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The concept of the Schwann cell by Louis Ranvier and his school: The 'interannular segment' as a cell unit

Jean-Gaël Barbara ^{a,b} and Paul Foley ^c

ABSTRACT

The hundredth anniversary of the death of French histologist Louis Ranvier (1835–1922) is an opportunity to reexamine his elaboration of the first concept of the Schwann cell. A loyal supporter of Theodor Schwann and his discoveries, and an attentive reader of the work of Albert von Kölliker, Ranvier studied the anatomic details of the myelinated nerve fiber with picocarminate staining. The diffusion of the dye into the nerve fiber at the cut ends and at the sites of the annular constrictions (Ranvier's nodes) set him on the path to defining a new cellular entity surrounding the axon, the "interannular segment," comprising a Schwann nucleus, myelin, and cytoplasm. Ramón y Cajal recognized in 1913 that this concept of the Schwann cell according to Ranvier and his pupil William Vignal had been a brilliant intuition, but it was widely rejected until it was rediscovered using electron microscopy in the 1950s. The article reconstructs the steps of Ranvier and Vignal in building this Schwann cell concept, as well as establishing bridges with the discoveries of the 1950s.

KEYWORDS

Kölliker; Ranvier; Schwann; Schwann nucleus; Schwann sheath; Vignal

Introduction

On the occasion of the centenary of the death of French histologist Louis Ranvier (1835–1922; see Barbara 2007; see Figure 1), we would like to revisit one of his most important achievements, often underestimated in the history of neuroscience. In 1913, the eminent neuroanatomist Ramón y Cajal (1852–1934) characterized Ranvier's elaboration of his initial concept of the structure of the Schwann cell as remarkable:

Ranvier had an intuition of genius when he put forward the notion of the interannular segment as a vast cellular unit within which are contained the nucleus, myelin, and axon. The modern histologists have confirmed this doctrine in all its essentials (Ramón y Cajal 1913–1914; as translated in Ramón y Cajal 1991, Part II, 44)

In this article we will discuss how Ranvier's work on the Schwann sheath and the nerve fiber led to an early and fruitful concept of the Schwann cell. We will also discuss why this concept was largely abandoned during the early twentieth century and forgotten, before electron microscopy reestablished in the 1950s that elements of Ranvier's concept were, in fact, quite prescient.



Figure 1. Portrait of Louis Ranvier (1835–1922). Courtesy of Collège de France.

The aim of our analysis is to not only revisit the work of Louis Ranvier, praised in his time but then neglected, but also to more broadly illustrate the complex history of concepts of glial cells by exploring a specific aspect, the recognition of the Schwann cell as a cellular entity that synthesizes myelin in its cytoplasm and envelops the peripheral nerve fiber in a dynamic cellular process.

This investigation requires an epistemological approach in order to understand ideas from each period about the nature of the complex relations between the anatomic *elements* of the peripheral myelinated nerve fiber, initially described in disparate ways—as myelin, the Schwann sheath, the Schwann nuclei, the Mauthner sheath, the axis-cylinder—and certain other histological details, such as striations and the intimate structures of the annular constrictions.

Our analysis of Ranvier's initial Schwann cell concept requires us to first consider the *anatomic arrangement* (French: *dispositions*) of the nerve fiber studied by histologists during the period preceding his work; that is, the spatial relationships between the elements of the nerve fiber and the interpretation of these relationships in the context of specific models of nerve development.

This type of history is particularly difficult because of the many and varied interpretations of the complex structural relationships between nerve fiber elements across time, often misinterpretations only gradually resolved with the aid of electron microscopy during the 1950s. Like the history of the neuron concept, that of the Schwann cell must take into

account a diversity of theoretical frameworks, techniques, standards of interpreting observations, and patterns of theoretical elaboration to understand the evolution of ideas that between the 1870s and the early twentieth century sometimes moved toward and sometimes away from the modern Schwann cell concept.

This historical approach is also necessitated by the fact that, even more than for the neuron concept, the interpretation of new observations often differed between authors because of differing theoretical presuppositions about how nerve fibers form, and also because of the different staining techniques used. This makes an epistemological approach that unravels this complex history useful for evaluating the contribution of Ranvier's work to the concept of the Schwann cell.

In this article, we will attempt to understand the genesis of new concepts by not restricting ourselves to chronologies of the contexts of enunciation and justification of new research findings, but by describing their contexts of discovery; that is, by establishing the order of the discoveries and the order of the construction of concepts, step by step.

Interestingly, we found, after we had completed the first draft of this article, that the introductory text of an 1897 treatise by French anatomist Mathias Duval (1844–1907) proposed just such an approach to Ranvier's complex concept of the interannular segment and the subsequent work of Ranvier's student, William Vignal (1852–1894):

Another character given, in the present volume, to the mode of exposition of the various questions, is what may be called *historical evolution*. It has often seemed to us that the only way to undertake an inclusive study was to follow the succession of ideas about its object that anatomists had provided. . . . This mode of proceeding often lends a singularly arduous question all the interest of a story that piques curiosity and impatience. Consider, for example, the constitution of the myelinated nerve fibers, the last word regarding which concerns the interannular segments of Ranvier and the cells of Vignal. Without doubt, were it only a question of recording in a few lines the present state of knowledge, in a dry and uninteresting inventory, we could simply characterize the constitution of the sheaths of the axis-cylinder as a series of casing segments, each having the value of a cell. But if we want an explicit presentation that identifies and highlights the value of each detail, I say that it entirely lacks didactic feeling if it does not proceed by precisely following the historical order, first showing us how the axis-cylinder and its sheaths were discovered, how Ranvier discovered the annular constrictions, which problems concerning the meaning of the corresponding interannular segments then arose, and how Ranvier himself provided the solution to these problems by showing that there is only one cell nucleus for each of these segments; then how Vignal's work on the histogenesis of the nerves confirmed these conclusions. The constitution of the nerve fibers then appears complete, unfolding in a logical chain of historical phases, and calling for new notions to be deduced or anticipated on the basis of the original ideas, namely those related to the degeneration and regeneration of sectioned nerves. (Duval 1900, xiv–xv)

We propose to unravel the contexts of discovery of Ranvier's concept of the Schwann cell by reconstituting the order of the discoveries and that of the construction of his concept. This will require a review of concepts of the elements of the peripheral myelinated nerve fiber since the earliest observations. First, it is necessary to understand the trend across time to dissociate ever more finely the elements of the nerve fiber for the sake of precision. A second historical anatomic direction then aimed to determine the relationships between these elements within theoretical frameworks for the development of the nerve fiber. Departing from these trends, Ranvier's research led to the start of the modern concept of the Schwann cell, which was initially well received, particularly in France. Finally, we will discuss the

reasons for the gradual abandonment of the concept, and how new findings with electron microscopy reestablished its relevance after it had largely been forgotten.

The structure of the myelinated peripheral nerve fiber and its development before Louis Ranvier

It would be erroneous to believe that the constituent elements of the Schwann cell—the Schwann nuclei, the Schwann membrane, myelin—were ever the objects of separate descriptions. As early as the work of Theodor Schwann (1810–1882) on the sheaths of myelinated peripheral nerve fibers (Schwann 1839), their relationship was discussed in the context of a theory of nerve development that explained the elaboration of tubular structures from primordial round cells.

However, the story of the myelinated peripheral nerve fiber began with the search for distinctions between its elements. The first characterization concerned local observations in longitudinal and transverse sections of nerve by microscopists with limited staining options. The initial differentiations were consequently in the transverse plane, distinguishing the internal and external elements of the myelinated fiber; that is, from the inside to the outside: the axis-cylinder, the Mauthner membrane, the myelin sheath, the Schwann sheath, the Schwann nuclei, and the external connective sheath.

This story was paralleled by that of models of the development of these structures within the broader theoretical frameworks of the globular, the fibrillary, and cellular theories of nerve formation. The two stories must be considered jointly, as they are inseparable at the epistemological level. Indeed, the observation of structures was partly determined by theoretical presuppositions that themselves were sometimes validated by other observations.

First distinctions between elements of the myelinated peripheral nerve fiber

The first distinction, facilitated by the development of microscopy in the seventeenth century, was the recognition of an elementary solid fiber, constitutive for the nerve tube. It was no longer possible to regard nerve elements as hollow tubes, analogous to blood vessels, that allowed the circulation of distinct humors. Malpighi, Leeuwenhoek, and Procháska found that nerves consisted mostly of solid fibers that might be considered semi-hollow (i.e, including longitudinal canals) and filled with a liquid, or as solid structures, as for example in the fibrillar theory of Alexander Monro (1697–1767; see Chvátal 2015, 275).

The second broad distinction was the recognition of a sheath surrounding the elementary fiber. From the seventeenth to the nineteenth centuries, a model emerged that regarded nerve structure in a manner we might today describe as fractal; that is, with structural analogies between different scales of structure, between microscopic fibers associated in bundles and nerves in nerve bundles. The sheaths of nerve fibers were correspondingly conceived as fine structures analogous to the sheaths of nerves. Czech anatomist Jiří (George) Procháska (1749–1820) was one of the first authors to focus in this way on the microscopic structure of these supposed thin sheaths. He recognized that even the thinnest nerves also have sheaths:

The cellulose nerve sheaths are at the nerves' beginning and around thicker nerves stronger and bulkier, while along the nerves the sheaths are getting thinner, so thin nerve endings and strands are surrounded only by very thin cellulose matter, through which the exposed nerve strands are shining (Procháska 1779, 52; as cited in Chvátal 2015, 273).

The meticulous observations of Florentine physicist Felice Fontana (1730–1805), published in 1781, went further, no longer focusing on a more or less hypothetical elementary fiber but rather on the direct observation of the primitive structure of the nerves; that is, its indissociable, elementary component, a “tortuous fiber” (*fiber tortueuse*) he termed the “primary nerve cylinder” (*cylindre nerveux primitive*). Just as nerves of different sizes, including the finest nerves, have a sheath of “cellular nature,” Fontana recognized that the primitive cylinder is itself surrounded by a “cellular tissue” made of “loose filaments” (*filaments déliés*) that dissociate in water, which he termed “the outer envelope of the cylinders.” These filaments reflect the behavior of myelin in water, as later also observed by Ranvier.

The distinction between the two parts of this sheath—the internal part, with a fatty and shiny substance, and the more external component—might seem to belong to the second half of the nineteenth century; Kölliker in 1850, for example, did not recognize it in Schwann's descriptions. However, Procháska had made the distinction in his 1784 treatise on the functions of the nervous system, commenting on Fontana's observations. He distinguished between two kinds of sheath, one of which can be removed from fine nerves, whereas the other cannot be detached but can be divided into threads:

The mentioned strands, already deprived of their fibrous sheaths, have a second, strong and flexible sheath, which is so tightly linked with the nerve mass by its membrane [*sepimentum*], that it can hardly be separated, and if we try to divide these strands along their length with a needle, [the] sheath would split into strings that were not previously present. (Procháska 1784, 162)

We find a similar description in Fontana, who spoke of the cellular tissue of the nerves that can be removed and of a sheath of “loose filaments,” even if, for Fontana, this latter sheath itself is cellular in nature.

