REVIEW/SYNTHÈSE

The behavioral and developmental physiology of nematocysts[1]

G. Kass-Simon and A.A. Scappaticci, Jr.

Abstract: Nematocysts are the nonliving secretions of specialized cells, the nematocytes, which develop from multipotent stem cells. Nematocysts are the means by which coelenterates capture prey and defend against predation. The 25 or more known types of nematocysts can be divided into to four functional categories: those that pierce, ensnare, or adhere to prey, and those that adhere to the substrate. During development a collagenous cyst, which may contain toxins, forms; a hollow thread, which becomes coiled as it invaginates, develops. Maturing nematocyte–nematocyst complexes migrate to their discharge sites and are deployed in specific patterns. The mechanisms of pattern determination are not clear. Discharge of nematocysts appears to involve increases in intracapsular osmotic pressure consequent upon release of bound calcium within the capsule; the eversion of the filament may depend upon release of structural tension consequent upon a loss of zinc from the thread. Evidence exists that discharge is initiated as a calcium-dependent exocytosis, triggered by an electrical signal resulting from the transduction of mechanical stimuli received at the nematocyte's cnidocil. Chemical signals transduced in adjacent sensory cells alter the frequency response of the nematocyte. In opposition to the nematocyte–nematocyst independent effector hypothesis, excitatory and inhibitory neuronal input appears to regulate discharge.

Résumé : Les nématocystes sont des sécrétions non vivantes produites par des cellules spécialisées, les nématocytes, qui proviennent de cellules souches multipotentes. Chez les coelentérés, les nématocystes servent à la capture des proies et sont des armes de défense contre les prédateurs. Les quelque 25 types connus de nématocystes peuvent se diviser en quatre catégories fonctionnelles : ceux qui percent, ceux qui servent de pièges, ceux qui adhèrent aux proies et ceux qui adhèrent au substrat. Au cours du développement, il se forme un kyste de collagène qui peut contenir des toxines; un fil creux se déploie en spirale en s'invaginant. Les complexes nématocytes–nématocystes migrent vers leur site de vidange et ils sont disposés selon un arrangement particulier. Les mécanismes qui régissent cet arrangement sont mal connus. L'expulsion des nématocystes semble se faire par augmentation de la pression osmotique intra-capsulaire consécutive à la libération du calcium lié dans la capsule; l'évagination du filament peut dépendre du relâchement de la tension structurale qui se produit lors de la perte du zinc du filament. Il semble, d'après certains indices, que l'expulsion des nématocystes soit d'abord une exocytose dépendant du calcium, un processus déclenché par un signal électrique résultant de la transduction de stimulus mécaniques perçus au niveau du cnidocil du nématocyte. Les stimulus chimiques modifiés par transduction dans des cellules sensorielles adjacentes modifient la fréquence de la réponse du nématocyte. En contrepartie de l'hypothèse d'un effecteur indépendant nématocyte–nématocyste, il faut envisager celle d'un contrôle nerveux à la fois excitatoire et inhibiteur de la vidange du nématocyte.

[Traduit par la Rédaction]

Introduction

Nematocysts have long been a source of fascination for the professional biologist and the ordinary layman. To the biologist they are a source of unending intellectual and experimental stimulation; for the rest of the world, the stimulation may only be the physically unpleasant sensation of being stung by a jellyfish. Nematocysts, which are the secretions of specialized cells that reside mainly in the tentacles of jellyfish, sea anemones, corals, and the polyps of hydroids, are the chief instruments by which these animals obtain food, defend against predation, and in the case of polyps, adhere to solid substrates during locomotion.

In response to appropriate stimuli, nematocysts are ejected

Received 11 December 2001. Accepted 16 May 2002. Published on the NRC Research Press Web site at http://cjz.nrc.ca on 19 November 2002.

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[1]This review is one of a series dealing with aspects of the phylum Cnidaria. This series is one of several virtual symposia on the biology of neglected groups that will be published in the Journal from time to time.

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 DOI: 10.1139/Z02-135

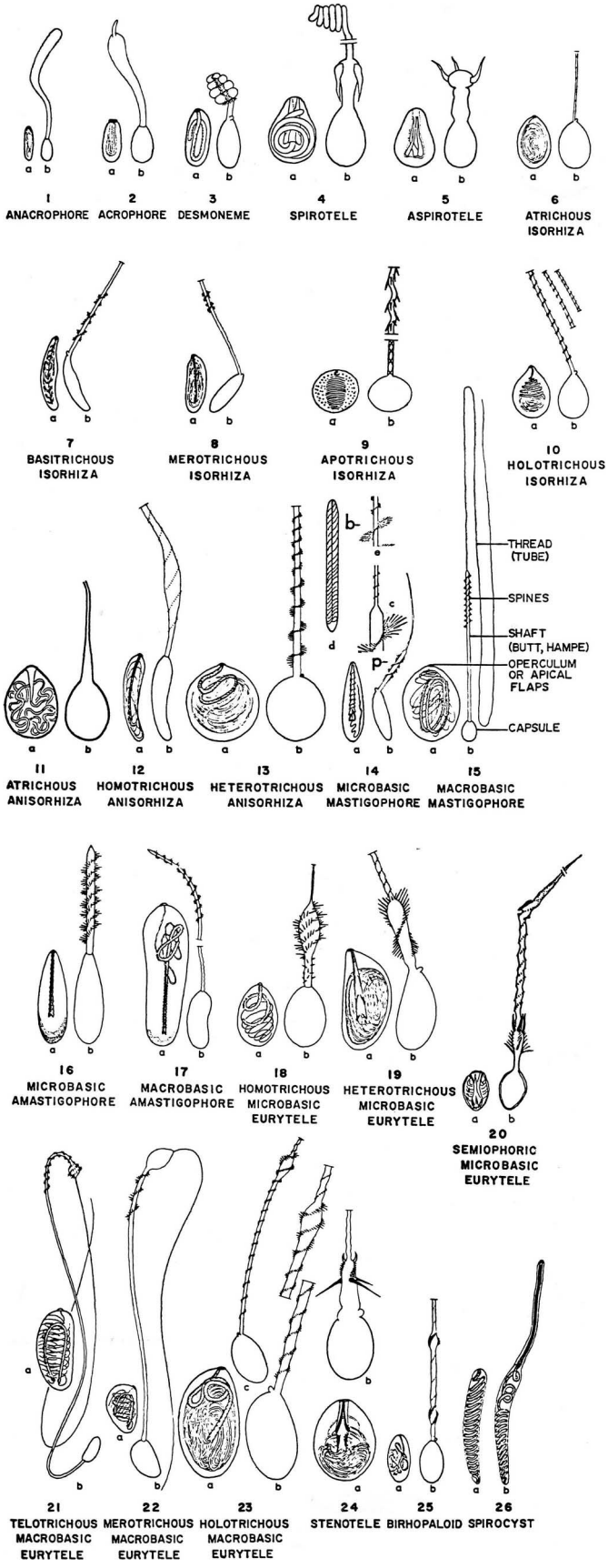


Fig. 1. Nematocysts and spirocysts. Slight variations in the distribution of spines on the basitrichous isorhizas, as well as the presence of spines on atrichous isorhizas, have been reported (Westfall 1966*b*). (From Mariscal 1974, reproduced with permission of Academic Press Inc. © 1974.)

from the polyp or jellyfish onto their target, where, depending upon the type of cnidocyst, they either entwine, pierce, or stick to the target. Strictly speaking, nematocysts are a subcategory of secreted organelles, known as cnidae, which distinguish the cnidarians from their non-cnida-bearing ctenophore cousins. There are 28 known types of morphologically distinct cnidae, which are divided into three subcategories, nematocysts (25 different types), spirocysts (2 types), and ptychocysts (Mariscal 1974; Mariscal and Bigger 1976; for a review see especially Mariscal et al. 1977) (Fig. 1).

One reason for their fascination is the idea, voiced from time to time, that perhaps nematocysts are independent effectors, acting entirely without recourse to central control systems or neuronal intervention. This notion has placed nematocysts squarely at the center of fundamental biological questions about the nature of tissue and organism and the extent to which an individual may or may not exercise control over its own body parts. (For a thought-provoking discussion of coelenterate organs see also Mackie 1999.)

Coelenterates are, for all intents and purposes, little more than guts with tentacles. The predominant location of nematocysts in the tentacles confers on the tentacles their role as primary sensor and effector, and effectively raises them to the rank of an organ specialized for feeding and predation. In the freshwater polyp *Hydra*, most nematocysts are found in highly modified ectodermal epithelial cells (Slautterback and Fawcett 1959), referred to as the battery-cell complex (Hufnagel et al. 1985), which reside only in the tentacle. In siphonophores, mature nematocysts are found concentrated in knobbed structures on the tentacles called cnidosacs (Skaer 1988). The tentacles of *Stephanophytes superba* (Chun 1891) and *Nanomia cara* (Mackie and Marx 1988; Mackie 1999) bear highly organized nematocyst batteries on numerous side branches (tentilla), which erupt when prey comes into contact with them. A large *N. cara* can have as many as 80 tentacles with some 1500 nematocyst batteries, six million nematocysts, and an effective circumferential spread of 3–4 m (Mackie 1999).

That the cnidarians have persisted in marine and freshwater niches since the Cambrian is due not least to the effectiveness with which their nematocyst-bearing tentacles act as lethal weapons of defense and predation.

Morphological distinctions

Although at least 25 or more distinct morphological types of nematocysts have been identified among the coelenterates, functionally there are in fact no more than three or four differentiated categories. Thus, two types of nematocyst are involved in feeding: those that pierce and simultaneously inject toxins into prey or predator, and those that ensnare prey. A third group of nematocysts consists of those used to adhere to substrates, especially during locomotion, and a fourth group consists of those that are specifically used in defense.

Light- and electron-microscopy studies of whole and discharged nematocysts reveal the architectures upon which their functioning depends. The representative nematocyst consists of a double-walled, capped capsule, which harbors an inverted hollow thread that everts explosively when appropriately stimulated (Mariscal 1974). Numerous studies of the capsule wall and thread in several genera, including *Metridium*, *Aiptasia*, *Physalia*, and *Hydra*, indicate that the capsules are composed of a collagen-like protein, containing proline, hydroxyproline, glycine, and cystein, linked by disulfide bonds. However, the cyst is impervious to digestion by collagenase, elastase, and other proteolytic enzymes (for a summary and discussion see Blanquet 1988).

Of the 25 known types of nematocysts, 22 are found in the class Hydrozoa, 17 of which are exclusive to the class. Four types are found in the class Scyphozoa and six types in the class Anthozoa, of which two are exclusive to the class; the Anthozoa also possess other cnidae that are classified as spirocysts (Mariscal 1974) (Fig. 1).

