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REVIEW ARTICLE

The early history of the synapse: From Plato to Sherrington

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ABSTRACT: One hundred years ago, in 1897, Sherrington adopted the name *synapse*. However, the concept of the synapse emerged from considerations of how muscles are contracted and so locomotion affected over a period of 2400 years, from the time of Plato and Aristotle in the 4th century BC to the early part of the 20th century. This early history is considered in the present review. In terms of duration of influence, the early history was dominated by Aristotle's concept of *vital pneuma*. This was derived from the ether which filled all space, taken in by the lungs, transformed to vital pneuma in the heart, and then conducted in the blood stream to be transmitted to muscles. The vital pneuma then initiated the final phase of the muscle's *psyche*, that is, its contraction leading to locomotion. Aristotle's ideas had to be modified with the discovery by Galen and his students in the 2nd and 3rd centuries AD that nerves arising from the brain and spinal cord are necessary for the initiation of muscle contraction. They modified the Aristotlean account so that the vital pneuma delivered by blood vessels to the brain was converted there to *psychic pneuma*, from whence it was conducted along nerves to be transmitted to muscle, so allowing the muscle to contract. There matters rested for about 1300 years until Descartes. Descartes rejected the idea of organs and muscles possessing a psyche with a final cause that was released by the conduction and transmission of psychic pneuma in nerves, emphasising that mechanical explanations must be sought when determining the function of an organ or muscle. He argued in his corpuscular theory that fine particles derived from the blood in the brain, which he gave the unfortunate name of *animal spirits*, were conducted and transmitted along nerves to enter muscle during transmission, so leading to the increase in width of the muscle fibres, their shortening and contraction. This description was elaborated on in great detail by Descartes, and by his contemporary Borelli, in the 17th century. In the 18th century, Swammerdam carried out a series of brilliant experiments that showed that the Descartes/Borelli theory could not be correct, muscles did not change their volume during contraction, and so could not be contracted by being swollen due to an influx of the corpuscles that made up the animal spirits. These results were published at about the time of the birth of Galvani (1737), whose work was to show that animal spirits were not corpuscular but electrical. The triumph of 19th century physiology, primarily due to Matteucci, du Bois-Reymond and Helmholtz , was to take Galvani's discoveries and show that nerves possessed a potential across their walls that could give rise to a propagating transient potential change which was transmitted to muscles with a finite velocity. Although Sherrington refined the concept and adopted the word "synapse" at the end of that century, it was not until the early part of the 20th century that a conceptual scheme for the synapse involving transmitters and receptors was developed. This clearly delineated a new period following the early history of synaptic transmission.   © 1999 Elsevier Science Inc.

In the beginning there were four elements, fire, air, water and earth. Various proportions of these composed the blood, muscle, bone, tendons and nerves from which the body or soma was constructed. The ingredients of the blood determined intelligence so that the heart was the basis of the intellect and of mental life. This pre-Socratic idea of the 5th century BC, principally due to Empedocles, was developed further by Democritus who considered that each of the four elements was composed of a different kind of particle. He argued that the psyche or soul was composed of the lightest, fastest moving and most nearly spherical particles which are to be found throughout the body, especially concentrated in the brain. Particles of a lesser quality were to be found in the heart, giving it a role in emotion whilst the most coarse particles were located in the liver, responsible for functions such as lust. Plato, in the 4th century BC, assigned specific geometrical shapes to each of the four kinds of particles. In addition he confronted the problem which these pre-Socratic ideas presented of how to relate the psyche to the body. A living thing for Plato was matter properly arranged to permit effectual intervention of the soul. Following Democritus, he claimed that there were three different kinds of psyche, namely that concerned with rational thought and behaviour which was associated with the head, that involved with passion and the emotions associated with the breast and the heart therein, and that concerned with desires which was associated with the liver. Only the rational psyche was immortal [34,53,105].

The problem of what form the association between soul and body took was formulated in terms of the geometrical principles that played such a large role in Plato's cosmology [20]. As he considered the fundamental units of the elements themselves to be geometrical figures, such as the triangle, so the body composed of these elements must ultimately be thought of in mathematical
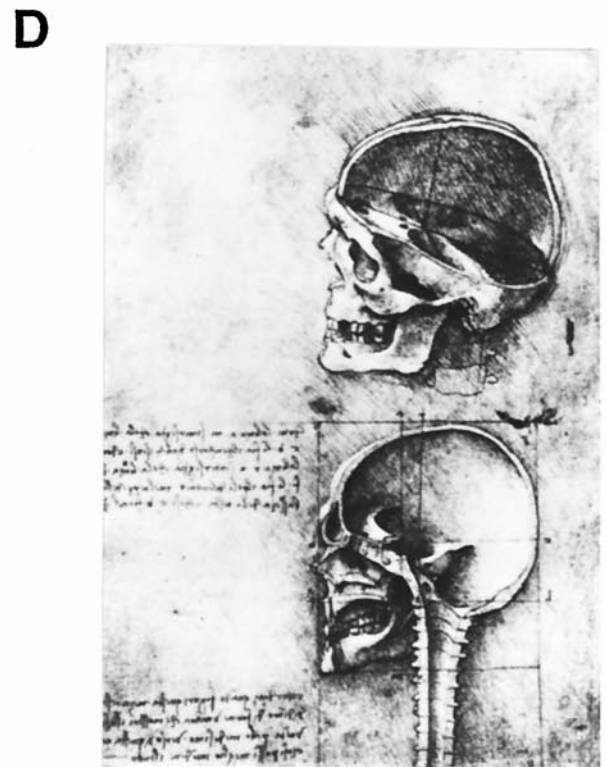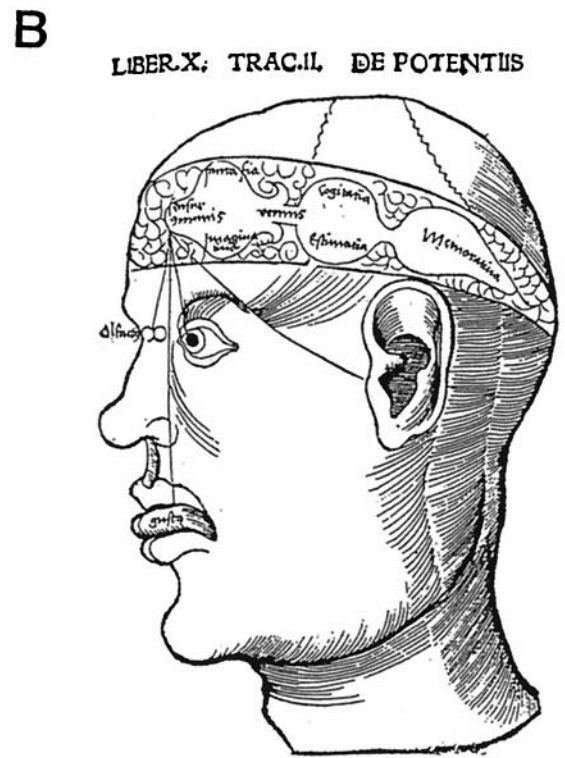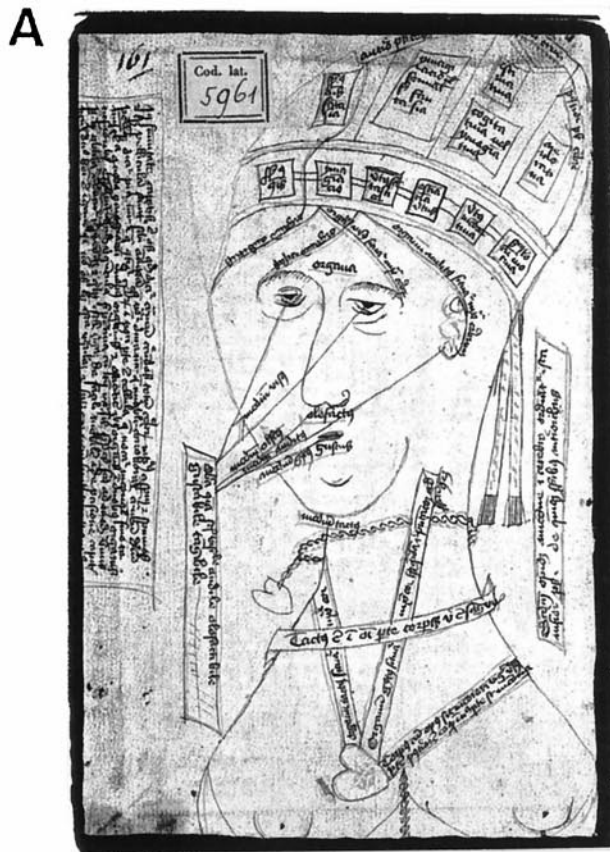
FIG. 1. Theories of the nervous system before Descartes: conduction and transmission of psychic pneuma. (A) This anonymous 15th-century drawing illustrates pre-Cartesian brain theories, which followed the views of Aristotle. The senses of touch and taste are shown connected to the heart, while the

terms. It was the appropriate organisation of these geometrical figures from which the body was ultimately composed that allowed the bonding of the soul to the body. It was only through such bonding that the soul-body complex could manifest life-as-action. Plato placed this bonding in what is now called the nervous system. In his "Timaeus" he describes the soul as bonded to a substance that is found in its purest form in the cranial and spinal cavities where it appears as "marrow", or what is now called brain and spinal cord. The marrow is the primary life stuff in which "were fastened the bonds of life by which the soul is bound to the body". This marrow is not composed of the four elements, or rather of the elementary geometrical figures which make up the elements, but of specially well-formed examples of those triangles which are the common components of these elements [54].

Thus Plato, following Pythagoras, developed the notion of the body as a temporary receptacle for a separate soul, which was associated with rationality, located in the marrow or nervous system, and which could pass from one body into another at death. The other kinds of soul, those associated with the emotions and desires and therefore with the heart and liver, were not capable of this transmigration. Physiological function of an organ was considered in terms of the associated psyche or soul giving life to the propensity of the organ to carry out its function. In this way, organs came to be seen as possessing faculties or propensities to carry out a physiological act that was energised by the psyche [85].

Aristotle, in the 4th century BC, developed radically different concepts concerning the functions of the body and soul that were to have a profound influence on physiological thought concerning the activation of organs and of muscle for 2000 years (see [1–3]; Fig. 1). The Aristotlean concept of the soul will be considered in some detail here as Aristotle's ideas are so different from those of Descartes, which embody a dualism like that of Plato which still dominates thinking on these issues to this day [21,33].

For Aristotle the soul or psuche or psyche was the form of the thing under consideration. This form constituted the reason for a thing being as it is and could be considered as providing explanations for what it is made of (the material cause), what actually makes it (the efficient cause), what shape is used to identify it (the formal cause) and the ultimate reason for its existence (the final cause). Thus in the case of a muscle, the material cause is the fibres that it is made of, the efficient cause is the grouping of the fibres in relation to each other, the formal cause is that this grouping is done to a particular design in order to produce a muscle of a particular shape and the final cause is the fulfilment of the purpose of the muscle, which is to contract and produce, say, the movement of a limb. In this way an organ's form or psyche is not material but is inherent in the organ and cannot exist separate from the organ. If then the constituents which make up the form are specified, so is the soul or psyche. In this way Aristotle lays stress on the activities of living things and on the distinction between "living" and 'dead' rather than in the distinction emphasised by Plato

between 'mental' and 'physical'. 'Mind' does not figure largely in Aristotle's work, perhaps because of his emphasis on the psyche, that is on the activities of living things such as organs. If the psyche disappears from an organ it then ceases to be such a thing except in name only. The loss of psyche, of the soul of a living thing, means it ceases to exist [54].

The concept of the psyche of an organ was not abandoned until Descartes. Meantime, the effect of Aristotle's ideas was to lead to the search for the form of an organ so that scholars sought to identify the psyche of an organ [19]. This had two effects: first, it lead enquiry away from the mechanical workings of the organ; second, it placed emphasis on the final cause component of the psyche, that is the potential of an organ to carry out its function, of how the potentiality of the psyche of an organ could be realised, a problem which will now be considered.

For Aristotle the heart was the central organ of perception, rather than the brain, as postulated by Plato. If an animal's perception gives rise to action, that is to the contraction of muscle leading, for example, to locomotion, it will occur as follows [33]: '. . . *if the region of the origin (i.e. the heart) is altered through perception and thus changes, the adjacent parts change with it and they too are extended or contracted, and in this way the movement of the animal necessarily follows*'. According to Aristotle, perception occurs in the heart with its particular psyche (Fig. 1A). Perception is not an activity that involves two different substances, as later suggested by Descartes, for the affections of the psyche are common to the psyche of the body. '*It is apparent that all the affections of the psyche are with the body . . . in all these the body undergoes some affection*'.

The central sense organ is therefore the heart, which is connected to the individual sense organs (Figs. 1A and 1C). When these are affected by their objects, the affections pass through the blood stream to the heart. Thus the movements around the heart bring about the movements of the limbs by acting through the blood stream. An organ ceases to be an organ if separated from the body, as its psyche no longer exists. It is only as a consequence of being part of the body that its psyche is intact, which includes the final cause or ultimate reason for the organs existence. Given that the heart is the centre of perception and of the appetites and responds to these by initiating animal motion it is responsible for the activation of the muscular organs. The key question which now arises is how does the psyche of the heart conduct and transmit through the blood stream, information to the psyche of the muscular organs which is responsible for their final cause, that is contraction.

