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NEUROID CONDUCTION AND THE EVOLUTION OF CONDUCTING TISSUES

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ABSTRACT

Neuroid conduction, as here defined, refers to the propagation of electrical events in the membranes of non-nervous, nonmuscular cells. Examples from protists, plants, and animals are described.

In the dinoflagellate Noctiluca, propagated membrane depolarizations accompany the spread of the luminescent response, and local electrical changes are associated with tentacle movement. The ability of Noctiluca to conduct is attributable to its peculiar geometry, in which much of the cytoplasm is confined to a thin peripheral layer surrounding the flotation vacuole, a condition that permits local current flow to develop.

Fresh-water algae of the family Characeae show propagated action potentials in which chloride efflux is the major event responsible for electrogenesis. Chloride spikes are presumed to be an adaptation to fresh water, following Grundfest (1966c).

Among the higher plants, Dionaea and Mimosa provide examples of neuroid conduction. The former also possess trigger cells which function in an analagous way to certain animal receptors. In Mimosa there is evidence that the cells responsible for conduction of electrical events are located in the vascular bundles and that propagation requires simultaneous activation of a number of cells lying parallel in the bundles, as in mammalian smooth muscle. In both cases transmission from cell to cell is thought to be electrical via low-resistance pathways.

In hydromedusae and siphonophores neuroid conduction occurs in the exumbrellar ectoderm and subumbrellar endoderm, the two layers being linked as a transmission pathway for excitation going to ectodermal smooth muscle systems. The "crumpling" behavior of medusae is transmitted by this system, but nervous components may be involved in the generation of the full response. Reverse locomotion in physonectid siphonophores (e.g., Nanomia) involves activation of neuroid pathways. In the siphonophore Hippopodius, neuroid conduction in the exumbrella is coupled to luminescent and blanching reactions. Neuroid conduction in all these forms provides a rapid and efficient method of information transfer. It is typically associated with the spread of protective and locomotory responses and is general rather than local in effect. The more complex and local responses are believed to be organized by the nervous system.

In ctenophores, recent work suggests that propagation of the ciliary beat between cells of the comb plates is neuroid, and that inhibition of ciliary activity is nervous. Certain cells in the ciliated grooves seem to represent neurons in process of evolution from non-nervous, ciliated cells.

*In the pluteus larva of an echinoderm, coordination of ciliary reversal is associated with electrical signals apparently of non-nervous origin. In another larval form, that of the toad *Xenopus*, neuroid conduction has been demonstrated in the skin at a stage before the nerve supply reaches the skin, giving the tadpole a precocious capacity for response.*

As for the evolution of conduction, conducting tissues probably arose independently in many lines of evolution.

Frequently the conducting tissue would have evolved from an epithelium in which the cells were connected by pathways serving for metabolic communication, the existence of these junctions predisposing the tissue for electrical transmission of propagated depolarizations. The effective conducting units in such tissues would have been groups of electrically coupled cells, rather than individual cells as such.

In animals, nerve and muscle tissues are considered to have arisen from primitive myoepithelial sheets in which transmission occurred through low-resistance intercellular pathways. With the need for increased specificity in the conduction and response system, the original tight coupling between the cells would be replaced by specialized synapses. While electrotonic synapses have the potential to perform many integrative functions of the nervous system, chemical synapses have in general prevailed.

INTRODUCTION

THROUGHOUT the animal kingdom nerve cells provide the common means for rapid transfer and organization of information, often doing so to the exclusion of other functions and without the help of other conducting systems. Conduction, however, is not an exclusively nervous property. In organs such as the vertebrate heart and in a number of other muscles, waves of excitation pass from cell to cell across the tissue, spreading the contractile response. This is referred to as "myoid" conduction. Further, certain non-nervous, non-muscular tissues are also known or suspected to be capable of conducting electrical events. Non-nervous conduction of this sort is termed "neuroid."

The term "neuroid conduction" has been applied to a variety of phenomena, not all of which can be explained on the same functional basis. In some cases the conduction in question may not involve propagated electrical changes at all, or such changes, if they occur, may have no significance in information transfer. These cases are excluded from the present discussion. We are here solely concerned with cases where there are propagated electrical changes in the membranes of the conducting cells. Such con-

duction occurs in plants, animals, and protists. It is probably a phenomenon of great antiquity that arose before the evolution of nerve cells took place, and it is therefore interesting for the light it may throw on the origin of nervous conduction.

Concepts of neuroid conduction may be traced back well into the last century, long before there was any understanding of the electrical basis of nervous transmission. Taking coelenterates as an example, we find that Kleinenberg (1872) proposed that the individual contractile cells of *Hydra* acted like combined neuromuscular units, receiving stimuli and transmitting the resulting state of excitation from the "sensory" pole to the contractile region, where the effector action took place. Chun (1897) developed this idea further by suggesting that conduction took place from cell to cell across the whole myoepithelial sheet. He even proposed that conduction could occur between epithelial cells even where no contractile elements were present, and cited as an example the exumbrellar epithelia of siphonophores. We now know that neuroid conduction does indeed occur here (Mackie, 1965).

