambical speech in honor of him who produced the best of his work among us in Barcelona. He was so absorbed in his work during those years of intense production, that his memoirs have not a single line mentioning

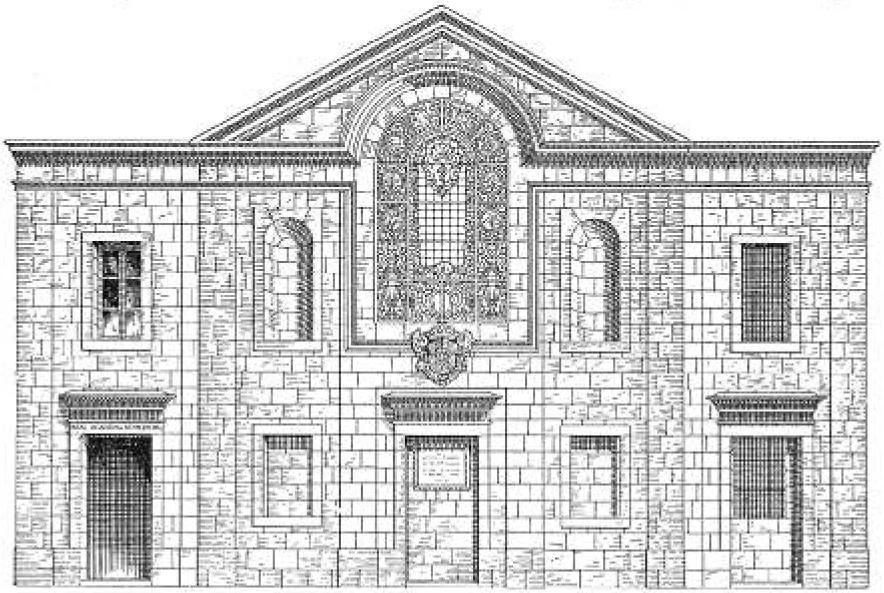

Fig. 2.—The Old Medical School of Barcelona where Ramón y Cajal taught histology between 1887 and 1892, the years of initiation into the researches in the central nervous system. The building—now the Academy of Medicine—was erected as the College of Surgeons in 1753.

the Exposition of 1888, one of the most brilliant moments in Barcelona's life.

As early as 1888, when starting the study of the brain structure, Ramón y Cajal cried out with enthusiasm: "The knowledge of the brain is equivalent to the knowledge of the material channel of thought and will; it is a brief history, which we may consider engraved in these neuronal coordinations of defense, reflexes, instinct and association of ideas."

Long before Harvey only meager details about arteries and veins were known, and nobody had formulated the doctrine of circulation.

The knowledge of structure facilitates that of the function derived therefrom, but does not necessarily lead to it, even if it is taken into consideration that in the nervous system, as Starling remarked so well, the relation between them both is more intimate. Facts have shown the error contained in the above words: Sherrington, Pavlov and Adrian have lately revealed the fact that the total physiology of the nervous system: peripheral nerve,. reflex, cortical association, and not one of them followed Ramón y Cajal's path. Letamendi, at that time Professor in Madrid, in his constantly lyric and boastful form, used to call these problems "a constellation of unknown quantities." Their explanation has not been derived from morphological facts. Claude Bernard noticed this, and later on Sherrington expressed his own physiological conception, opposed to that of Ramón y Cajal, in the following words:

> The chains of neurones, the conductive lines, have been especially in recent years, by the methods of Golgi, Ehrlich, Apathy, Cajal, and others, richly revealed to the microscope. Anatomical tracing of these may be likened, though more difficult to accomplish, to tracing the distribution of blood-vessels after Harvey's discovery had given them meaning, but before the vasomotor mechanism was discovered. The blood-vessels of an organ may be turgid at one time, constricted almost to obliteration at another. With the conductive network of the nervous system the temporal variations are even greater, for they extend to absolute withdrawal of nervous influence.