From the eighteenth century onward, the nerve fiber is conceived as being hollow and filled with a transparent jelly (Fontana) or as solid (the fibrillar theory applied by Alexander Monro to the nerves). In both cases, it is surrounded by a shiny sheath that forms threads in water when disrupted (the “outer envelope of the cylinders” or myelin sheath), and itself covered by another sheath of connective tissue that can be removed with a needle.

The cellular nature of the nerve fiber according to Theodor Schwann

Uncertainty about whether the nerve fiber was hollow or solid persisted until the development of achromatic microscopy in the 1830s. This uncertainty was reflected in Theodor Schwann's 1839 description of nerve fibers, despite recent observations by Christian Ehrenberg (1795–1876) and Robert Remak (1815–1865). Ehrenberg had noted in 1836 that the white color of certain fibers (*markführende Röhre*) was attributable to the fatty “sheaths” (*Nervenmark*) adjacent to the “double contour” (*doppelter Wandung*) of the nerve tubes (*Hirnröhre*), while in 1837 Robert Remak described primary nerve bands (*primitive Bänder*) surrounded later in their development by white matter of external origin.

Schwann agreed with Remak that the nerve fiber is a pale band surrounded by a white sheath that could be removed by pressure (Schwann 1839, 169). On the other hand, he still thought that Remak's *Primitivband* might only be the solid content of a hollow nerve tube of white matter. In either case, the elements were part of the same functional entity, so the ambiguity was of little theoretical consequence.

Schwann also adopted Procháska's distinction between two sheaths around the nerve fiber: a membrane surrounding the white matter, which might contain nuclei (the Schwann sheath), and a second, more external sheath of cellular tissue. Schwann described the inner sheath as a strange, finely granular membrane seen as a clear, narrow border that contrasted with the double dark contours of the white matter.

At the functional level, Schwann associated both sheaths with a single entity that included the nerve fiber and the white sheath. Most important to Schwann from the beginning was to show how this entity and its constitutive elements arose from *cells*, analogous to what he had already achieved with his model of sarcolemma development in muscle tissue. This cellular perspective made Schwann particularly sensitive to identifying the different nuclei he noted in the cellular and Schwann sheaths. For Schwann, these nuclei were necessarily those of cells that had participated in the formation of the nerve fiber, derived from round formative or "primary cells," because of his observations in embryonic tissues that these nuclei were more abundant at this stage of development. The disappearance of nuclei in the Schwann sheaths during development convinced him of their origin in primary cells; those that persisted were interpreted as indicating that the Schwann sheath was the membrane of a secondary cell formed by the coalescence of primary cells.

Schwann's attention to the cellular elements surrounding the axis-cylinder was recognized with varying degrees of praise by later generations of investigators. Louis Ranvier, a friend and ardent supporter, ranked this work among Schwann's most important when he cited it in the inaugural lesson of his chair of general anatomy at the Collège de France in Paris in 1876, mentioning Schwann's "two important discoveries . . . the membrane of the nerve-tubes and the sarcolemma" (Ranvier 1876, 12).

The new interpretation by Albert Kölliker

Swiss anatomist Albert Kölliker (1817–1905) adopted, with less reservation than Schwann, Remak's concept of the nerve fiber as a cylinder-axis surrounded by a myelin sheath (Figure 2). Kölliker concentrated his critique of Schwann's work on his concept of the sheaths and modified his interpretation of nerve fiber formation (Kölliker 1868).

Kölliker was convinced by the anatomic continuity between the elements he had observed that nerve fibers developed from nerve cells. According to his model of nerve tissue development, the delicate Schwann sheath was not derived from the primitive nerve cells, and Kölliker also rejected the alternative interpretation of Jakob Henle and Charles Robin that it was a connective tissue element (i.e., part of the neurilemma). Kölliker sought an interpretation of the sheaths that was consistent both with his view that the nerve fiber initially develops without a sheath and with Remak's observations. For this reason, he examined the sheaths in greater detail than his predecessors.

Kölliker did not believe that inspecting nerve tubes in their fresh state allowed detailed study of their sheaths (Kölliker 1868, 315), opposing the view of most histologists, including those of the French school at the Collège de France. For this reason, he developed

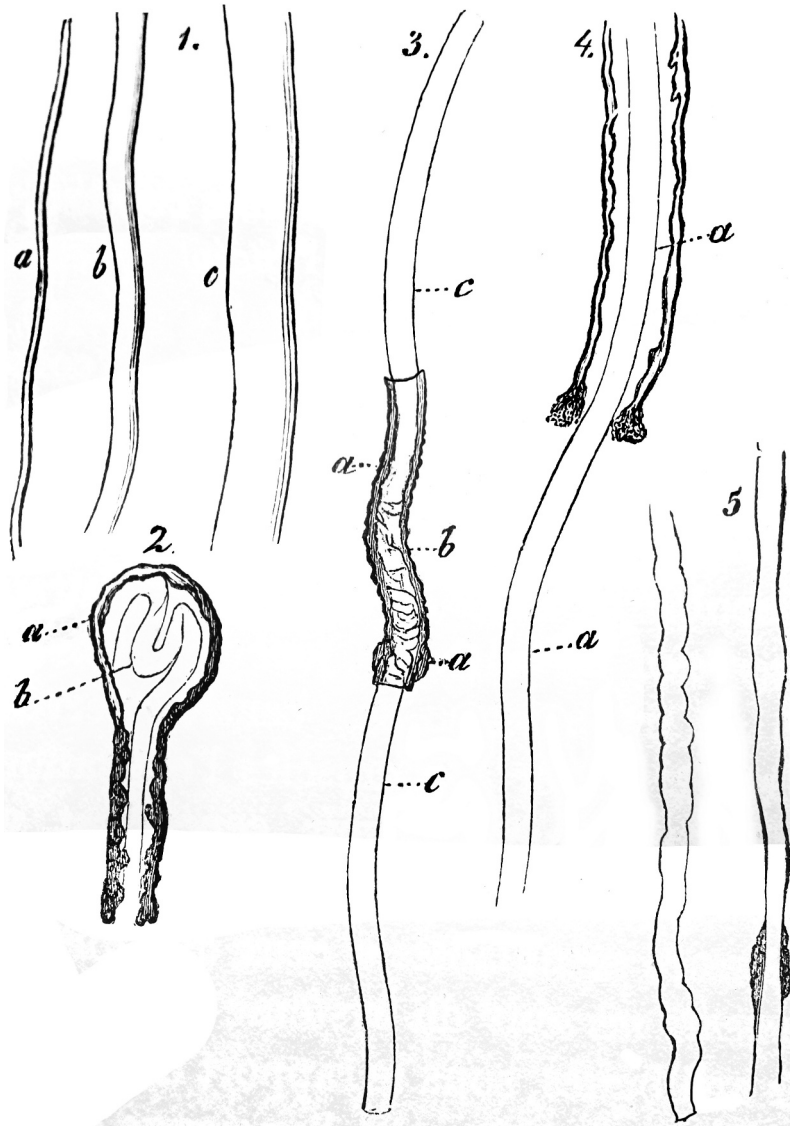


Figure 2. Nerve fibers according to the observations by Kölliker (1850) at $\times 350$ magnification. 1. Nerve fibers in their natural state from dog and rabbit; a. thin tube; b. tube of intermediate size; large tube from a peripheral nerve. 2. Nerve fiber from a frog placed in serum, a. a drop of marrow (myelin) flows out of the tube with the fiber inside b. 3. Fresh nerve fibers from the human spinal cord in serum; a and b. double-contoured medullary sheath; c. axis-cylinder. 4. Nerve fiber with a double contour from the fourth ventricle (human); a, axis-cylinder with a portion outside of the tube. 5. Two isolated tubes from the spinal cord of man. The first shows undulating contours while the other shows small bulges and some marrow attached.

procedures for treating nerve tubes, boiling or exposing them to strong acids to dissolve the axis-cylinders and the connective sheaths, allowing the isolation of hollow sheath tubes: “many fragments of somewhat swollen sheath, completely empty” (Kölliker 1868, 241). He saw this as the primitive myelin sheath, for “the fat is seen to flow out of the tube in the form

of pale droplets, the axis-cylinder dissolves, and the yellowish sheaths remain behind empty, broader and with swollen walls” (Kölliker 1868, 241, [Figure 2](#)). Kölliker further observed that this primitive sheath included nuclei, and he doubted Schwann could have clearly distinguished them from those of an external connective tissue sheath.

Kölliker perhaps saw an analogy between the fatty Schwann sheath and the adipocyte. He believed that an adipocyte was derived from a primordial cell, its membrane thickening with the formation of lipid that almost completely replaced the cytoplasm and formed a central fat drop. Kölliker insisted that the transformation of the membrane of the primordial cell modifies its chemical properties such that the resulting fat cell becomes refractory to acids and alkali (Kölliker 1868, 45). This is precisely the test that Kölliker applied to the sheathed nerve fiber, isolating empty sheaths consisting of a lipid that protected them from dissolution while the surrounding structures disappeared.

As for the modes of formation of the two sheath types, Kölliker initially adopted Schwann’s view, but he clarified it with regard to the external connective sheath (endoneurium), which he interpreted as derived from the membranes of the “formative cells” (Kölliker 1867, 241). Further, as a result of his observations concerning the “developmental history” of the sheaths, he considered both sheath types to be cell membranes and thus cellular elements, not connective tissue. In fact, Kölliker proposed that the sheaths are initially formed from round cells that fuse to envelop the axis-cylinder and the myelin sheath. But these cells, unlike the myelin sheath, did not form a tube, as he had once believed: “Formerly I thought that the nerve fibers were inside the cavity of these cells; but now it seems more likely to me that the cells are flattened . . . and only surround the nerve fibers on the outside” (Kölliker 1867, 241).

Kölliker saw the Schwann sheath and its nuclei as composed of a collection of flat cells around the nerve fiber and its white sheath. This model resembles that of the epithelial cells of the fine blood capillaries, but an analogy with the flat epithelial cells of the endoneurium is also possible. The nerve fiber is therefore covered by a viscous substance that is itself covered by a sheath of flattened cells, in turn covered by a sheath of cellular tissue. The Schwann sheath consisted of cells, but whether these cells contained white matter was unclear. Kölliker’s model did not really move from the transverse arrangement of the nerve fiber elements, from the axis-cylinder in the center to the outermost cellular tissue, but he did entertain the idea of the Schwann sheath comprising cells that encircled the nerve fiber after its formation and associated with the white matter covering the nerve fiber.