The actual expression, "neuroid," seems to have originated with G. H. Parker, who used it to describe the spread of excitation in the

tissues of sponges, a form of conduction which he believed "represents without doubt that elemental property of protoplasmic transmission from which true nervous activity has been evolved" (Parker, 1919, p. 64). He also applied the term to conduction in ciliated epithelia, following earlier authors who had regarded this as a form of non-nervous propagation. Unfortunately, there is still no evidence that information transfer in sponges involves propagated electrical events and, if specialized conducting cells do occur, they have not been identified with certainty, so the term neuroid conduction in the sense defined above cannot confidently be applied to sponges, although "neuroid conduction" in some other sense might be supposed to occur. In the case of ciliary transmission, electrical changes in the membranes of the ciliated cells themselves seem to be the triggering events in a few cases, but generally the issue is in doubt. Some forms of ciliary transmission are thought to be entirely mechanical (Sleigh, 1966), and therefore fall outside the present definition.

It is not possible here to review the whole history of concepts of non-nervous conduction nor to allude to all the instances where it is believed to occur. The intention here is to consider recent work where electrical recordings give evidence of neuroid conduction and to choose certain specific examples which seem to be especially significant. Thus, this review is selective rather than comprehensive.

CONDUCTION IN A UNICELLULAR ORGANISM (*Noctiluca*)

Noctiluca is a member of the Order Dinoflagellata, well known for the luminescence of certain of its species. It is large enough for recording electrodes to be inserted into the interior and for external recordings to be made simultaneously, as well as for stimuli to be applied either externally or internally (Eckert, 1965a, b, 1966; Eckert and Sibaoka, 1967a, b, 1968).

Potentials recorded from the interior resemble nerve action potentials except that their polarity appears at first sight to be anomalous: they are negative-going rather than positive-going events. This is now known to be due to the fact that the "internal" electrode is not

really in the cytoplasm at all, but lies in the flotation vacuole which occupies the center of the cell. The vacuole is separated from the cytoplasm by the cell membrane, so the fluid in it is effectively an extracellular medium. When the inner, active membrane depolarizes the vacuole becomes negative with respect to the sea water, so the event is recorded as a hyperpolarization by an electrode in the vacuole. Recordings from within the perinuclear cytoplasm show a conventional positive-going polarity.

Two main types of electrical event have been recorded from *Noctiluca*. One is associated with the food-gathering movements of the tentacle, the other with propagation of the luminescent flash. Each time the tentacle beats, whether in response to stimulation or spontaneously, a potential change is recorded. A prespike pacemaker potential is recorded first, lasting about three seconds, during the latter part of which the tentacle flexes. Then comes the spike, followed after one or two seconds by extension of the tentacle. When the organism is placed in calcium-free sea water the tentacle movements stop but the cyclical electrical changes continue, indicating that the recorded signals are no mere byproduct of the mechanical activity. Evidently, in fact, they are excitatory pulses similar to those recorded from muscle cells prior to contraction. They are probably not propagated over the whole cell but are confined to the region around the tentacle. As local, nonpropagated events, these potentials fall outside the strict definition of conducted neuroid events, but they are included here because they are interesting as an indication of the differing electrical properties of different parts of the cell membrane, a condition foreshadowing that of nerve cells in higher animals.

When *Noctiluca* is touched or electrically stimulated it gives off a flash of light. Unlike the tentacle response, flashing does not happen spontaneously. Recordings taken during flashing show that the flash takes place a few milliseconds following a spike potential, which is propagated all over the organism at about 6.0 cm/sec. Flashing is never seen without the preceding spike potential. The latter, once evoked, is propagated on an all-or-none basis, but local, graded responses can be obtained

with subthreshold stimulation. This capacity on the part of the excitable membrane for graded response as well as for nondecremental propagation, and the properties of potentiation, summation, and fatigue shown by the luminescent response, all find parallels in conventional neuromuscular physiology.

The discovery of propagated electrical changes in *Noctiluca* raises questions concerning conduction in protistans, in general. Propagated events have not been recorded in other protistan forms. Electrical changes have been described in a number of cases, but they are not propagated events. In *Paramecium*, for example, action potentials are recorded when there is a change in the direction of ciliary beating, but these potentials do not spread progressively (i.e., propagate) — they occur uniformly over the whole surface at the same moment (Naitoh and Eckert, 1969).

The key difference between *Paramecium* and *Noctiluca* seems to lie in the peculiar geometry of the *Noctiluca* cell, consisting as it does of a thin layer of cytoplasm surrounding a fluid vacuole. The layer of cytoplasm presumably has a high core resistance, so that local current flow, and hence propagation, become possible. In *Paramecium*, by contrast, the interior is essentially isopotential. Current flow initiated in any region will achieve nearly the same density throughout the interior and across all parts of the membrane, so that when the depolarization threshold is reached, it is reached simultaneously all over the cell. Propagation is impossible in spherical or subspherical cells with isopotential interiors. If *Paramecium* were longer, thinner, or flatter, it might be capable of propagation. Thus, in attempting to explain why a given cell does or does not conduct we have to consider not only the electroionic properties of the membrane, but the shape of the cell as a whole.