In the same year 1888 Ramón y Cajal formulated his four laws of the nervous system: (1) end of collateral and terminals of axons by free arborizations, not through a diffused net; (2) those arborizations apply themselves against the cellular body and against dendrites; (3) therefore cellular bodies and dendrites take a part in conduction; (4) the nervous impulse is transmitted by contact and induction.

It is curious to note Golgi's position in view of the third of these laws, one proof still of how the knowledge of structures may, at the outset, give an orientation in the study of functions, but nothing else. Golgi had fully described dendrites and their free arborizations, and even though their position and relation with regard to the other fibers seemed to point out a conductive part, he denied it attributing to them only the function of nutrition.

The four laws above mentioned give the scheme of all later researches and discussions. They include the theory of the neurone, in opposition to Gerlach's reticular hypothesis, that is, a sort of historical evolution quite the reverse of the process of the facts pertaining to the capillaries. Before knowing the paths following the large trunks, the existence of a communicatory net was presumed. Starting with the conception of a reticule, the objective study of the terminal behavior is not necessary; it is enough to state that, after a few divisions, the last fibers are lost in the interstitial net. For circulation the opposite obtains: the routes of arteries and veins was well-known, just as is the fact that blood had necessarily to pass from the first to the second, but no one had thought about a capillary net until Malpighi described it. It is very likely that the classical notion of the capillary net led to the theory of the nervous terminal net; nothing so simple as the identification of sensitive nerves with arteries—the centers being considered organs for the transformation of the nervous influx—and motor nerves to veins. Reflexes would be—one might say—the equivalent of the change of arterial to venous blood.

The thesis that "everything communicates with everything" could bear some appearance of truth and clearness, but would have made absolutely impossible the actual physiological notions about the nervous system with the concepts of facilitation, summation and inhibition which at that time were unknown terms. It particularly disagrees with the pregnant theory of the final common path. The valuable help lent by the learned Spaniard, in destroying the reticular theory and laying the foundations for the theory of the final common path, may well be considered his best contribution to the knowledge of physiology of the central nervous system.

The thesis of dynamical polarization was formulated one year later (1891) simultaneously by Cajal and Van Gehuchten. Ramón y Cajal had for a long time been in constant communication with the Louvain histologist and both were interested in the same problems. The question was clear enough: Is the nervous impulse transmitted in all directions, just as sounds or luminous vibrations, or only in one direction, just like water on the slope of a mill channel or a train on a railway? An important fact was known beforehand: Bell and Magendie had formulated the law of rachidian roots, and it was known that in motor axons the nervous discharges provoked by the medullar forehorn cells could only be transmitted in cellulifuge direction, that is to say, from the cell soma to the peripheral motor plate. Some neurologists, such as Bechterew, Kölliker, Waldeyer, had in theory generalized this type of axonic conduction. On the other hand, no criterion existed about conduction in dendritical endings, and it has already been shown that some, Golgi for example, did not attribute to them even a conductive rôle.

Ramón y Cajal's idea was based on the resemblance between the peripheral prolongations of sensitive ganglion cells and olfactive and retinian bipolar cells with protoplasmatical prolongations of the motor neurones. Since the first lead to the cellular body, there is nothing against