The concept of the interannular segment of Louis Ranvier

Louis Ranvier adopted and advanced the analogy of the adipose cell with the Schwann sheath cell, but he arrived there indirectly, only after having discovered the annular constrictions on nerve fibers, the Ranvier nodes (Barbara 2007, [Figure 3](#)). Here we will highlight the links between his research into annular constrictions and his concept of the Schwann cell in an explicit analogy with the adipocyte.

Ranvier’s initial investigations of the peripheral myelinated nerve fiber are often described by neuroscience historians as studies of a detail, the node of Ranvier, with the aim of determining its physiological importance. This is indeed the impression conveyed by reading Ranvier’s articles in their order of publication (Barbara 2007). Nevertheless,

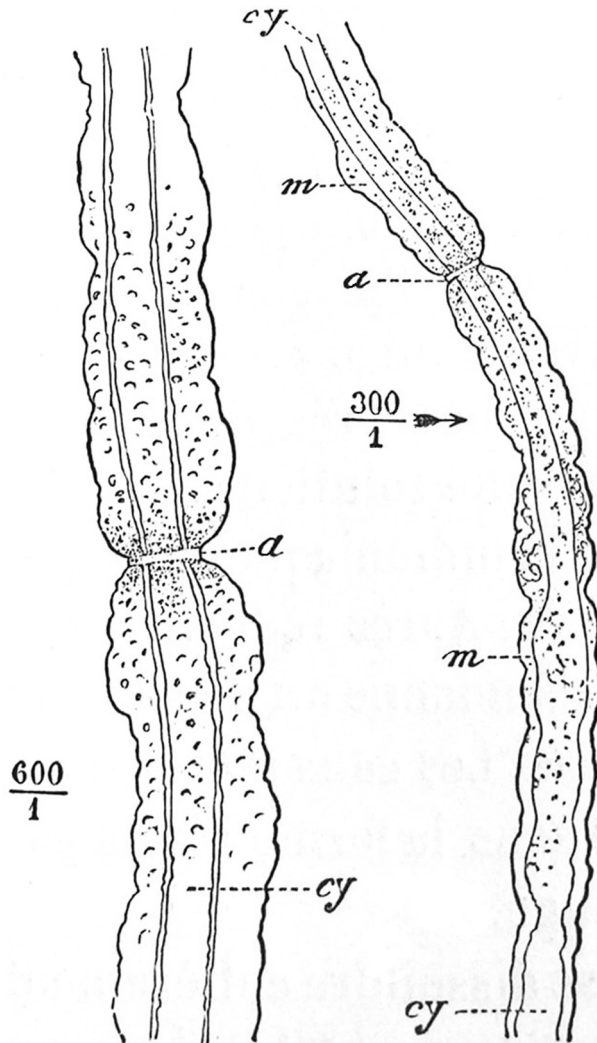


Figure 3. Large sciatic nerve tube dissociated in picocarminate ammonium (1%) by Ranvier. Tubes were drawn after one hour incubation. Red picocarminate staining is indicated by dots. Axis-cylinder is stained in red near the annular constrictions (a), indicating picocarminate penetrates the nerve tube at this level, $\times 600$ magnification. Adapted from Ranvier (1875).

epistemological analysis should aim to differentiate between the contexts of enunciation and justification and the contexts of discovery, in order to better understand the genesis of new concepts and their modes of constitution, free of a *posteriori* rationalization for facilitating their reception.

Analysis of texts in the history of science typically and naively follows the order of publication and accepts the reconstructed rationality proposed by the authors across these publications. But some scholars follow instead the order of the discoveries if they judge it of greater pedagogical value for the exposition of the genesis of a concept. Mathias Duval adopted this approach with reference to Ranvier, as did the Lyons histologist Joseph Renaut (1844–1917) in 1899 when discussing Ranvier's

intercalary segment: “[I]n my description, I shall follow precisely the reverse order [to proceeding from cylinder-axis to the annular constrictions], because my main concern is clarity in the exposition of facts which, at present, are no longer disputed by anyone, but which, on the other hand, are not always well understood” (Ranvier 1899, 808).

We will accordingly show that Ranvier’s work was primarily concerned with elucidating the nature of the Schwann sheath as a cellular entity, whereas the physiological interpretation of the node of Ranvier as an anatomic detail developed only later, as the physiological justification of histological research conducted in the school of French physiologist Claude Bernard (1813–1878) with a view to attracting the interest of the physiologist community (Barbara 2007).

In order to understand Ranvier’s concept of the Schwann cell, it is consequently necessary to highlight the specific context of its development relative to Ranvier’s observations and changes in his interpretation of the Schwann sheath. Ranvier’s studies took a new epistemological turn, devoted to establishing vertical discontinuities in the myelinated nerve fiber, such as the interruptions of the myelin and Schwann sheath at the Ranvier nodes, in contrast to the prevailing view that the nerve fiber and its sheaths were continuous from the nerve cell of origin.

Moreover, Ranvier’s epistemological turn concerned not only vertical structural discontinuities but also horizontal arrangements of nerve fiber elements. Instead of pursuing distinctions between elements in the horizontal plane, Ranvier sought to establish, by careful observations, local forms of horizontal continuity between the Mauthner, the myelin, and the Schwann sheaths. Ranvier established such histological relationships by observing invariance in the cytoplasmic granulation patterns that accounted for protoplasmic continuities between different elements of the nerve fiber. Ranvier was thereby able to define the limits of a new cellular entity in the Schwann sheath, characterized by its specific cytoplasmic granulation profile.

Importance of the kinetics of staining of the myelinated nerve tubes with carmine

In the 1869 treatise he coauthored with Victor Cornil, Ranvier described the structure of the “medullary nerve tubes” (*tubes nerveux à moelle*) by repeating in broad outline Kölliker’s descriptions, both structurally and in terms of their origin from nerve cells (Cornil and Ranvier 1869). But from the outset, Ranvier emphasized the importance of staining with carmine, which allowed him to affirm that the nuclei of the Schwann sheath were “included in the membrane” and surrounded by a “lenticular mass of protoplasm” (Cornil and Ranvier 1869, 26). Ranvier also insisted on the ability of carmine to stain the axis-cylinder of medullary nerve tubes when the “carmine solution comes into contact with it” (Cornil and Ranvier 1869, 27).

Intact medullary nerve tubes (i.e., those not damaged during dissociation of the nerve) do not rapidly stain in a carmine solution. However, it was clear to Ranvier that the axis-cylinder has an affinity for carmine, for “those that escaped from their sheaths [during dissociation] stain to their full extent and in an almost instantaneous manner” (Cornil and Ranvier 1869, 27). Ranvier further observed that, in unstained tubes, staining with carmine spreads by diffusion from the cut ends: “When a section of nerve tube is placed in the carmine liquid . . .

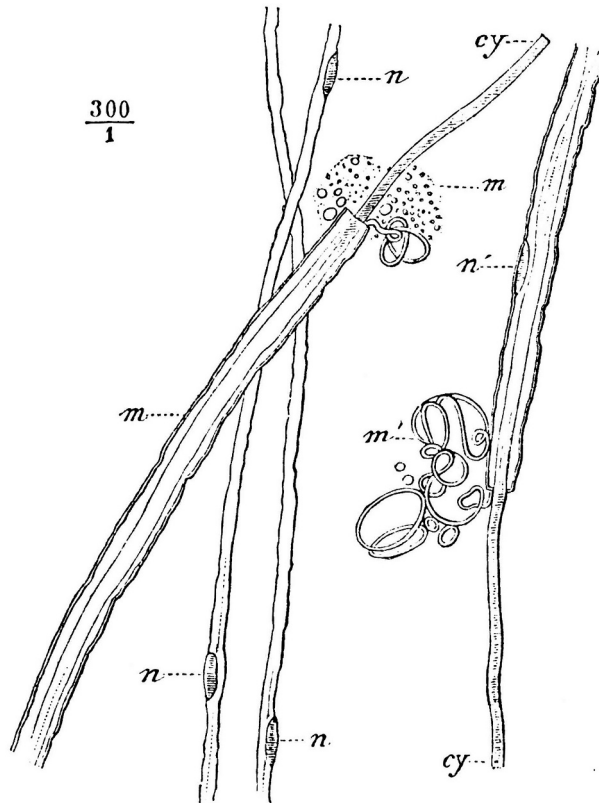


Figure 4. Sciatic nerve tubes dissociated in picocarminate ammonium (1%) by Ranvier. Myelin flows outside the sheath. Picocarminate stains the naked axis-cylinder and invades the inner portion of the nerve tube at cut ends of the sheath only, showing myelin is impermeable to picocarminate; cy, cytoplasm of the axis-cylinder stained, (m, m') myelin, (n, n') nucleus of the interannular segment. Adapted from Ranvier (1875).

staining of the axis cylinder shows itself at the two [severed] ends of the tube and proceeds gradually, so as to be complete only after two or three days" (see Figures 3 and 4).

At the November 11, 1871 meeting of the *Société de Biologie*, an anonymous correspondent similarly mentioned,

[I]f, like M. Ranvier, ... one preserves [fresh nerves dissociated in 1% neutral ammoniac picocarminate], one sees after a few minutes the free axis-cylinders are colored in their full extent; then the axis-cylinders still enclosed by their myelin sheaths become colored for one- or two-tenths of a millimeter at the severed ends of the nerve tubes. (Ranvier 1871a, 131)

The myelin sheath seemed to constitute a barrier to the passage of carmine into the axis-cylinder, but Ranvier did not yet draw this conclusion. Instead, he restricted himself to a simple description of a phenomenon that did not seem to have been previously reported. It would, however, have great importance for the furtherance of Ranvier's work.

The discovery of the annular constrictions of Ranvier

Ranvier's conclusion about the impermeability of the myelin sheath to carmine is found in a later article: "The impermeability of myelin is demonstrated by the fact that carmine in solution cannot pass through it to reach the axis-cylinder, which nevertheless has a great affinity for this coloring matter" (Ranvier 1871b, 1169). This formulation indicates that Ranvier was specifically interested in carmine as a microscopy stain for investigating the physicochemical properties of histological elements. This interest led Ranvier to improve his staining process to facilitate more quantitative studies by developing a solid form of carmine for preparing aqueous solutions of known concentration.

Ranvier had used carmine for many years in the form of "Gerlach's dye" (Ranvier 1875, 96), particularly in his studies of connective tissues. In 1868, he published the results of his systematic use of picric acid, previously used as a fixative and dye for plant and animal tissues. He combined carmine with picric acid to form the compound *picrocarminate*, a dye he described as invaluable for the study of delicate elements, as "these retain their shape and size; each of their parts can be colored with extreme ease, according to their degree of affinity for carmine"; "the cells remain transparent, their nuclei and protoplasmic granulations can be clearly distinguished" (Ranvier 1868, 321). In these studies, Ranvier prepared picrocarminate crystals, allowing him to control the concentration of the dye (he generally used a 1% ammoniac solution in water; see Ranvier 1872, 131).