AN ALTERNATIVE TO THE SODIUM SPIKE

The Characeae

The internodal cells of freshwater algae of the family Characeae are used extensively for electroionic studies similar to those carried out on the squid axon, and for the same reason: the large size of the cells in question facilitates their study. Action potentials can be evoked

by suitable stimulation, and are found to travel at velocities of up to 40 cm/sec in cells bathed in media of suitably low resistance (work reviewed by Sibaoka, 1966). The significance of these propagated events in the biology of the Characeae is unknown. There are no known effectors coupled to the transmitting system. The only noticeable change is that cytoplasmic streaming is temporarily suspended following the passage of an "impulse." Excitation can jump from one cell to another, probably by low resistance pathways or cytoplasmic bridges in the junctional region.

The action potential in several of these algae is now known to involve primarily the chloride ion (Bradley and Williams, 1967; Raven, 1967). The central vacuole of the cell is about 150 millivolts negative to the outside in the resting condition, but is about 15–20 millivolts positive with respect to the cytoplasm. The high resting potential of the cell is brought about by the accumulation of chloride within the cell cytoplasm by active transport. When the cell is stimulated, a rapid efflux of chloride takes place, to the accompaniment of a recorded action potential of considerable magnitude (over 200 millivolts in *Chara*). The net effect is similar to that observed in the squid axon, where active outward transport of sodium and a transitory sodium influx are the analogous events.

As Grundfest points out (Grundfest, 1963, 1966a), the development of chloride spikes would appear to be a logical adaptation in cells surrounded by fresh water, since the concentration of cations in the medium would be too low to permit the rapid influx needed for a spike depolarization. The chloride anion by contrast can be accumulated gradually by steady pumping in the resting cell to a level sufficient to allow rapid efflux when the conductance change associated with spiking takes place.

Dionaea: A PLANT WITH SENSE ORGANS, "MEMORY," AND BEHAVIOR

The terminal part of the leaf in *Dionaea* (Family Droseraceae, the Venus' fly trap) is divided into two semicircular lobes hinged together by the midrib. Under appropriate stimulation, a wave of excitation crosses the leaf

causing turgor changes in the cells around the midrib, and the two lobes then move together. As is well known, the plant can catch small insects by this means.

The upper surface of the leaf has six trigger hairs reminiscent of the tactile sensillae found in various animal groups. An action potential is generated at the base of a trigger hair when the latter is moved, and spreads from there all over the leaf. Transmission may be as fast as 17 cm/sec (Sibaoka, 1966).

Using a technique adapted from methods introduced for investigating insect sensillae, Jacobson (1965) has shown the existence of nonpropagated receptor potentials which precede the propagated event, and which act, in effect, like the generator potentials found in animal receptors. Jacobson draws the analogy with the Pacinian corpuscle in particular, where receptor potentials generate single propagated action potentials in the nerve leading out from the corpuscle.

It usually takes two action potentials coming within a period of about twenty seconds to call forth the closure response. When it takes place the response occurs quickly, generally within a second of the arrival of the second potential. The interval between the two potentials is not critical in determining the response latency. "How the lobes memorize the reaction due to the first action potential is still unknown" (Sibaoka, 1966, p. 56).

Sibaoka (1966) showed that passage of the first potential facilitates passage of the second in terms of conduction velocity, for the second potential travels at three or four times the velocity of the first if it follows the latter within a few seconds. Since neither the identity of the conducting cells nor the mode of junctional transmission is understood, it would be premature to compare this phenomenon with superficially similar mechanisms in animals.

Mimosa: THE EFFECTIVE UNIT OF CONDUCTION

The *Mimosa* leaf has flexible joints operated by pads of parenchyma cells. The cells are usually distended, holding the joint stiff. When appropriately stimulated they suddenly lose fluid from the vacuole, and the joint bends. This reaction takes place with a short latency following damaging stimulation to the leaf,

and is termed "seismonasty" by plant "psychologists." To the student of animal behavior it would appear to have adaptive value as a protective response, like the tentacular withdrawals and closure responses of marine invertebrates. A distinguished botanist, however, asserts that "it is very difficult to see any ecological significance" in the response (Strasburger, 1965, p. 63).

Sibaoka (1966) has described several sorts of propagated phenomena from *Mimosa* leaves. These include rapidly conducted action potentials, the impulses which trigger the seismonastic response. A search for the excitable cells revealed that they are located in the vascular bundles. Elongated parenchyma cells in both xylem and phloem carry the impulses. Transmission must occur from one cell to another on an all-or-none basis within through-conducting portions of the leaf, since no single cell would be long enough to span the entire distance.

Sibaoka's experiments show that transmission must take place not only longitudinally from cell to cell, but also laterally between adjacent cells in the vascular bundle. Generation of a propagated impulse seems to require *simultaneous activation of a number of excitable cells*. From these observations it is concluded that the effective unit of conduction in *Mimosa* is not the individual cell or linear series, but groups of adjacent, electrically interacting cells. The larger the number of cells activated, the stronger would be the electrotonus generated. This would help to explain the finding that the most rapid conduction occurs in those parts of the leaf having the greatest cross-sectional diameter.

Cases where, as in *Mimosa*, the effective conducting unit is *more* than one cell also occur in animals. Mammalian smooth muscle conducts slowly without the aid of nerves. If a strip of muscle is cut down to about 100 micra, equivalent to two or three hundred cells in parallel, conduction ceases (Burnstock and Prosser, 1960). Low effective resistance between adjacent cells is secured by their close apposition, which reduces the possibility of dissipation of the current in the extracellular fluid, and by the development of pathways of low resistance between the cells, or "nexuses," first described by Dewey and Barr (1962).