Nematocysts are classified not according to the phylogenetic group to which they belong but according to the structure and appearance of their discharged threads (Carlgren 1940; Cutress 1955; Hand 1961; Mackie and Mackie 1963; Werner 1965; Deroux 1966; Lacassagne 1968*a*, 1968*b*; Mariscal 1972; see the classic review by Mariscal 1974 summarizing the work of Weill 1934, 1964). The group is first divided according to whether the cyst possesses a thread that is open or closed at the tip. Threads that are open at the tip are called stomocnidae; those that are closed are called astomocnidae. Stomocnidae, with open threads, such as the stenotele or penetrant, are thought to deliver toxins to prey; astomocnidae, with closed tips, such as the desmoneme, are likely to be used to adhere to substrates and entangle prey. Nematocysts are further subcategorized according to differences in the morphology of the shaft and thread; their classification depends on whether or not spines are present on the thread or whether the shaft is well defined or present at all. Since differences in architecture are not correlated with phylogenetic classification, the question arises as to whether the subtle differences in the architecture of the thread and shaft reflect differences in function. This question has not yet been experimentally addressed.

Classified separately from the nematocyst is a type of cnida called a spirocyst (Mariscal 1974), which is found in the zoantharian anthozoans. Spirocysts are designed to adhere to prey and non-prey and are distinguished by a thin capsular wall with a long spirally coiled thread that has no apparent shaft or spine; upon discharge, the capsule and thread become transparent. Nematocysts are thick-walled and basophilic; spirocysts are thin-walled and acidophilic. Whether or not the distinction between nematocysts and spirocysts reflects differences in basic function or merely differences in evolutionary development is not known.

Other differences in capsule architecture among nematocysts have also been noted, but have not been considered from the perspective of functional anatomy. Thus, the operculum that covers the inverted thread has been found to differ in various coelenterate classes (Westfall 1966*a*, 1966*b*; Mariscal 1974). Within the Hydrozoa and Scyphozoa the operculum is a sealed convex window. In the Anthozoa the operculum comprises a series of apical flaps (Westfall and Hand 1962; Westfall 1965; Westfall 1966*a*, 1966*b*).

Functional distinctions

Feeding and locomotion

In the most widely studied hydrozoan, the freshwater polyp *Hydra*, four types of nematocysts exist: two for feeding, one for locomotion, and one for defense. All four types are found in *Hydra*'s tentacles, which are the primary instruments of its feeding and peripatetic behavior. In the tentacle, all nematocysts are arranged in battery-cell complexes that contain the entire complement of *Hydra*'s nematocysts plus sensory cells and ganglion cells, along with the myonemes, the cell's muscular contractile elements (Westfall et al. 1971*a*; Hufnagel et al. 1985; Hufnagel and Kass-Simon 1988; Westfall 1988). In a typical battery-cell complex, the large toxin-containing stenotele is positioned in the center of the complex with the smaller, ensnaring desmonemes and adherent isorhizas surrounding it concentrically (Fig. 2).

Prey capture is accomplished by the desmonemes. The thread of the desmoneme is tightly coiled and appears spring-like when discharged (Fig. 1). Once the prey is ensnared, as it struggles to free itself, its vibrations cause the cnidocil of the stenotele, which has a higher threshold of discharge, to be deflected (personal observation). The stenotele, a stomocnidum (thread open at the tip) is discharged into the prey, allowing its toxins to enter the prey's body (cf. Ewer 1947). Stenoteles have an elaborate design that makes them effective instruments of penetration and toxin delivery. Their tubule, typically with three stylets and prominent spines, arises from a salient shaft that becomes thinner as it tapers from its base, thereby classifying stenoteles as heteronemes. Their morphology has been compared to that of an arrowhead, which, once having entered its target, is difficult to dislodge (Mariscal 1974).

In contrast to the penetrant, the desmoneme (the ensnaring nematocyst) is an astomocnida, whose thread is closed at the tip and which does not release toxins. The threads of desmonemes are tightly coiled (placing desmonemes in the category spironemes) and do not arise from well-defined shafts (thus classifying the desmonemes as haplonemes) (Mariscal 1974). In addition to desmonemes and stenoteles, holotrichous isorhizas (spine-bearing astomocnidae) are apparently used primarily for defense; discharged holotrichous isorhizas were found in paramecia, considered to be irritants or parasitic predators, although other commensal ciliates that live among *Hydra*s and are similar in size did not evoke a defensive response (Ewer 1947).

*Hydra*s can be made to perform somersaults over a surface when presented with a distant source of light. When the animal's tentacles come into contact with the substrate, atrichous isorhizas (astomocnidae, without spines), which allow the tentacles to adhere to the substrate, are discharged. By directing *Hydra*s to walk up a glass wall and subsequently staining the discharged nematocysts with methylene blue, Ewer (1947) was able to determine that only atrichous isorhizas were discharged. Interestingly, Ewer (1947) also showed that discharge of atrichous isorhizas was completely inhibited by prey extracts.

Fig. 2. Schematic representation of a battery-cell complex. The three types of nematocysts, a sensory cell, and a ganglion cell (with its cilium) are imbedded in the battery cell. Attenuated regions of adjacent battery cells are coupled by gap junctions and connected by septate junctions. (From Kass-Simon 1988, reproduced with permission of Academic Press Inc. © 1988.)

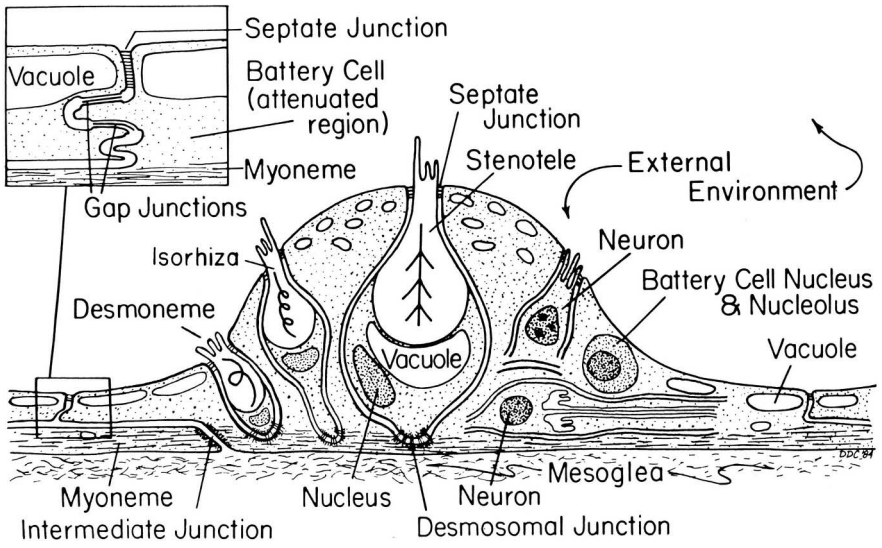
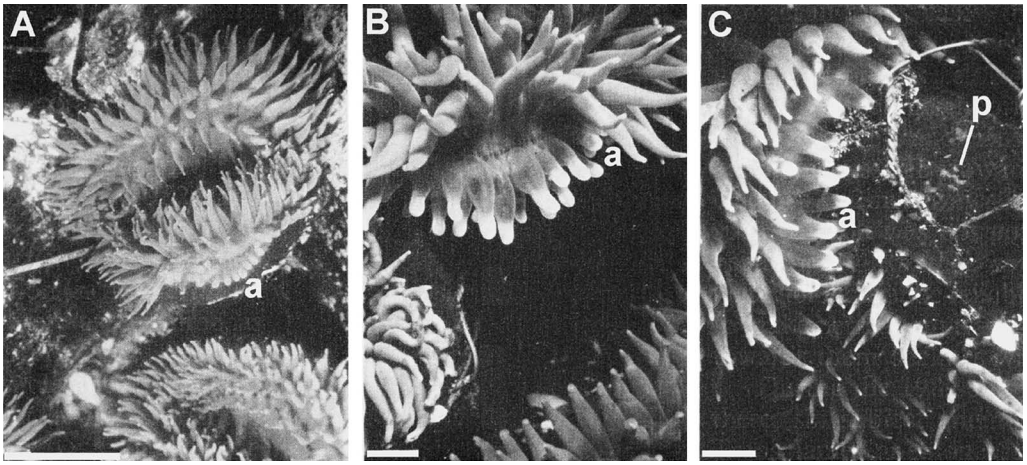


Fig. 3. (A) An agonistic encounter by *Anthopleura xanthogrammica*. The individual at the top has its acrorhagi (*a*) inflated on the side facing its neighbor. Scale bar = 5 cm. (B) Acrorhagi (*a*) of a subject anemone prior to contact with an experimentally transplanted anemone. Scale bar = 1 cm. (C) Ectoderm from the tips of acrorhagi (*a*) (light patches (*p*)) adhering to the column of a transplanted anemone (peeling). Scale bar = 1 cm. (From Sebens 1984, reproduced with permission of Biol. Bull. (Woods Hole, Mass.), Vol. 166, © 1984 Marine Biological Laboratory, Woods Hole, Mass.)

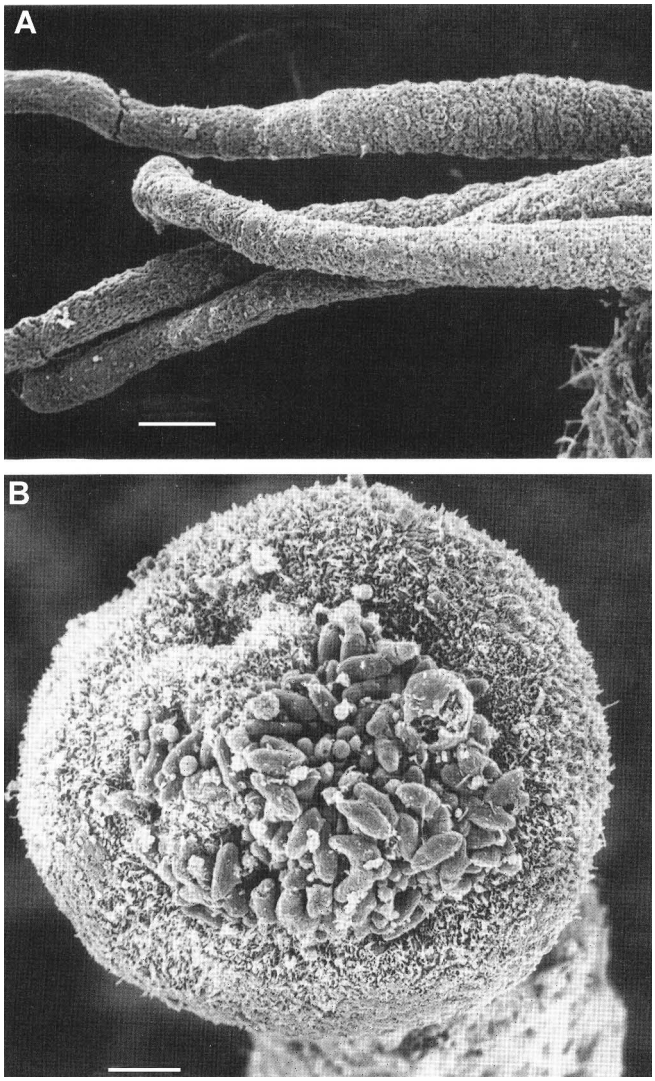


Aggressive and defensive behavior

This is best understood in the Anthozoa. Sea anemones and corals have developed several specialized structures used to defend against territorial invasion by conspecifics or coelenterates of other species. Three of these structures, acrorhagi, catch tentacles, and sweeper tentacles, are modified tentacles; the other structure is a modified element of the mesentery, the mesenteric filament (for a review see Bigger 1988).