The emphasis of Aristotle on the natural world rather than the Platonic mathematical world led him to consider the most likely method for conduction and transmission from the heart to a muscle through the blood stream in terms of the elements. To the organs whose substance was made up of the four elements (fire, air, water and earth) he introduced a fifth element. This

boxes on the head are the "cerebral cells" where mental faculties such as memory and fantasy are located. Anonymous, 15th Century, Bayerische StaatsbibliotheK. Munich (From [86]). (B) A 15th century illustration due to Gregor Reisch, showing the four routes of communication connecting the organs of taste, smell, seeing and hearing to the anterior cerebral ventricle. This is divided into sensus communis, fantasia and imaginativa. The vermis connects it to the second ventricle, with the two faculties called cogitativa and estimativa, whereas the faculty spoken of as memorativa is in the third. The curving lines around the ventricles can be interpreted as representations of the brain's convolutions (from Biblioteca Nazionale Centrale, Florence. See also Corsi, 1991; The Enchanted Loom). (C) In the 4th century AD and for several hundred years to follow, the faculties of the mind were thought to be housed in four ventricles of the brain as in (B). A 15th century illustration, with indistinct lettering, designed to illustrate the 1494 edition of Aristotle's de Anima. Four regions of the brain are labelled: sensus communis, virtus cogitativa, virtus imaginativa, and memoria (Courtesy of the Incunabula Collection at the National Library of Medicine, Bethesda; From [14]). (D) Leonardo da Vinci's localization of the sensus communis. In the lower left of the figure his own words state: "Where the line a-m is intersected by the line c-b there the meeting place of all the senses (senso commune) is made". (Courtesy of the Royal Library at Windsor Castle; From [14]).

element was not restricted to this world only but also belonged to the stars and heavens, so that it permeated the entire universe: he named it the 'ether'. The concept of the ether was to have a major impact on both the physical as well as the biological sciences. Aristotle considered that the ether element was taken into the body during breathing and conveyed from the lungs to the heart in which it was transformed to 'vital pneuma' or 'vital heat' [83]. This vital pneuma was then distributed from the heart throughout the body by blood vessels, where it was able to mediate between the psyche of the heart and the psyche of the organs including muscles. It is then vital pneuma that is conducted from the heart along the blood vessels to be transmitted to the muscles and in so doing initiating their final cause, contraction [54]. Aristotle had in one brilliant stroke introduced a means for mediating between the psyche of the heart and the psyche of muscles by introducing a fifth element that was not just of this world but seemed to possess a heavenly property associated with the stars. But the great contribution here is the introduction of the concept of a substance of a kind, be it of somewhat mysterious qualities, which had to be conducted to an organ to allow it to function, even though this function was taken to be simply the ability of the organ to release its propensities to action as dictated by the final cause of its psyche.

GALEN: PNEUMA IS CONDUCTED AND TRANSMITTED FROM NERVE TO MUSCLE

Galen and his students, in the 2nd and 3rd centuries AD, greatly refined the concept of the conduction of pneuma to the organs of the body [see 42–44]. They retained Aristotle's conceptual scheme with the four elements constituting the tissues and organs of the body, and a fifth composing the vital pneuma acting as a mediator for the psyche to give life to the organ and allowing it to release its propensities for action. Erasistratus argued that the pneuma of the inspired air became vital pneuma as it passed from the bronchioles of the lungs via the intrapulmonary veins to the pulmonary vein and into the heart. The heart on dilation sucked in the pneuma from the pulmonary vein and on contraction forced the vital pneuma to the rest of the body through the arteries. Blood is carried by veins not arteries. The vital pneuma which reaches the brain in this way is converted to 'psychic pneuma' there *from which it travels outwards along nerves* [41]. The brain, rather than the heart, becomes once more the centre of perception in this scheme. Galen had already established that nerves arise from the brain and spinal cord, that conduction of psychic pneuma is necessary in these nerves for sensation and motor action, for if they are cut or damaged there is no sensation or movement, and that there are two classes of nerves, one motor (if damaged no motor action) and the other sensory (if damaged no sensation). It was therefore established that sensitive psyche possessed its own nerve supply as did the locomotor psyche.

These observations and speculations of Galen and his students set the stage for the consideration of the mechanism of conduction of psychic pneuma along motor nerves and of the transmission of pneuma into muscle. Galen comments '*All muscles require to receive a nerve from the brain or from the spinal cord and this nerve is small to behold but by no means slight in power*'. Three possibilities for the conduction of the effects of psychic pneuma were entertained: one, that the psychic pneuma flows along the nerves like a liquid along a conduit; second, that the psychic pneuma in the brain pushes the pneuma resident in the nerve so that some is released at the ends of the nerves; finally, that there is only a flow of 'potency' through the psychic pneuma that is resident in the nerve. This last is akin to nerve conduction as we

understand it today. However, Galen did not speculate further on which of the three modes of psychic pneuma conduction was most likely to occur. The next problem concerns that of the transmission of the psychic pneuma into the muscle necessary for the muscle psyche, in Aristotle's scheme, to realise its final cause and so contract. All that Galen says on this is that transmission must be such as to allow the psychic pneuma to reinforce and initiate the muscles intrinsic propensity to contract, that is to achieve its final cause. However, he did entertain the possibility that this might occur by the psychic pneuma being pushed out of the end of the nerve [54]. It was this idea that was to pave the way for a revolution in the approach to conduction and transmission which followed 1300 years later, and is due to Descartes.

DESCARTES: THE REPLACEMENT OF PNEUMA BY MECHANICAL CORPUSCLES

The great contribution of Descartes (1596–1650; Fig. 2A) was to dismantle the concept due to Aristotle 2000 years earlier that all manifestations of life, such as locomotion, nutrition and sensation are to be attributed to the psyche; engagement of the causal entity then leading to the expression of the inherent capacity of a particular organ to be expressed. As he pointed out [24]:

The error is that, from observing how all dead bodies are devoid of heat, and consequently of movement, it has been thought that it is the absence of the soul which has caused these movements and this heat to cease; and thereby, without reason we have come to believe that our natural heat and all the movements of the body depend on the soul. What, on the contrary, we ought to hold is that the reason why soul absents itself on death is that this heat ceases and that the organs that operate in moving the limbs disintegrate.

The psyche, as elaborated by Aristotle, was abandoned. This opened up for enquiry the mechanisms of how organs move and heat is produced, cessation of which leads to death. It made transparent the fact that the idea of each organ possessing a psyche, which had prevented the development of physiology for 2000 years, was merely a means of declaring an ignorance concerning the mechanisms of how a particular organ functioned. The loss of the psyche as the causal agent meant that psychic pneuma was no more, leaving open the questions of what is conducted along nerves and transmitted into muscle and how does conduction and transmission occur. To these questions Descartes gave detailed answers, based on his new mechanistic philosophy. In this the body consists of a set of corpuscularly constituted mechanically interacting parts, so that the ultimate level of analysis concerns corpuscular motion. Each part of the body can be activated by the transfer to it of motion that is ultimately derived from heat, which itself is just the agitation of particles engaged in fermentation. Descartes thought this took place in the heart and therefore involved blood particles. This description has a modern ring about it, except of course for the placing of heat generation in the heart.

In Descartes scheme, large blood particles when they reached the brain were used to nourish it, whereas fine blood particles were transformed into a different kind of particle that could be used by the brain for the purposes of conduction along the nerves leaving the brain and spinal cord. This different kind of fine particle to that found in the blood he referred to as animal spirits. Such a name tends to remind one of the psychic pneuma, but in Descartes' case, the animal spirits were fine particles and accessible to physiological enquiry. Descartes own dissections of the nervous system in his early 20s led him to describe nerves as hollow tubules with a sleeve-like double outer sheath, the inner and outer membranes of the sheath being continuous with the inner and outer meninges of the brain. Each nerve tubule contained a central marrow of longitudinal fibrils, surrounded by animal spirits moving outward from
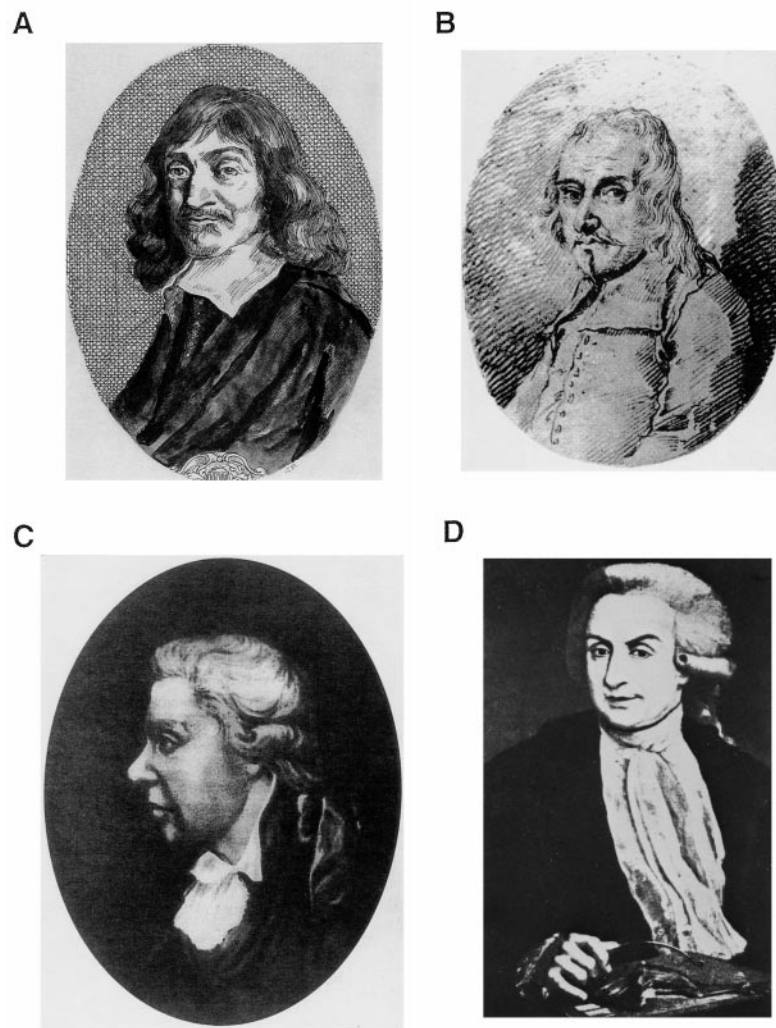
FIG. 2. The principal contributors to our understanding of nerve conduction and transmission in the 17th and 18th centuries: from corpuscles to electricity. (A) R. Descartes (1596–1650) (From [6]. Reprinted with permission). (B) Giovanni Alfonso Borelli (1608–1679) (From [13]. Reprinted with permission). (C) Felice Fontana (1733–1805) (From [7]. Reprinted with permission). (D) Luigi Galvani (1737–1798) (From [13]. Reprinted with permission).

the brain, the animal spirits being composed, as we have commented, of highly volatile material particles derived from the blood. In Descartes own words (see [25]; Fig. 3A):

Now in the same measure that spirits enter the cavities of the brain they also leave them and enter the pores or conduits in its substance, and from these conduits they proceed to the nerves. And depending on their entry or their mere tendency to enter some nerves rather than others, they are able to change the shapes of the muscles into which these nerves are inserted and in this way to move all the members.

Conduction in nerves involves the passage of small particles derived from the heart. Transmission is due to these particles leaving the ends of the nerves and entering the muscle. In order to make sure that the reader is aware of the mechanism of conduction and transmission that he is proposing Descartes comments:

But to make you understand all this distinct, I wish to speak to you first of the fabric of the nerves and the muscles , and to show you how from the

sole fact that the spirits in the brain are ready to enter into certain of the nerves they have the ability to move certain members at that instant.

This description is worth quoting at some length as the first detailed account of conduction and transmission [24]:

Observe in Fig. 3A [Fig. 3A of present manuscript], for example, nerve A whose external membrane is like a large tube containing several other small tubes, b, c, k, l, and so on, composed of a thinner, internal membrane; and observe that these two membranes (outer and inner) are continuous with the two, K(pia) and L(dura), that envelop the brain MNO. Observe also that in each of the little tubes there is a sort of marrow composed of several very fine fibrils which come from the actual substance of the brain N and whose two extremities end one at the internal surface of the cavities of the brain and the other at the membranes and flesh on which the tubule containing them terminates. But because this marrow is not used to move the members, it will suffice for now that you know that it does not completely fill the tubes containing it but leaves room enough for animal spirits to flow easily through them from the brain into the muscle whither
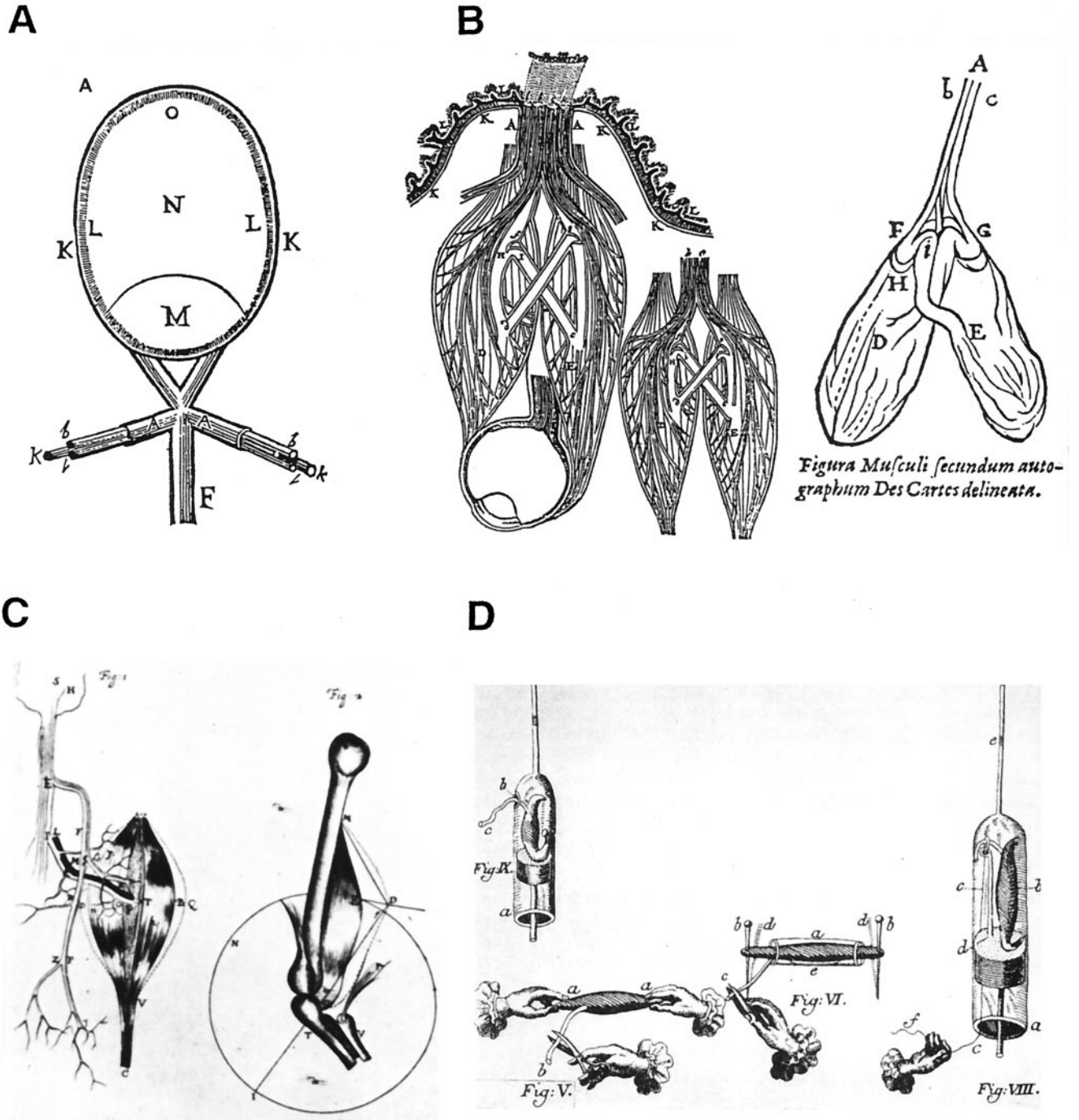
FIG. 3. The elucidation and refutation of the corpuscular theory of transmission in the 17th and early 18th centuries. (A) The Cartesian model of the nerves cast a long shadow into the 19th century. Descartes (L'homme, 1664) conceived of motor impulses conveyed in the space between the pipes and outer sheath while sensory impulses were conveyed in the inner pipes. For a full description of this figure see the text (From [24]). (B) On the left is the Cartesian model of how the nerves proceed to a muscle and control its shortening. In Descartes words 'Next observe how the tube or little nerve bf proceeds to muscle D, which I assume to be one of those that move the eye, and how it there divides into several branches composed of a loose membrane which can extend, enlarge and shrink according to the quantity of animal spirits that enter or leave it, and whose branches of fibres are so arranged that when animal spirits enter therein they cause the whole body of the muscle to inflate and shorten and so pull the eye to which it is attached, while on the contrary, when they withdraw, the muscle disinflates and elongates again. Observe further that in addition to the incoming nerve-tube bf there is still another, namely ef, through which the animal spirits can enter muscle D, and another, namely dg, through which they can leave it. And quite similarly that muscle E, which I assume is used to move the eye in the contrary direction receives animal spirits from the brain through nerve-tube cg from muscle D through dg, and sends them back toward D through ef' (From [24]). On the right is the original sketch by Descartes illustrating "the canals by which the spirits of one muscle can pass into that which opposes it". Valves in the canals, "i" can open or shut as required for reciprocal innervation (From [14]). (C) Croone's diagram depicting the route (EFG) by which nervous fluid flows from the brain (H) to little bladders

these little tubes, which should be thought of as so many little nerves, make their way.