Ranvier used his new procedure to study dissociated nerve fibers in even greater detail. He isolated with a needle a nerve bundle from a fragment of nerve placed into picrocarminate, then tore its connective sheath to dissociate the nerve tubes. He then noted the kinetics of carmine staining of the various elements. In addition to staining axis-cylinders that had escaped their myelin sheaths and the fiber extremities close to the severed parts of the sheaths, Ranvier noted that other parts of the axis-cylinder could also be stained two to three days after certain accidents of preparation (Ranvier 1872, 133). For example, in a preparation in which a nerve tube with its sheath was artificially twisted to form a handle, the axis-cylinder slightly moved away from its sheath on the convex side and was stained, as if the carmine solution had accumulated in the newly exposed space:

If, at the time of dissociation, a nerve tube has been twisted to form a loop, its axis-cylinder no longer occupies the axis of the tube; on the concave side, it has moved closer to the Schwann membrane and sometimes even touches the membrane. The axis-cylinder, which at this level [but on the opposite side] is no longer surrounded by myelin, becomes colored to a certain degree. (Ranvier 1872, 133–134)

Ranvier was clearly attentive to accidents of picrocarminate staining of the axis-cylinder, which in this case he correlated with a local defect in the impermeability of the myelin sheath. Further, he deliberately conflated here the Schwann membrane with the myelin sheath as a single entity, as later confirmed by his use of the expression, "double contour of the Schwann membrane." For Ranvier, this membrane was an envelope containing the myelin, the inner side of which was in contact with the axis-cylinder.

It was in the context of such observations that Ranvier noted that at high magnification (800× with immersion objectives) the axis-cylinders also presented small staining points, equidistant constrictions of the myelinated nerve tube, at places that he immediately hypothesized were local zones of interruption of the myelin sheath, accidental or not. He first published these observations in 1871, proposing that these zones constituted the

pathway by which oxygen could enter the axis-cylinder. He found that these zones constituted local interruptions of the myelin sheath, with a ring structure that he did not consider an artifact of preparation (Ranvier 1871b).

Ranvier's interest in the regular constrictions in the myelinated nerve tube was not solely provoked by a histological detail that had previously been depicted by many authors, including Ranvier himself, without drawing much attention. He initially approached the constrictions from a histological perspective with possible physiological implications, and his interest was primarily in understanding whether they were accidents of staining or a physiological pathway for axis-cylinder nutrition. The second hypothesis could not be conclusively confirmed using picrocarminate staining alone. Indeed, French histologist Jean Nageotte (1866–1948), Ranvier's successor at the *Collège de France*, later considered the diffusion of the dye to be accidental, consistent with his view that the Schwann membrane was continuous at the annular constrictions (Nageotte 1911a, 70–71). Conversely, Ranvier's view was consistent with his concept of interruptions of myelin and the Schwann sheath, and his interpretation of the diffusion of picrocarminate was more intimately related to the question of the nature of the Schwann sheath than to the discovery of a nutritive pathway.

The nature of the constrictions was therefore of great importance. Ranvier was all the more aware of this because he knew that they could be artefactual, and he was familiar with changes in the organization of myelin in water, which “loses its refractive power and becomes slightly grainy, while the axis-cylinder takes on a yellowish color” (Ranvier 1872, 132). Such modifications could explain local changes in permeability to the dye. They were observed during the two or three days of maceration of nerve tubes in aqueous picrocarminate solution required for the dye to diffuse throughout an interannular segment. This process itself could conceivably modify the local permeability of the myelin sheath. For this reason, Ranvier paid close attention in his descriptions of the kinetics of picrocarminate staining to morphological changes in the nerve tubes as staining progressed. In particular, he verified that the constrictions were visible before they took up stain, when the axis-cylinders were already stained slightly yellow. He was also careful to preserve his preparations during maceration by sealing the flask containing the microscope slides, whereupon he observed that the axis-cylinder stained red at each ring, whereas the ring itself was not stained (Ranvier 1872, 132). The presence of the annular constrictions before staining and their implications for the staining of the axis-cylinders showed Ranvier that they were real structures and not artifacts.

The study of the arrangement of the annular constrictions and their significance

Ranvier then devoted a long study to the annular constrictions and their arrangement (*disposition*); that is, to their structural relationships with the elements of the medullary nerve tube—namely, the Schwann membrane and nuclei, and the myelin sheath.

His first question naturally concerned the structure of the interruption of the myelin sheath at the constriction and its ring structure (*anneau*). He tried to answer this question with the use of picrocarminate and high-magnification immersion lenses (800×). He observed a depression at the level of the constrictions that was obscured by a shadow when the focus of the lens was slightly shifted. He interpreted it as a concave body, similar to the hollow depressions of red blood cells:

It is known that convex bodies, examined under the microscope in a less refractive medium, remain brilliant when the objective is moved below the distinct view, while concave bodies, such as red blood cells seen from the front, become obscure under the same conditions (Ranvier 1872, 134).

The shadow observed at the level of the annular constrictions must therefore correspond to a hollow seen from the front, or to a narrowing of the tube seen in profile, or to a constriction presenting itself to the eye as a concave surface. When Ranvier tracked the double contours of the myelin sheath under the microscope, he observed its disappearance at the level of the shadow—that is, in the constriction:

By focusing the lens on the edge of the nerve tube, which the observer can do by guiding themselves along the double contour of the Schwann membrane, which can be seen only in this way, the membrane disappears in the constriction, and the constriction becomes a dark line in the microscope field. When we move the lens away, this line becomes bright. (Ranvier 1872, 134)

He was convinced that these observations confirmed the absence of myelin in the constriction itself. But, according to Ranvier, one must also imagine that the space without myelin is occupied by a pierced disk or by a ring through which the axis-cylinder passed (hence, “annular constriction,” *étranglement annulaire*), because “the narrowest portion of the annular constriction is wider than the corresponding axis-cylinder” (Ranvier 1872, 134).

Ranvier had offered two types of argument regarding the interruption of the myelin sheath at regular intervals: a functional argument (based on picocarminate staining) and a structural argument. A summary of his 1871 work clearly noted these two aspects:

If we observe the action of the reagent [picocarminate] as it develops, we see that an ever increasing length of the axis-cylinder becomes apparent on each side of the annular depression. It is therefore at this depression that the reagent penetrates, and it is from this point that it spreads by diffusion. Twenty-four or forty-eight hours later, the axis-cylinder is colored red at the points that were initially only colored yellow. (Ranvier 1871a, 133)

Ranvier was able to rectify a rather common misconception among histologists that the myelinated nerve tube did not show any significant functional or morphological distinction along its course—that is, in the vertical plane:

The myelin or nerve marrow of the broad tubes of the peripheral nerves completely hides the axis-cylinder, and if it formed a continuous layer, as histologists still hold, it would create a considerable obstacle to the exchange of materials [with the blood] (Ranvier 1871b, 1169).

Ranvier had noted that German physiologist Otto Funke (1828–1879; see Ranvier 1871a, 130) and German–Italian chemist Ugo Schiff (1834–1915) had respectively reported oxygen consumption and an increase in temperature in nerves, both of which were characteristic of combustion and implying the exchange of materials between the nerve and its environment. In posing the question as a preamble to his study of annular constrictions—“[W]hat is the path taken by oxygenated plasma from the blood to the axis-cylinder?” (Ranvier 1871b, 1169)—Ranvier aligned himself with Kölliker, for whom oxygen entering the cells was the principal exciter of “ordinary nutritive movement,” by considering his nodes as the portal for oxygen and other materials necessary for the nutrition of the fiber.

The arrangement of the annular constrictions relative to the Schwann nuclei according to Ranvier

Ranvier's study of annular constrictions was a physiological advance, but above all the culmination of a series of discoveries on a strictly histological level. It was the first observation of a morphological discontinuity in the course of peripheral myelinated nerve fibers. The vertical morpho-functional distinctions of the myelinated nerve tube by Ranvier thereby constituted an epistemological turning point, although it should be noted that myelin discontinuities had also been described in 1875 by Heidelberg zoologist Ernst Calberla (1847–1878; see Calberla 1875; reviewed in Foley *in press*).

Conversely, Ranvier initiated another epistemological shift by breaking with the traditions of horizontal distinctions of the structures of the nerve fiber and advocating relations of continuity between the Schwann sheath, the Schwann envelope, the Schwann nuclei, the myelin sheath, the Mauthner sheath, and the axis-cylinder. However, we want to show here that these are, in fact, two parallel turns that placed Ranvier on the path to his initial concept of the Schwann cell.

Ranvier first wondered about the disposition of Schwann nuclei relative to the other structures of the myelinated nerve fiber. In his first study of annular constrictions, he seemed to agree with Kölliker, interpreting the nuclei as belonging to epithelial flat cells covering the myelin:

These [Schwann] nuclei are lodged in depressions in the Schwann membrane, and they detach very easily. I think they belong to flat cells that have hitherto escaped my observation (Ranvier 1871b, 1171).

This view of peripheral nuclei, detachable from the myelin sheath, proved persistent. Ramón y Cajal still subscribed to it in 1912, arguing that myelin was so firmly attached to the nerve fiber that it must be secreted by it (Boullerne and Barbara 2020). Ranvier initially adopted this view because he sometimes saw nuclei detached from the myelin, but later he considered it an erroneous interpretation of the more distal nuclei of the endoneurium.

Ranvier also had a theoretical motivation for supposing the existence of flat cells: It was consistent with his interpretation of the diffusion of picrocarminate at the annular constrictions. He believed that diffusion into the axis-cylinder followed a “colloidal pathway” through a serous-type space; the dye accumulated between two serous-type sheets and entered the axis-cylinder via a window in the inner sheet that connected the axis-cylinder with the serous space containing the picrocarminate.

For Ranvier, the flat cells covering the myelin constituted an inner and the endoneurium an outer cellular sheet. He envisaged an analogy between the myelin sheath, the Schwann sheath, and the connective sheath (the endoneurium) and the arrangement of a serous membrane, such as the pleura of the lungs. The outer parietal layer lining the interior of the thoracic cavity was analogous to the connective sheath (the endoneurium), the inner layer or visceral pleura wrapping the lungs analogous to the myelin and Schwann sheaths in contact with the axis-cylinder (Figure 5).