Here then, as in *Mimosa*, groups of electrotonically interconnected cells appear to constitute the functional unit of conduction, acting in concert or not at all, like a "three dimensional core-conductor" (Dewey, 1965). [Myoid propagation via nexuses is found not only in vertebrates but also has been demonstrated in the tunicate heart (Kriebel, 1968).]

In respect to tissue homeostasis, it is now clear that cells are usually subordinate to the epithelia of which they form a part. Small molecules can pass freely between cells via intercellular pathways. As Loewenstein (1966) has expressed it, "the entire connected cell system, rather than the single cell, constitutes the functional unit." Doubtless in some cases the same pathways which permit metabolic exchange between cells also allow them to communicate electrically. Indeed, propagation of the impulse between cells may first have arisen in such epithelia, and it may have arisen as a property of a cell population rather than as a property of individual cells. This argument is developed below (p. 327 ff.).

THE COLLABORATION OF NERVOUS AND NEUROID SYSTEMS IN THE ORGANIZATION OF BEHAVIOR

Hydromedusae

Hydrozoan coelenterates have a simple, two-layered construction, but they are active, predatory animals with well-developed nervous systems and surprisingly complex behavior. In the medusae of this group, and in the medusoid nectophores of certain siphonophores, it has been found that large areas of the body are lacking in nervous tissue but have, instead, an excitable epithelium which transmits impulses resembling nerve impulses (Mackie, 1965; Mackie, Passano, and Pavans de Ceccatty, 1967; Mackie and Passano, 1968). Several species have been investigated, and a general picture of the significance of neuroid conduction in the group is emerging.

Hydromedusae exhibit *neuroid* conduction in *simple* epithelia and *myoid* conduction in *myoepithelia*. This distinction is somewhat artificial because myoepithelia may merge into simple epithelia through transitional zones in which the myofibrils are rudimentarily developed, and impulses may cross such zones quite freely. Myoepithelia contract when they con-

duct an impulse; simple epithelia have no contractile ability.

In the jellyfish *Sarsia*, the swimming muscle in the subumbrella is a myoid conducting tissue. Contraction of the myoepithelial cells composing it results in the constriction of the bell-shaped body, producing the locomotory jet of water. It can be shown that the excitation for this response is conducted in the muscle sheet itself. Nerves play a part in the process, however, acting apparently as the pacemakers which initiate the rhythmical swimming beat, and serving also to transmit the excitation rapidly around the margin so that all four quadrants of the muscle sheet will receive excitation at the same time. Transmission in the muscle sheet is at a velocity of less than 10 cm/sec. In the marginal nerves it is about five times as fast.

On the outer, exumbrellar, side of the bell, the ectoderm forms a simple epithelium without muscle fibrils, except in a restricted area near the margin, where a sphincter muscle is developed. Stimulation of the epithelium by electrical or tactile means gives rise to propagated action potentials which travel at about 15 cm/sec in all directions from the site of stimulation. On reaching the margin, they pass around it on the subumbrella, probably travelling via special bridging cells which span the jelly-like mesogloea, and are relayed via the endoderm sheet to various ectodermal muscle systems—not the same systems which are active during swimming. The behavioral response associated with excitation in this system, first described by Romanes (1876), is a general one, involving inward retraction of the margin, shortening of the manubrium and tentacles, and closure of a marginal sphincter muscle. It is evidently protective in nature, serving to withdraw and enclose the more vulnerable regions of the medusa. It is not exhibited spontaneously, but only in response to abrupt or damaging stimulation.

A feature of special interest in this "crumpling" response is the secondary involvement of the nervous system. The transmission of the response to the tentacles involves nervous pathways and pacemakers. The transmissions of the responses to the subumbrellar effectors may be obtained under experimental conditions without the participation of nerves, but the

full response exhibited under normal conditions appears to involve neuropacemakers in the margin and possibly at some of the effector sites. Thus, excitation can pass from the neuroid epithelium to nerves and back again to non-nervous myoepithelial effectors.

Siphonophores have neuroid exumbrellar epithelia similar to those of medusae, serving what appear to be modified versions of the crumpling response. In one case, *Nanomia*, the contraction of asymmetrically placed radial muscle fibers, evoked by stimulation of the exumbrellar epithelium, occurs simultaneously with swimming, with the result that the opening from the bell is distorted during emission of the water jet, and the direction of locomotion changes. What in "conventional" medusae is a protective closure here becomes an escape reaction (Mackie, 1964).

In *Hippopodius*, another siphonophore, propagation of excitation in the exumbrellar epithelium has two interesting side-effects: (a) in the dark, a transient luminescence is seen to accompany passage of the wave; and (b) in the light, opacification or "blanching" of the mesogloea adjacent to the epithelium is seen. Opacity is caused by the sudden appearance of small, light-scattering granules. The granulation persists for several minutes before it disappears, allowing the organism to resume its normal transparent condition. While both luminescence and blanching are associated with neuroid conduction in the epithelium, they appear to be quite distinct processes, the one occurring intracellularly and the other extracellularly (Mackie and Mackie, 1967).