Descartes goes on to say, with respect to Fig. 3B:

And consider that although there is no evident passage through which the spirits contained in muscle D and E can leave them except to go from one to the other nevertheless because their particles are very small and indeed because they are made incessantly finer through the force of their agitation, some always escape across the membranes and flesh of the muscle while others return through the two nerve-tubes bf and cg to replace those that escape.

It will be noted that Descartes retained the basic Galenic idea that the heart was the source of the material used to allow conduction by the nerves, after its transformation in the brain. In the case of Galen and his students that material passed from the heart as vital pneuma, was transformed in the brain to psychic pneuma whence it was used by the nerves that leave the brain and spinal cord for conduction. For Descartes, coarse and fine particles in the blood leave the heart and are sorted by the brain in such a way that the coarse particles are used to nourish it whereas the small particles cease to have the form of blood and become animal spirits. These are able to enter the 'pores and conduits' of the brain from which they are guided eventually into appropriate nerves to mediate a particular motor action. The Galenic and Cartesian schemes are very similar except that in the latter we are dealing with definite particles, sorted in a definite way by the brain, with the properties of the particles and their passage in the brain and nerves open to further physiological enquiry.

It seems likely that Descartes conceived that conduction of the particles occurs by the mechanism favoured by Galen for psychic pneuma, namely that the particles are forced out of the peripheral end of the nerve in the muscle as a consequence of the entry of particles into the central end of the nerve. As for transmission, it probably required the direct entry of particles from the nerve endings into the muscle cells on which they impinge. However, Descartes does not make these points explicit, commenting in relation to the nerves that *animal spirits flow . . . easily through them from the brain* without specifying whether this is to be thought of as a travelling wave in time. Indeed it was taken to be a wave of infinite velocity until the experiments of Helmholtz in the19th century. As for transmission from nerve to muscle, he comments in relation to the nerve fibres in the muscle that *animal spirits enter therein they cause the whole body of the muscle to inflate and shorten and so pull . . . while on the contrary, when they withdraw, the muscle disinflates and elongates again.* This certainly seems to imply that there is direct flow of animal spirits into the muscle that causes the inflation, although that is not specified and explained in detail until the work of Borelli a few years later.

BORELLI: A CORPUSCULAR DESCRIPTION OF CONDUCTION AND TRANSMISSION

The Cartesian hypothesis concerning the mechanism of conduction and transmission was taken up and elaborated on in great detail in the new tradition of physiological enquiry by Borelli (1608–1679; Fig. 2B), a young contemporary of Descartes who outlived him by some 30 years. Borelli's description of the animal spirits used for conduction by the nerves follows closely that of Descartes [12]:

In the animals, besides liquids such as blood, there is another extremely spirituous fluid substance which is the direct motive cause of the animal body. This appears from the effects of this substance. This spirituous humour is not wind or air but has a liquid consistency such as spirit of wine. It is generated from blood in the brain and diffused by the nerves. All modern authors admit this point. The exact structure and composition of the nervous juice, although unknown, can be surmised somewhat from its motions through the nerves.

The mechanism of conduction of the animal spirits along the nerve is due to the compression of the spirits at the central end leading to secretion of spirit at the peripheral end [12]:

The spongy cavities of these nervous fibres thus are conceived as being always soaked and filled up to turgescence by some juice or spirit transmitter from the brain. In a bowel full of water and closed at both ends, impulse at an extremity compressed and slightly percussed is instantly transmitted to the other extremity of the turgid bowel. The adjacent elements of the liquid are aligned in a long row. By pushing and shaking each other, they transmit the movement to the extremity of the bowel. Similarly, as a result of some slight compression, jolt or irritation at the origins of the canals of the nervous fibres which are in the brain itself, these fibres thus shaken and activated must secrete some drops of this juice which swells their internal spongy substance, into the fleshy mass of the muscles.

Transmission involves the movement of the spirituous juice from the nerve endings in the muscle directly into the muscle cells [12]:

The distal orifices of these nervous fibres are scattered everywhere in the mass of the muscle although they are open, the spongy structure itself with which the fibres are provided plays the role of valvules. Indeed droplets hanging from wet sponges do not flow out. A shaking force is required to express them. This may be the cause why the nervous juice is secreted and instilled in all the mass of the muscle by order of the will.

The cause and mechanism by which nervous juice is instilled in the muscles with a convulsive force by an order of the will and produces their instantaneous swelling, are deduced from what was said above. Contraction will continue as long as the cause of the bursting is present i.e. the instillation of nervous juice. When it stops, the turgescence of the muscles disappears, as light disappears when the flame which continuously renews it is removed.

In summary, Borelli conceives conduction and transmission thus [12]:

Consequently, this slight motion of the spirits provoked by the will in the brain can shake or excite the fibres or spongy ducts of some nerves turgid with spirituous juice. As a result of this convulsive irritation which shakes all the length of the nerves, some spirituous droplets can be expressed and spilled from the orifices of their extremities into the corresponding muscle. This results in the boiling and bursting by which muscle is contracted.

At the end of the 17th century, William Croone summarised for the Royal Society of London the revolution in understanding of conduction and transmission that had taken place that century, involving rejection of the concept of psychic pneuma for that of juices consisting of corpuscles. Figure 3C shows his diagram of the mechanism of conduction along motor nerves and transmission to muscle. What is now called the nervous fluid flows from the brain along the motor nerves to inflate small bladders in the muscle which cause it to expand and shorten [22].

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which inflate the muscle to expand from contour ABCD (solid line) to AQV (dotted line). On the right is a diagram of the direction of forces when bending the elbow (From [14,22]). (D) Swammerdam's experiments including the one by which he proved that muscles were not swollen by an influx of nervous fluid when they contracted. Fig. V is of an experiment to show the change in shape of a muscle when stimulated by pinching its nerve. Fig. VI illustrates the pulling together of the pins holding the tendons when the muscle contracts. Fig. VIII is the crucial one in which a drop of water is imprisoned in the narrow tube projecting from the vessel enclosing the muscle. Further description of this experiment is given in the text (Biblia Naturae, Amsterdam, 1738; From [13,95]).
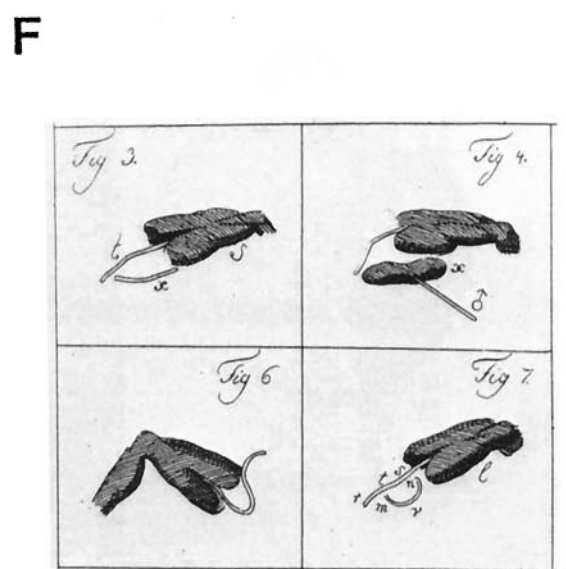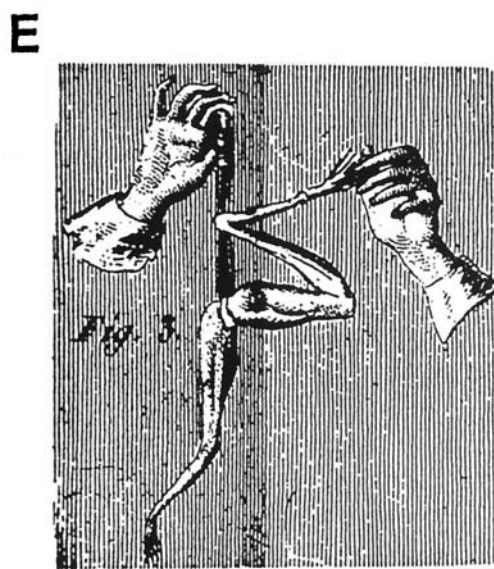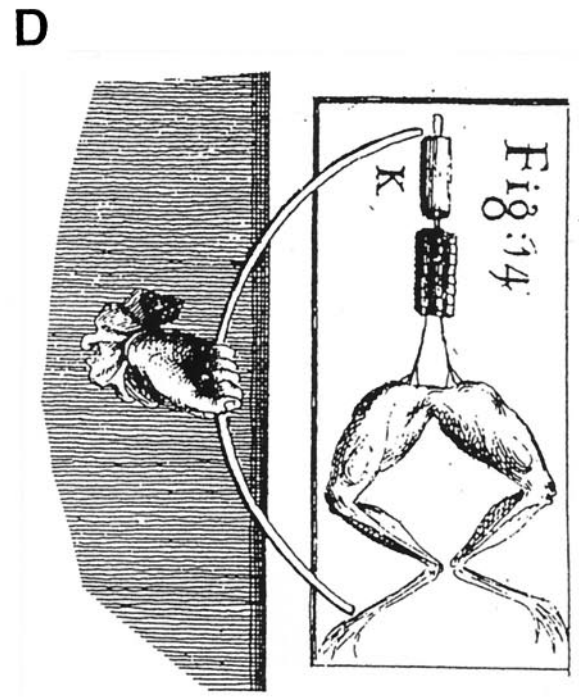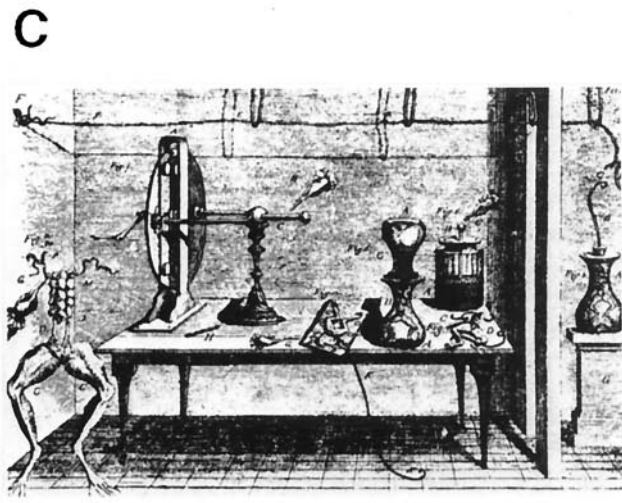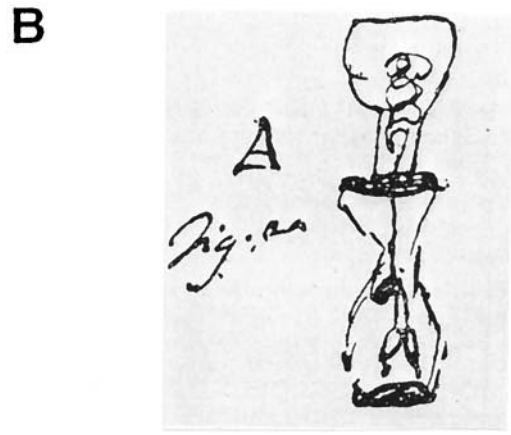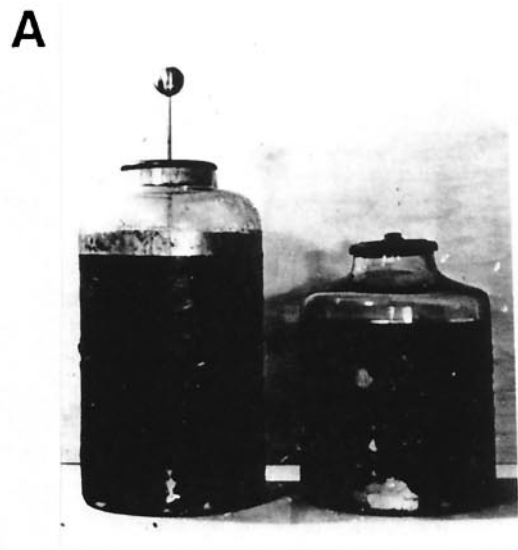
FIG. 4. The emergence of the concept in the late 18th century that electricity is conducted by nerves. (A) Two early Leyden jars in the collection from the Boerhaave Museum, Leyden. (Photograph by courtesy of the Boerhaave Museum). (B) Galvani's sketch of his preparation of inverted flasks containing

FONTANA: NERVES ARE COMPOSED OF MANY CYLINDERS ALONG EACH OF WHICH CONDUCTION OCCURS

The composition of the nerves along which conduction occurs was illuminated in the 18th century. At its beginning the Dutch microscopist Antoni van Leeuwenhoek (1632–1723) used his one lens microscope to give a description of the composition of nerves, commenting that '*Often and not without pleasure, I have observed the structure of the nerves to be composed of very slender vessels of an indescribable fineness, running length-wise to form the nerve*' (Fig. 5A). These vessels were taken to be hollow tubes, in agreement with the Cartesian concept that animal spirits flowed in nerves [98,99]. The relation between these hollow tubes and the nerve was spelt out in detail through the nerve dissections of Felice Fontana (1730–1805; Fig. 2C). These were performed, after immersing the nerve threads in water, with very sharp needles under a magnification of × 700, and allowed Fontana to claim that (see [35]; Fig. 5B):

The basic structure of nerves is as follows: a nerve is formed of a large number of transparent, uniform, and simple cylinders. These cylinders seem to be fashioned like a very thin, uniform wall of tunic which is filled, as far as one can see, with transparent, gelatinous fluid insoluble in water. Each of these cylinders receives a cover in the form of an outer sheath which is composed of an immense number of winding threads. A very large number of transparent cylinders together can form a nerve so small that it is barely visible but which shows the white bands on the outside. Several of these nerves together form the larger nerves seen in animals. I am fully convinced by my own observations, which I repeated many times with the same result, that the cylinders I have described are the simple and first organic elements of nerves, for I have not succeeded in dividing them further, no matter what investigations I carried out with the help of the sharpest and finest needles. I could easily tear and break them here and there; but they always remained indivisible. I could strip them off their sheaths and separate the winding cylinders of which they are formed, although they were very small. The primitive nerve cylinder then appeared transparent, homogeneous, and of equal diameter everywhere.