Thus, some sea anemones possess, in addition to their usual tentacles, hollow structures known as acrorhagi, which are located at the margin of the body column (Rapp 1829; Sebens and Paine 1978; Sebens 1982, 1984; for a review see Bigger 1988) (Fig. 3). When such anemones make physical contact with one another, usually with their tentacles, after initial tentacle withdrawal, if the anemones do not perceive each other as inert objects and if they are unable to avoid further contact with one another (e.g., by bending or releasing their pedal discs from the substrate and passively floating away), an acrorhagial attack takes place (Abel 1954; Bonnin 1964; Brace and Pavey 1978; Francis 1973*a*, 1973*b*; Bigger 1980, 1988; Brace 1981). After making contact, the acrorhagi expand and are repeatedly applied to the target organism. During application, the ectodermal tissue of the acrorhagus lifts away from its underlying mesoglea (the acellular collagenous secretion that separates the ectodermal and endodermal cell layers), nematocysts are discharged, and the acrorhagial ectoderm adheres to the target organism. This process is called peeling. As a result of continued nematocyst discharge into the victim, the tissue beneath the acrorhagial peel becomes necrotic and dies. Contact with the

Fig. 4. (A) Scanning electron micrographs of sweeper tentacles of *Erythropodium* sp. (a gorgonian octocoral). Note the knobbed tip (acrosphere) of the sweeper tentacle. Scale bar = 100 μm. (B) Enlarged view of the acrosphere from a sweeper tentacle with a central cluster of large nematocysts most of which are holotrichous isorhizas. Scale bar = 10 μm. (From Sebens and Miles 1988, reproduced with permission of Biol. Bull. (Woods Hole, Mass.), Vol. 175, © 1988 Marine Biological Laboratory, Woods Hole, Mass.)



target animal causes simultaneous massive discharge of the acrorhagial nematocysts, which are primarily holotrichous isorhizas (Bigger 1988). Specific molecules, which have not yet been identified, on the ectoderm and endoderm of the target animal are the apparent initiators of the behavior. However, the same substances have not been found to elicit nematocyst discharge in experiments, which suggests that they may be qualitatively or quantitatively different from substances which cause nematocyst discharge (Bigger 1976, 1982).

Catch tentacles, which have been described for some sea anemones, are also specialized tentacles that are distinguished from the more slender feeding tentacles by their opacity and their blunt, wide form (Williams 1975; Purcell 1977; for a review see Bigger 1988). Catch tentacles develop from feeding tentacles that undergo a morphological change when an anemone, such as *Metridium* sp. or *Haliplanella* sp., comes into contact with appropriate conspecifics or other sea anemone species. Over the course of several weeks, feeding tentacles alter their morphology and their complement of cnidae, which now become different from those of its other tentacles (Hand 1955; den Hartog 1977; Purcell 1977). Feeding tentacles contain mainly spirocysts and mastigophores (penetrants with well-defined shafts, classified as stomocnidae) (Fig. 1), while catch tentacles, at least those of *Haliplanella* sp., contain small holotrichous isorhizas (Richardson et al. 1979; Sheppard 1981; Chornesky 1983; Watson and Mariscal 1983*a*, 1983*b*; Hidaka and Miyazaki 1984; Logan 1984; Hidaka et al. 1987). Catch tentacles do not adhere to potential food objects such as living brine shrimp, and when touched with a prey animal, actually retract (Purcell 1977).

Another modified tentacle used in defense is the sweeper tentacle of scleractinian corals, whose tips, referred to as acrospheres, contain a large number of holotrichous isorhizas (den Hartog 1977; Richardson et al. 1979; Wellington 1980; Bigger 1988; Sebens and Miles 1988) (Fig. 4). The tentacle tips of *Montastrea cavenorsa* contain approximately 63% holotrichous isorhizas and those of *Galaxea fascicularis* contain almost 50% microbasic b-mastigophores and 40% spirocysts (Hidaka and Miyazki 1984; Hidaka and Yamazato 1984). Like catch tentacles, sweeper tentacles differentiate in response to weeks of contact with corals of another species (Chornesky 1983; Hidaka 1985; Hidaka et al. 1987; Sebens and Miles 1988). Sweeper tentacles extend at night and, as their name implies, flail or undulate (Bigger 1988; from Richardson et al. 1979). They can reach 5–10 times the length of feeding tentacles.

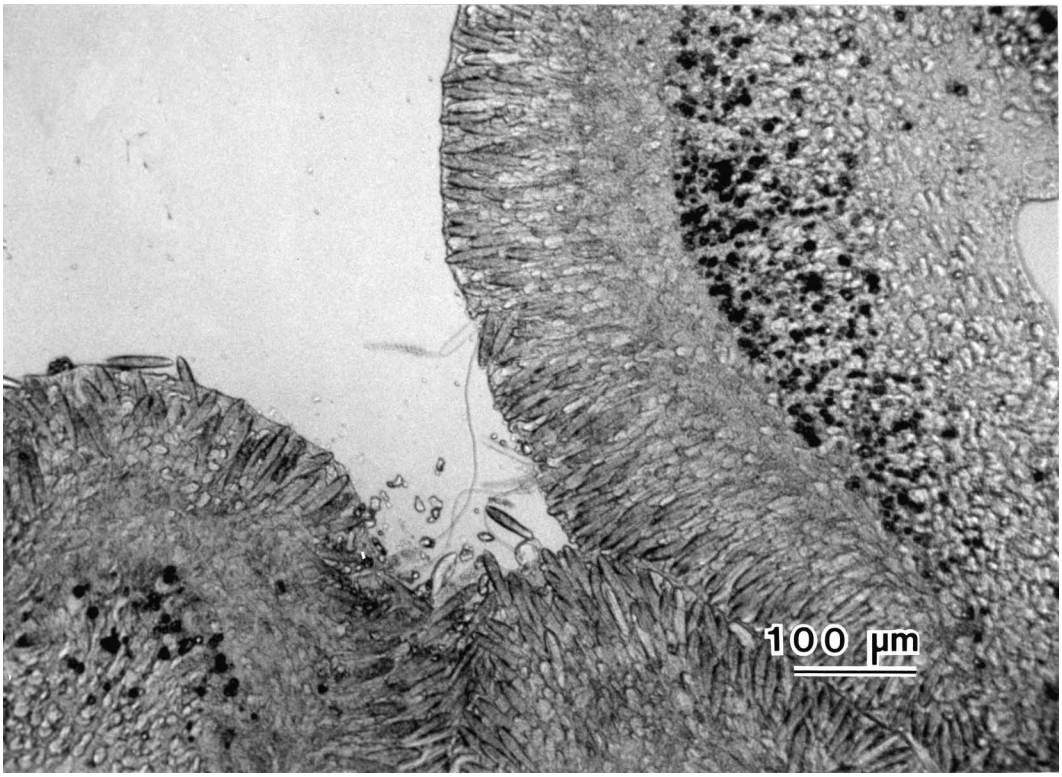
Another structure, which is used as a weapon of aggression and defense in corals, is the digestive mesenterial filament. Mesenterial filaments can be extruded through the body wall or oral cavity onto adjacent corals (Lang 1973). Although digestion by the filaments appears to be the major source of injury to the target organism, the great numbers of nematocysts (of unknown type) they possess no doubt contribute to the filaments' effectiveness as a weapon (cf. Bigger 1988) (Fig. 5).

Nematocyst development

Nematocysts are the secretions of developing nematocytes, the specialized progeny of a group of interstitial cells that, at least in *Hydra*, exist throughout the ectoderm and endoderm of the body column (David and Challoner 1974; David and Gierer 1974), although Bosch and David (1991) seem to suggest that interstitial cells grow and differentiate mainly in the interstices of ectodermal cells.

Interstitial (i-cells) cells destined to differentiate into nematocyst-bearing nematocytes develop from multipotent stem cells. These i-cells occur as clusters of 2*n* cells and arise from smaller clusters of two to four larger interstitial cells (David 1973). Clusters of 4, 8, and 16 interstitial cells elaborate nematocysts, with all cells in a cluster synchronously forming the same type of nematocyst capsule (Lehn 1951; Rich and Tardent 1969; David and Challoner 1974). Differentiation occurs only in the gastric region (David and Challoner 1974). How nematocysts and nematocytes develop

Fig. 5. A mesenterial filament "squash" of the coral *Fungia scutaria*. Note the numerous nematocysts. (From Bigger 1988, reproduced with permission of Academic Press Inc. © 1988.)



and differentiate, how they find their way to their ultimate location in the cells of the organism, and how their population is maintained continue to be subjects of intense inquiry. Not all the evidence is consistent and not all workers agree on its interpretation. The questions have been skillfully and extensively reviewed in papers by H.R. Bode, R.D. Campbell, E.A. Robson, and R.J. Skaer in the 1988 symposium volume *The Biology of Nematocysts*, edited by D.A. Hessinger and H.M. Lenhoff, and the present article relies heavily on these reviews. But it should be made clear that the questions raised in 1988 have not been completely answered in 2002 and continue to be a source of debate and discussion.

Where does the nematocyte–nematocyst complex come from?

It is generally agreed, at least for the forms which have been studied, that nematocysts and their encapsulating nematocytes arise from precursor cells that differentiate into the mature nematocyte–nematocyst complex in a series of steps, and that either the differentiating nematocyte or the complex of its precursor cells migrates from its birth site to its usage site in a series of more or less similar steps (cf. Bode 1988; Campbell 1988; Shimizu and Bode 1995).