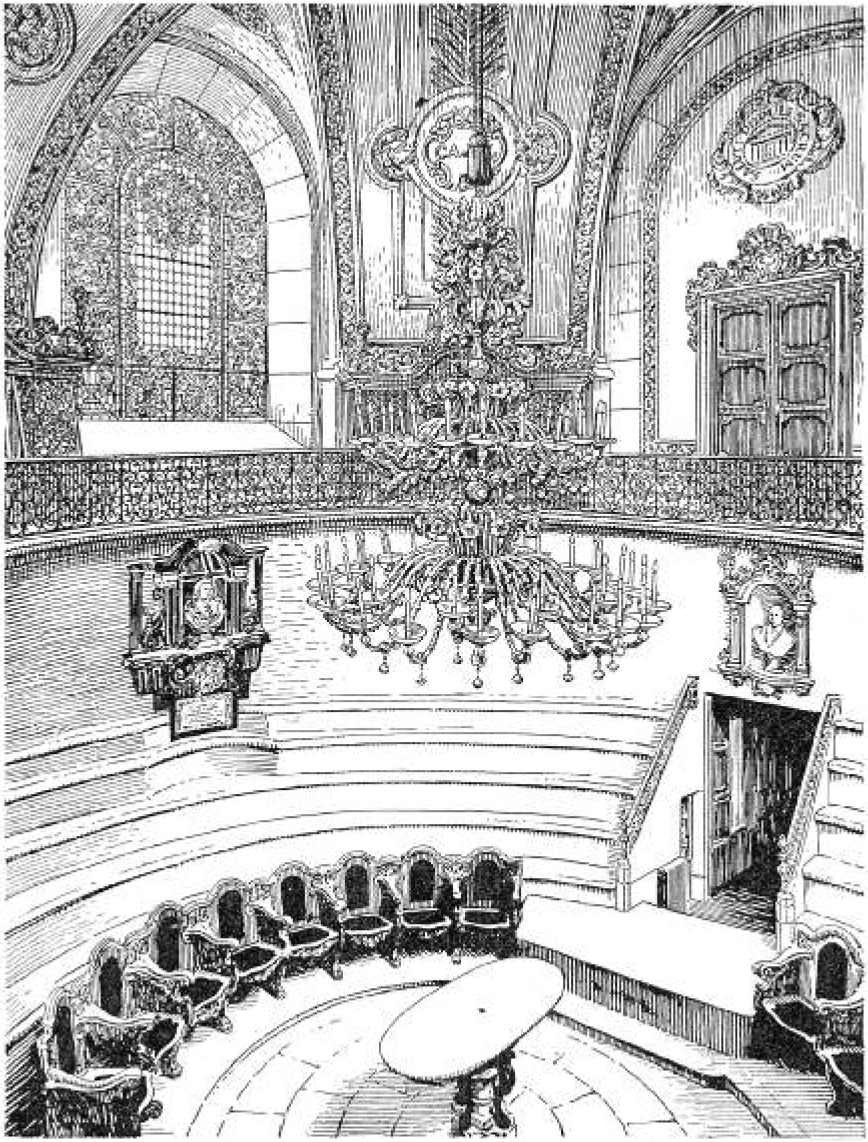

Fig. 3.—Amphitheatre of the Old Medical School. In the dome the names of Cajal (in front), Gimbernat, Servet and Mata; in the center the table of dissection of Antonio de Gimbernat (1734-1816) who gave here his anatomy course in the time of the College of Surgeons.

a conduction in the same direction within the similar structures in the motor neurones. He stated from the start that his problem might be foreseen, but could not be solved by histological means only. It may be added that he never found anyone to help him with any other means.

The theory of dynamical polarization was definitely settled by his further interpretation, the theory of axipetal polarization: "The soma and dendrites possess an axipetal conduction, that is to say, they lead impulses towards the axon. On the other hand, axon is characterized by a somatofuge or dendrifuge conduction, and it forwards the impulses received from the soma or the dendrites towards the terminal nervous arborizations." (1) This interpretation implies in a general law different cellular types: monopolar, bipolar and multipolar cells. It is not necessary that the soma acts as a conductor in the first, but it is certainly so in the two last.

The general trend that has extended even to the present attaches small importance to cellular bodies in the nervous function. A nutritional and conservative function was only allowed to them as a consequence of the studies on Wallerian degeneration, without admitting in them a direct part in these functions—conductive and integrative—particular to the nervous system.

The theory of dynamical polarization represents a definite landmark in this devalorization: the soma, when finding itself in the way of conduction (bipolar and multipolar cells) will act as another conductive element, when being situated out of its way (monopolar cells) its part is not exactly known. Bethe, in 1897, possibly with the idea of arguing against Ramón y Cajal's ideas, states that cellular bodies never act as conductors, although he does not attribute to them any special separate function, apart from the vague and ill-defined trophic activity. Bethe descends one step more in the devalorization of cellular bodies. Sherrington, in his classical book, follows the same line, but being always worried about integrative functions he says that the neuronal body is the nodal point in conduction, the place of summation in the space, a kind of final common path, therefore an integrative path for currents coming from various protoplasmatical endings, transmitting impulses proceeding from various neurones, to be finally reduced to one common and only path, the axon.