He goes on to say that:

After having dissected a very small nerve and its minimal nervous threads made of the different nervous primitive cylinders I have extensively dealt with in my work, I succeeded in stripping from the inner sheath, or rather from the tortuous threads, some nervous primitive cylinders. These were transparent, homogeneous, not empty, as I had found them in previous occasions.

As to the constituents that made up the cylinders, that were 'not empty', Fontana in 1781 describes the microscopic features of the axoplasm extruded from the cut end of an axon as [38]:

. . . glutinous, elastic, transparent material, insoluble in water, that decomposed itself into very little round grains of a diameter four or five times less than a red blood globule.

I am not sure that Physiologists would be willing to consider those little grains as animal spirits, and the mechanical principle of all movements. This hypothesis would not explain the instantaneous speed of animal movements, since those little grains seem too lazy to move inside the nerve, where they form instead a viscous and inert glutine. Animal movements would be easier to explain considering that such grainy material is elastic, and continuous along all the nervous canal, as the observation in fact demonstrates. The movement

could be transmitted at the moment that would follow a mechanical alteration of the nerve or any of its parts.

These descriptions of the larger nerves as composed of smaller nerves which are not divisible further and which contain '*a glutinous, elastic, transparent material*' has modern resonances. However, Fontana produced this description in the year that Galvani began his most important discoveries. These were to identify electricity as the conducting material for nerves rather than the Cartesian corpuscles of fine particles derived from blood. Fontana then adheres still to the Cartesian *animal spirits* and so has difficulty in reconciling the size of the *lazy particles* in the nerve cylinders with that of the speed of animal movement. He then comes to emphasise the possibility favoured by Galen that it is the extrusion of the particles at the peripheral ends of the nerves following the entry of particles at the central ends of the nerves that provides the appropriate speed for nerve action [36,37].

GALVANI: ELECTRICITY IS CONDUCTED AND TRANSMITTED NOT CORPUSCLES

Borelli had commented in relation to the idea of the flow of a nervous fluid in nerve to muscle that '*All modern authors admit this point.*' Indeed when Boerhaave produced the first figure of the neuromuscular junction in the early part of the 18th century (see [11]; Fig. 5C), it emphasised continuity between the nerve ending and muscle, as expected if there was to be a direct flow of nervous fluid into the muscle required for muscle shortening. This whole conceptual scheme was dealt a major setback with the brilliant physiological experiments of Swammerdam, published in 1738. These showed that muscles were not swollen by an influx of nervous fluid during contraction. In this work, illustrated in Fig. 3D (VIII), he placed a muscle with its nerve supply in a narrow tube which was then filled with water in such a way that water could be expelled from the tube if the muscle swelled on contraction [95]. A wire attached to the muscle nerve in the tube was then pulled on to excite the nerve and contract the muscle. The result was unequivocal, muscle contraction did not lead to the expulsion of water from the tube, so that muscle swelling could not have taken place. Nervous fluid could not, by flowing directly into a muscle, cause contraction. The whole concept of a nervous fluid, consisting of small Cartesian corpuscles, was now thrown into doubt. What could be the nature of the substance that was conducted by nerves?

The science of electricity emerged in the 16th and 17th centuries. William Gilbert (1544–1603) had constructed the first electroscope, consisting of a suspended needle that was attracted to static electricity, so that it turned on being brought near a piece of rubber amber. This apparatus allowed the amount of attraction due to the static electricity to be given in quantitative terms according to the extent of deflection of the needle. Gilbert used the electroscope to detect static electricity in a number of other rubbed objects consisting of glass, wax and sulphur. This led to the invention by Otto von Guericke (1602–1686) of the frictional machine which was constructed from a sulphur ball mounted on a spindle and rotated by hand to generate large quantities of static electricity. The opportunities for the discovery of animal electricity were in place with the subsequent invention of the Leyden jar for

the frog's nerve muscle preparation from an experiment dated December 10, 1781 (From [14,49]). (C) This figure shows Galvani's frictional machine, a Leyden jar, and a wire strung across the room to collect the charge (From [14,46]). (D) An artist's depiction of Galvani's favourite preparation published as part of the first illustration to the famous Commentary published in 1791. (From [14]) (E) The critical experiment by Galvani on muscle contraction in the absence of all metals (From [14,32]). (F) Von Humboldt's experiments in which he demonstrated contraction of nerve-muscle preparations in the absence of any metals. His Fig. 3 depicts a frog nerve-muscle preparation to which he applied a tube of glass (x), producing a contraction. His Fig. 6 shows an experiment in which he turned back the nerve against the muscle without interposing the glass rod (From [14,97]).
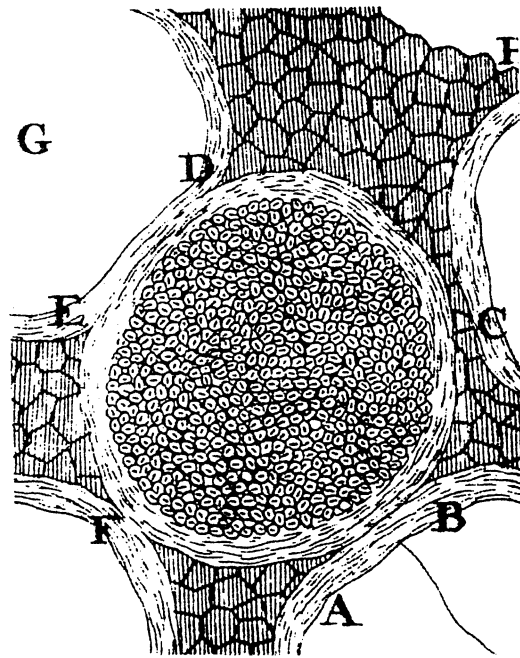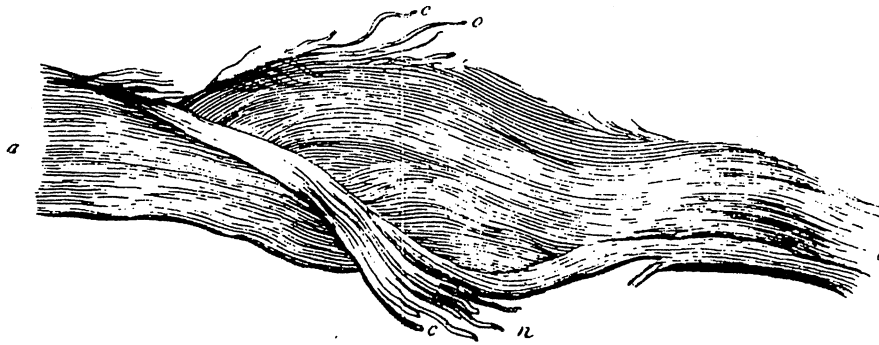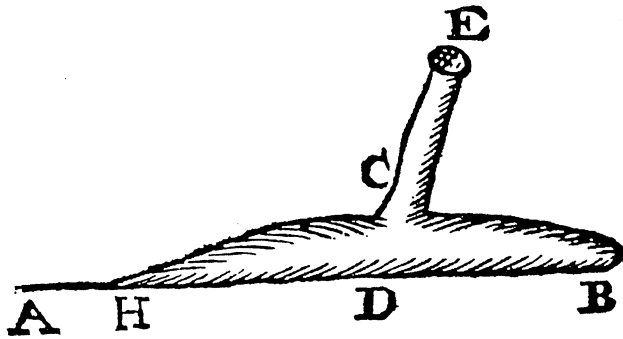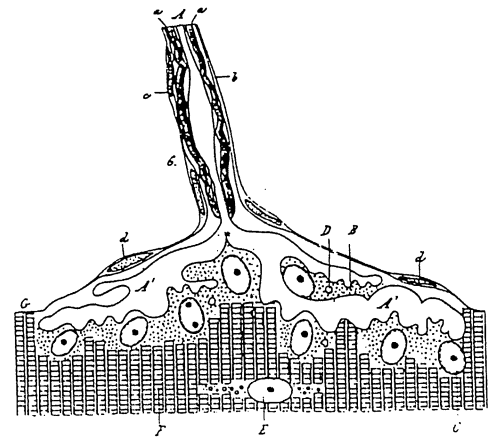
FIG. 5. Anatomical identification in the late 18th century of nerve fibres and their junctions with muscle. (A) Leeuwenhoek's drawing of a small nerve (ABCDEF) composed of many "vessels" in which "the lines or strokes denote the cavities or orifices of these vessels". This nerve is surrounded in part by five other nerves (one of which is labelled G), in which only "external coats" are represented. (From [7,98]). (B) Nerve fibres drawn by Fontana. The drawing illustrates "a nerve torn with a needle, to determine the continuity of the primitive nervous cylinders." a indicates the "two ends of the nerve", c,n,o indicate "several of the primitive cylinders" (From [7]). (C) Boerhaave's concept of the neuromuscular junction. He believed that the nerve (EC) flowed directly into the substance of the muscle (HB) (From [11,14]). (D) Schematic summary view of the mammalian neuromuscular junction (From [66,91]).

storing static electricity by Petru van Musschenbroek (1692–1761; Fig. 4A). Indeed speculations that electricity might compose the Cartesian animal spirits were made at this time by the mathematician Christian August Hausen (1693–1743).

Luigi Galvani (1737–1798; Fig. 2D) discovered 'animal electric fluid', a phrase reminiscent of the 'animal spirits' used by Descartes in his mechanical description of nerve conduction. This story begins on the famous occasion during which one of Galvani's collaborators touched with a lancet the exposed nerve of a frog muscle near a frictional machine (Fig. 4C), which occasionally sparked giving rise to the transfer of charge by induction to the frog's nerve and thereby a twitch contraction. Galvani investigated this phenomenon further using the apparatus shown in Fig. 4C [46]. This consisted of a frog's exposed spinal cord-leg preparation suspended in a sealed jar by means of a wire passed through the spinal cord and then through a seal at the top of the jar; lead shot was present in the bottom of the jar (right hand side of Fig. 4C). A wire was then strung across the ceiling to pick up the charge from a frictional machine and convey it to the wire from which the spinal cord was strung, as shown in Fig. 4C. This apparatus allowed for the unequivocal demonstration that when the machine sparked the legs twitched. From this Galvani concluded that frog nerves conduct electricity. Animal spirits had become electricity.

Galvani devised a number of other experimental procedures in the years 1781 to 1791 which showed the existence of electrical conduction in nerves [45,46,47,49]. In one experiment he used a pair of jars in one of which there was enclosed a frog spinal cord-leg preparation suspended over lead shot as before by means of a fine iron wire; this wire then lead into another jar which in turn had a layer of lead shot, together with a coil of attached wire to collect the discharge from the frictional machine, as shown in Fig. 4B. This discharge was accompanied by sparking in the upper jar and twitching of the frogs legs in the lower jar, due to what Galvani described as the passage of 'electric fluid' down the wire in the upper jar and down the spinal cord and nerves into the leg muscles. His conclusion from these experiments was that there must be a nervous 'electric fluid'. That this electric fluid must flow along individual nerves and not just the spinal cord was confirmed by work in which the sciatic nerve of one leg of a frog was dissected and used in the experimental apparatus instead of the spinal cord. In this case the leg twitched on discharge of the friction machine as had been the case with the isolated spinal cord-leg preparation.

An investigation of Galvani's in 1794, which was to have far-reaching repercussions in the following century in the hands of du Bois-Reymond, involved experiments that were to lead to the discovery of 'animal electricity', that is, the existence of electricity generated by nerve and muscle itself [46]. In this experiment, Galvani placed the severed end of a nerve, belonging to a leg-muscle preparation, on the intact portion of the nerve and obtained movement of the leg (Fig. 4E; see also [32]). This showed the existence of electrical potential in nervous tissue and that electrical flow could occur in nerves as a consequence of the nerves producing a potential. He published this work anonymously as '*Dell' uso e dell' attivita dell'Arco conduttore nelle contrazioni dei muscoli*' (On the application and activity of the Arco conduttore in the contraction of muscle). In 1797, Galvani showed that if he allowed one nerve of a nerve-leg preparation to fall from a glass rod on which it was suspended onto the cut region of another nerve from the same frog then the legs moved [48]. It was not then necessary that the same nerve be used to excite itself, but that any injured nerve would suffice. Indeed, electricity could be lead by a suitable conductor from the cut end of the spinal cord where the potential was generated to the leg directly in order to obtain a twitch (Fig. 4D).

One of Galvani's most famous demonstrations of the flow of electricity in nerve involved the observation that frog's legs twitched when hung from brass hooks to an iron railing even in the absence of a thunderstorm. Galvani interpreted this as due to the generation of animal electricity rather than, as Volta was later to show, to the flow of current between dissimilar metals connected in a circuit. However, Volta went further and attempted to analyse all of Galvani's experiments as an artefact due to this phenomenon [100,101]. It was left to Alexander von Humboldt (1769–1859) to confirm Galvani's experiments and show that they occurred independently of any current flow due to dissimilar metals being incorporated into the experimental design, something which Galvani himself had shown (see Fig. 4E). Galvani met Volta's criticism by cutting both sciatic nerves of a frog where they leave the spinal cord. He then lifted the cut end of one nerve with a glass rod so that it touched the other nerve with its cut end. When this occurred the muscle of the touched nerve contracted. Figure 4 (F3) shows one of von Humboldt's experiments in which he applied a charged tube of glass to the nerve of an isolated frog nerve-muscle preparation and obtained a contraction. Figure 4 (F6) shows another experiment in which he turned the cut end of the nerve against the muscle and obtained a contraction, a variation of the Galvani experiment in which the cut end of a sciatic nerve was placed on another sciatic nerve [97]. None of these experiments were open to the kinds of criticism that Volta had aimed at Galvani.