In *Hydra*, multipotent interstitial stem cells give rise to the four types of nematocyst-containing nematocytes, to three types of secretory cells, and to several types of neurons (David and Murphy 1977; Bode et al. 1987; Bosch and David 1987; Shimizu and Bode 1995). The type of nematocyst elaborated by the nematoblast appears to depend upon the axial position at which the differentiation occurs (Bode and Smith 1977; for a review see Fujisawa et al. 1986). Thus, stenoteles are found mainly in the proximal regions of the body column and decreasingly along the column towards the distal regions, whereas desmonemes are produced mainly in the distal and middle regions; the hypostome and the base of peduncle are not involved with nematocyte differentiation.

In *Hydra*, the differentiation sequence, as illustrated by desmoneme differentiation (Shimizu and Bode 1995), begins when a multipotent stem cell undergoes three to five cell divisions that yield 8–32 cells which are connected to each other by cytoplasmic bridges to form a syncytial nest or cluster (Slautterback and Fawcett 1959). The progeny from each successive cell division decrease in size and alter in shape (David 1973; Shimizu and Bode 1995). When cell division is complete, the cells of the nest synchronously undergo differentiation, i.e., the nematocyst begins to form and develop (Slautterback and Fawcett 1959). In *Hydra*, nematocyte differentiation occurs exclusively in the body column (Bode and David 1978). When differentiation is complete, the bridges between the cells disappear. After this, the mature nematocytes migrate up the body column among the epithelial cells into the tentacles (Tardent and Morgenthaler 1966; Campbell 1967*a*, 1967*b*, 1988; Herlands and Bode 1974).

Shimizu and Bode (1995) suggest that commitment by the pluripotent i cell to become a nematocyte, and to become a specific type of nematocyte, occurs early in the differentiation pathway. Their arguments rely on the finding that the cells of a cluster differentiate into nematocytes bearing the same type of nematocyst, and that the G2 phase is significantly different for stenoteles and desmonemes. However,

other workers have suggested that for nematocytes, commitment to type is similar to commitment in the neuronal pathway, where it occurs later, during the last cell division (Fujisawa and David 1981, 1982).

In normally growing *Hydra*, the origin of the multipotent interstitial cells that ultimately differentiate into nematocytes and nerve cells is other interstitial cells. However, studies of regenerating *Hydra* have shown that already differentiated cells can dedifferentiate and redifferentiate into other types of cells. Thus, if the endoderm of *Hydra* is isolated by stripping away the ectoderm, the endodermal gland cells that, as part of the lining of the gut, would have been involved in the secretion of digestive enzymes, dedifferentiate and then redifferentiate into ectodermal epithelial cells and interstitial cells. These interstitial cells subsequently differentiate into nerves, sperm, and nematoblasts (Davis et al. 1966). Cell division by nematoblasts that already bear nematocysts (i.e., that were presumably mature and postmitotic) has also been documented (Davis 1970).

Secretion and differentiation of nematocyst structures

Although nematocysts, like horns and feathers, are merely the inanimate secretions of living cells, the complexity and ingenuity of their design, upon which their functioning depends, astonish. The best and most detailed analysis of the how their architecture develops has been given in a series of penetrating studies on siphonophores by Picken and Skaer (Picken 1953; Skaer and Picken 1965, 1966; Skaer 1973; Picken and Skaer 1966; Robson 1988; Skaer 1988). The description that follows is drawn from various workers and is a derived outline of their work. The analysis has been essentially confirmed, albeit with variations of detail, in later ultrastructural and kinematographic studies on *Hydra* (Holstein 1980).

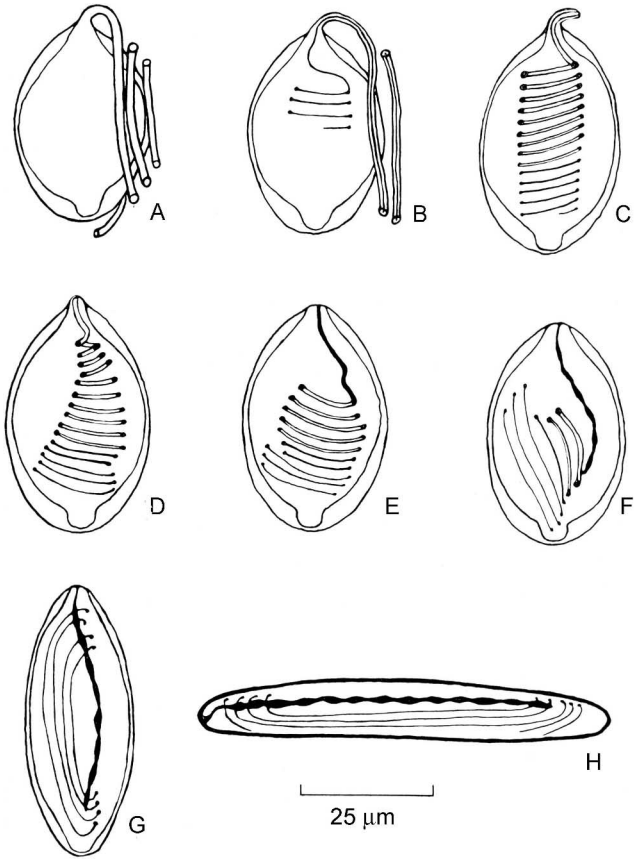
Using phase-contrast microscopy, Skaer (1973) tracked and continuously photographed the development of individual cnidoblasts of all four types of nematocysts in the living gastroid of the siphonophore *Rosacea cymbiformis*. There are four types of nematocysts in this species, all of which follow essentially the same sequence as that given for the large microbasic mastigophores (Fig. 1). The first sign of differentiation is the appearance of an ovoid vesicle that eventually forms the capsule of the nematocyst within the secretory cell, the nematoblast. The nematocyst material is synthesized in the rough endoplasmic reticulum and Golgi complexes to form the ovoid secretion product (Gupta and Hall 1984). The nematoblast secretes the molecular components of the nematocyst as a mass of macromolecules into the membrane-bound secretion vesicle. Gupta and Hall (1984) point out that this material must contain at least the glutamic and aspartic acid-rich peptides and the toxins of the capsule fluid, the collagenous material of the capsule, the sulfur-containing metalloproteins for the hollow filament, proteins to form barbs and spines, and material to form the operculum. In the leptomedusa *Eirene viridula*, Germer and Hundigen (1980) describe the formation of a large vesicle containing electron-dense material, whose membrane bears an outer coat; the vesicle is the primordium of the nematocyst. As the vesicle grows by fusion with other Golgi vesicles, the outer coat of the vesicle membrane is lost. A tube, external to the capsule, grows out of the vesicle by accretion of secretory droplets, apparently produced by the Golgi apparatus of the cell's cytoplasm (Skaer 1973). The droplets fuse onto the tip of the tube. In microbasic mastigophores, the length of the fully developed tube, which narrows towards its tip, may be as much as 7–10 times that of the capsule. In *E. viridula*, the walls of the capsule, which consists of two layers, become thinner. The capsule wall does not extend over the growing external thread, which is bounded by two unit membranes and surrounded by microtubules (Germer and Hundigen 1980).

The tip of the external tube then inverts and passes back down itself into the capsule. As the tube becomes internalized, the invaginated tube coils to form a helix about the long axis of the capsule. How such an inversion begins is not known, and while it is plausible to attribute the helical coiling of the tube to the inherent properties of its collagenous molecules, it is more difficult to attribute the initial invagination to such a property. A number of authors have interpreted the disappearance of the external tube as a regression and the differentiating structures appearing within the capsule as the primordium of a differentiating internal tube (e.g., Weill 1934; Westfall 1966*b*; Günzl 1971; Germer and Hundigen 1980; Campbell 1988). At first, approximately three coils are added every 4.5 min, but later they are added more slowly. Coiling is apparently an inherent property of the tube, as it lies suspended within the capsule without touching the capsule wall (Skaer 1973; see also Gupta and Hall 1984) (Fig. 6). As the internal tube forms, the volume of the capsule increases; finally, when about 15 coils have been formed within the capsule, the tube is completely invaginated within the capsule. As the nematocyst matures, the coils near the tip gradually become more lax and are repositioned to lie along the longitudinal axis of the capsule at the same time as the coils near the point of attachment to the capsule straighten out. The capsule continues to elongate as the thread begins to differentiate into two regions. At this stage, in those nematocysts that have one, a small operculum forms at the point of attachment of the thread to the capsule.

Using measurements made on electron micrographs of holotrichous isorhizas (in various stages of discharge) of the sea anemone *Corynactis viridis* to construct paper, velvet, and cellophane models, Picken and Skaer reconstructed the development of the thread's functional morphology and presented a vivid portrayal of its changing configuration as it is discharged (Picken 1953; Skaer and Picken 1965, 1966; Picken and Skaer 1966; for a comprehensive summary see Skaer 1988). The thread of the undischarged nematocyst becomes pleated during inversion, as it twists in upon itself, creating "a torsion which gives it the shape of a deeply cut infinite screw thread" (Bretschneider 1949). When the nematocyst is discharged, the pleats are smoothed out. In *C. viridis*, three pleats run around the thread in left-handed helices (Fig. 7). The core of the inverted thread in holotrichous isorhizas is comprised of barbed spines whose bases are inserted into pockets of the thread. The rows of barbed spines form helices around the thread. In the undischarged thread the tips of the barbed spines overlap each other and are evenly spaced around the circumference of the tube (Fig. 8).

After the operculum forms, the capsules migrate to their final site in the batteries of the tentacles, where they undergo final maturation. The whole process of development of

Fig. 6. Diagram of the development of a microbasic-mastigophore nematocyst, based on phase-contrast microscopy of living specimens. None of the formative cell is shown and much of the external thread has been omitted. The internal thread is shown in optical section. (A) Formation of the cylindrical thread in the cytoplasm. (B) Entry of the thread into the capsule. (C) Coiling of the thread in the capsule. (D–F) Remodeling of the thread in the capsule. (G) Stage at which migration occurs. (H) Mature nematocyst. (From Skaer 1973, reproduced with the permission of J. Cell Sci., Vol. 13, © 1973 The Company of Biologists Ltd.)