Although no mention is made of it, this implies a capacity of selection, summation, etc., on the part of the cellular body. If several impulses simultaneously reach the axon, and only one of these can pass by it, the soma will decide the priority of one or the other of the impulses. Many years later when Sherrington and his disciples published their chemical theory of excitation and inhibition, a theory which Fulton has defended with special enthusiasm, they attributed to the cellular body the formation of the excitant and inhibitive substances, studying in each different instance the alterations of Nissl's bodies and of the terminal branches adhering to the motor neurones. This structure had also been described by Ramón y Cajal, who was also the first to talk hypothetically about a possible chemical action in nervous activities. Perhaps the importance attributed to this chemical action was excessive, but no doubt its results have been very fertile.

Let us point out the identity of the chemical hypotheses about synaptical functions with Rijland and Demoor's modern theories concerning heart conduction. This is also effected through quick steps alternating with springs and time losses. These ideas are approached by the chemical conceptions about excitation and inhibition, those about the origin of excitations in the sympathetic and parasympathetic endings and in the terminals of the effector nerves of the extero-ceptive field, and the hormonal alterations implied by these excitations. A great general doctrine about excitation and inhibition through humoral intermediaries is being actually established.

Gad (1884) had already been on the point of formulating the theory of dynamical polarization, when he stated that dendrites only lead impulses *towards* the axon and never *from* the axon. There is here a clear idea about valvular conduction. Several later experiments of Kühne on peripheral nerves—only to mention the most elemental and popular—and of other authors about central zones, have shown that nervous fibers conduct indifferently in both directions, so that conduction, which is reversible in the intraneuronic space, becomes irreversible when becoming interneuronic. This implies the existence of a structure acting as a valve, called synapse by Sherrington and Foerster. With regard to this indifference of neurones towards the direction of current, another English physiologist, Bayliss, described one year later two facts that, at least in some special cases, rejects the theory of neuronal polarization, namely, the existence of axonic reflexes and of the antidromic conduction. Langley has availed himself largely of these two facts in his own doctrines. It is not only a question of a fiber that may conduct current in both directions, but of normal activity of indifferent conduction towards the soma or coming from the soma. However, dynamical polarization as a function of synapse constitutes today an undeniable fact.

In 1894, Ramón y Cajal went to London to give the Croonian Lecture. He made there the acquaintance of the English physiologists who later on were to make such a profitable use of the morphological bases he had discovered. It is interesting to notice in his memoirs the admiration he shows when describing an experiment he witnessed made by Langley. We get the impression that a new world had been opened to his eyes: "How, after such a tremendous traumatism—exposition and excitation of the sympathetic chain on one side—the heart was still beating and all the vital functions of the animal were almost fully preserved, is for me an unfathomable mystery." A few years later he might have seen Cannon extirpating the complete chain in both sides and the animals living undisturbed for weeks and months. Ramón y Cajal's ideas about physiological techniques are revealed in his description of the instruments necessary for physiological research in his *Rules and advice to young researchers,* First Spanish edition, Madrid, 1905.

The cellular theory of the nervous system, which is known today under the name of the neuronal theory, and its consequence, the communication between neurones only by contiguity, is another of Ramón y Cajal's doctrines which aroused sharp discussion. The Master left this world worrying about the lot that would befall his thesis, and in a posthumous publication, he studied the evolution suffered in the ideas and derivations of his doctrine. A brief review of this work of his will help us in our task on this point (2).