We may sum up the features of physiological importance in neuroid conduction in the hydromedusae as follows (Mackie and Passano, 1968):

(1) Both ectodermal and endodermal layers may conduct independently, doing so regardless of the presence or absence of nerves and of whether or not the cells possess contractile elements.

(2) Neuroid conduction is typically all-or-none, is unpolarized, and takes place at velocities up to 35 cm/sec in medusae and up to 50 cm/sec in siphonophores. It may be slightly slower than nervous conduction in the same forms, but this is not in itself a sufficient criterion for distinguishing it from the latter. A

short refractory period of a few milliseconds has been recorded in one case. In general, for purposes of simple information transfer, the neuroid systems appear no less efficient than nervous.

(3) The neuroid systems in medusae show no evidence of pacemaker capability, this function apparently being restricted to the nervous system. In the hydroid *Tubularia*, on the other hand, the spontaneous potentials recorded in the hydranth may originate from non-nervous pacemakers (Josephson and Mackie, 1965); and in *Hydra* the pacemakers associated with the contraction pulse system, which manifests itself in the form of epithelial depolarizations, are not known and might be non-nervous (Josephson, 1969). Because both the origin and the transmission of these events in hydroids may involve nerves, they have not been given prominence in the present review.

(4) Neuroid conduction is typically found in rather simple, generalized responses, involving rapid activation of whole muscle sheets or of interrelated effector blocs all over the animal. The more complex, graded, and local movements are evidently organized by the nervous system. The non-muscular effector responses described above (blanching and luminescence) are also of a generalized, wide-spreading kind.

(5) Neuroid epithelia have tactile sensitivity, but their chemoreceptive and photoreceptive capacities are uncertain. The only indisputable receptor organs in these animals are linked with the nervous system and are composed of neurosensory cells.

Why have these animals developed neuroid conduction to such a high degree when they have perfectly good nervous systems? The answer must lie in that important biological principle—the avoidance of redundancy. Where a response can be spread efficiently by an epithelial layer that already exists, there is no need for nerves to invade the area. For the overall, spreading type of response there may be no need for the development of specific pathways of excitation. The excitation can travel in the effector cells themselves or in epithelial cells connected with them. The widespread occurrence of myoid conduction in hearts and other muscles illustrates the same principle.

Where specific excitation of local effector units is called for, where special rapid conduction routes are needed, where spontaneous activity needs to be generated, or where sensory information needs to be translated into complex motor output, there is a clear need for specialized conducting cells, insulated from neighboring cells and to some extent from each other. Such cells have arisen in the Hydrozoa, and they may have arisen quite independently in other animal groups. If so, convergence has obliterated the traces of their independent origins. A single word, "neuron," is applied to them all.

Ctenophores

Here we have a group of large planktonic metazoans which swim by ciliary action. Recent work suggests that the waves of ciliary activity are propagated in a neuroid manner by the ciliated cells themselves (Horridge, 1965a, b).

In a form like *Pleurobrachia*, the cilia are arranged in eight rows of comb plates running down the sides of the animal from an apical center which includes a balancing organ. The pacemakers which initiate the ciliary beat are located in the apical organ, but cells elsewhere in the comb plate system have the potentiality to assume pacemaker function.

A nerve net is present all over the surface, and elements of the net run under the comb plates, making specialized contacts with the ciliated cells. When regions between the comb plates are stimulated, the ciliary beating is inhibited. This inhibition is presumably due to activity in the nerve net. In *Beroë*, ciliary inhibition is accompanied by activity in certain muscles, also attributable to excitation transfer via nerves.

The picture which emerges, albeit tentative in certain respects, is of a double transmission system: *neuroid* transmission of a simple response (the ciliated beat); and *nervous* transmission of other, more complex or local activities, including ciliary inhibition. Thus, in a general way the ctenophore resembles the hydromedusan. The inhibitory effect of the nervous system on the neuroid system is a feature peculiar to the ctenophore.

Of particular interest are the curious, elongated cells of the ciliated grooves that

connect the upper ends of the comb rows with the apical balancing organ. These cells form part of the series of ciliated epithelial cells making up the comb row, but their cilia are vestigial. The cells are shaped rather like bipolar neurons, and there is good reason to suppose that, like neurons, they conduct impulses. And yet, on other grounds, they appear to be part of the neuroid transmitting system rather than part of the nervous system proper. It would seem, as Horridge (1965a) has suggested, that these cells represent an independent evolutionary step in the direction of the neuron.

There is, of course, no reason why neuroid epithelial cells should, in general, bear any physical resemblance to nerve cells, for their unpolarized form is appropriate to unpolarized conduction, and they have other functions to fulfil which call for a conventional shape. The cells would be expected to become elongated and to assume a nerve-like form where, as in Horridge's example, conduction is directionalized.

LARVAL FORMS OF HIGHER METAZOANS: PRECOCIOUS EXCITABILITY

It would be logical to look for non-nervous conduction in certain aquatic larvae, known to be responsive and capable of movement but lacking the generalized innervation they will later develop. With this in mind, Mackie, Spencer, and Strathmann (1969) studied the pluteus larvae of the echinoderm *Strongylocentrotus*.

The larva shows ciliary reversals when placed in water containing particulate matter. At the same time various muscular movements may be exhibited, particularly in the oral region. The net effect is that the larva swims backward for a brief period, simultaneously ejecting material from the gullet region.