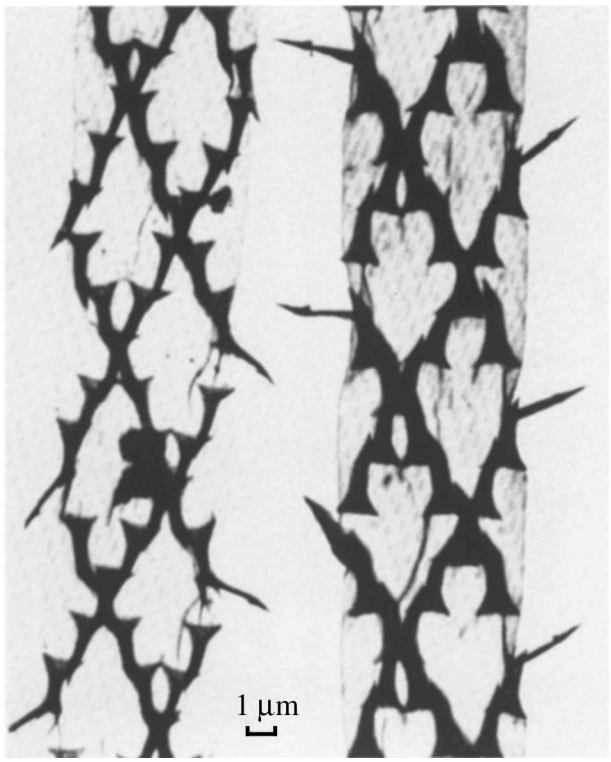
R. cymbiformis cnidoblasts from the completion of the external tube to migration takes about 4 h (Skaer 1988).

How are nematocyst-containing nematocytes deployed?

Nematocysts do not simply migrate randomly to their sites of discharge; indeed, in those forms in which the question has been studied, it appears that specific nematocyst-bearing nematocytes are deployed to form unique and precise patterns at their destinations. Thus, in *Hydra*, the cnidocytes in the battery-cell complex (Westfall et al. 1971*a*; Hufnagel et al. 1985; Hufnagel and Kass-Simon 1988; Westfall 1988) are organized so that a single stenotele is positioned at the center of the complex and is surrounded by an outer ring of desmonemes and isorhizas (Fig. 2). In siphonophores, a very complex pattern arises as a result of migration and as a consequence of a series of cell sortings that takes place after the cyst-bearing nematoblasts have developed (Skaer 1988) (see below).

In mature, growing *Hydra* there appear to be at least two complementary ways in which the nematocyte–nematocyst

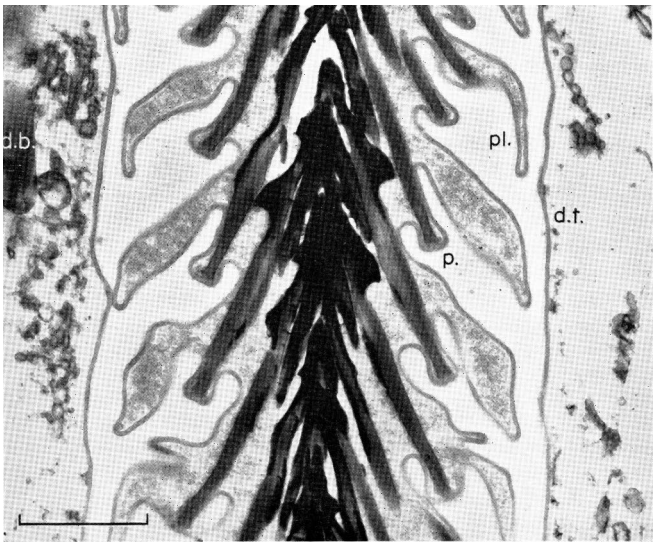
Fig. 7. Air-dried discharged threads from two holotrichous isorhizas, flattened to different extents, showing barbed whorls and the staggering of the whorls, so as to form three rows of barbs. (From Skaer and Picken 1965, reproduced with permission of Philos. Trans. R. Soc. Lond. B Biol. Sci., Vol. 250, © 1965 The Royal Society.)



complex arrives in the battery-cell complexes of the tentacle. According to the summary given by Campbell (1988), there is convincing evidence from many sources, including filmed microscopy studies of various forms, that the nematocyst-containing nematocyte actively migrates as an amoeboid cell between the cells of ectoderm to its final location (Schneider 1894; Hadži 1911; Lipin 1911; Weiler-Stolt 1960; Tardent and Morgenthaler 1966; Günzl 1971; Carré 1974; Rahat and Campbell 1974; Campbell and Marcum 1980; Campbell 1988 and references therein; Skaer 1988) (Fig. 9). In *Hydra*, studies indicate that the developing nematoblasts migrate to preordained places within the battery cell and make a desmosomal connection with this specialized region. This region, in turn, makes a hemidesmosomal connection with the mesoglea (Wood and Novak 1982; Novak and Wood 1983; Hufnagel et al. 1985; Wood 1988); however, such complexes have also been found in the absence of nematocysts (Hufnagel and Kass-Simon 1988).

In experiments in which the axial distribution of differentiating nematocysts was studied, stenoteles, in nematoblasts, were distributed in a distal–proximal capsule-size gradient; when *Hydra* heads (hypostome and tentacles) and basal discs were transplanted to their opposite poles, the gradient became reversed. The stenotele size gradient was abolished when the head was repeatedly removed from regenerating *Hydra* but not when the basal disc was repeatedly ablated (Rich and Tardent 1969; Tardent et al. 1971). Tardent et al. (1971) suggest that the gradient is due to some factor or fac-

Fig. 8. Median section of the thread of a holotrichous isorhiza arrested in discharge. This region is within a few micrometres of the dart. *pl.*, pleats; *p.*, barb pocket; *d.t.*, discharged thread; *d.b.*, barb detached from the discharged thread. Scale = 1 μm. (From Picken and Skaer 1966 with permission of Academic Press Inc. © 1966.)

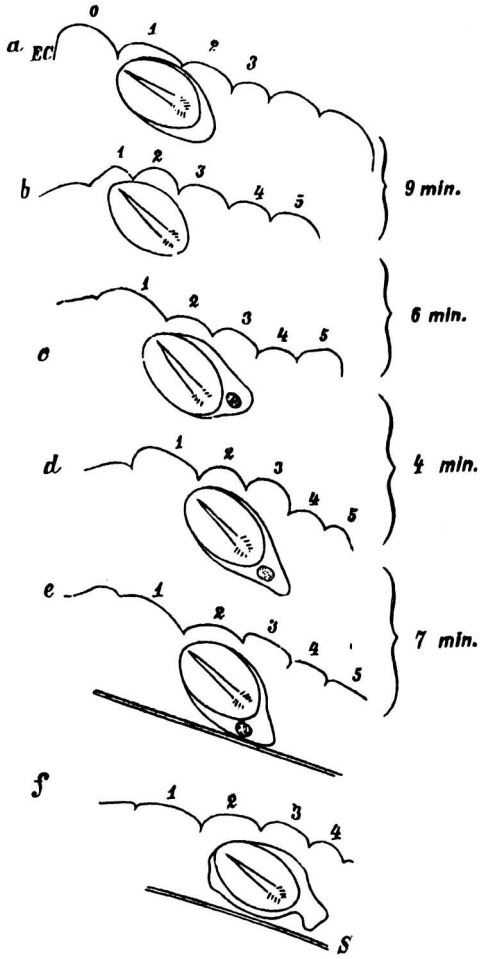


tors produced by the head. Bode and Smith (1977) also found that the nematoblasts of the different types of nematocysts in *Hydra* are differentially distributed along the animal's axis. Nematoblast-bearing stenoteles were distributed in a distal–proximal gradient; desmonemal and isorhizal nematoblasts were found mainly in the upper half of the body column. The authors suggested that the determination of the type of nematocyte that would be differentiated was position-dependent. By grafting column sections of *Hydra*s devoid of dividing nematoblasts and interstitial cells onto sections of normal, vitally stained *Hydra*s and sampling the interstitial cells that had migrated at various periods, Heimfeld and Bode (1984) reported that migration does not appear to be random, but rather, because of the presence of the head, there is considerable movement of migrating interstitial cells towards the head (Herlands and Bode 1974); in budding animals there is migration in the direction of the bud as well.

In colonial hydroids, nematocytes have been found to develop in stolons and then migrate into the hydranths. In *Polypodium hydriforme*, nematocytes migrate distally into the tentacle from their origin at the tentacle base (Lipin 1911), and in siphonophores they arise in a thickening near the tentacle base and migrate out along the tentacle (Schneider 1894; Carré 1974; Skaer 1988).

Many workers have suggested that the pathway of migration is unidirectional and distal, away from the body into the tentacles. Thus, in *Hydra* grafts, larger numbers of radioactively labeled nematocytes migrated from basal donor to apical host than from apical donor to basal host (Campbell 1967*a*, 1967*b*; Herlands and Bode 1974). However, time-lapse movies made by Günzl (1971), Rahat and Campbell (1974), and Campbell and Marcum (1980) indicate that migration is bidirectional but not, or only rarely, circumferential, at least in the tentacles of *Hydra* (Campbell and Marcum 1980).

Fig. 9. Stenotele nematocyst migrating along the tentacle of *Pennaria cavolinii*, a hydrozoan, observed and drawn by Murbach (1895). Frames *c–e* show relative positions of the single anterior pseudopod, nucleus, and backward-directed capsule; frames *e* and *f* show the mesoglea. (From Campbell 1988, reproduced with permission of Academic Press Inc. © 1988.)



The second way in which the nematocyte–nematocyst complex may get to its ultimate destination in the base and tip of *Hydra*'s tentacles is by the simple growth and sloughing-off processes that have often been described, and have been the focus of a number of studies (e.g., Campbell 1967*a*, 1967*b*; David and Plotnick 1980).

In *Hydra* the nematocyte–nematocyst complex arises in the column from a population of interstitial stem cells, of which 60% divide to make further stem cells, 10% ultimately become nerves, and 30% become nematocytes in each stem-cell generation (David and Gierer 1974). Differentiating stem cells, which are embedded in the ectodermal epithelium, are moved distally to tentacle and peduncle regions as the *Hydra* grows and older cells are sloughed off (Bode et al. 1973; David and Plotnick 1980; Campbell 1988). The nematocyst-containing nematocytes can migrate from their site of origin in the ectoderm of the gastric region to their final destination in the developing battery cells of the constantly self-renewing tentacles, which are elaborated at the base of the hypostome (Kanaev 1952; Campbell 1967*a*, 1967*b*). By tracing the movements of differentially labeled

ectoderm and endoderm cells into the hypostome and tentacles of *Hydra*, Dubel (1989) determined that the battery cells of the tentacle, containing nerves and nematocytes, were derived from ectodermal stem cells of the gastric region. The developing stem cells move into the stationary area at the outer periphery of the hypostome near the bases of the tentacles. From the stationary zone, the cells move towards either the mouth or the tentacles. If they are migrating towards the tentacles, they differentiate into nematocyte-containing battery cells.