W. His (1886-1898) and Forel (1887) stated that nervous expansions end freely in the gray substance and in the sensitive organs. Not many years later, Ramón y Cajal verified the accuracy of this theory in histological preparations, mainly of cerebral cortex, terminal baskets and climbing fibers, and Waldeyer in 1891 invented the word "neurone." Golgi had already shown (1885) that dendrites end freely in the gray substance, without attributing to them, as already said, any conductive function. The neuronal theory has been amply discussed with histological, neurogenetic and physiological arguments, especially by Apathy and Bethe, and Held recently. Concerning histological proofs, Ramón y Cajal states that in thirty-five years of work, he never has seen any dendro-dendritical or axo-axonical connections. They are always axo-dendritical or axo-somatical. Levi, in his *Tratato d' histologia* (1927), affirms the possibility of the existence of such communications, studying at the same time the cases of direct continuation through neurofibrils, as described by Held in the chalices of the trapezoïdal body, and Boecke (1910) in the thin filaments united on one side to the nervous fibers of motor plates and on the other to striated fibers. The last resurrection of these doctrines is represented by Held's theory about the fundamental reticule, to which he attributes a conductive capacity. Ramón y Cajal remarked, fitly, that Held's conception creates great difficulties for the doctrine of physiological localization and to all acceptable interpretations of propagation of the nervous impulse through the gray substance. Any attempt to establish the direction of the current would thus become an inaccessible enterprise.

The neuronal theory was specially attacked by Bethe and Apathy.

The arguments of both investigators, especially those of Bethe, were of a morphological and physiological order. Under the aspect of histological technique, it appears that the Strassburg Professor was far below Ramón y Cajal; some preparations he sent to him, in order to show him the existence of neurofibrils, greatly disappointed Ramón y Cajal.

The arguments of neurogenetic or functional order were stronger. The discussion about the origin of nervous fibers and about the form of regeneration of cut nerves lasted for several years, giving way to the publication of Ramón y Cajal's classical book about nervous degeneration and regeneration, which showed plainly the unicellular origin of fibers. On the other hand, Cajal counted in favor of his thesis the results of researches on the histogenesis of nervous elements. These results show very clearly the morphological individuality of each cell.

Bethe and Apathy insist mainly that nervous conduction takes place through small fibers passing from one cell to another. This may be true for some Medusae, with which animal Bethe worked specially; possibly also for the nervous intestinal plexi, and perhaps for other visceral sympathetic terminals in the superior vertebrates and even in man. But it must be considered that these tissues present also special physiological conditions. Without mentioning it specifically Sherrington explains this point in his book (3):

> Refractory phase is obviously an essential condition in coordination . . . But there is one significant difference between refractory state in the scratch reflex and in the swimming mechanism of Medusa. In the latter, as in the heart, the refractory state is a property not relegated to a central nervous organ remote from the peripheral tissue in whose function it finds expression. It is located in intimate connection with the peripheral organ itself. From observations of Bethe it seems likely that refractory phase in Medusa is a function of the nerve-net. Magnus has recently shown that the refractory phase of the beat of the isolated intestine is referable to the local nerve-plexus (Auerbach's) lying in the gut wall. In these cases the refractory state seems to belong to the nervous elements, but to nervous elements diffused through the peripheral tissue. But in the scratch-reflex the site of the refractory state is central, intraspinal.

This means that were there any closed nervous nets existing in certain special cases, these would also give way to special physiological responses, but spinal and other central reflexes in superior animals can only be explained by the neuronal theory, inasmuch as a great part of physiological features in those reflexes can only be interpreted by the existence of synapse, where conduction is quantitatively and qualitatively altered. This is so obvious that physiologists who have studied these problems have perforce been led to the hypothesis of the existence of an intermediary substance, Langley's receptive substance, Sherrington's synaptical substance. The object of the admission of a resistant pericellular substance is in order of the admission of a resistant pericellular substance to explain the delay in the propagation of impulse, when it has to spring from one cell to another.