Whenever ciliary reversals take place, electrical potentials can be recorded from the patches of ciliated epithelium known as "epaulettes." These events are recorded synchronously, or almost so, in different epaulettes, so presumably we are dealing with conducted impulses.

By analogy with ctenophores, one might suppose that the ciliary reversals represented

nervous influence on a basically neuroid system. However, nerves are reported to occur only in limited regions near the apex and around the mouth, these points being remote from the epaulettes. Removal of the regions said to contain nerves does not affect the capacity for reversal, nor block the potentials. There is no evidence of a nerve plexus or of nervous connectives of any sort between the epaulettes. There is therefore a strong possibility that the potentials represent neuroid impulses coordinating ciliary reversal.

In another aquatic larva, that of the toad *Xenopus*, Roberts (1969) has described propagated electrical events in the cuboidal epithelial cells of the skin. These impulses are evoked by tactile stimulation and spread at 5–11 cm/sec in all directions from the site of stimulation. It is reasonable to assume that these events are non-nervous because they can be recorded in larvae in which nerve processes extend only a short distance from the central nervous system. Wintrebert (1920a, b) postulated neuroid conduction in the skin of amphibian larvae on the basis of behavioral experiments, but he believed it to be superimposed on nervous excitability rather than to precede the latter.

The adaptive significance of neuroid conduction in these tadpoles is not established with certainty, but it presumably endows them with a precocious capacity for response in the period before the skin is innervated. Roberts (pers. commun.) now has evidence that the epithelial cells are electrically coupled, so impulses may be assumed to spread by direct current flow.

THE EVOLUTION OF CONDUCTION AND THE ORIGIN OF NERVE CELLS

In order for a cell to conduct, certain basic conditions must be met. The cell must have excitable membrane, it must be surrounded by a fluid medium of suitably low resistance, and its shape and core properties must be such as to allow current flow to be concentrated regionally.

No attempt has been made to review current concepts concerning the physicochemical basis of membrane excitability, but this the subject of an important recent book (Duncan, 1967). Its author proposes that membrane permeability is controlled by an adenosine triphospha-

tase (ATPase) mechanoenzyme complex whose molecular configuration may change as a function of the balance between ATP and ATPase. This model is applied to a wide variety of cells, from simple ones like *Amoeba* up to the evolutionarily advanced receptor cells, nerves and muscles. While it may be true that there is a single fundamental principle underlying the various types of membrane excitability, it is nevertheless remarkable that the actual ions whose movement is responsible for electrogenesis vary considerably among different groups of organisms, even, in some cases, within a single organism (Gundfest, 1959, 1961, 1963, 1964, 1966a, b). Thus in *Helix*, some neurons require sodium for spike electrogenesis while others do not. In several sorts of arthropod muscle, spike electrogenesis seems to depend on an influx of divalent cations, particularly calcium, rather than on sodium. The chloride spikes of the Characeae have already been mentioned (p. 322). Chloride spikes can be evoked in *Raja* electroplaques; potassium spikes, in *Tennebrio* muscle. In both of the latter cases we are dealing with electrogenesis under artificial conditions, but the fact that it can be achieved at all with these ions is revealing.

The lesson which we should draw from this diversity of ionic mechanisms is clear: conducting ability has been evolved repeatedly and independently in evolution. It has been evolved in more than one way and serves a variety of purposes.

Probably most cells, both now and in the past, have been electrically inexcitable. Excitability would develop by adjustment of the magnitudes and time courses of conductance to various monovalent and divalent ions. The "elemental property" which Parker (1919) referred to may be found in some such system as Duncan (1967) proposes, but the ways in which the property has found expression are heterogeneous. No one species of electrogenesis stands out as primitive. Grundfest (1967) refers to "the usefulness of studies in primitive forms [such as *Ascaris*] in which the record of evolutionary experimentation may still be preserved" (p. 1955). It does not follow, however, that the mechanisms in so-called primitive forms represent tentative or incomplete attempts at the mechanisms found in higher animals. Florey (1967) has justly observed that "there are no

higher and no lower kinds of physiology" (p. 2). For similar reasons, I find it hard to follow Bishop (1956) and Grundfest (1959) in viewing graded conduction as more primitive than self-propagating conduction. Both are adaptive in different circumstances.

How did conduction evolve in multicellular organisms? It is probably no accident that in *Mimosa* (and presumably in other higher plants) the cells which conduct electrical events are located in the vascular bundles — "conducting tissues" in the sense that they also conduct water and metabolites. These metabolites include specific chemical factors capable of evoking tropistic responses in target areas. Response latency could be shortened considerably, if instead of the slow flow of a chemical, the rapid passage of an electrical impulse were the triggering event. Originally we may suppose that communication was entirely chemical. However, the passage of chemical factors through the cells of the vascular bundle would often be accompanied by bioelectric events in the same cells. Sibaoka (1966) has cited examples of such electrical manifestations of chemical movement. The potentials need have no significance in information transfer. They presumably represent transmembrane ionic adjustments induced locally by certain active metabolites. They might, however, have been the evolutionary starting point for true impulses such as we find in *Mimosa*, and whose function is to communicate information otherwise conveyed by chemical factors, or to supplement this method.