According to this interpretation, the nerve tubes would have access at the annular constrictions to the space between the two sheets filled with blood plasma—that is, to the space between the myelin/Schwann sheath and the connective sheath. This is how Ranvier interpreted the fact that the membrane of the axis-cylinder could be in contact with this

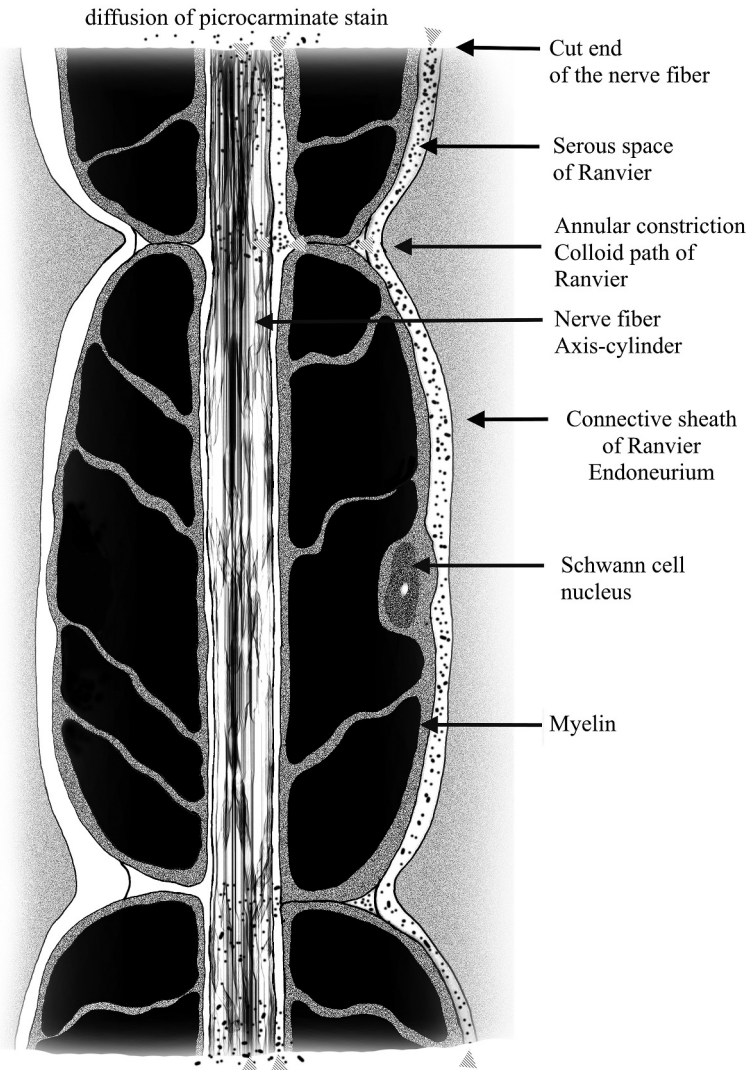


Figure 5. Model of Ranvier for explaining the diffusion of picocarminate at cut ends of the nerve fibers and at their annular constrictions. Picocarminate diffusion is represented by dots and the direction of diffusion by arrows. Ranvier observed picocarminate penetrating the axis-cylinder at cut ends. He explained the slow staining at annular constrictions by a “colloidal pathway” that he conceived as a serous-type space. Accordingly, Ranvier envisaged an analogy between the myelin sheath, the Schwann sheath, and the connective sheath (the endoneurium) and a serous membrane, such as the pleura of the lungs. The outer parietal layer lining the interior of the thoracic cavity was analogous to the connective sheath (the endoneurium), the inner layer or visceral pleura wrapping the lungs analogous to the myelin and Schwann sheaths in contact with the axis-cylinder. Ranvier thought the dye accumulated between the two serous-type sheets and entered the axis-cylinder via a window in the inner sheet that connected the axis-cylinder with the serous space containing the picocarminate. Adapted by the authors from [Figure 8](#) in Berdal (1899, 247).

space, filled with carmine by diffusion and necessary for the passage of nutrients. He concluded,

The nerve tubes are immersed in a serous cavity, the nutritive fluids circulate in this cavity and come into contact with the axis-cylinders via the colloidal pathway of the annular constrictions of the nerve tubes (Ranvier 1871b, 1171).

But Ranvier was gradually moved to revise his concept of flat epithelial cells covering the myelin after he began using osmic acid staining, introduced into histology by Bonn anatomist Max Schultze (1825–1874). Ranvier initially used osmic acid because of its affinity for myelin; with its help, he studied the shapes of the annular discs, the bi-concave menisci of the constrictions, and even their fine striations. Most importantly, osmic acid staining allowed him to resume quantitative studies of the arrangement of the Schwann nuclei at lower magnification—that is, more globally. He found that a nucleus was present in the middle of each interannular segment, as Schwann had already seen (Foley *in press*), and that it was lodged in a depression in the myelin sheath: “these nuclei are shown . . . merging on their outer side with the Schwann membrane and pushing back the myelin, which forms a sort of nest for them” (Ranvier 1872, 139).

Ranvier then paid particular attention to the tracking of granulation types along the tubes, which he interpreted as patterns of granules of protoplasmic (cytoplasmic) substances. He observed, like others before him, a protoplasmic mass around the Schwann nuclei and their “nests.” But he still distinguished a thin layer of protoplasm between the myelin and the Schwann membrane along the entire length of the inter-annular segment, especially in small depressions that did not contain nuclei:

The Schwann membrane does not follow the myelin in all the depressions it forms. Between this membrane and the underlying myelin there is an albuminoid substance, slightly grainy, that is not colored by osmium and most probably consists of protoplasm (Ranvier 1872).

However, he also observed the continuity between the protoplasmic mass around the Schwann nuclei and that between the Schwann membrane and the myelin, leading him to conclude:

This layer [between the Schwann membrane and myelin] is an expansion of the protoplasm of the nucleus; it doubles the Schwann membrane, lines it throughout its extent, and continues at the annular constriction, along the wall of this constriction (Ranvier 1872, 140).

This had previously been overlooked. Kölliker, for instance, did not seem to have noticed it, and even a similar but simpler example did not draw his attention: He had insisted that the internal fat droplet of the adipocyte almost entirely displaces the cytoplasm of its primordial generating cell, without insisting that the cytoplasmic remnants formed a sheet around the droplet. For Kölliker, “the cytoplasm [of the fat cell] is reduced to a thin layer surrounding the nucleus, the remainder of the cell cavity being occupied by a drop of fat” (Kölliker 1868, 31), this layer being only “traces of the cytoplasm” (Kölliker 1868, 34). This suggests that Kölliker was not sensitive to the arrangement of the thin protoplasmic layers he regarded as secondary residues of the primordial cells involved in the formation of specialized cells.

In Ranvier’s view, Kölliker overlooked the thin cytoplasmic layer between the fat droplet and the adipocyte membrane. Ironically, Ranvier would revisit the Kölliker

model of the adipocyte, with consequences for his interpretation of Schwann and myelin sheaths. Moreover, Kölliker may not have developed such an interpretation of Schwann sheaths and myelin because his model of the adipocyte was overly simplistic. Even had he noted scattered granulations in the Schwann sheath, Kölliker would have interpreted them as necessarily belonging to the very thin, flat epithelial cells, not to a cellular entity enclosing the myelin. It is thus clear that general conceptions of the arrangement of histological elements interfered with interpreting their structures, and that theoretical concepts influenced what was seen under the microscope.

Ranvier's interpretation of the interannular segment

Ranvier accepted Kölliker's implicit analogy between the adipocyte and the Schwann sheath and myelin. Ranvier tended to deliberately confuse the Schwann and myelin sheaths; he used the term "Schwann membrane" as a specific concept for a membrane that covered the myelin sheath externally, but is also inserted between the axis-cylinder and the myelin, where a thin protoplasmic layer, the Mauthner membrane (now termed "the axolemma"; its existence was still questioned by many authors at this point) was seen. For Ranvier, the Schwann membrane was thus a cell membrane that completely encompassed the myelin of an interannular segment. This interpretation, now essential to the Schwann cell concept, was somewhat speculative at the time, for which reason it was subsequently abandoned until the 1950s.

This interpretation seems to have derived entirely from Ranvier's adoption of the analogy between the hypothetical cell unit of the interannular segment and his own concept of the adipocyte, in which a layer of cytoplasm completely surrounded the lipid inclusion and separated it from the membrane of the adipocyte (Ranvier 1871b). However, Ranvier's use of "Schwann membrane" was not as innovative as it might appear. It can be traced back to Kölliker's concept of the "primitive sheath," which included the myelin sheath. Kölliker indeed wrote,

Within the primitive sheath, which on all nerve tubes includes—apparently on its inner side, but probably actually within its breadth—cell nuclei of oblong shape, we find the nerve marrow (medullary sheath, . . . white matter [myelin] . . .) . . . which forms a cylindrical tube, enveloping the central fiber (Kölliker 1868, 238).

Ranvier offered a broad view of a Schwann membrane that encompassed myelin and possessed a nucleus in each interannular segment. From this position, the continuity between the protoplasmic mass of the Schwann nuclei and the thin layer of protoplasm between the Schwann membrane and myelin suggested that the nucleus belonged to a cell, the membrane of which is the Schwann membrane of the interannular segment. Ranvier concluded, "[I]t follows from these facts that the interannular segment of the nerve tubes is a cell. This is comparable with the fat cell, as I have understood it in a recent communication" (Ranvier 1872, 141ff.; Figure 6).

For Ranvier, the structures of the nerve tube between two annular constrictions constituted a single cellular entity. His concept of the adipocyte induced his research into the protoplasmic continuities that facilitated his elaboration of the concept of the cell of the interannular segment, but Ranvier did not use the term "Schwann cell."

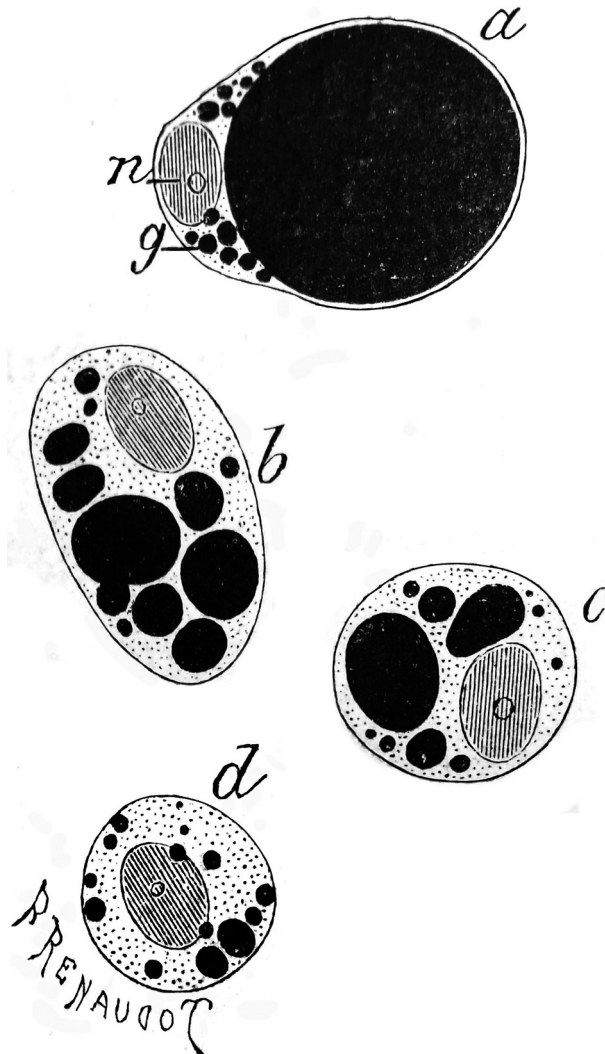


Figure 6. Adipose cells from the subcutaneous conjunctive tissue of an ox embryo of 45 cm, after interstitial injection of osmic acid by Ranvier; a. almost fully developed cell with a large fat globule colored black by osmium; n. nucleus; g. fat granules; b and c. intermediate stages of development; d. adipose cell at the beginning of the formation of fat globules; magnification x500. From Ranvier (1975, 416).