The development and deployment of nematocysts during larval development and metamorphosis appear to follow an analogous, albeit not yet fully described itinerary (Martin and Archer 1997). In the early free-swimming planula larva of the hydroid *Pennaria tiarella*, interstitial cells that arise during gastrulation are distributed throughout the endoderm. The cells begin to divide and find their way into the base of the ectoderm. They increase in number in both ectoderm and the endoderm. At the onset of metamorphosis, the interstitial cells located in the mid and basal regions of the larva move down into the ectoderm and endoderm of the region that will attach to the substrate. Later, by the time the metamorphosing polyp begins to develop its presumptive head and tentacle region, the distribution of interstitial cells takes on its final adult pattern, with the majority of interstitial cells concentrated in the head region. The mechanisms guiding these migrations are not known, nor have individual interstitial cells been followed to their final destination and ultimate state of differentiation. Nonetheless, Martin and Archer (1997) have characterized the distribution of nematoblasts in the various developmental stages. Nematoblasts are found in both the endoderm and the ectoderm in all stages, appearing in the ectoderm 14 h after fertilization. In the free-swimming planula larva, they migrate from apical endoderm to ectoderm as single cells, which apparently do not divide to form clusters or syncytial nests. In the mature larva, fully differentiated nematocytes are present, mainly at the apical surface. As the planula attaches, nematoblasts move into the surface ectoderm and endoderm of the apical attachment region, where they remain, leaving the growing stalk of the polyp without either nematoblasts or nematocysts. Later, by the time the incipient head and tentacles form, the complete adult complement of nematocytes (stenoteles, desmonemes, microbasic heterotrichous b-mastigophores, and later, microbasic heterotrichous b-mastigophores with inclusions) can be found in the head region. Thus, during metamorphosis, nematoblasts migrate apically in large numbers, whereas in the still undifferentiated planula migration occurs primarily transversely from endoderm to ectoderm. Martin and Archer (1986) point out that since the planula larva is oriented "upside down" when it metamorphoses into the adult polyp-bearing stage, the embryonic distribution of cells is completely reorganized, which suggests that since nematoblasts are found in the endoderm as well as the ectoderm of the adult polyp, migration of the adult in multiple directions is probable.

In siphonophores, nematocysts are born in closely associated but not attached nematoblasts, in a cuff situated at the top of the gastrozoid (Carré 1972; Skaer 1973; Skaer 1988). But unlike *Hydra* (Rich and Tardent 1969), where groups of nematoblasts elaborate the same type of nematocysts, in siphonophores, closely adjacent nematoblasts may elaborate any type of nematocyst (Skaer 1988). However, as the individual nematocyst-bearing nematocytes travel out of the gastrozoid to their ultimate destinations, the types are sorted into distinct and precise patterns. The patterns are formed during migration, when clumps of specific cell types are formed (Figs. 10, 11). Migration itself appears to provide the mechanism by which the cell clusters, of the correct cell number and type, are constructed (although other workers have suggested that the destiny of each nematocyte is regulated and determined in the cnidogenic band in the gastrozooid (Carré 1974, cited by Mackie 1999). After migration, when the cells are adherent and in contact with one another, and are dye-coupled, they form an invariant and exact geometric pattern, which might require the sort of positional information postulated for the placement and docking of nematocytes in *Hydra* (Wood and Novak 1982; Novak and Wood 1983), or which might arise by means of the self-assembly of interlocking surface molecules on the nematocyte (for a comprehensive description and discussion see Skaer 1988).

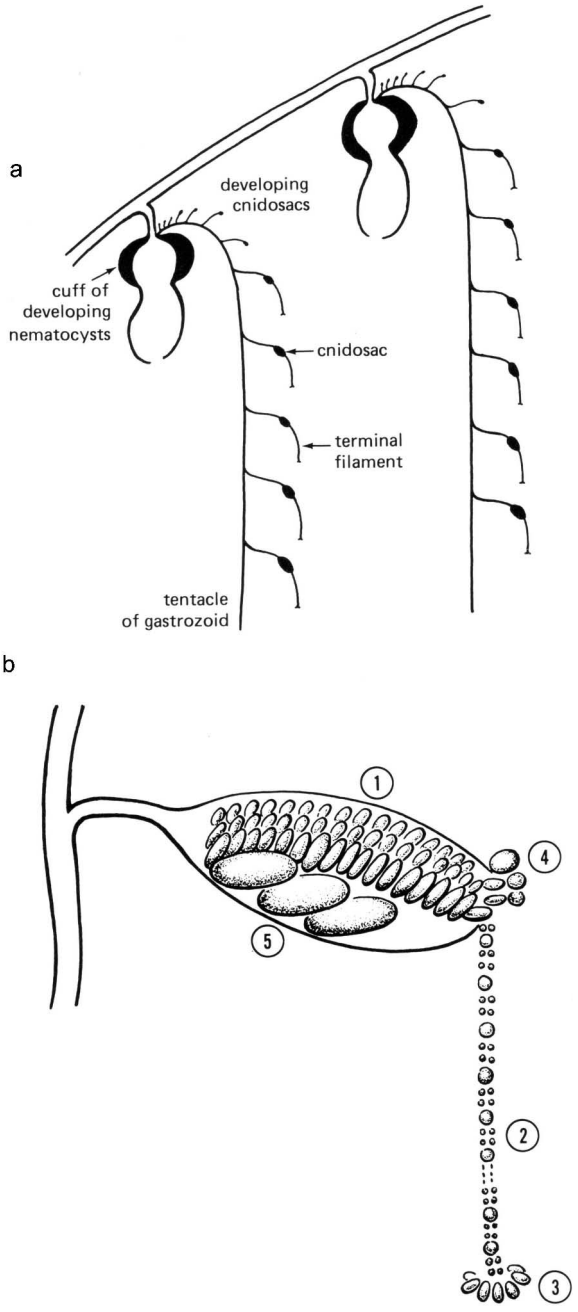
Physiology of nematocyst discharge

Explosion dynamics

An unparalleled analysis of the events that constitute stenotele discharge in *Hydra* has been made by means of ultra-high-speed cinematography and experimentally slowed discharge by Pierre Tardent and co-workers (Holstein and Tardent 1984). The description that follows is taken largely from Tardent's (1988) summary. To capture the morphological changes that occur in the less than 3 ms of discharge, Tardent's group discharged stenoteles from intact *Hydra*s or from isolated tentacles into gels of various densities. In this way the discharge could be blocked at various stages of eversion and the behavior of the stylets and lamellae studied with light and scanning electron microscopy (Tardent and Holstein 1982) (Fig. 12).

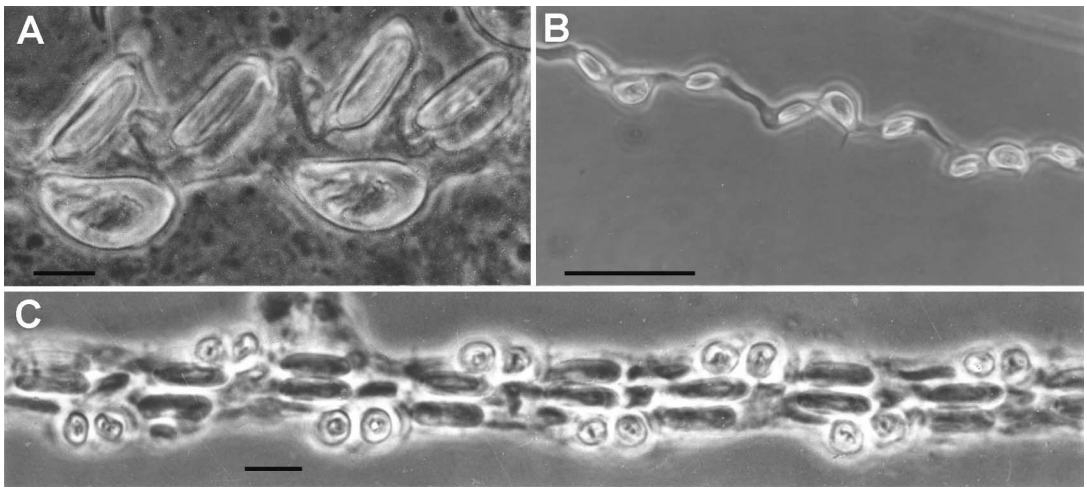
Stenotele discharge can be broken down into a series of events. The first visible response to an electrical stimulus (after about 30 μs) is the opening of the nematocyst's triangular operculum, which is immediately followed by the extrusion of the basal part of the tubule, including the short, broad shaft and the three stylets, which form the pointed arrowhead that penetrates the prey. Just prior to opening (after about 60 μs), the cyst increases in volume, presumably as a result of water rushing into it (Holstein and Tardent 1984). Opening of the operculum can take place in isolated cysts and must therefore be a property of the capsule itself (Tardent 1988). These events take about 10 μs and since the tip of the stylets travels a distance of about 20 μm, the average velocity of 2 m/s suggests an acceleration of 40 000 × g at the moment when the stenotele hits its target and pierces it. This phase of discharge is accompanied by a 25% decrease in the total volume of the cyst. In the next phase there is an apparent backward movement of the stylets as they are withdrawn to clear the way for evagination of the rest of the tubule. The backward motion of the stylets is presumed to result from the eversion of the shaft's conical section. Finally, the long, slender tubule is completely everted. As the tightly twisted tubule everts, its coils are relaxed, so that the tubule approximately doubles its resting length (e.g., in anemones; Godknecht 1985). The energy stored in the twisted

Fig. 10. (*a*) A typical arrangement of gastrozoids in a siphonophore, each gastrozoid having one tentacle. Tentacles grow near their site of insertion on the gastrozoid and cnidosacs form from outpushings of the tentacle. Cnidosacs are filled with cnidoblasts that originated in the thick cuff around the top of the gastrozoid and then migrated into those cnidosacs that are at an appropriate stage of differentiation. The single tentacle represents a "frozen" time sequence in the development of cnidosacs and their nematocyst patterns (the youngest cnidosac is proximal; the oldest is distal). (*b*) A typical calycophoran cnidosac, showing the dorsal cnidoband (1); terminal filament (2); sinker (3); dorsal array of desmonemes (4); and large lateral microbasic mastigophores (5). (From Skaer 1988, reproduced with the permission of Academic Press Inc. © 1988.)