Surprisingly, few higher plants appear to have evolved the capacity for impulse propagation. One must suppose that rapidity of response was rarely of importance in plant evolution. Where rapid responses were advantageous, as in insectivorous plants, we find impulse conduction and advanced transduced devices like the trigger hairs of *Dionaea*.

The origin of specialized conducting tissues in animals may have proceeded along lines similar to those proposed here for plants. In plants it is well known that most of the cells are connected by cytoplasmic bridges which serve for the transfer of metabolites. It has been suggested above that such bridges served also for electrical communication and permitted impulse conduction to become established in whole populations of communicating cells, on

the three-dimensional core-conductor principle. In animals too it is now known that the cells in many epithelial tissues are electrically and metabolically coupled through special pathways of communication (Loewenstein, 1966). Quite large molecules can pass between the cells, and such interchanges are undoubtedly vitally important in tissue homeostasis. The condition must be assumed to be of extreme antiquity, probably as old as the Metazoa.

The same pathways which in the ancestral metazoan served for metabolic exchange would have permitted electrical current to flow between the cells. I have suggested elsewhere (Mackie, 1965) that conduction originated in tissues of this sort. Whether it did or not, it will be generally conceded *that the evolution of conduction is inseparable from the evolution of junctional specialization and that both are subject to the requirements of tissue homeostasis*.

I envisage the starting point for a metazoan conducting tissue as something resembling a myoepithelial tissue sheet in a coelenterate, a sheet consisting of a single type of cell, and each cell having its own contractile myofibrils (Fig. 1A). The cells would not resemble neurons morphologically. They would conduct graded or all-or-none events, contracting as they conducted, and their ability to do so would depend on the presence of pathways of communication between the cells, pathways which also serve for metabolic exchange. As in plants, the effective conducting unit would presumably be a group of cells rather than single cells.

From such a primordial epithelium, the cells of which were capable of reception, transmission, and contraction, specialized muscle tissues would have arisen by the sinking in and isolation of contractile cells (Fig. 1B). Systems of neurons and neurosensory cells would have become segregated in the same way, losing their contractile component but providing for excitation of the evolving muscle tissues and for the coordination of their responses (Fig. 1C, D). In some places, the primordial sheet would retain its conducting ability, either along with contractile ability or without it, giving us myoid and neuroid epithelia respectively, such as we find in the coelenterates. Elsewhere, conducting ability would be lost, as the presence of nerves would make neuroid conduction unnecessary.

Neuroid conduction could, however, be reestablished in tissues secondarily.

Horridge (1966, 1968) has analyzed the possibilities for the development of increasing complexity in simple neuromuscular systems. He stresses (1966) that "specificity emerges from randomness and becomes more precise only in so far as is made necessary by the presence in the same locality of pathways which must be kept separate for functional reasons" (p. 264).

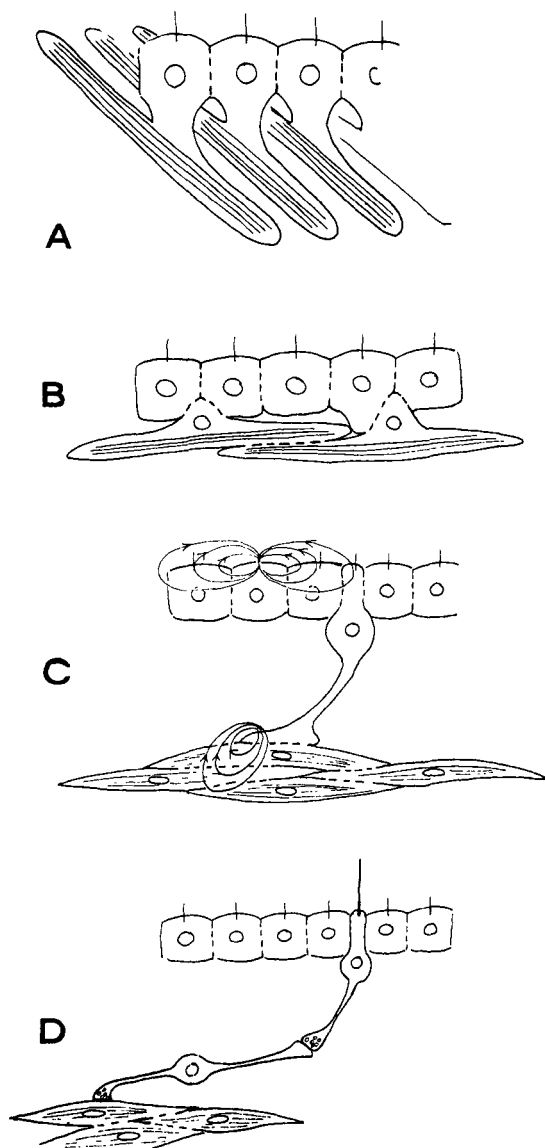


FIG. 1. SUGGESTED STEPS IN THE EVOLUTION OF NERVE AND MUSCLE CELLS

Nerve nets in which the functions of the individual units are not specified occur in many animal phyla, but nervous systems have generally tended to evolve in the direction of increasing specificity. By contrast, neuroid conducting systems, such as those of ctenophores and hydromedusae, are largely unspecified, resembling undifferentiated nerve nets in this respect. By the time a neuroid system has developed specificity, however, it would probably no longer be recognizable as non-nervous, since the conducting elements would have assumed the morphological character of neurons. What we seem to see happening in the ctenophore's ciliated groove may have taken place repeatedly.