As we have seen, at the end of the 17th century, nerves were thought to conduct animal spirits rather than psychic pneuma, with the former envisaged as corpuscular in nature, derived from fine particles of blood. Galvani died at the end of the 18th century, by which time he had shown that nerves could conduct electricity and further that the potential for generating electricity could be found in nerve and muscle itself [15]. It was generally accepted after this work and that of von Humboldt that the conduction of electricity in nerve was like the way in which metallic wire conducts voltaic electricity. Animal spirits had become electricity.

MATTEUCCI AND DU BOIS-REYMOND: TRANSIENT ELECTRICAL CHANGES ARE CONDUCTED (THE ACTION POTENTIAL)

The triumph of 19th century physiology was to take Galvini's discoveries and show that the nervous primitive cylinders of Fontana possess a potential across their membranes that could give rise to a propagating transient potential change, the action potential.

As is so often the case in the history of neurophysiology, the development of concepts concerning electricity in nerve and muscle at the beginning of the 19th century was dependent on advances in instrumentation. Gilbert's use of a suspended needle to detect electricity permitted only slight deviations from the meridian because of the earth's magnetic field. In 1820, Schweigger, following Oersted's discovery that a magnet tends to set itself at right angles to a loop of bent wire carrying an electric current [81], designed the galvanometer. In this instrument many turns of wire were wound on a rectangular frame inside which a compass needle was placed that was balanced on a vertical pivot or in some cases suspended from a thread. Leopold Nobili in 1825 manufactured the first astatic galvanometer in which he wound two coils of wire on the rectangular frame of Schweigger in opposite directions, so as to cancel the effects of the earth's magnetism. Nobili used this instrument in 1827 to detect currents passing up the body of a frog away from the legs towards a cut spinal cord and in this way made the first measurement of animal current, or as he called it the 'intrinsic current'. However, he attributed the current to a thermoelectric effect caused by the unequal cooling of nerve and muscle
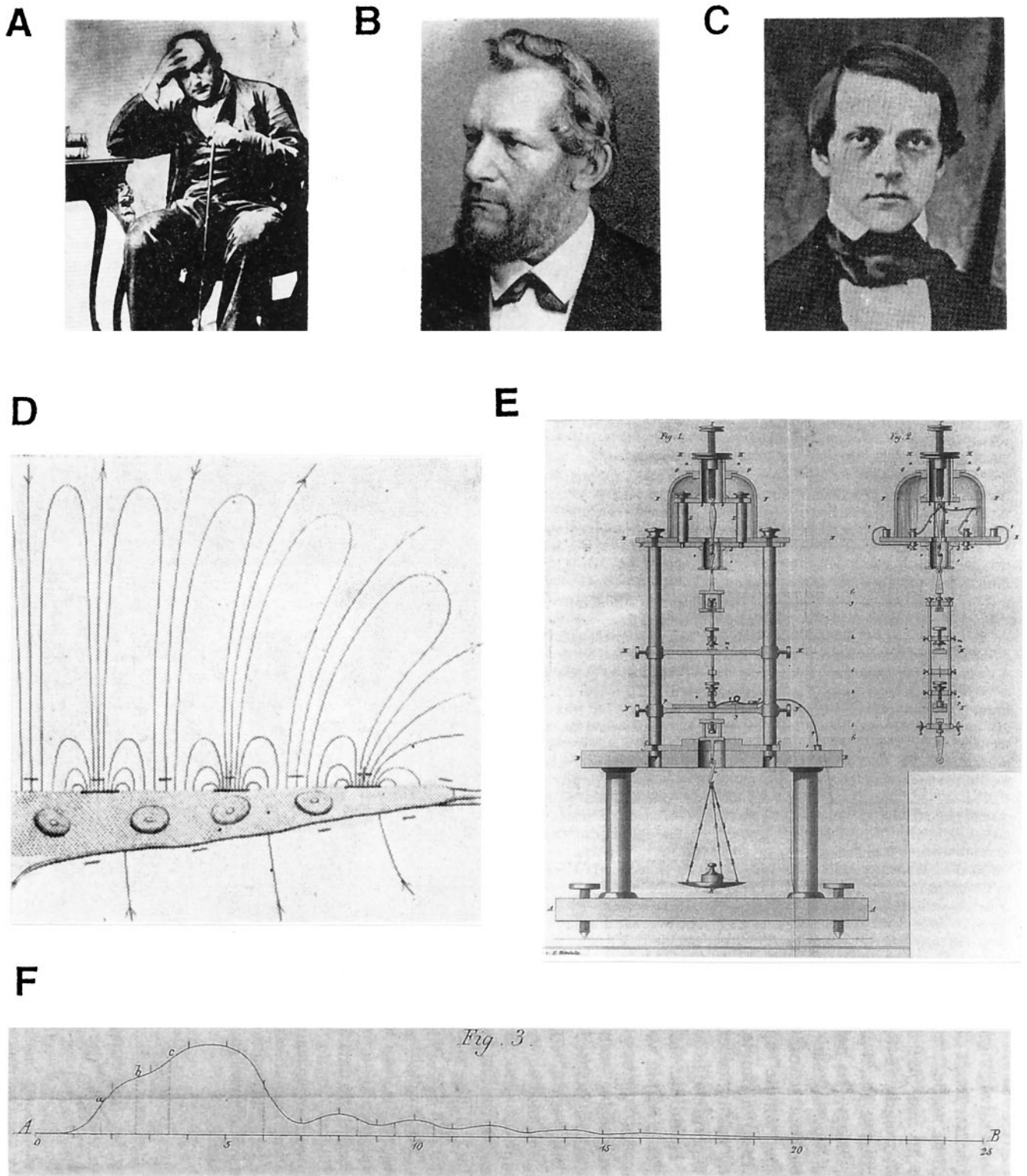
FIG. 6. Identification of the action potential as the electrical means of conduction. (A) Carlo Matteucci (1811–1865) (From [13]). (B) Emil du Bois-Reymond (1818–1896) (From [13]). (C) H. von Helmholtz (1821–1894) shown as a young man when he made his greatest contribution to the understanding of impulse conduction in nerve (From [13]). (D) Schemata of du Bois-Reymond's postulated method for transmission at the motor end plate (From [29]). (E) Helmholtz's apparatus for measuring the time course of muscle contraction and the propagation velocity of the nerve impulse. On the left, Figure 1 shows the entire apparatus; on the right, Figure 2 shows the arrangement when the nerve w is attached and more than one point on the nerve can be stimulated (From [16,55]). (F) Helmholtz's muscle curve (From [16,55]).

produced by evaporation rather than due to an intrinsic biological phenomenon [79,80].

Carlo Matteucci (1811–1865; Fig. 6A) used the Nobili galvanometer to great effect on isolated nerve-muscle preparations. Although not well known, he may be considered to be a founding father of electrophysiology. Matteucci showed that a twitching muscle generated current sufficient to stimulate the nerve of another muscle laid across it and so produce a twitch in the other muscle. Importantly he detected current flow between the cut end of a muscle and the intact end. These currents were correctly interpreted as generated by the muscles themselves [69,70]. This was emphasised by his experimental technique of preparing a pile of sectioned frog's thighs arranged in a series so that the intact surface of one thigh was in contact with the sectioned surface of the next one. The currents generated were in proportion to the number of thigh sections in the pile. However Matteucci's most important observation was that the current between the cut end of a muscle and the intact end declined during a tetanus caused by strychnine, that is, there was a negative variation in the current. Thus excitability was associated with a decrease in the potential that gives rise to the current. Although Matteucci was unable to detect with his instruments a negative variation in the nerve current, his observations laid the ground work for the emergence of the concept of the action current and of the action potential (see [68,71,72] and also [73].

du Bois-Reymond (1818–1896; Fig. 6B), confirmed Matteucci's experiments on nerve-muscle preparations, and on muscles isolated from their nerve supply, calling current flow in the latter case 'muscle current'. Most importantly the negative variation or 'negative Schwankung' of the muscle current during a tetanus was shown in 1843 to be produced by other means than strychnine, for instance, by direct faradic stimulation. du Bois-Reymond, using more sensitive instrumentation than that available to Matteucci, was able to detect in 1834 the negative variation in nerves as well as muscle. The concept of the action potential with its action current showing up as a negative variation was clearly envisaged by du Bois-Reymond [26,27]. He hypothesised that a resting potential existed between the middle of muscle cells at positive potential and that of the tendons at negative potential: it was this potential which decreased during stimulation so that a negative variation was recorded. He went on to develop the concept of 'electromotive particles' or 'electrical molecules' [30]. These possessed a positive charge in their middle and a negative charge at each of the polar regions. He postulated that these were situated along the length of the surface of muscle cells and nerve fibres and that it was these that gave rise to the polarisation of the cells (Fig. 6D). At rest these molecules were postulated to be arranged in an ordered longitudinal array, so that if a nerve or muscle was sectioned transversely this gave rise to the muscle or nerve current between the injured regions and the intact surface. An electrical stimulus was envisaged to perturb the ordered longitudinal array, producing an electrotonic disturbance leading to the initiation of the negative variation.

In this 'molecular hypothesis' muscle and nerve fibres are composed of strings of so-called peripolarelectric molecules, each of which possess an equator corresponding to the electropositive metal zinc and two poles corresponding to the electronegative metal copper. The current attributed to the internal potential difference thus created could be led off by placing one end of a conductor on the 'natural longitudinal section' of a nerve or muscle and the other end on the 'natural cross section'; in this case the longitudinal section acted as the positive pole and the cross section as the negative pole. The term 'natural cross section' as applied to muscle refers to the tendon covered ends of the muscle, regarded as prisms or cylinders, while the term 'natural longitu-

dinal section' refers to the lateral surface of these prisms or cylinders. The corresponding artificial cross section and longitudinal section are obtained by dividing the muscle lengthwise or crosswise. In this sense the proximal cross section is the upper one, and the distal cross section the lower one. The same applies mutatis mutandis for the nerve. The negative variation involved the discharge of this electromotive force, an idea that clearly presaged the concept of the resting membrane potential and its depolarisation during the action potential ([28,29]; for a recent detailed account, see [84]).

Matteucci had discovered the negative variation in muscle that accompanies activity and du Bois-Reymond that in nerve. Although it seemed very likely that this negative variation of electrical polarisation was the animal spirit of Descartes, it was still endowed with the mysterious property that it could travel at infinite velocity. This was accepted by all the leading physiologists of the first half of the 19th century. For example, in 1846, E. Weber summarised his observations on the conduction of the action current in muscle nerves with the comment that [104]: '*When one stimulates a muscle through a motor nerve*' its movement '*occurs at the same moment*' that is '*the movement begins and ends with the stimulus*'. Muller's comment was that [74,75]: '*the time the stimulus takes to travel to the brain and back is infinitely small and unmeasureable*'. The existence of such a phenomenon as a travelling wave with infinite velocity left the mechanism of conduction opaque to further analysis, rather in the way that the idea of the psychic pneuma had until the time of Descartes. This impasse was broken through the experimental skill of Helmholtz (1821–1894; Fig. 6C).

HELMHOLTZ: THE ACTION POTENTIAL HAS A FINITE VELOCITY

In 1848 Helmholtz began, in his own words [16]:

. . . to study the processes occurring in the simple contraction of a muscle; by such an action I mean one that results from a stimulus of vanishingly small duration. I have now finished building my frog-tracing machine and have already carried out a few tracing experiments on mica sheets. Instead of the frog muscles, I inserted a spring. The weight hung from it, oscillated up and down, and recorded its movements. The traces are much prettier than the earlier ones, very fine and regular [see Fig. 6F]. *The previously unknown fact that in animal muscles too, as in the case in much longer time intervals in organic muscles, the energy of the muscle does not develop completely at the moment of an instantaneous stimulus. Rather, in most cases after the stimulus has already ceased, it increases gradually, reaches a maximum, and again subsided.* [Fig. 6F]. *The force of the muscle was not strongest directly after the stimulation, but rather increases for a time and then falls.*

In October 1849 he set out to give a more accurate account of this apparent delay between the electrical stimulus and the muscle's response, with its implications for a finite velocity of conduction of the nerve action potential. To this end he used a method for measuring small time intervals based on the fact that the length of the arc through which the magnetic needle of a galvanometer moves when a transitory current passes through its coil is proportional to the duration of the current. The time interval in question was then measured by ensuring that this movement was led to the deflection of a mirror. Helmholtz next arranged his apparatus so that the beginning and end of the time interval marking the currents duration coincided with the time interval that began with the application of the stimulus and ended with the onset of the muscle's mechanical action. The latter was obtained by the mechanical action of the muscle lifting a weight which then placed a break on the electrical current.