tubule, which is considered to represent a major part of the driving force that carries out the eversion, is thus released (see also Dujardin 1845; Jones 1947; Carré 1980) (Fig. 12). Based on X-ray microanalytical data, Gupta and Hall (1984) point out that during eversion, the filament (which has high concentrations of zinc, copper, and sodium and low concentrations of potassium and chloride, different from the concentrations of these ions in the capsule wall and fluid) loses most of its zinc but not its copper component. They suggest that this removal of zinc results in the removal of allosteric restraints in the filament's structure, causing a release of kinetic energy, which permits the explosive untwisting and uncoiling of the filament during eversion. Thus, as Gupta and Hall (1984) point out, referring to the thought first iterated by D.W. Fawcett (see Discussion by D.L. Slautterback in Lenhoff and Loomis 1961), eversion appears to be the rapid behavioral converse of the slow developmental act of invagination. The final phases of eversion are accompanied by another 25% drop in capsule volume. Experiments with naked cysts indicate that the fluid in the capsule is under positive pressure relative to the external milieu and that its volume increases once the firing of the cyst is triggered. Passive uptake of fluids with molecular masses up to 7000 Da has been observed by Tardent and his group. In the sea anemone, the onset of discharge appears to be accompanied by the release of previously bound calcium within the capsule and the influx of water (Lubbock and Amos 1981; Lubbock et al. 1981; Gupta and Hall 1984). The role of calcium in effecting discharge remains problematic. In the undischarged capsule, calcium forms salt links with negatively charged polypeptides rich in glutamic and aspartic acids (Blanquet 1970, 1988; Mariscal 1974). High concentrations of intracapsular calcium and magnesium (above 1 M) that do not wash out support the idea that these ions may be bound to capsule proteins, peptides, or glycoproteins (Tardent 1988). Gitter and Thurm (1993) provide evidence that calcium channel blockers inhibit nematocyst discharge and that electrically induced discharge requires the presence of ionic calcium (Gitter and Thurm 1993; Gitter et al. 1994). In agreement with Lubbock et al. (1981), who proposed that cell-surface receptors induce electrical activity in the apical membrane of the nematocyte that causes exocytotic fusion of the apical cell membrane with the vacuole surrounding the nematocyst, they suggest that discharge, like neurotransmitter release in nerves, is a calcium-dependent exocytosis (Skaer 1973) mediated by voltage-gated calcium channels at the apical surface of the nematocyte (see below). However, the calcium required for exocytosis would presumably be used in the process of exocytosis at the nematocyte membrane, which might be responsible for the extrusion of the nematocyst from the nematocyte, whereas increases in intracapsular free calcium (and magnesium) would be responsible for increases in intracapsular osmotic pressure and the concomitant inrush of water, which, perhaps by opening the operculum, would release the tensile energy stored in the coiled and twisted tubule (for discussion see especially Gupta and Hall 1984 and Tardent 1988). Interestingly, it appears that uptake of water by the capsule depends upon the presence of a surrounding nematocyte. By immersing cyst-bearing nematocytes and cleaned nematocysts in methylene blue solution, Tardent and co-workers have shown that when electrically stimulated,

Fig. 11. (A) High-power photomicrograph of a terminal filament of *Abylopsis* sp., showing the paired rhopalonemes on each side of the (larger) desmoneme. Note the pattern of two rhopalonemes, one desmoneme, and two rhopalonemes. Phase contrast. Scale bar = 10 μm. (B) The same as A but extended in vivo. Scale bar = 100 μm. (C) Terminal filament of *Forskalia* sp., showing the repeat unit of two rhopalonemes, two desmonemes, and two rhopalonemes. Phase contrast. Scale bar = 10 μm. (From Skaer 1988, reproduced with permission of Academic Press Inc. © 1988.)



naked cysts do not take up the solution, whereas nematocysts enveloped by their nematocytes do (Tardent 1988). The mechanisms by which the nematocyte controls the cyst's uptake of water remain unknown.

Control of discharge

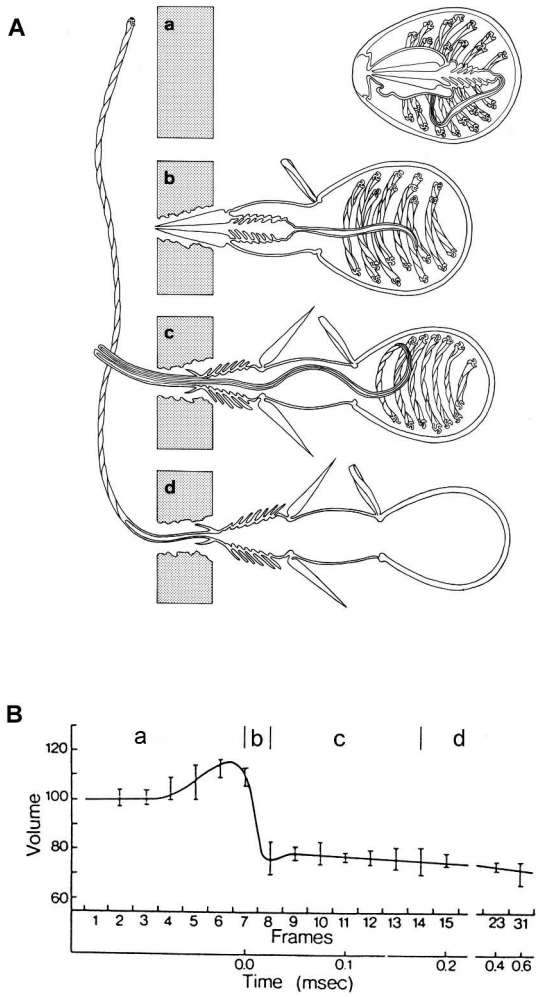
What orchestrates the discharge of nematocysts in response to prey and predator? Nematocysts are made to discharge by the combined effects of chemical and mechanical stimuli. This statement, which continues to be supported by current work, arises from early studies of feeding in *Hydra* and sea anemones (Parker and Van Alstyne 1932; Pantin 1942; Ewer 1947) and more recent studies of aggression (Hand 1955; Williams 1975; Purcell 1977). In his classic monograph *The Elementary Nervous System*, Parker (1919) argued compellingly that nematocysts were independent effectors whose discharge was controlled only by external stimuli. This view of nematocyst functioning has prevailed among many biologists over the years. However, there is a growing body of evidence that indicates that nematocytes are innervated and responsive to signals received and transduced elsewhere, in other parts of the animal (Ewer 1947; Ross and Sutton 1964; Hufnagel and Kass-Simon 1988; Kass-Simon 1988; Westfall 1988; Westfall et al. 1998, 1999), which argues against the hypothesis and suggests that nematocyst behavior is at least modulated, if not completely controlled, by the nervous system.

In *Hydra*, when a small animal such as a nauplius larva of *Artemia* sp. or a *Daphnia* swims against a tentacle, the animal responds by discharging its nematocysts, some of which pierce the prey, causing it to exude its metabolites around the *Hydra*. Certain of the released substances cause additional nematocysts to be discharged and these or other metabolites simultaneously induce the tentacles to bend towards the mouth, which opens to receive the prey. The entire response is coordinated by the interaction of chemical and mechanical stimuli. Food extract (Ewer 1947), or more specifically, reduced glutathione (GSH) alone, is sufficient to cause mouth opening (Loomis 1955; Lenhoff 1961, 1981) or "tentacle-ball" formation (in *Hydra japonica*; Hanai 1981). However, while mechanical stimulation of the tentacle by itself is sufficient to elicit nematocyst discharge, many more nematocysts are discharged when the mechanical stimulus is coupled with a chemical one (Ewer 1947; Watson and Hessinger 1989*a*; Thurm and Lawonn 1990). Although Tardent and Holstein (1982) have shown that naked nematocysts (without nematocytes) can be discharged in vitro by direct electrical stimulation, in vivo, mechanical and chemical stimulation act synergistically to elicit discharge. This is also true in the sea anemone *Anemonia* sp. (Conklin and Mariscal 1976). In *Haliplanella* sp., the chemical stimulus, acting through chemoreceptors, apparently sets the frequency response of the mechanoreceptors (Watson and Hessinger 1991), while in the sea anemone *Anthopleura* sp., GSH alters the direction of ciliary currents in the oral region and asparagine controls the contraction and bending of tentacles that bring food to the mouth (Lindstedt 1971). Our own current work indicates that in *Hydra*, the vibrations of the prey first cause the tentacles to move in the direction of the vibrations. Subsequently, nematocysts are discharged when the tentacles are sufficiently close to the prey to allow the force (or pressure) produced by the prey's movements to be transmitted to the cnidocil of the nematocyte; a single impact of adequate force is sufficient to cause discharge (Scappaticci and Kass-Simon 2001) (Fig. 13).

When feeding has proceeded to satiation, the ability to elicit nematocyst discharge is markedly reduced (Burnett et al. 1960; Sandberg et al. 1971; Smith et al. 1974). Inhibition of the discharge in *Hydra* (Smith et al. 1974; Ruch and Cook 1984; Grosvenor and Kass-Simon 1989) and the sea anemones *Calliactis* sp. and *Epiactis* sp. (Mariscal 1973) is chemically mediated by food substances. In *Hydra*, nematocyst discharge can be inhibited by a non-GSH-containing molecular fraction of food extract that is also a competitive inhibitor of GSH binding at the membrane receptor (Grosvenor and Kass-Simon 1989; Grosvenor et al. 1992).

Although neither the chemoreceptors, nor the mechano-

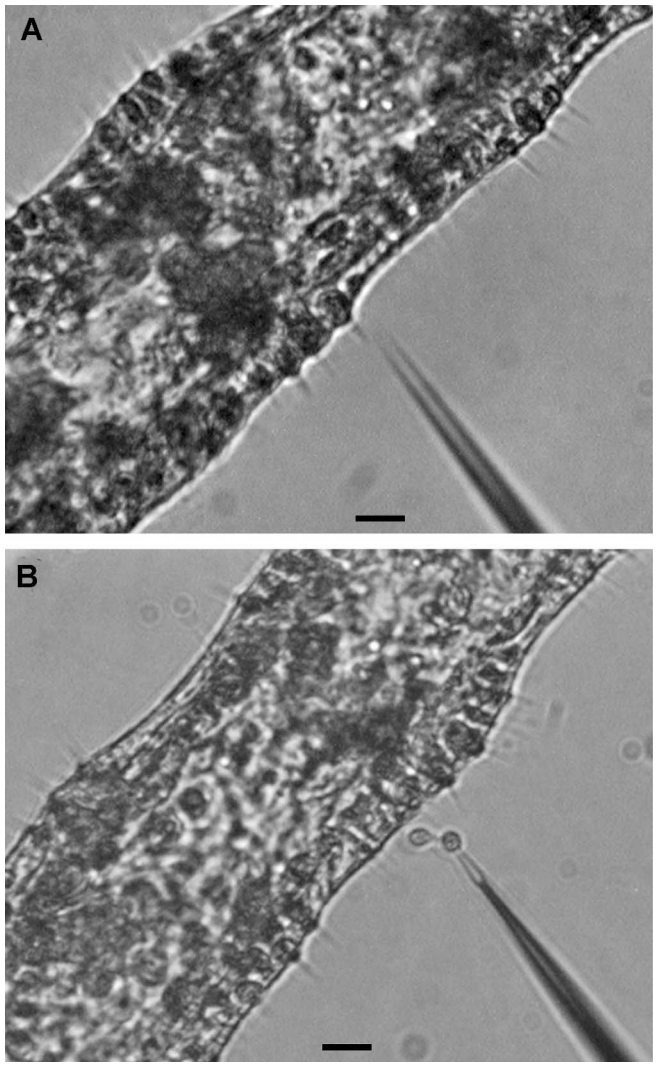
Fig. 12. (A) Four stages of the discharge of a *Hydra* stenotele hitting and perforating the cuticle of a prey and everting its tubule into the target. (From Tardent and Holstein 1982, reproduced with the permission of Cell Tissues Res., Vol. 224, © 1982 Springer-Verlag.) (B) Average values (n = 5) of volumetric changes (expressed as a percentage of the initial value) of the stenotele cyst after triggering and during the subsequent phases of the process of discharge. The calculations are based on high-speed film sequences. Note that the time sequence *a–d* in B corresponds to the stage of discharge *a–d* in A. (From Tardent 1988, reproduced with the permission of Academic Press Inc. © 1988.)



receptors, nor the neuronal connections controlling nematocytes have been definitively described, a number of studies have begun to reveal the mechanisms and receptor sites that are responsible for the chemical and mechanical coordination of nematocyst discharge (for a review see Kass-Simon and Hufnagel 1992).