We must mention that in advancing his thesis, Ramón y Cajal was greatly confused by conductibility and excitability conditions (he designates the latter *"crontaxia de la pic".*)

The classical features of reflexes according to Sherrington may now be mentioned: (1) slower speed as measured by the latent period between application of stimulus and appearance of end-effect, this difference being greater for weak stimuli than for strong; (2) less close correspondence between the moment of cessation of stimulus and the moment of cessation of end-effect, *i.e.,* there is a marked "after-discharge"; (3) less close correspondence between rhythm of stimulus and rhythm of end-effect; (4) less close correspondence between the grading of intensity of the stimulus and the grading of intensity of the end-effect; (5) considerable resistance to passage of a single nerve-impulse, but a resistance easily forced by a succession of impulses (temporal summation); (6) irreversibility of direction instead of reversibility as in nerve-trunks; (7) fatigability in contrast with the comparative unfatigability of nerve-trunks; (8) much greater variability of the threshold value of stimulus than in nerve-trunks; (9) refractory period, "Bahnung", inhibition and shock, in degrees unknown for nerve-trunks; (10) much greater dependence on blood circulation, oxygen (Verworn, Winterstein, von Baeyer, etc.); (11) much greater susceptibility to various drugs (anesthetics).

Features 1, 3, 5, 6 and 7 would be very difficult to explain without accepting the neuronal theory. The other features imply at least an important alteration in the quantitative conditions of impulse. These alterations, of course, are not to fall necessarily on synaptical or other equivalent substances, they might also be produced in the intermediary nets, or in the nervous tissue itself, somewhat altered.

In 1903 Ramón y Cajal published some "Critical remarks about Bethe's theory on the structure and connections of nervous cells." The main arguments were the following: (1) the real and morphological connections of neurones once known, we cannot estimate, as Bethe and Apathy do, that neurofibriles are the only conductive substance in the nervous protoplasm; (2) Bethe's method, on account of the lack of tinction of pericellular arborizations and nervous collaterals, is not appropriate for the study of interneuronal connections. Ramón y Cajal did not for a single moment worry about the physiological problems established by these questions. However in one of Dr. Tello's works there is a question of studying alterations of neurofibrils under the influence of innervation.

Very little remains at the present moment of Bethe's theory as a general doctrine. In some special cases there may be communicative fibers, but he himself has ceased insisting on these general doctrines. In Fulton's book (4) there is a good summary of the actual state of problems of nervous conduction: "The so-called neurofibrils along which conduction is believed by some to pass, are held by Mott to be artefacts, having no real existence in living nerve. Certain observers notably Vernon, regard the evidence for the absence of neurofibrils as inadequate, since the ultramicroscopic method employed by Mott differentiates structures only so long as they have different refractive indices. The fact remains, however, that no one has ever demonstrated neurofibrils in normal living nerve fibers, and Macdonald stated that he has observed their formation within the axis cylinders of nerve fibers following, *i.e.,* during early stages of disintegration. It is therefore difficult to place confidence in theories of conduction which call upon the neurofibrils."

Other functional conceptions and theories of Ramón y Cajal have exerted less influence and been less widespread than the two above discussed, possibly since they refer only to associated aspects of nerve physiology or their not being based on such solid ground of well-established morphological facts. An exception must be made on behalf of the growth of neuroblasts and nervous regeneration as a whole, inasmuch as these researches may be considered a consequence of the discussions about the neuronal theory. The first of these two groups may be represented by the morphological descriptions of the striated body and the optical thalamus, which have lately been confirmed by clinical and experimental studies.

Ramón y Cajal repeatedly endeavored to explain physiology by anatomy, as did the Renaissance anatomists. His success in these attempts was uneven. We may find, especially in his early years, many hypothetical speculations about possible functions, speculations which nowadays are absolutely obsolete. Such is, for instance, his publication "Some remarks about the anatomical mechanism of association, ideation and attention" (1895). He himself criticized this work twenty-five years later in his memoirs. He excludes from his criticism his theory of nervous avalanches, according to which the number of neurones taking part in conduction increases progressively from the periphery to the brain and *vice versa.* Were this true, things would happen just the reverse of the concentration of paths, which is a special feature of motor functions, and more particularly of reflexes. His ideas about the mechanism of conduction and interruption of currents through synapses, starting from the principle of contacts, are also erroneous. Mathieu Duval complicated this theory still further by pretending to give an explanation even of sleep, which gave rise to many researches about the so-called amoeboism of cellular terminals. Nothing of all this is accepted at present, and considerations deriving from the study of latency time