He had used interstitial injections with silver nitrate to show that the adipocyte had three distinct parts: an enveloping membrane, a layer of protoplasm lining the whole deep surface of the membrane and enclosing a lenticular nucleus, and the central fat droplet. He concluded that the droplet is separated from the membrane by a continuous layer of protoplasm. He added that the adipose cell represented, with its nucleus, a flat cell similar to connective tissue cells (Ranvier 1871c, 125). This formulation of his concept of the adipocyte is exactly what he applied to the cell of the interannular segment, retaining Kölliker's concept of a flat cell. But for Ranvier, the protoplasm between the axis-cylinder

and the myelin was part of the flat cell that encompassed the myelin as a protoplasmic inclusion. That is, he saw the large flat cell as a cellular entity extending between two annular constrictions, including the myelin he considered a lipid inclusion.

If we place this perspective of Ranvier in the context of earlier models of the Schwann membrane and myelin for interpreting the structures of the medullary nerve tube, we can better understand the path he took by synthesizing the reasons for his interpretative choices.

Schwann had opened the way to this type of cellular interpretation with his novel explanation of how tubular structures could develop from round primitive cells. For Schwann, the tubes were cells of a secondary type, formed by the union of primary round cells. For the nerve tube, Schwann's nuclei were interpreted as the residua of the primary cells, largely because he had noted that these nuclei were much more numerous during embryogenesis. In reality, Schwann, like Kölliker and even Ranvier, was not always able, at least in the early stages of his studies, to differentiate Schwann nuclei from those of the endoneurium, although Kölliker was eventually able to isolate the primitive Schwann sheath with its own nuclei using specific methods.

Kölliker initially approved Schwann's model, but in his 1850 treatise he explained a change of view after his developmental studies. He now considered the Schwann sheath to consist of flat cells arising from the fusion of round cells. However, his position remained vague: Did the flat cells of the Schwann membrane constitute only the surface layer of the Schwann sheath? Or did these flat cells constitute the Schwann sheath, encompassing the myelin sheath?

Ranvier's response to this question was to regard the Schwann sheath as having an outer membrane (in contact with the endoneurium) and an inner membrane (in contact with the axis-cylinder) that delimited a serous-type space with a role in nutrition. For him, the two membranes joined at the level of the annular constriction to delimit a single cellular entity encompassing the myelin and including a single nucleus between

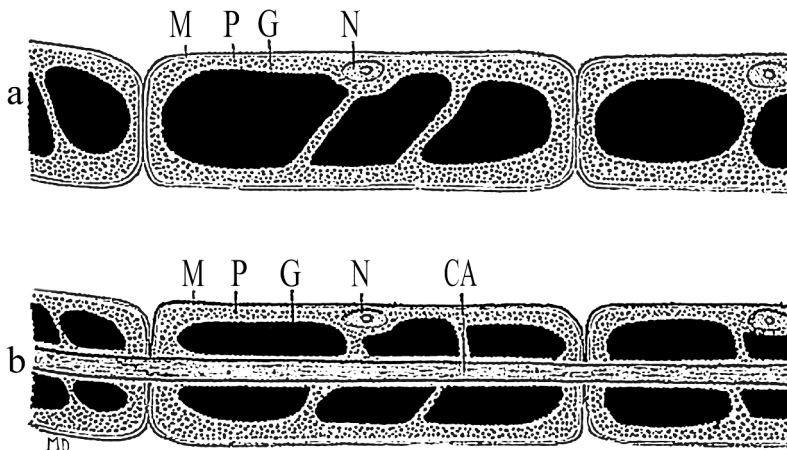


Figure 7. Comparison of the interannular segment of Ranvier with the adipose cell according to Duval. A, three elongated adipose cells positioned end to end. M. cell membrane; P. cytoplasm (protoplasma); G. fat (*graisse*); N. nucleus. B. three interannular segments. M. Schwann sheath (cell membrane of the Schwann cell); P. cytoplasm (protoplasma); G. fat (*graisse*); N. nucleus; CA. axis-cylinder. From Duval (1900, 817).

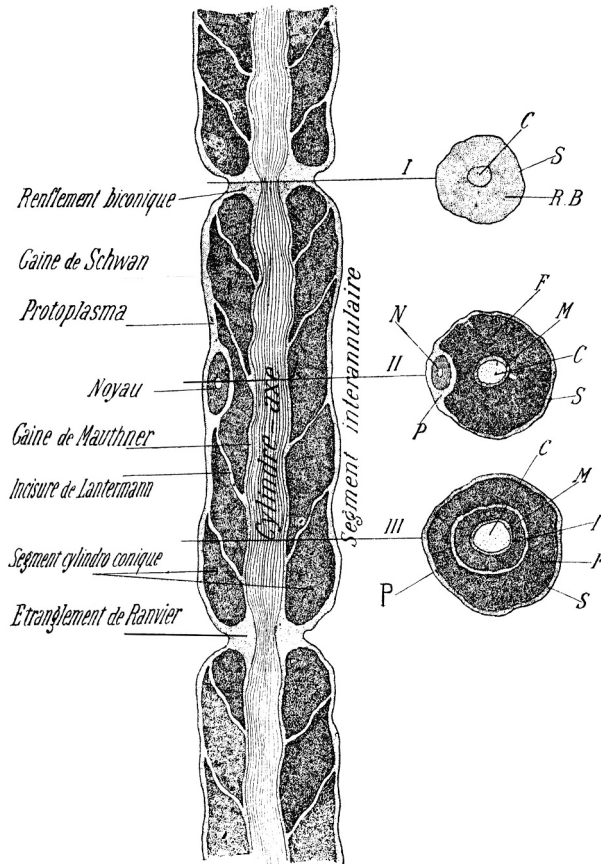


Figure 8. Ranvier's model of the myelinated peripheral nerve fiber with interannular cells (Schwann cells). *Gaine de Schwann*, Schwann sheath; *renflement biconique*, biconic dwellings of Ranvier; *Noyau*, nucleus; *Gaine de Mauthner*, Mauthner sheath; *Incisure de Lantermann*, Lanterman incisure; *Segment cylindro-conique*, cylindro-conic segment; *Étranglement de Ranvier*, Ranvier's constriction. Three sections are shown at three levels of the nerve fiber. I. upper section, at the level of the constriction. II. middle section at the level of the Schwann cell nucleus. III. bottom section of a region of the Schwann cell near the constriction at the level of a Lanterman incisure. C. axis cylinder; S. Schwann cell membrane; R.B. biconic swelling; M. cytoplasm strip (Mauthner sheath); F. bands of Frommann (?; not explained in the original); N. Schwann cell nucleus; P. peripheric cytoplasm strip. I. Lanterman incisure. From Berdal (1899, 247). Berdal presents this model as incorrect, in keeping with the concepts of Nageotte and his contemporaries (Berdal 1899, 246). For the same reason, Berdal depicts the cytoplasm of the Schwann cells as continuous, contrary to the model of Ranvier with adjacent but distinct cell units.

two constrictions. The argument of cytoplasmic continuity between the cytoplasm around the Schwann nuclei, on the one hand, and the cytoplasm between the Schwann sheath and the myelin, on the other, established the continuity of the cell of the interannular segment and made it possible to propose an analogy with Ranvier's concept of the adipocyte (Figure 7). In this way, one can better appreciate the importance of Ranvier's work on annular constrictions, considered as elementary vertical distinctions, that led him to conceive the Schwann cell as a specific cell of the interannular segment.

In his 1875 *Traité technique d'histologie*, Ranvier again discussed his concept of the interannular segment as an adipocyte-like cell (Ranvier 1875, 775), because new information seemed to confirm his intuition. Indeed, Charles Rouget (1875) and Hector Leboucq (1876) had described, in the tadpole tail, the progressive formation of myelin in the protoplasm of annular segments by the conjoining of fatty granules, in a manner similar to that which Ranvier had described in the adipose cell (Ranvier 1875, 414–418, 775).

Ranvier then defined his concept of the interannular segment cell more precisely, in the context of theories of nerve tube growth during development. He noted that German physiologist Theodor Engelmann (1843–1909) had adopted his concept of an interannular cell entity, but with the aim of defending Schwann's developmental theory in which nerve fibers are formed by cells placed end-to-end—that is, Engelmann argued that Ranvier's interannular cells showed that nerve fibers are formed from chains of cells. To counter this model, Ranvier argued that the interannular segments could not be the progenitors of the nerve fiber because “the interannular segments indeed correspond to cells, but to cells that are merely added to the nerve fiber itself. . . . These cells surround the axis-cylinder, which passes through them without being part of it, as a thread would pass through a string of beads” (Ranvier 1881, 27). Ranvier had previously presented his model in this way: “Picture an elongated adipose cell, filled with this particular fat we call myelin, and crossed by a body foreign to it, the axis-cylinder: we have the interannular segment” (Ranvier 1878, 119).

In the same lesson, Ranvier drew theoretical consequences from his interannular segment model. First, he adopted a new terminology according to which the interannular segment would have a genuine “histological individuality” (Ranvier 1878, 112), the “morphological significance” and functions of which were yet to be understood. He again specified the role of the analogy with the adipocyte in forging this concept, reflecting the analogical mode of rationalization common among histologists of his time. But his particular rationality is in this case imbued with obviously Bernardian perspectives. For example, Ranvier insisted that a general synthetic capacity, in this case the production of fat, could not be specific to a certain cell type (Ranvier 1878, 112), in keeping with Claude Bernard's ideas about several cell types having glycogenic capacity. Ranvier deduced that the interannular segment could be considered a particular “connective cell” that synthesizes its own fatty material. Ranvier also insisted on the chemical diversity of the fats of different cell types, suggesting, in agreement with Claude Bernard, that the function of a cell type is defined more by its biochemical composition than by its morphological character, as shown by the case of the alpha and beta cells of the pancreas.