It is worthwhile analysing the apparatus that Helmholtz used for this experiment, both for the beauty of its design and for the
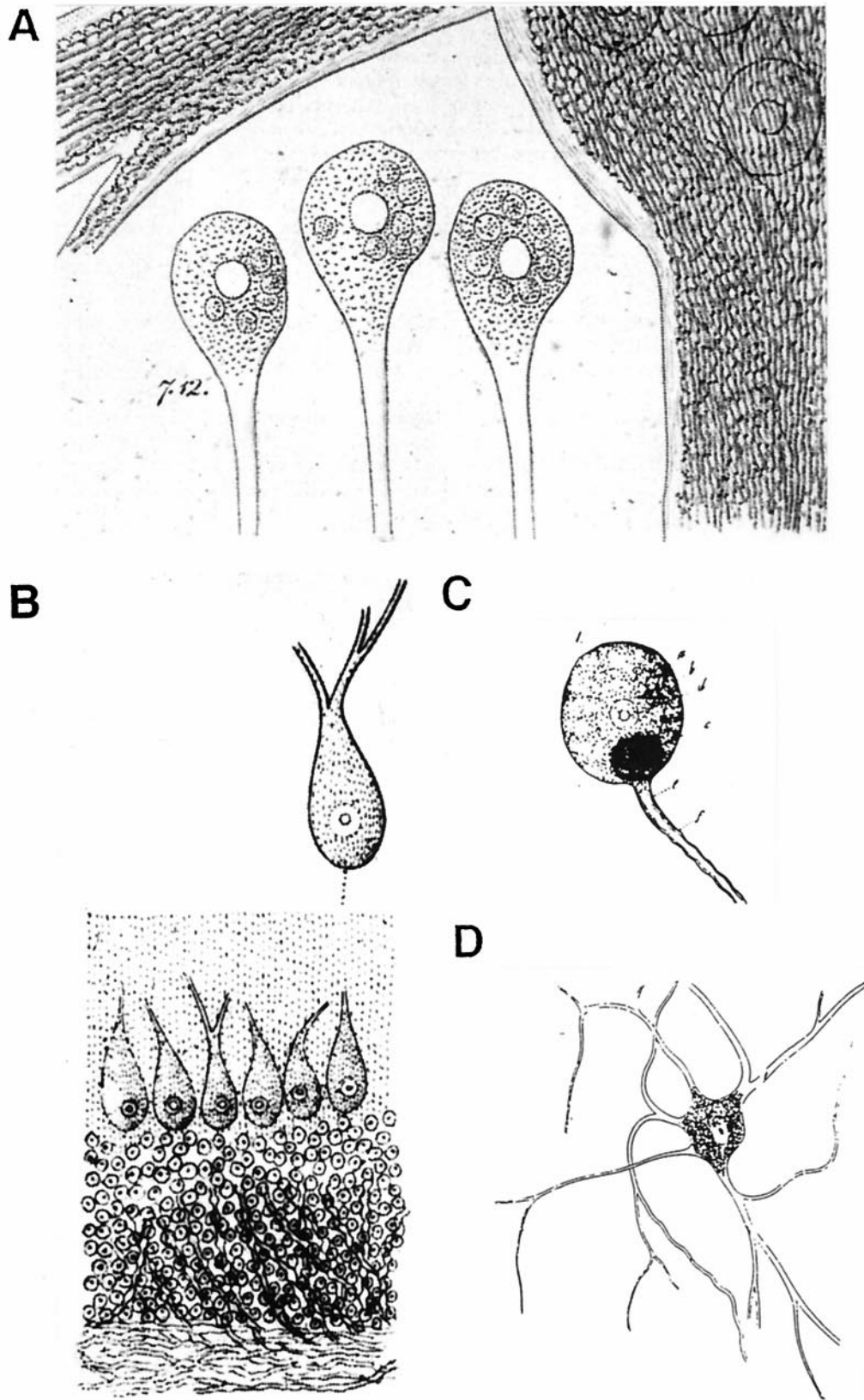
FIG. 7. Identification in the first half of the 18th century of the neuron as the cell body g iving rise to the nerve fibre or axon. (A) Single neurons from the leech nervous system representing one of the first two illustrations of a neuron (From [31]). (B) The large corpuscles of the cerebellum, which became known as Purkinje cells after their discoverer, giving the other first illustration of a neuron. This was also the first published view of the cellular composition

unequivocal outcome that it led to, namely the accurate measurement of the velocity of the action potential. With reference to Fig. 6E, and following the description of Cahan [16]:

. . . a muscle was hung suspended from a screw I to which was attached a series of screws and contact surfaces that would break the flow of the current when the muscle raised the weight suspended on the scale pan K. The apparatus was placed in a container with humidity enriched air in order to prevent the muscle from drying out; this set up remained in a usable state for three to four hours. At a certain point following stimulation of the nerve w [see the enlargement on the right hand side of Fig. 6E], *where v is the current carrying wire to the nerve, the energy of the muscle would equal the load suspended from its lower end. After that point, any increase in the energy of the muscle would elevate the load a little and separate point m from the point n on the apparatus; if, however, weights were put on the scale pan K, such that the muscle was acted upon by an additional overload, then the stimulated muscle could raise the combined weight only if its energy (elastic Spannung) equaled the sum of the weights of the load and the overload. Helmholtz arranged his apparatus so that the current, whose time interval was to be measured, would break when the elastic Spannung of the muscle increased by an amount sufficient to raise the weight of the overload.*

With this approach Helmholtz discovered that the time interval between a stimulus applied to the nerve and the moment when the muscle produced enough force to lift the overload depended on the distance between the point of stimulation of the nerve and the muscle. A method for measuring the velocity of propagation of the action potential was now available. On 29 December 1849, Helmholtz measured the velocity of propagation as 30.8 metres per s. The curves obtained in these experiments (Fig. 6F) showed that the velocity was finite and the apparatus (Fig. 6E) that this velocity could be measured ([55,56,57; see also [82]). Helmholtz had made the great discovery which transformed the nervous system from consisting of cylinders through which animal spirits flowed with infinite velocity to one which was amenable to quantitative measurement for the testing of hypotheses [58,59]. He knew that '*as long as physiologists insist on reducing the nerve effect to the propagation of an imponderable or psychic principle, it will appear unbelieveable that the velocity of the current should be measurable*'. Although the mechanism by which this propagation of the action potential occurred was not indicated by these experiments, Helmholtz proposed the first hypothesis to be tested, namely that the process was the same as that of '*the conduction of sound in the air and in elastic matter or the burning of a tube filled with an explosive mixture.*

J. Bernstein (1839–1917) began the use of quantitative measurement of nervous phenomena to investigate the mechanism of propagation of the action potential in 1868 with his measurement of the time course of the potential, its latency, rise-time and decay [8]. This led him to his famous theory that the membrane of nerve and muscle is normally polarised at rest with an excess of negative ions on the inside and of positive ions on the outside. The action potential then becomes a self-propagating loss of this polarisation or a depolarisation. Injury currents arise as a consequence of the loss of the polarisation at some point in the membrane due to its injury. Bernstein was led to this theory by comparing the negativity of the current arising from an injured nerve and that of the action current [9]. As the former was attributed to the inside of the tissue becoming continuous with the outside it was conjectured

that a transient exposure of the inside to the outside occurs during the action current [10]. The fact that the action potential could conduct in the orthograde or anterograde directions followed from this theory of the polarization of the nerve and muscle cell membrane.

Perhaps the most original contribution of Bernstein was his theory of the origin of the polarization of the membrane of muscle and nerve, which was based on Nernst's concept of the diffusion potential developed at about the same time [77,78]. In this theory, the potential arose as a consequence of the high permeability of the membrane to potassium compared with other ions. Given that the concentration of potassium is higher inside than outside a negative polarization of the inside of the membrane with respect to the outside is generated.

KUHNE AND AUERBACH: IDENTIFYING THE STRUCTURE OF NERVE ENDINGS ON MUSCLE AND NEURONS

The advent of superior histological stains allowed the first descriptions of neurons to be given in 1836–1837 by C.G.Ehrenberg for single nerve cells in the leech nervous system (Fig. 7A) and by J.Purkinje for the large nerve cells of the mammalian cerebellum named after him (Fig. 7B; see also [87,88,89]). Sixteen years later, A. Kolliker (1817–1905; Fig. 10A) showed that the nerve fibres of Fontana originated from nerve cells with a description of the beginnings of the acoustic VIII nerve, or in his words in relation to Fig. 7C:

Nerve-cell with the origin of a fibre (from the acoustic VIII nerve) of the Ox; a, membrane of the cell; b, contents; c, pigment; d, nucleus; e, continuation of the sheath region of the nerve-fibre; f, nerve-fibre.

In the same year of 1852 he described how motor nerves originated from the anterior horn nerve cells of the spinal cord (Fig. 7D). The question then arose as to the relationship between these motor nerves and the muscle cells on which they impinge. R. Wagner showed in 1847 that the terminal branches of nerves going to the electric organ of the electric ray split into ever finer branches when they entered the electric organ until nothing was left of them in the fine-grained parenchyma of the organ [102]. He extended this by analogy to the nerve supply of muscle. W. Kuhne (1837–1900) described histological differences between the end of the motor nerve and the muscle cell on which it abuts in frogs in 1862, namely at the end-plate (Fig. 5D; see also [64–66]). However, this did not illuminate the functional problem of how the action potential was transmitted from motor nerve to muscle any more than did the diagram of the motor endplate by Boerhaave's some 140 years earlier (Fig. 5C) indicate how animal spirits left the nerve to enter the muscle. Boerhaave had simply acquiesced in the current physiological concept of Descartes, developed by Borelli, that animal spirits passed directly from the nerve into the muscle to increase the muscle volume and so shorten it. Kuhne, likewise, took the current physiological paradigm of the action potential and suggested that the action current of the nerve invaded the muscle at the endplate. This idea was developed in some detail by W. Krause in 1863, who drew attention to the similarity between the nerve endings in muscle and the electric plate in the organ of the electric catfish, which was taken to act as a Leyden jar. He argued

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of the histological layers within a brain region. From below: fibres, granules, large corpuscles (Purkinje cells), molecular layer (From [87,91]). (C) A nerve originates from a cell body. A nerve cell with its nerve in Kolliker's Handbuch der Gewebelehre des Menschen (1852). In his words: "Nerve cell with the origin of a fibre from the acoustic VIII nerve of the Ox; a, membrane of the cell; b, contents; c, pigment; d, nuclear, e, continuation of the sheath region of the nerve fibre; f, nerve-fibre. . . ." (From [63,91]). (D) Another nerve cell from Kolliker's (1832) Textbook for comparison with Fig. C. This is a "large nerve cell with processes from the anterior cornua (horn) of the spinal end in man" (From [91]).
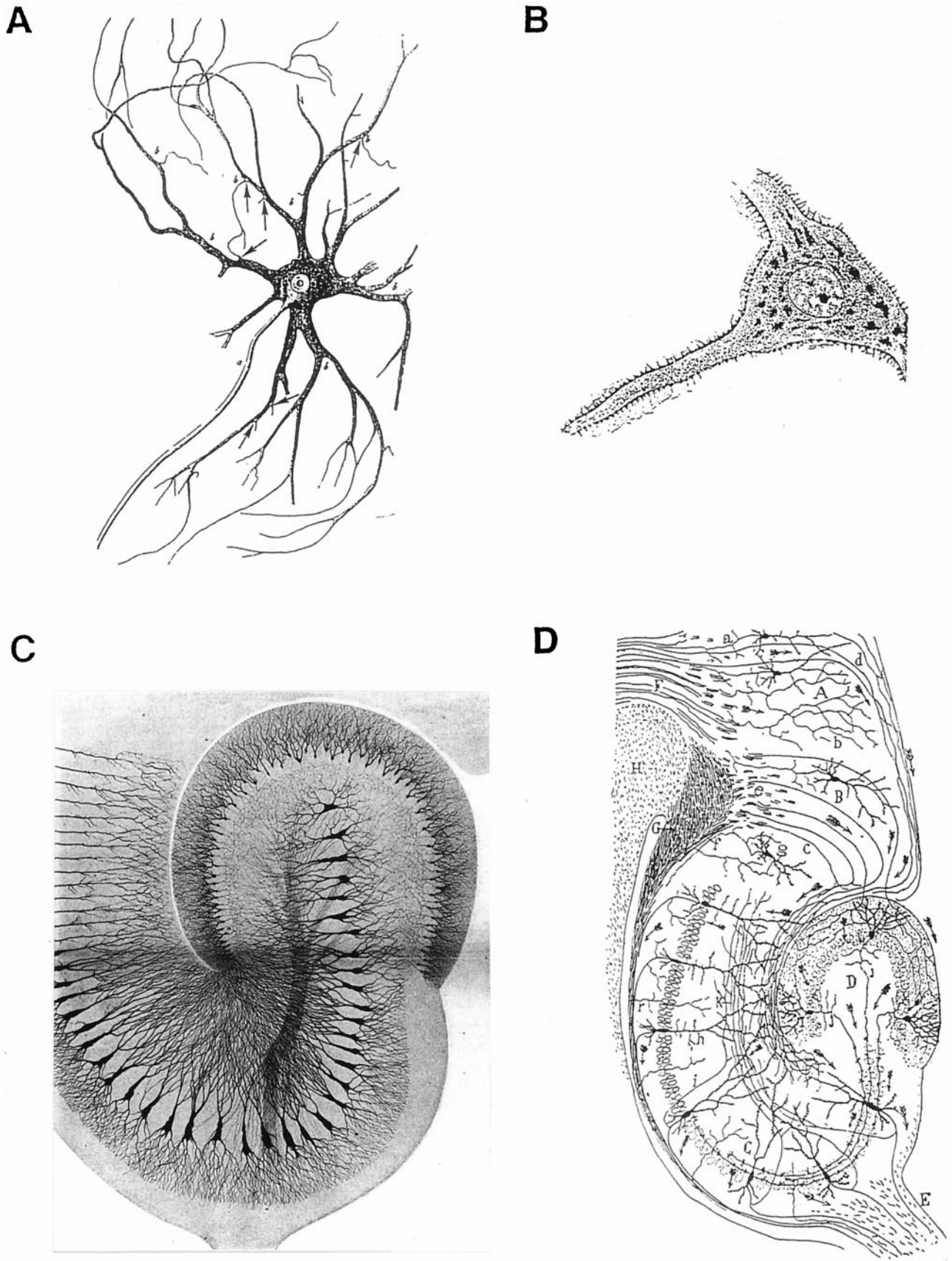
FIG. 8. The search during the second half of the 19th century for nerve endings in the brain. (A) The concept that protoplasmic processes (b) and the axis cylinder (a) are different prolongations of the same cell was represented by Deiters in 1865 in a neuron dissected from the spinal cord of an ox (from Max Schultze, 1870). Deiters thought that input to the protoplasmic processes (dendrites) was via fine fibres connecting by means of a trumpet-like expansion

that the nerve ending, the nerve endplate, charged like an electric plate when the nerve was excited, giving to the contractile substance of the primitive muscle fascicle an electric shock so stimulating it to contract.

Once it had been established that nerve fibres originate from nerve cells, the question arose as to the relationship between the nerve fibre endings in the nervous system and nerve cells. Given that the histological methods using silver staining as well as microscopical techniques current at that time were not able to give an appropriately detailed account of the relationship between nerve ending and muscle at the endplate, they were certainly not able to illuminate the question of the relationship between nerve ending and nerve cell. This area of study was ripe for speculation, without necessarily furthering understanding, and as a result controversy followed. In 1865, O. Deiters [23] showed that dendrites (or as he called them protoplasmic processes; these were named dendrites by W. His in 1889 [61]), in addition to nerve fibres (or as he called them axis cylinders; these were termed axons by Kolliker in 1896 [63]), arose from the nerve cell (named the neuron by Waldeyer in 1891; [103]), a fact that he illustrated beautifully with his drawings of neurons dissected from ox spinal cord (Fig. 8A). He noted in passing that the dendrites possessed trumpet-like expansions on their surfaces attached to very fine fibres (Fig. 8A), which he speculated could represent the input to the dendrites. In 1898, L. Auerbach showed, with silver stain, the 'end bulbs' of nerve fibres on the surface of neurons in the facial nucleus, which he unequivocally identified as such (Fig. 8B; [4]). He also subscribed to the Cartesian/Borelli idea that there was continuity in the propagation from nerve to target cell, commenting that [4]:

As I understand that theory, the axon terminals exert their effects on the cell surface of the ganglion cell by means of close contact of the end bulbs, without intervention of any intermediate substance.