An essential feature in the transformation of the primordial conducting sheet into specialized nervous and muscular units is the modification of the junctions between the units. The free two-way "cross-talk" characterizing the tightly coupled cells in the original system would usually be inappropriate to the needs of evolving nerves and muscles, since the very essence of integration lies in the fact that unpolarized one-for-one transfer of information between cells does *not* occur. Furthermore, because of the high capacitance inherent in a coupled-cell system, it would presumably be hard to excite and thus rather insensitive to stimulation of a more delicate or localized kind. [In some special situations this very property of low excitability might, however, be advantageous—see, for example, the coupled

A, primordial myoepithelium.

B, protomyocytes start to forsake the epithelium, sinking into the interior.

C, protoneurons evolve, conveying excitation to the myocytes from the exterior. All cells are still shown as electrically coupled. Current flow around depolarized regions of membrane involves groups of electrically interconnected cells. These groups are the effective conducting units.

D, Neurosensory cells and neurons evolve. They are usually connected to one another and to the myocytes by chemically transmitting, polarized junctions. Electrical coupling persists in many epithelia and muscles. In some cases these tissues retain the ability to conduct impulses, neuroid and myoid respectively. However, conduction of impulses becomes increasingly a property of the nervous system, and individual neurons are the effective conducting units.

Broken lines at junctions between cells indicate low resistance pathways through which action currents can flow, as indicated in C.

trigger cells in the *Tritonia* brain (Willows and Hoyle, 1969). A striking property of this system is that it serves to filter out weak neural activity and to set a relatively high threshold for the escape response which it triggers.]

Transmitting junctions in existing animals fall into two categories, electrotonic and chemical synapses. The simpler types of electrotonic synapse correspond to the ancestral type of junction proposed here. It is becoming clear, on the other hand, that some electrotonic synapses are quite specific in the types of information they will or will not pass, and are thus potentially suited to a role in integration similar to that assumed by chemical synapses (Bennett, 1966, 1968). They can, indeed, "exhibit all the properties classically associated with synaptic transmission" (Bennett, 1968, p. 112). In discussing the question of why, with this potentiality, electrotonic synapses are so much less common than chemical ones, Bennett suggested that the selective decoupling of the tightly coupled cells of the early embryo may pose special problems that would make chemical transmission an easier solution. If this argument has merit, it could be rephrased in phylogenetic terms for our present purposes. However, there are probably other reasons why chemical synapses have proved preferable; for example, their potential for signal amplification, and their superiority for inhibition and for synaptic activity spread over a long time-course. Their preponderance may be explained on some such basis.

Whatever the cause, junctional evolution in nerve cells generally went in the direction of chemical transmission rather than electrical. The introduction of chemical synapses need have involved no drastic or macroevolutionary steps. Secretion of biologically active substances may well have been a major function of primitive nerve cells, as Lentz (1968) has stressed. In certain cell lines we must imagine a progressive curtailment of free pathways of communication between cells along with the secretion of chemical factors into the intercellular spaces, these factors serving to coordinate metabolic activities and to control morphogenesis. In fact, as in plant vascular cells, the elongated shape of the "protoneuron" may have been related as much to the need to transfer metabolites to specific

points as to provide a linear pathway for impulse transmission.

We may suppose that the final transformation to nerve cells, as we now see them, was achieved in cases where groups or chains of these cells, instead of propagating electrically to one another, gradually lost this ability and at the same time developed the ability to excite electrogenesis in one another by the transmitter action of the chemical factors they secreted. The secretory property would have become specialized *pari passu* with the restriction of junctional permeability and the loss of low resistance pathways across the synapses.

It goes without saying that a conducting system of this sort would not have arisen *in vacuo* but would have been accompanied by concurrent specialization of the effector systems. Horridge (1966) has commented that Parker's well-known evolutionary sequence (Parker, 1919), which starts with independent effectors such as muscle cells and then adds sensory units and finally neurons, is open to objection on the grounds that "conducting systems must be developed before the independent effectors which we know become possible and before sensory cells can activate areas large enough to give a significant response" (p. 264).

There appear to be no neuroid systems in which junctional transmission is achieved chemically. Chemical transmission seems to be unique to junctions involving nerve cells. It has been argued here that electrical transmission was probably the more primitive method, but it is a method which could also have arisen *de novo* on many occasions in epithelia in which the cells were connected by low-resistance pathways serving for exchange of metabolites. Since a great many (perhaps the majority of) epithelia possess low-resistance junctions of this type between some or all of their cells, it would not be surprising if neuroid transmission proved to be of much more widespread occurrence than we now suspect.

Conducted electrical events are usually significant in the context of behavioral physiology: indeed, observations on behavior have typically provided the original clues which led to the demonstration of neuroid conduction. We cannot, however, at this stage rule out the

possibility that neuroid impulses may sometimes serve purposes quite unrelated to behavior in the usual sense—for instance, the coordination of secretion or other metabolic processes within groups of similar cells. There is at present no direct evidence of such a function, but very few workers have investigated epithelia with this possibility in mind.

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