Finally, without reference to Claude Bernard, Ranvier drew on the consequences of the analogy between the annular segment and the adipocyte to interpret the Mauthner sheath as a protoplasmic layer of the interannular segment against the axis-cylinder, which explained the picrocarminate staining pattern on transverse sections:

It is therefore easy to understand why the axis-cylinder, studied in transverse sections stained with carmine, has a colorless peripheral part. This corona, to which, as we have seen, Mauthner drew attention, obviously corresponds to the reflected part of the protoplasmic lamina, the remnant of the protoplasm originating in the cell. (Ranvier 1878, 120)

In this case, Ranvier adopted Kölliker's position on thin layers of protoplasm as remnants of primary cells because he saw no particular function for this layer. He also interpreted

Schmidt's incisures in myelinated fibers as interlocking protoplasmic layers, similar to that of the large lipid inclusion in adipocytes (Ranvier 1878, 120).

Finally, Ranvier's work on the degeneration and regeneration of nerve fibers after sectioning, which followed his work on the structure of the myelin fiber in the same collection of lessons, built on new anatomic information while reinforcing the concept of the interannular segment cell and its role in nerve regeneration (Barbara 2022). In particular, his observations of the re-myelination process in the distal stump and the establishment of new interannular segments, with a different interannular distance from the original, reinforced the idea that the interannular segment is established by new connective cells produced by cell division that surround the axis-cylinder and form the myelin sheath. This process confirmed Ranvier's model in which the myelin sheath is established by the apposition of connective cells at regular spaces along the nerve fiber (Figure 8).

After Ranvier: From William Vignal and Jean Nageotte to electron microscopy

Ranvier's concept of the interannular segment cell was widely accepted in France soon after its publication, and was then expanded with the concept of the "Vignal cell," named for William Vignal, a student of Ranvier, and disseminated by French anatomist Matthias Duval (1884–1907) in his textbooks. In 1874, the French translation of the *Compendium der Physiologie des Menschen* by German physiologist Julius Budge (1811–1888) incorporated large excerpts from Ranvier's articles on the interannular cell, although Ranvier was not cited in the German edition. German cytologist Theodor Boveri (1862–1915) supported a concept close to Ranvier's by recognizing that two protoplasmic layers on either side of myelin belonged to the same cellular entity (Boveri 1885). Boveri was opposed to the idea of a connective cell pierced by the axon, but this description by Ranvier was more a metaphor intended to convey an idea of the relative location of the nerve fiber and myelin sheath than an actual description of how their apposition arose. During the 1880s, Vignal further clarified Ranvier's concept with his study of a special arrangement discovered by the histologist Joseph Renaut (1844–1917): the short interannular segment.

Renaut's 'short interannular segment' (1881)

In 1881, Renaut published a study on the structure of nerves undertaken in his new histology laboratory in the Lyons medical faculty. He made a surprising observation in degenerating nerve tissue from horses and donkeys: interannular segments that were shorter than others, located amid segments that were larger and more consistent in size.

Renaut was a Paris medical intern and colleague and student of Ranvier; he had worked in Bernard's *Collège de France* histology laboratory in the early 1870s and was a *répétiteur* (tutor) in the laboratory during 1872–1875 (Laios et al. 2014; Renaut 1887). Appointed professor of general anatomy in Lyons in 1877, a year after Ranvier received a similar chair in Paris, Renaut founded his own school of histology in a new laboratory.

While Renaut had made a name for himself in Paris for his work in pathological anatomy, his 1881 study of "certain features of the histology of nerves" was a work of comparative anatomy in the horse and the donkey (Renaut 1881, 162ff.), conducted in collaboration with his colleagues from the veterinary school of Lyons, Auguste Chauveau

(1827–1917) and Saturnin Arloing (1846–1911; see Renaut 1881, 163, note 2). Renaut argued that the study of “the constitution of the nerve cords in a series of similar organisms” made it possible to examine variations in detail that facilitated recognition of the morphological significance of certain parts and to discover new arrangements (Renaut 1881, 162).

While studying degenerating nerve nets in mixed nerves of old horses and donkeys, Renaut discovered a new arrangement that he termed “short intercalary segments” (Renaut 1881, 175, note 1), the presence of which was an exception to Ranvier’s supposition that nodes were located at regular intervals along a nerve fiber:

A large myelin tube is formed by successive interannular segments of equal length and diameter. At the level of a constriction, an interannular segment of infinitely lesser diameter and length than the preceding one arises. The myelin sheath of this segment is thin. . . . The short segment measures one-half, one-third, one-quarter, even one-fifth of the preceding ones; it has a nucleus in its exact middle. Rarely, it is followed by a small and short segment similar to it; most often, the nerve tube beyond it resumes its previous dimensions: the interannular segments then return to their length and width. (Renaut 1887, 77)

Renaut interpreted this new arrangement as reflecting a developmental mechanism for elongation of the nerve fibers “in their continuity” (Renaut 1881, 78, 174–175), during which small spaces arise through stretching of the nerve fiber during growth. These spaces are then colonized by small cells that become the short interannular cells. According to Renaut, nerve fibers elongate along their course, and not only at their free end, and are myelinated in a process involving a new connective cell that is inserted between two interannular segments, the short intercalary segments.

The dynamic nature of the establishment of intercalary segments was confirmed in the twentieth century, notably by the *in vivo* microscopy studies of American anatomist Carl Caskey Speidel (1923–1964). Speidel observed an interannular segment degenerating and being replaced by a new one (Speidel 1964), consistent with the observations of Renaut. But as early as the 1880s, observations of short intercalary segments suggested that they were cells with dynamic properties that could regularly appose themselves along the axis-cylinder or interpose themselves between other segments during development and regeneration.

William Vignal after the work of Joseph Renaut

The dynamic nature of intercalary segments was discussed during the 1880s. It was therefore quite natural that William Vignal, then a medical student in Paris and student of Ranvier, sought to identify short intercalary segments in embryos while investigating the development of nerve tubes.

Vignal was a *répétiteur* in the Collège de France histology laboratory after the departure of Renaut in 1876 (Laboratoire d’histologie au Collège de France 1876). His scientific and political career is representative of a generation of young French scientists who did not hesitate to turn to German science after defeat in the Franco–Prussian War, believing that the loss reflected the scientific superiority of Prussia. Vignal had interrupted his studies to join the army and was wounded and imprisoned, but immediately after the war he went to Bonn to study with Max Schultze.

Vignal was familiar with the work of Renaut, whom he met at the *Société de Biologie*; he had also worked with one of his students, Auguste Rigal (1839–1915). It was in this context

that Vignal became interested in the short intercalary segments, that he indeed identified in embryos (Vignal 1883a), inspiring his hypothesis regarding the elongation of intercalary segments during embryonic development (Vignal 1883b). For Vignal, Ranvier's theory that nerves grow by elongation of each intercalary segment was quantitatively insufficient to explain nerve growth during development. Rather, elongation of the interannular interval must be accompanied by another mechanism, such as the addition of intercalary segments.

Vignal was aware that Renault regarded the role of the interannular segments as replacing degenerated segments, a role later confirmed by Speidel (1964). But degeneration of interannular segments was very rare. Consequently, Vignal believed that intercalary segments were also important as the origin of the new interannular segments that appeared during embryonic development (Vignal 1883b, 545).

To understand this mechanism, one must know, as Speidel (1964) later reported, that a nerve fiber can sometimes sprout a collateral at the level of a Ranvier node, with a small local elongation of the main part of the fiber where a new short intercalary segment establishes itself. Vignal could not visualize the process as sharply as it was observed *in vivo* by Speidel, but he could nevertheless imagine that a connective cell could first position itself at the level of a node and locally induce growth of the axis-cylinder, allowing intercalation of a new short interannular segment.

We can thus understand how Vignal imagined a connective cell as the origin of a very dynamic intercalary segment, later called the "Vignal cell" by Mathias Duval. The Vignal cell was, however, only one aspect of Vignal's broader concept of "embryonic connective cells that penetrate nerve fiber bundles and proliferate until they come into contact with the axis-cylinders to form a "special envelope by surrounding them and fusing with them" (Vignal 1883b, 532); about four months later, myelin appears in thin blades or balls and invades almost the entire length of the interannular segment.

Criticism of the Ranvier model by Jean Nageotte, and its disappearance

The Vignal cell concept was best established in France, with the support of Matthias Duval. Some other histologists also adopted the model, including Kölliker (1886), Wlassak (1898), and Ariëns Kappers (1903), but the dominant view remained that the myelin sheath was formed by the axis-cylinder itself (for an overview, see Foley *in press*). One argument was the apparent absence of satellite cells in myelinated central fibers, which led Kölliker to reject Ranvier's adipocyte analogy (Kölliker 1896). Nevertheless, Kölliker retained a Schwann cell model as an anatomic and physiological entity that included the myelin sheath and contained the axis-cylinder (Kölliker 1886, 33), and he upheld Vignal's view that the Vignal cell participates in the formation of the myelin sheath (Kölliker 1886).

The hypothesis that the axis-cylinder secretes myelin gradually gained ground during the first half of the twentieth century (Foley *in press*). Even Jean Nageotte, initially sympathetic to the views of Ranvier and Vignal, became firmly opposed to their model: "[T]he model of Ranvier, which compares the interannular space to an adipose cell crossed by the axis-cylinder, should no longer be accepted, because it does not correspond to the reality of the facts" (Nageotte 1911b, 10; Berdal 1899, 246). For Nageotte, myelin was not a simple fatty substance but a complex structure, a "living protoplasm" with trabeculae continuous with the axis-cylinder, structures that in the following decades would become the important themes for investigations of "living myelin" (*myéline vivante*) with auto-organizational

properties revealed by the *in vitro* self-organization of artificial lipid mixtures reported by Nageotte.

Nageotte was inspired by the model of nerve fibers of Russian histologist Anton Vitalievich Nemiloff (1879–1942), based on methylene blue staining, according to which Schwann cells with a nucleus were flat cellular entities distinct from the Schwann membrane, which he termed the “medullary membrane” (Foley *in press*). From this point, myelin was viewed as having a complex structure with lamellae and an endoskeleton in which the cellular extensions of the Schwann cells participated. At the beginning of the twentieth century, the molecular orientation of the structural study of myelinated fiber cytology focused on subcellular structures and their biophysical and biochemical characterization, leading to increasingly complex models of myelin structure and formation, encouraged by developments in spectrography, polarimetry, and electron microscopy. Studies using these techniques greatly complicated concepts of the molecular scheme of myelin organization (e.g., Schmitt, Bear, and Palmer 1941), even though the central idea of the model generally adopted was in conformity with that of Vignal—that is, an arrangement based on the lamellar association of a lipid body and proteins. The critical point of the new ideas concerned the nature of the relationship between myelin and the Schwann cell.