CAJAL: NERVE ENDINGS ARE NOT CONTINUOUS WITH THE CELLS ON WHICH THEY IMPINGE

The use by C. Golgi (1842–1926; Fig. 10A) in 1886 of a silver stain in which potassium bichromate and silver nitrate are applied to produce a black impregnation of neurons did not help resolve the nature of the region of nerve fibre endings on cells. On the one hand, Golgi claimed that he could detect intracellular neurofibrils in nerves with his silver technique and that these extended from the end bulbs of the nerves into the neurons on which they ended, providing continuity for the transmission of the action potential [50,51]. No better illustration of the implications of this continuous reticular network of neurofibrils through nerve fibres, end bulbs, and neurons is provided than that of Golgi's drawing from his stained material of a transverse section through the hippocampus (Fig. 8C). Golgi emphasises in the legend to this figure that the axons ending on the granule cell neurons (upper right part of the figure in the fascia dentata; axons of the pyriform pathway) merge with the dendrites of the granule cells and that the nerves which emerge from the granule cell neurons (the mossy fibre axons,

shown converging to form a single nerve in area CA3) merge with the dendrites of the CA3 pyramidal neurons. In his words [51]:

The diagram illustrates particularly the mode by which a fascicle of nerve fibers comes in relation to the small ganglion cells of the fascia dentata. Between the fascicle of nervous fibers still maintaining themselves as individual elements and the nervous prolongations (axons) of the small cells, exist a complicated network, occupying a semicircular area, which, especially toward the deep part, has indeterminate borders. It is on entering into this network, that, ramifying, a part of the nervous prolongations (axons) lose themselves, as well as the fibers deriving from the fascicle. The latter, issuing from the semicircle formed by the fascia dentata, traverse the zone of the grey layer of the convolution, occupied by the bodies of the cells which belong to this layer, and go to join the fibers of the Alveus and Fimbria.

The conceptual framework here is that of Descarte/Borelli for the neuromuscular junction, namely with continuity between nerves and the structures on which they end. However, in 1866, when Golgi stated that continuity existed between nerves, quite different conclusions were being reached by other histologists [34]. W. His suggested, on the basis of Kühne's description of nerve endings on muscle fibers [64,65], that '*the motor endplates give the indisputable example of transmission of a stimulus without continuity of substance*' [60]. In 1887, F. Nansen, using Golgi's silver-staining technique on the nervous system of invertebrates, concluded that '*a direct combination between ganglion cells, by direct anastomosis of the protoplasmic process, does not exist*' and that '*the branches of the nervous processes do not anastomose*' [76]. Finally, A. Forel in 1887 used the Golgi technique to show that after a lesion '*total atrophy is always confined to the processes of the same group of ganglion cells, and does not extend to the remoter elements in merely functional connections with them*' [39]. None of these observations gave clear evidence one way or the other as to whether nerve endings are continuous with the cells on which they impinge, although the research of Forel on the effects of a lesion paved the way for the definitive work on this problem by a remarkable neurohistologist.

S. Ramon y Cajal (1852–1934; Fig. 10B) learnt of Golgi's silver-staining technique in 1887 and applied it to blocks of the cerebellum in 1889. From this earliest work, Cajal claimed that the terminal baskets of the stellate neurons could be seen to envelop the Purkinje neurons on which they ended without any sign of their being in continuity with the neurons. He developed from this the neuron doctrine, namely that each neuron is an independent cell that does not anastomose with surrounding cells [18,19]. This doctrine is deservedly attributed to Cajal for two reasons: one is the trenchant way in which he defended it against the contrary claims of other neurohistologists, which he did by using their experimental techniques to show how their claims were based on artefacts; the other was his definitive degeneration studies in which he showed that the loss of a particular neuron type could leave behind the synaptic terminals that impinge on it, indicating that the latter were not in continuity with the former. Examples of his forceful style in relation to the defence of his work claiming that

(arrows added by another author) (From [23,62,90]). (B) The first representation of synaptic endings (Endknopfchen) in the central nervous system (facial nucleus; reduced silver preparation; paraffin section). From Leopold Auerbach (1898). He concluded that this was evidence in support of the contact theory of nerve connections. (From [4,62]). (C) A diagram by Golgi of the nervous elements of the hippocampus and fascia dentata. (From [50,91]). (D) A diagram by Cajal illustrating the structure and connections of the hippocampus and fascia dentata. A, retrosplenial area: B, subiculum; C, Ammon's horn; D, dentate gyrus; E, fimbria; F, cingulum; G, angular bundle or dorsal hippocampal commissure (crossed temporo-ammonic path); H, corpus callosum; K, recurrent collaterals from pyramidal cells to the stratum lacunosum of Ammon's horn (Schaffer collaterals); a, axon entering cingulum ; b, cingulum fibres ending in the retrosplenial area; c, fibres of the perforant or direct temporoammonic path; d, perforant fibres of the cingulum; e, plane of dorsal perforant path fibres; g, subicular cell; h, pyramidal cells in field CA1 (regio superior) of Ammon's horn; i, ascending (Schaffer) collaterals of large pyramidal cells; r, collaterals of alvear fibres. (From [18]).
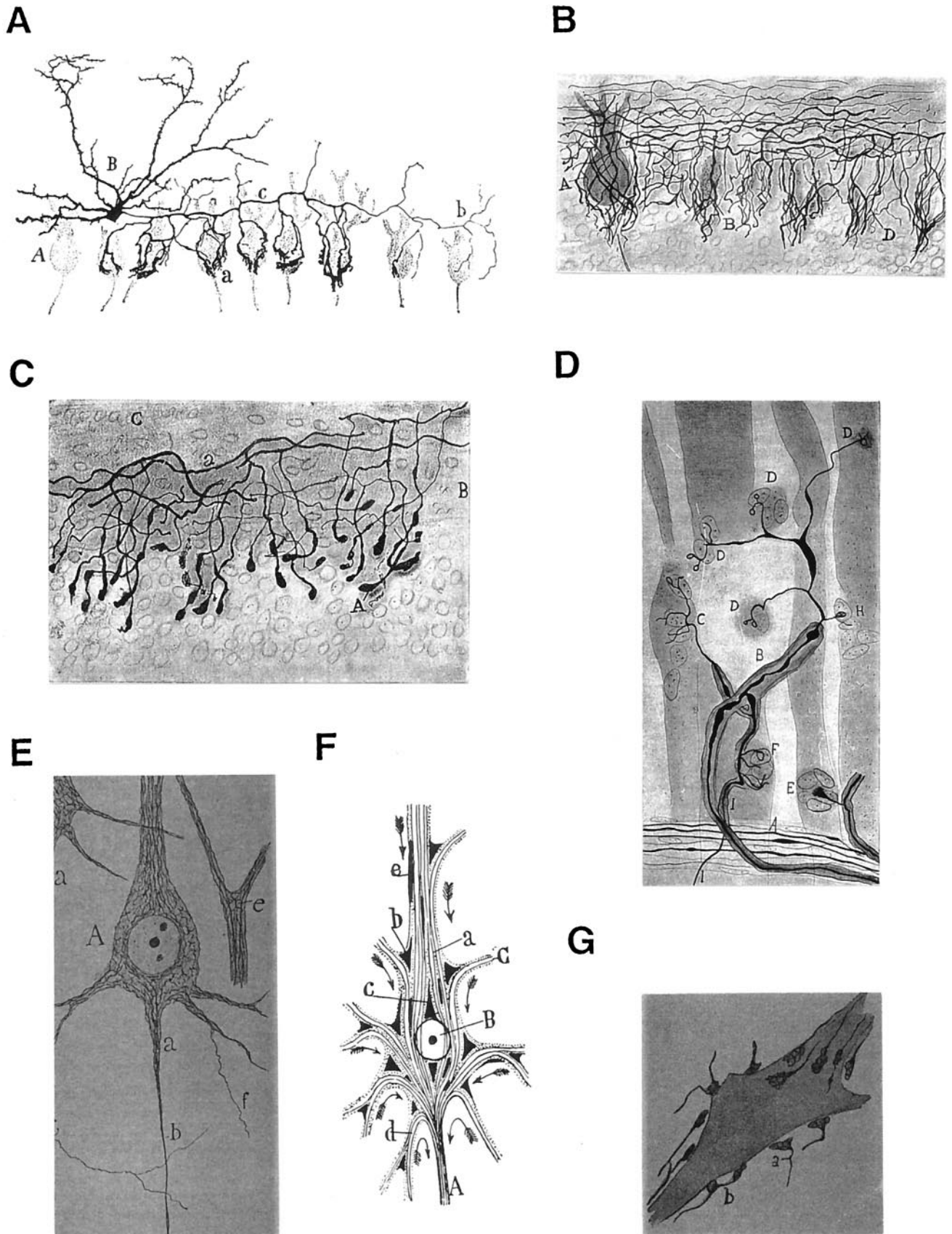
FIG. 9. Evidence at the end of the 19th century that nerve terminals are not in continuity with the cells on which they impinge. (A) The endings of cerebellar basket cells in the albino mouse viewed using the Golgi method. A, Purkinje cell stained with osmic acid. B, basket cell. a, b, pericellular axonal ramifications forming baskets. C, axon. (From [18]). (B) The endings of cerebellar basket cells in a cat (25 days old) 24 hours after axotomy of the Purkinje

nerve terminals can be shown in silver stained material to abut but not anastomose with neurons are as follows [18]:

'Gerlach concluded that certain axons anastomose at their endings with the tips of dendrites, and, thus that central axonal arborizations do not end freely but instead merge with dendrites.' 'Because Golgi thought that central axonal arborizations do not end freely but anastomose instead, his hypothesis is actually based on Gerlach's theory.' 'To demolish the theory, it was necessary to show by direct observation in the adult brain that axonal arborizations terminate freely, and in the final analysis to do so under conditions that no one could object to because observations were in embryonic material or because material was improperly stained. We were the first, in 1888, to demonstrate unequivocally and irrefutably that terminal arborizations end freely.' 'One need only recall the varied and often profound alterations that occur in dendrites stained with Ehrlich's method giving varicosities, cyanophilic masses and abnormal thickenings, which may condense or fuse with one another. When this happens the resulting images look so much like anastomoses that they may readily be mistaken for them.' 'In the embryonic and adult spinal cord, in the cerebellum, cerebral cortex, Ammons horn, striatum, and olfactory bulb, in the autonomic nervous system, in the spinal ganglia, retina, and elsewhere, the terminal arborizations of axons and dendrites invariably end absolutely freely—a fact that can be demonstrated equally well by the Golgi and the Cox methods.'

He therefore concluded that [18]:

. . . the only opinion that is in harmony with the facts (is) that nerve cells are independent elements which are never anastomosed, with by means of their protoplasmic expansions (dendrites) or by the branches of their prolongations of Deiters (axons), and that the propagation of nervous action is made by contacts at the level of certain apparatuses of dispositions of engagement.

In 1892, Cajal gave his description of the nerve networks of the hippocampus using the Golgi silver technique, 6 years after Golgi himself had described the network (Fig. 8C). Cajal's work could not be more different (compare Fig. 8D with 8C in which the sections through the hippocampus are oriented in the same way, with the fascia dentata uppermost). Here neurons are clearly circumscribed according to the neuron doctrine that each neuron is a separate cell, rather than in continuity with other cells through a neurofibrillar network that joins them all together at the site of the end bulbs. The neurofibrils were intracellular to the neuron according to Cajal (Fig. 9E), and did not extend out of the terminal boutons into the neurons on which they abutted (Fig. 9G). With Golgi and many other neurohistologists these neurofibrils were both intracellular and intercellular, joining the terminal boutons to the neuron on which they ended, and so giving rise to a reticulum of neurofibrils that gave continuity to the entire neural network in places such as the hippocampus (Fig. 8C). On technical grounds it is not easy to say unequivocally that Cajal had objective proof for his doctrine. This was particularly the case when considering the speculations which he and other neurohistologists engaged in concerning the role of the neurofibrils in the conduction of the action potential. For example, Cajal comments that [18]:

The existence of a conductive pathway in the cytoplasm was also postulated on the basis of observations made with the Nissl method. . . . So that the reader may judge the extent to which the discovery of the neurofibrillar network justifies these assumptions, we shall reproduce a drawing (Fig. 9F published long ago and based on the work of Bethe). Neurofibrils are the sole conductors of neuronal activity. They form bundles in the dendrites and axon, and course between the Nissl bodies as they cross the perikaryon on their way from one process to another without anastomosing among themselves. Long neurofibrils, most of which converge on the axon, are not the only type found in the cell.

Cajal went much further in this conjecturing, for which there was not a scintilla of physiological evidence, that the arrangement of the neurofibrils within a single neuron is such that the conduction of the action potential could only occur from dendrites to soma to axon (Fig. 9F). This then led him to place arrows of action potential flow on so many of his drawings summarising the results of silver staining of a particular block, such as that of the hippocampus (Fig. 8D). The fact that these have ended up being approximately correct does not mean that Cajal should be credited for their discovery, which would be for profoundly wrong reasons, namely based on the conduction of action potentials by neurofibrils. It might be commented on in passing that Cajal's work was not subject to review until towards the end of his life, as it was published privately. In summary then the neuron doctrine could not be considered to be definitively supported by this silver-stain work.

An entirely different conclusion may be reached when considering Cajal's work on degeneration of neural centres which does give definitive support to the neuron doctrine. Again the major evidence was provided by the relationship between terminals on Purkinje cells in the cerebellum and the state of the terminals when the Purkinje cells degenerate [18]:

'As an example of a convincing and well known case let us mention the disappearance of the Purkinje cells in general paralysis with maintenance of the basket and stellate cells of the molecular layer. This persistence, revealing the independence of the baskets and the cells they surround, can also be produced experimentally by sectioning the axons of the Purkinje cells at the level of the granular layer or even below as is shown in Fig. 9B (compare with the normal in Fig. 9A). This remarkable conservation of the baskets, despite the disappearance of the cells in connection with them. . . . , 'The basket cells resist pathological influences much more that do the Purkinje cells.' 'The baskets in young traumatised animals appear nearly normal, even at the level of regions where the cells have disappeared (Fig. 9B(D)).' 'Baskets of the Purkinje cells . . . are perfectly formed in animals from twenty to thirty days old, while they are constantly altered in the vicinity of wounds, although they never react so actively and energetically as the axons of the Purkinje cells. The lesions most commonly found are as follows: (a) Baskets whose descending appendices have terminal balls. As can be seen in Fig. 9C(A), the Purkinje cells have been resorbed, and the descending branches of the baskets, notably thickened and intensely stained, end in a terminal ball or in a series of clubs.'