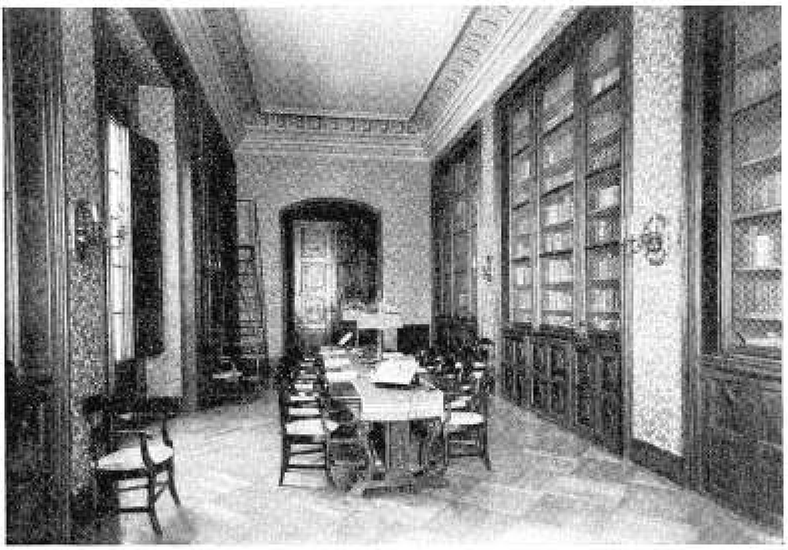

Fig. 4.—The library preserved exactly as in the old time of the College of Surgeons.

and of the incremental capacity of reflexes have finally cleared up all doubts that might still remain about the likelihood of these ideas. Ramón y Cajal and his school's suggestions about the part played by neurological cells in the synaptical contact and about the isolating action of neuroglia have also been refuted.

On the other hand, he was right in his attempts to explain professional ability and functional dexterity derived from practice and from the frequent repetition of the same acts, both by the progressive strengthening of nervous paths and their constant excitation through the repeated passage of the same wave (a conjecture suggested by Tanzi and Lugaro), and by the growth of new cellular appendices and dendrites, elongation and arborization of non-congenital nervous collaterals, which give a better finish to the adjustment and extension of those paths, and which are even able to establish new relations between neurones primitively unconnected. These opinions, which contain the seed of modern doctrines about facilitation in the centers, are also expressed by Ramón y Cajal in his Croonian Lecture.

In connection with all the above should be mentioned the idea that the functional preeminence of the human brain is intimately bound to the "wonderful abundance and unusual extravagance of short axon neurones," to the profuseness of dendritical arborizations and to the large extension of the associated zones (1899).

The law of the unity of function in neurones corresponds with the present knowledge about corresponding points. This is a special feature to be mentioned among others in the case of the crossing of the optical paths in connection with the retinian distribution of fibers—by which one can see that the accurate study of morphology and deep meditation upon structures are indeed powerful helps in the interpretation of function. But it does not reach farther than that.

Another fact still: the discovery of appropriate histological dispositions and features in the various projecting centers of the brain cortex and the correspondence with the afferent and efferent paths is a most powerful argument on behalf of cerebral localization, so much discussed at the moment when this work was published (1899). It is interesting to note that, in this problem of localization, always so much discussed and with more intensity today, Ramón y Cajal's theses are still triumphant. In fact, the localization criterion is not as strict now as it was a few years ago, we know that some parts of the cortex influence the others, without possessing by themselves a well-defined function—the premotor area may be mentioned in this connection. The activity of these zones is always bound to specific functions, which have been established through direct excitation or experimental eradication, and which are sustained through a large number of associating fibers. It must be remembered also that it was Ramón y Cajal who insisted before anyone else that associating fibers have their part in insuring accuracy and outlining shades in all functions, and that the true characteristics of superior animals are on one side a greater precision in the localization of cortical projection areas and on the other a considerable increase of the associating zones.

Let us mention now the so-called law of commemorative assymmetry, "Sensorial and motor spheres in the brain cortex are symmetrical, but not so the representative or ideal zones (association centers of Flechsig), which lie absolutely localized in each hemisphere. Thus can the existence of the callous body and other commisural and intrahemispherical paths find its explanation, for they are meant to concentrate in each commemorative isodynamical and unilateral focus the sensorial residues produced at the perceptive centers at both sides." These suggestions have also found echo in further researches.