These biophysical studies indicated that the myelin sheath possessed such a complex molecular organization that it must be attached to the axon, with which it appeared to be continuous, both morphologically and functionally. In fact, the first electron microscopy studies concluded that no cell membrane separated the axon from the inner surface of the myelin sheath (Fernández-Morán 1950; Rozsa et al. 1950). As a result, the “Schwann cell” was reduced until the early 1950s to a thin cytoplasmic layer external to the myelin sheath; myelin lay outside the Schwann cell, consistent with Schmitt’s polarimetry data from the 1930s (Foley *in press*), a concept identical to that which dominated at the beginning of the twentieth century.

It was only gradually that doubts grew about these views. Studies of the myelination process in embryonic peripheral fibers facilitated a return to ideas closer to those of Ranvier and Vignal, without naming them, and some aspects of their model with respect to the relationship between axons and Schwann cells were rediscovered, but the Ranvier–Vignal model itself seemed forgotten.

Electron microscopy revives the Ranvier–Vignal model of the Schwann cell

The contribution of electron microscopy to clarifying the Schwann cell concept was primarily made in the United States, but its analysis owed a debt to the research of Ranvier and Nageotte in recognizing the nature of the relationship between the Schwann cell, myelin, and the axon.

The electron microscopy work of Betty ben Geren, working with Francis O. Schmitt at the Massachusetts Institute of Technology biology department, established that the Schwann cell wrapping around the axon underlay the myelination process (Ben Geren 1954). Ben Geren later described how this interpretation was aided by the mesaxon concept of Herbert Gasser (Boullerne 2016).

This concept, not always well understood, had a definite link with the work of Ranvier and Nageotte on unmyelinated nerve fibers. In order to understand this relationship, we must consider its origin. Nobel Prize winner and former director of the Rockefeller Institute

for Medical Research in New York, Gasser (1888–1963) had chosen to resume, after his retirement, his earlier research into the structure–function relationships of C-type amyelinated fibers of the dorsal roots of the spinal cord. His aim was to understand the mechanism of their slow conduction through anatomic analysis of their axons. Technical problems had previously hindered him accurately quantifying the diameter of these axons by light microscopy using silver nitrate staining. The Rockefeller Institute had in the meantime acquired an electron microscope, moving Gasser to take up the question again. At the 1952 Cold Spring Harbor Laboratory symposium on *The Neuron*, he delivered his preliminary findings in the discussion that followed the presentation by Finnish–Swedish physiologist Bernhard Frankenhaeuser on saltatory nerve conduction (Gasser 1952). Gasser described his electron microscopy micrographs and drew attention to the structure of the amyelinated fibers in accordance with Ranvier’s earlier descriptions of the Remak fibers and in agreement with the work that led Nageotte to his concept of the compound amyelinated fiber. Ranvier had undertaken detailed studies of Remak fibers, developing ideas that diverged from the views of Kölliker (Ranvier 1875, 747) and Henle (Ranvier 1875, 748). Ranvier concluded that the Remak fiber was compound in nature—that is, it included multiple axons:

Whatever nerve is considered, the islands corresponding to the fibers of Remak appear in transverse sections to be formed by a very large number of small circles of approximately equal diameter, colored red, and arranged one next to the other. These circles do not correspond to the Remak fibers themselves, but to the fibrils that constitute them. (Ranvier 1875, 751)

In 1911, during the debate between the neuronists and reticularists about the nature of central nervous system nerve cells, Jean Nageotte himself had defended Ranvier’s position against general opposition to it. Nageotte came to this view during his studies on nerve degeneration. He had developed a new technique for staining degenerated fibers that he found useful for examining Remak fibers. He concluded that his histological observations were in complete agreement with “the hypothesis of Ranvier”:

Following the example of Ranvier, I have called Remak’s fiber a *complexus*, containing a multitude of neurites, the fiber of Remak, and I believe that this expression is correct because it is aimed at a morphologic unit that would be imperfectly designated by any other name. But it is necessary, in order to avoid any ambiguity, to give a definition of this unit. What is a *nerve fiber*? In the central nervous system, the nerve fiber is identical with the neurite, which is naked. In peripheral nerves, it is not the same; the nerve fiber, an element that can be isolated by dissociation and which possesses an indisputable anatomic and pathological individuality, is made of: 1° a properly nervous part; 2° a protoplasmic sheath which, as we know, is of ectodermal origin. The myelinated fiber contains only one neurite, it is a simple fiber; the fiber of Remak contains several, it is a *compound fiber*. (Nageotte 1911b, 921)

Nageotte consequently used the term “compound amyelinated fibers” in the title of his article, a concept verified by Gasser using electron microscopy (Gasser 1952). At this stage, Gasser agreed with Ranvier and Nageotte in that he conceived the amyelinated fiber as a fiber with a Schwann membrane including one or more axons, but with at most a single myelin sheet, as this was not visible, in accordance with the opinion expressed by Ranvier (Ranvier 1875, 747–751, 776–777). But Gasser could see in his micrographs that each axon seemed to be connected to the inner edge of the Schwann cell by a kind of ligament of “gossamer fineness.” Gasser initially interpreted this ligament as an invagination of the

inner membrane of the Schwann cell into the lumen of the tube (i.e., of the C-type amyelinated fiber), and therefore proposed that the axons were located inside the cytoplasm of the Schwann cell, floating in it and attached to it by a ligament. His designation for this ligament, the mesaxon, refers to an analogy with the mesentery (Chase and Hunt 1995, 166; Foley *in press*).

However, the relationship between the concepts of mesentery and mesaxon is not unambiguous. First, in order to interpret the ligament he had seen, Gasser used the same analogy as Ranvier had made between the Schwann cell membrane and a serous membrane with parietal and visceral layers. This analogy is the key to the “mesaxon” concept, as the mesaxon is analogous with the sections of the dorsal mesentery that attach cavity organs such as the colon (mesocolon) and stomach (mesogastrum) to the abdominal wall. However, these organs are not located in the peritoneal cavity (i.e., between the parietal peritoneum and visceral peritoneum), but are enclosed within invaginating sacs, and the peritoneum only covers them (i.e., they are “peritonealised”). This point is important because, according to this analogy, the axons are not inside the Schwann cell but, instead, surrounded by a closed sac—that is, by the Schwann cell. The ambiguity of Gasser’s mesaxon concept lies in the fact that, by considering the axons as cytoplasmic inclusions of the Schwann cells, he did not draw all the consequences of his analogy.

The intracytoplasmic location of the axons became difficult to defend in the context of nerve impulse conduction by C fibers. Contrary to Ben Geren and Schmitt (1954), who proposed a model accepting Gasser’s intracytoplasmic axons, Gasser finally understood that the axons were outside the Schwann cell, just as the colon (attached to the mesocolon) and the stomach (attached to the mesogastrum) were outside the peritoneal cavity. To be

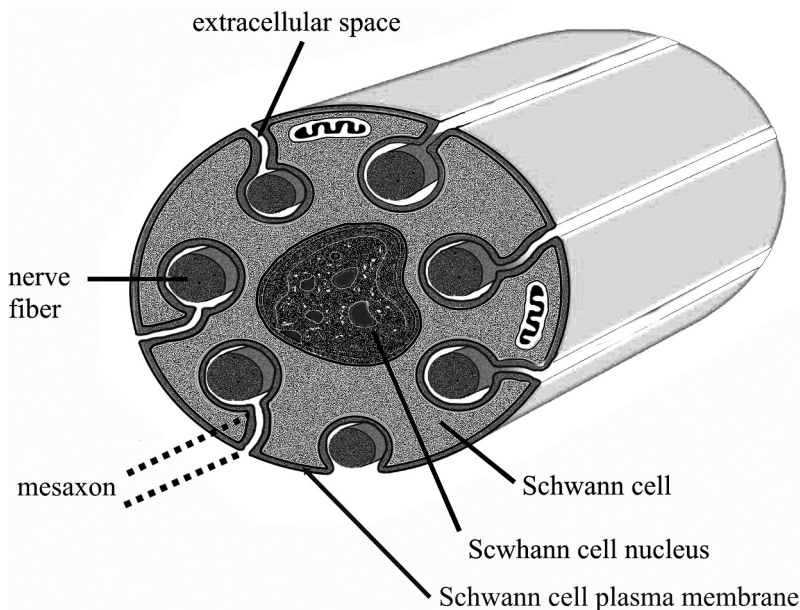


Figure 9. Structure of the peripheral amyelinated fiber. A Schwann cell wraps several nerve fibers in contact with the extracellular space. The mesaxon is the small linear invagination of the Schwann cell membrane connecting each fiber to the extracellular space.

consistent with the electrophysiological data and allow the ionic gradients needed for conduction, the axons could only be immersed in an extracellular medium inside the tube constituted by the Schwann cells. Gasser concluded, “The axon is *not* in the Schwann cell. It is *outside*. The outer surface of the axon plasma membrane is turned toward the outer surface of the Schwann plasma membrane, as infolded” (Gasser 1955, 714; italics in original; Figure 9).

Gasser may have corrected his interpretation of the mesaxon by considering the dynamic model of Schwann cell-winding around the axon that Ben Geren proposed in 1954 (Ben Geren 1954). Ben Geren was interested in myelin formation at the beginning of the 1950s, and found that the myelin sheath formed by the addition of successive lamellae (Ben Geren and Raskind 1953). However, she noted in embryonic nerve fibers a special arrangement of the Schwann cell in relation to the nerve fibers that was close to the concepts of Vignal and Ranvier:

The Schwann cells in the early (14-day) embryonic nerve trunk are extremely large compared to the size of the individual myelinating fibers which appear as large Schwann cell cytoplasmic inclusions. This is in marked contrast to the satellite type of appearance of the Schwann cell around the adult nerve fiber. . . . The forming myelin consists of concentric lamellar structures arranged as a sheath around the axon as it courses in the cytoplasm of the Schwann cell. (Ben Geren and Raskind 1953, 882–884)

Ben Geren continued her study with Gasser’s concept of the mesaxon in mind. She later described how one night, at two o’clock in the morning, she finally saw the mesaxons of Gasser in her electron microscopy images. From that moment on, she understood that the mesaxon corresponded to the initial position of the Schwann membrane before it rolled up. She realized that the pictures were explained by different degrees of winding and depicted the same process, the same cellular dynamics of the Schwann cell wrapping around the axon. This cellular mechanism shared the dynamic property of the Ranvier–Vignal concept of a cell enclasping one or several axons.

The electron microscopy investigation of the Schwann cell naturally owes little to the nineteenth century, but epistemological threads connect the two eras, highlighting the long-term value of the work of Ranvier and his school on the Schwann cell concept, parallel with our epistemological analyses of its genesis and complexity.

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