One may entirely agree with Cajal in his comment that [18]:

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cells, which destroy them. A, almost normal Purkinje cell. B, Purkinje cell undergoing atrophy and granular in appearance. D, baskets surrounding the empty spaces previously occupied by Purkinje cells that are now destroyed (From [17]). (C) The endings of cerebellar basket cells in a rabbit (2 months old) 30 hours after axotomy of the Purkinje cells. A, terminal clubs. B, molecular layer. a, transversal fibres of this zone (From [17]). (D) Motor endplates on skeletal muscle fibres during reinnervation of the muscle by the motor nerve. Different stages of restoration are shown. A, nerve. B, fibre that gives rise to several plates. E, H, plates as yet without ramifications. C, F, plates with a well-developed arborization (From [17]). (E) The concept of a neurofibrillary network within a individual neuron, that was taken to conduct impulses by Cajal and others. Shown is a giant pyramidal cell (10-day-old dog). A, is a cell with a pericellular plexus. A, axon. B, summit of the axon hillock. F, dendritic branch with a single neurofibril (From [18]). (F) Diagram due to Cajal showing the presumed direction of conduction of impulses along the neurofibrillary network with a cortical pyramidal cell. A, axon. B, nucleus. a, channels or pathways for the neuronal currents of the impulses. b, Nissl bifurcation cones. c, nuclear hood. d, recurrent path of currents in a process bordering the axon. e, elongated Nissl body. Arrows indicate the direction of current flow (From [18]). (G) Terminal boutons surrounding a funicular neuron in the spinal cord (From [18]).
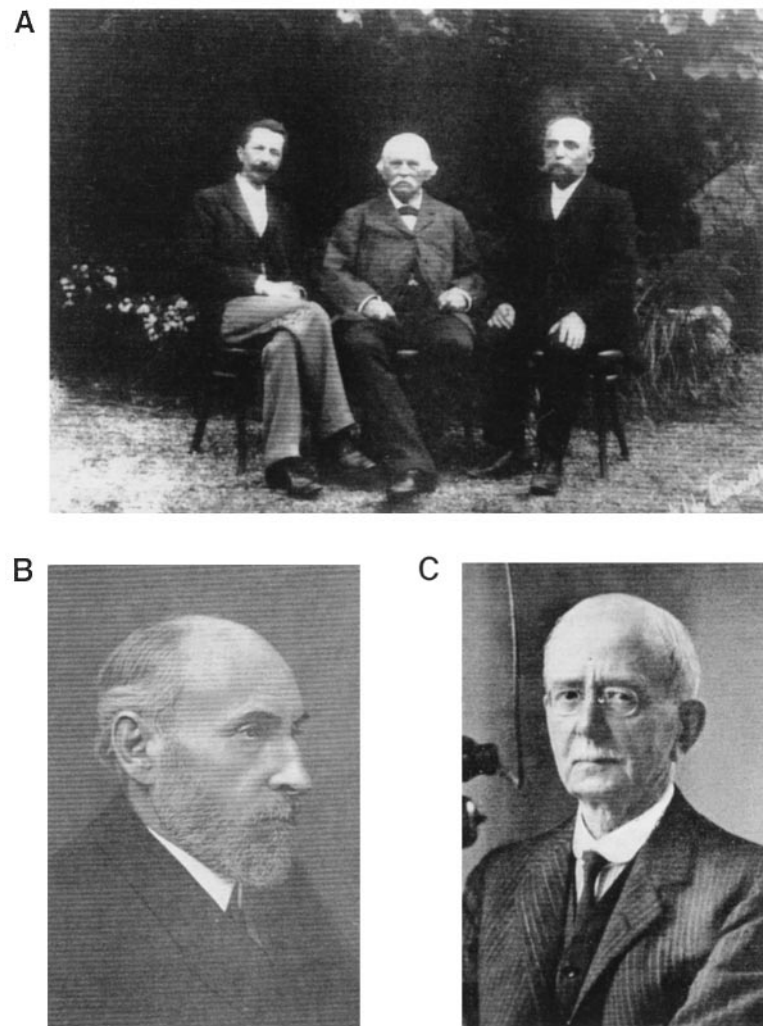
FIG. 10. Major figures at the end of the 19th century responsible for the emerging definition of the synapse. (A) From left to right, Guilio Bizzozero (a friend of Golgi), Albrecht Kolliker (1817–1905) and Camillo Golgi (1844–1926) at Golgi's home in Padua in 1887 (from Prof. P. P. C. Graziadei; From [91]). (B) Santiago Ramon y Cajal (1852–1934) (From the frontispiece in [18]). (C) Charles Scott Sherrington (1858–1952) (From [52]).

The neuron doctrine is compatible with the well-documented phenomenon of secondary degeneration in neural centers. In fact, if neurons were not completely independent, it would be impossible to account for the precise localisation of degeneration following ablation of cell groups or fiber tracts.

Cajal's speculations concerning the physiological role of neurofibrils had led him to his polarisation of the neuron doctrine, namely that action potential flow was only from terminal bulb to dendrite (or sometimes soma), and then from soma to axon. However, it was a physiologist, namely Sherrington, who supplied the experimental findings which showed that the region of contact between the end bulb and neuron might only allow the direction of action potential transmission in one direction through the end bulb.

SHERRINGTON: THE ADOPTION OF THE WORD 'SYNAPSE'

Sherrington (1858–1952; Fig. 10C), as a consequence of his

work on spinal reflexes in the 1890s, had reached the conclusion that transmission of the action potential across the end bulbs of sensory nerve terminals to neurons in the spinal cord involved different principles to that of the conduction of the action potential along nerve fibres (see [67]).

The nerve centre exhibits a valve like function, allowing conduction to occur through it in one direction only. How securely the circuits of the nervous system are valved against regurgitation is shown by the Bell-Magendie law of the reactions of the spinal nerve roots.

It was work on spinal reflexes that had led to the idea of the 'valve like function' of the region of apposition between the end bulbs and the neuron, and so distinguished this region from the rest of the nerve fibre. This is reminiscent of Descartes model of the nervous mechanism of reciprocal inhibition of voluntary movement which was based on the idea of a flow of animal spirits in hollow nerve fibres; in this case valves could differentially alter the flow through

anastomoses between nerves to antagonistic muscles, e.g. lateral and medial rectus muscles of the eye (see Fig. 3B). As Michael Foster said in 1901 [40]:

If we judge Descartes from the severe standpoint of exact anatomical knowledge, we are bound to confess that he, to a large extent, introduced a fantastic and unreal anatomy in order to give clearness and point to his exposition. . . . If we substitute in place of the subtle fluid of the animal spirits, the molecular changes which we call a nervous impulse, if we replace his system of tubes with their valvular arrangements by the present system of concatenated neurons. . . . Descartes' exposition will not appear so wholly different from the one which we give today.

How far then did the work on spinal reflexes in the late 19 century allow for a new principle to be enunciated concerning the operation of the region where end bulbs impinged on neurons, different from the speculations of the 17th century?

Sherrington's emphasis on some kind of discontinuity at the region of apposition between end bulb and neuron mostly rests on the results obtained from degeneration studies. He says [92,93]:

The evidence of Wallerian secondary degeneration is clear in showing that process observes strictly a boundary between neurone and neurone in the reflex arc. The characteristics distinguishing reflex-arc conduction from nerve-trunk conduction may therefore be largely due to inter-cellular barriers, delicate transverse membranes.

He goes on to comment that:

. . . the characteristics distinguishing reflex arc conduction from nerve-trunk conduction may therefore be largely due to intercellular barriers, delicate transverse membranes. . . . If the conductive element of the neurone be fluid and if at the nexus between neurone and neurone there does not exist any actual confluence, there must be a surface of separation. Even should a membrane visible to the microscope not appear, the mere fact of non-confluence of the one with the other implies the existence of a surface of separation. Such a surface might restrain diffusion, bank up osmotic pressure, restrict the movement of ions, accumulate electric charges, support a double electric layer, alter in shape and surface tension with changes in difference of potential, alter in difference of potential with changes in surface tension and in shape, or intervene as a membrane between dilute solutions of electrolytes of different concentration or colloidal suspensions with different sign of charge. It would be a mechanism where nervous conduction, especially if predominantly physical in nature might have grafted upon it characteristics just such as those differentiating reflex-arc conduction from nerve-trunk conduction. For instance, change from reversibility of direction of conduction to irreversibility might be referable to the membrane possessing irreciprocal permeability.

In Foster's textbook of 1897 he goes on to comment on the nervous impulse 'sweeping along' the axon of one neuron until it is [40]:

. . . brought to bear through the terminal arborisation on the dendrites of another neuron where 'the lack of continuity between the material of the arborisation of the one cell and that of the dendrite (or body) of the other cell offers an opportunity for some change in the nature of the nervous impulse as it passes from one cell to the other'.

There is no doubt that the results of Wallerian degeneration pointed to the likelihood of end bulbs possessing membranes as did the rest of their parent nerve fibre. The problem then presented itself of how such a membrane might relate to the membrane of the underlying neuron membrane on which the end bulb impinged. It was to this region then that the irreversibility of nerve transmission must be ascribed and an explanation sought. It was the histological work on Wallerian degeneration together with the physiological discovery of the irreversibility of transmission that indicated the special nature of this region. It was clear that this region deserved a name that might focus the attention of experimenters and so help delineate its properties.

In Foster's textbook of 1897 Sherrington provided the name [40]:

So far as our present knowledge goes, we are led to think that the tip of a twig of the arborescence is not continuous with but merely in contact with the substance of the dendrite or cell-body on which it impinges. Such a special connection of one nerve cell with another might be called a 'synapsis'.

The origins of this use of the word 'synapsis' or as it became 'synapse' can be found in letters Sherrington wrote to his colleagues Sharpy-Schafer in 1897 and Fulton in 1937, in reply to enquiries concerning the derivation of the word. To the former he wrote (see [92–94]):

'As to nomenclature—its sole object is I take it clearness combined with brevity. . . . Definition is wanting when a penny has to pass for 5 and 3 farthings as well as for 4: the one symbol is then too little. . . . All I think we ought to be careful not to do is "commit barbarisms", e.g., impossible adjectival form, using prefixes and affixes with false signification or in impossible ways—that simply adds new terms which like other "monsters" can't live long, and may be misleading during life, does all of us harm as giving the impression of carelessness or ignorance'. 'As to "junction" I feel we are less easily reconcilable. If a latin form capere not jungere should be the root. The mere fact that junction implies passive union is alone enough to ruin the term. . . . I think it does not want the gift of prophecy to foretell that it [the word junction] must become more and more obviously inapplicable as research progresses. Synapse, which implies a catching on, as e.g., by one wrestler of another—is really much closer to the mark. But I am not a bit wedded to the word: if you could suggest an English word containing the notion which is not already overburdened with applications. I have been trying to find one but cannot. Conjunction is even worse than junction'.

Sherrington wrote to Fulton that [94]:

'You enquire about the introduction of the term "synapse"; it happened thus. Michael Foster had asked me to get on with the Nervous System part (Part III) of a new edition of his Textbook of Physiology for him. I had begun it, and had not got far with it before I felt the need of some name to call the junction between nerve-cell and nerve-cell (because that place of junction now entered physiology as carrying functional importance). I wrote him of my difficulty, and my wish to introduce a specific name. I suggested using "syndesm" (συνδεσμοζ). He consulted his Trinity friend Verrall, the Euripidean scholar, about it, and Verrall suggested "synapse" (from συνα πτω), and as that yields a better adjectival form, it was adopted for the book.

The concept at root of the need for a specific term was that, as was becoming clear, conduction which transmitted the impulse along the nerve fibre could not—as such—obtain at the junction, a membrane there lay across the path, and conduction per se was not competent to negotiate a cross-wise membrane. At least so it seemed to me then, perhaps A. V. Hill and Gasser and Bishop could tell us differently today.

I do not know when the term "synapsis" was introduced for a phase of the karyokinetic process. Neither Foster nor I knew of it in that connection. I fancy Salvin Moore, a cytologist, put it forward. He once told me he had not known the term was in use in physiology. I think that your proposed synaptic knobs would be very clear and helpful. Pace Verrall's memory (Verrall was a delightful and charming man). "Synapsis" strictly means a process of contact, that is, a proceeding or act of contact, rather than a thing which enables contact, that is, an instrument of contact. "Syndesm" would not have had the defect, that is, it would have meant a "bond".'

The credit for the word "synapse" then goes to a classical scholar at Cambridge (for a detailed outline of this claim, see [96]).

Although the word 'junction' was abandoned by Sherrington as appropriate to describe the functional relationship between the end bulb and neuron it was preserved for that between motor nerve and muscle at the endplate. Here Wallerian degeneration had also indicated the discreteness of the nerve terminal from the muscle at the endplate, suggesting that neither Boerhaave nor Kuhn were any more correct than Golgi in ascribing continuity between the end of

nerve terminals and the cells on which they impinged. The research of Tello, working in Cajal's laboratory, was particularly persuasive on this issue, as it showed the postjunctional endplate apparatus was intact in frog muscle after denervation, and that reinnervating nerve fibres could be found at different stages of terminal formation on these regions of the muscle (Fig. 9D; see [17]).

Sherrington's prescient comment that [94]: '. . . *conduction per se was not competent to negotiate a cross-wise membrane*' was followed by the caveat that '*At least so it seemed to me then, perhaps A. V. Hill and Gasser and Bishop could tell us differently today*'. Sherrington's claim that conduction could not per se negotiate the synapse was soon challenged by K. Lucas and later his colleague E. D. Adrian. They produced credible biophysical explanations of how conduction *per se* could negotiate a cross-wise membrane. Their theory showed how even the process of inhibition at synapses could function without the necessity of evoking any new principles other than those involved in the conduction of the action potential.

Cajal's use of arrows showing the direction of action potential conduction on his drawings of silver-stained neurons seem to independently support Sherrington's notions, with conduction only possible in one direction across the synapse. But of course Cajal's arrows are placed according to an erroneous idea of conduction by neurofibrils. Too much importance has been placed in the history of neuroscience on Cajal's arrows and Sherrington's introduction of the work 'synapse'. These researchers made great contributions to the delineation of the types of neurons to be found together with their spatial relationships on the one hand and to that of the excitatory and inhibitory processes which these neurons participate in on the other. However, one must turn to the research of other investigators in order to find the observations which warrant the use of the words 'junctions' and 'synapses'. Such research was supplied in the 20th century, and is the subject of a more contemporary history (see [5]).

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