From all the above it can be seen that many of Ramón y Cajal's discoveries about the structure of various organs constituting the central nervous system have given useful leads in the interpretation of results arrived at through experimental methods. In other instances, the opposite has been true, and clinical observations and physiological data have given a functional value to structural details which were seen by Ramón y Cajal without his having established their histology, or only mentioning their probable function in view of their anatomical relations, without being able to prove that function. There are many instances of this, among others the case of the optical thalamus and the striated bodies; clinical exploration with autopsy data and physiological researches later furnished results which agree with the structure.

In the structure and functions of the sympathetic system, Ramón y Cajal's studies, dating from 1891, have also exerted a profound influence during the last forty years, and in a certain way they have formed the foundation of many ideas now well-established. This is especially true of the work of physiologists with Gaskell and Langley in the forefront. Ramón y Cajal's doctrine is still the doctrine of today; an efferent sympathetic system with ganglionar synapses between a preganglionic fiber with its origin in the center, and the dendrites of a sympathetic neurone, the axon of which—or postganglionic fiber—reaches the organs. The afferent vegetative innervation would be entrusted—as Kölliker also thought—to fibers belonging to sensitive neurones of the spinal ganglions or cranial nerves, which reach the organs through direct trajects, just as is the case with the pathways of exteroceptive sensibility.

We still find this scheme in all anatomy and physiology textbooks and objections are only now beginning to arise, especially in regard to the legitimacy of deductions starting from the so-called specific action of nicotine on ganglionar synapses, an absolute specificity which does not exist in the form that Langley supposed. Nicotine acts especially on the ganglion, but it also alters conduction in the fiber, and therefore schemes based on that action, considered as exclusive, must be taken as only provisional. But as far as what will remain permanent in all this—and probably it will be a great part—this constitutes another example of how physiologists have been the ones to reinforce the Cajalian theories, and to establish new research methods: the degeneration and regeneration of fibers after nervous sections.

We have endeavored to point out what we think are the most interesting contributions of Ramón y Cajal to the knowledge of neurophysiology, particularly what concerns the centers, and what at the same time has led to physiological researches and to the strengthening of the fundamental ideas of the Master. We have already seen that both influences—mutual influences—have been important, but they would have been more so had Ramón y Cajal been assisted by a physiological school. We must insist upon Ramón y Cajal's isolation. Some illustrious disciples gathered around him, who have followed the same anatomical current without worrying at all about the functional aspects. When Cajal arrived in Madrid in 1892 he found an atmosphere propitious to anatomy and clinic, physiological curiosity was absolutely non-existent. On the other hand, when leaving Barcelona the interest in physiological studies was just budding there. After the physiological awakening took place many years passed before a corps was constituted in Madrid which took an interest in these problems.

It is for this reason that we feel justified in regretting that, in spite of the greatness of Ramón y Cajal's work, as laid down in four big books and in the thirty-five volumes of his *Review,* it was not more impregnated with physiological substance. The work of the English physiologists of recent years should by right be the work of our own physiologists, having contact with the Master and being stimulated by him. Here is the extraordinary fact that the discoveries of an anatomist have given rise to important progress in physiology, and that by a just correspondence, physiology is now the support and justification of a whole life of exemplary work. Ramón y Cajal's struggle and discussions with physiologists lasted for over ten years, and did not come to an end until other physiologists appeared, stating that the experimental results they had obtained confirmed the main interpretations—not the morphological and scarcely ever discussed discoveries—of Ramón y Cajal. He could not be aware, because of the limited scope of his own training, of how other people's points of view might often be quite different from his own. He was surprised by objections and later on surprised again by coincidences.

This aspect of the scientific life of Ramón y Cajal is of such interest that we feel that the best homage which physiologists could render to the great Master would be to point out the influence of Dr. Ramón y Cajal's work in the production of physiological doctrines of the present times.

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