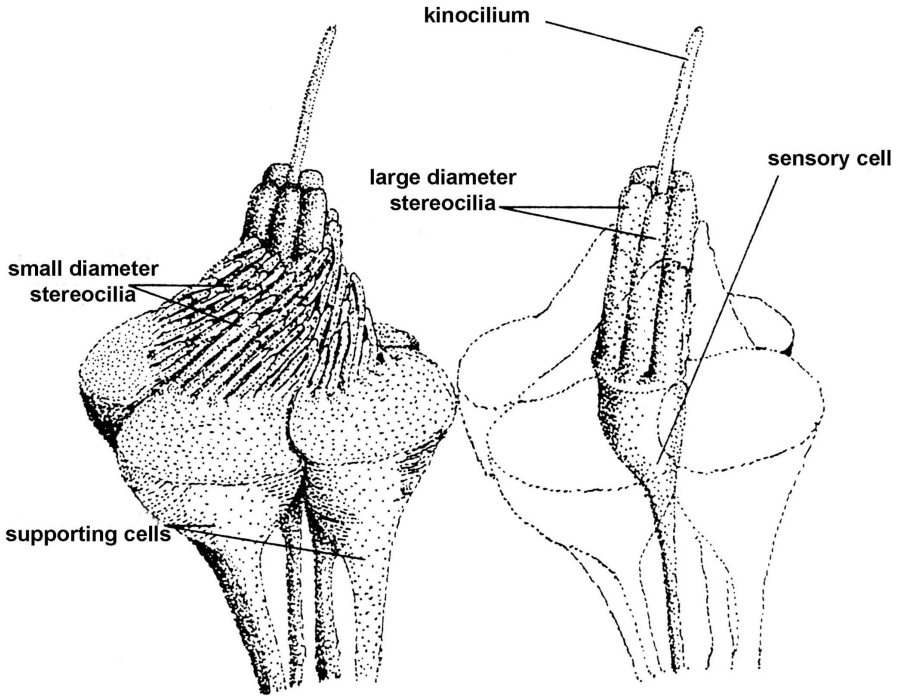
Structurally distinct receptor complexes are associated with the cnidocytes of each of the three classes of coelenterates. The receptor complexes may be formed entirely by the cilia and microvilli of the nematocyte housing the nematocyst or may include the projections of the cells surrounding the nematocyte (Fig. 14). A kinocilium, with a typical 9 + 2n microtubule cytoskeleton (the cnidocil) surrounded by stereocilia, is usual, but variations may include the absence

Fig. 13. (A) A piezoelectrically driven glass probe placed 1 μm from the cnidocil of a desmoneme nematocyte on a tentacle of *Hydra attenuata* is made to vibrate at 15 Hz. (B) A desmoneme nematocyst discharges and winds around the glass probe immediately after a single strike of the cnidocil. The images are from original videotapes. Scale bars = 10 μm.



of a kinocilium and the presence of more than one type of stereocilium. In the hydrozoans (*Hydra* and marine relatives), the receptor complex associated with the nematocyst is called the cnidocil apparatus or complex; in scyphozoan jellyfish (e.g., the genus *Cassiopeia*) it is also called the cnidocil complex, or flagellum–stereocilium complex (Mariscal and Bigger 1976); in the anthozoans (sea anemones and corals) these receptor complexes are called ciliary cones and are conspicuous by the absence of a cnidocil. Although the cnidocil apparatus is distinguished by name from the scyphozoan cnidocil complex and the anthozoan ciliary cone, the three structures are clearly similar and have homologous parts. Some efforts have been made to distinguish among the complexes on the basis of presumed differences in the motility of the kinocilium, but as Mariscal (1974) has pointed out, there is no convincing evidence for such distinctions.

Fig. 14. Drawing of a sensory cell / supporting cell complex (SNSC). At the left, the entire SNSC is stippled. Numerous small-diameter sterocilia originate from supporting cells and converge onto surface structures of the sensory cell. At the right, only the sensory cell is stippled. Large-diameter sterocilia and a centrally located kinocilium project from the surface of the sensory cell. (From Watson and Roberts 1995, Cell Motil. Cytoskeleton, Vol. 30, copyright © 1995, Wiley–Liss Inc., reproduced with permission of John Wiley & Sons, Inc.)



Although recent studies support the idea that the cnidocil apparatus forms the mechanoreceptor, initiating nematocyst discharge, there is growing evidence in the literature that the chemoreceptors, modulating the discharge, do not, at least in some cases, reside on the nematocyte itself, but rather on associated sensory or epithelial cells (Thorington and Hessinger 1988; Marcum 1989; Watson and Hessinger 1989*a*).

Apart from recent studies on *H. japonica*, using monoclonal antibodies, which suggest that some of the receptors involved in tentacle-ball formation in response to GSH may be localized on cnidocils of certain nematocytes, while others may be on the associated battery-cell surface (Sakaguchi et al. 1991), there is no other histological evidence that the modulatory chemoreceptors are localized on the nematocyte itself. Studies in *Hydra* that indicate that the probability of discharge is increased in a dose-dependent manner when the cnidocils of desmonemal nematocytes are directly stimulated with a vibrating probe in the presence of bath-applied mucin (Scappaticci and Kass-Simon 2001) do not differentiate between the nematocyte and the sensory cell as possible chemoreceptive sites. However, Thurm and Lawonn (1990) have demonstrated that the probability of causing nematocyst discharge is increased when *Artemia* extract is used to coat a probe that mechanically stimulates stenoteles in *Hydra* by direct contact of the cnidocil.

Recently, the work of Watson, Hessinger, and colleagues has revealed two distinct receptor sites that alter the threshold of the discharge of microbasic p-mastigophore nematocysts in *Haliplanella luciae.* Bath-applied *N*-acetylneuraminic acid (NANA) increases the length of the hair bundles (which were thought at first to be those of the nematocyte-supporting cell complex, but have more recently been considered to belong to nearby sensory-supporting cells; see below) by polymerizing the actin of the hairs. The actin polymerization causes the hairs to elongate, thereby tuning them to vibrations at lower frequencies and smaller amplitudes. The response to NANA is antagonized by proline, which causes the hair bundle to shorten, thereby increasing the discharge threshold of the hairs (Watson and Roberts 1995). The frequency response of discharge is abolished by cytochalasin B (Watson and Hessinger 1991). The chemoreceptors for N-acetylated sugars were initially thought to occur at the apical surface of the supporting cells surrounding the nematocytes. The receptors have been found to cycle by means of receptor-mediated endocytosis, so that the number of bound receptors changes as nematocysts are discharged (Watson and Hessinger 1989*b*). Colloidal gold antibody tagging of the proline receptor indicated that it was located on the supporting cells adjacent to the nematocyte, which suggested that at least some inhibitory control must come from cells other than the nematocyte (Watson and Hessinger 1994; Watson and Roberts 1994). More recently, Mire-Thibodeaux and Watson (1994*a*) and Watson and Roberts (1995) provided evidence that the frequency-responsive hair bundles belong to a group of cells, referred to as sensory-supporting cell complexes, that communicate by means of interneurons of the nerve net (Peteya 1975) with the supporting cells of the nematocyte, termed the nematocyte-supporting cell complexes (Watson and Roberts 1995) (Fig. 14).

Further analysis of chemoreceptor-mediated nematocyst discharge in *H. luciae* reveals that if the anemone is bathed in NANA prior to mechanical stimulation with agar-coated

Fig. 15. Electron micrographs of tentacles and nematocytes of the capitate hydropolyp *Coryne tubulosa*. (A) Scanning electron micrograph of a polyp. Around the peristome (*p*) the body column of the polyp bears two whorls of four capitate tentacles (*c*) each. Cnidocil complexes of nematocytes are marked by arrowheads and cilia of concentric hair cells by an arrow. (B) Scanning electron micrograph of a capitate tentacle. The ciliary complexes of nematocytes are marked by arrowheads and concentric hair cells by arrows. (C) Nomarski interference-contrast image of a living capitate tentacle. The arrowhead points to the cnidocil complex of a nematocyte, the arrows indicate long cilia of concentric hair cells at the base of the tentacular head, and the curved arrow indicates the tubular thread of a discharged nematocyst; *m*, mesoglia. (D) Electron micrograph of a cross-sectioned tentacular sphere. The arrowhead points to the cnidocil complex of a nematocyte and the arrow indicates the stereovilli enclosing the cilium of a concentric hair cell. *en*, endoderm; *m*, mesoderm; *n*, nematocysts; *v*, vacuole within the supporting cell. Scale bars: 50 μm in A; 10 μm in B, C, and F. (From Holtmann and Thurm 2001*b*, J. Comp. Neurol., Vol. 432, copyright © 2001, Wiley–Liss Inc., reproduced with permission of John Wiley & Sons, Inc.)

vibrating probes, there is a high discharge rate of the microbasic b-mastigophore type at lower frequencies and smaller amplitudes (Watson and Hessinger 1989*a*; Watson and Hudson 1994). The shift in response frequency is correlated with the polymerization of actin located in the stereocilia of hair bundles, which results in a 1- to 2-μm elongation of the hair bundle. In phalloidin-stained specimens, the polymerization is manifested as an increase in the intensity of fluorescence correlated with an increase in f-actin density (Mire-Thibodeaux and Watson 1994*a*; Watson and Roberts 1995). Upon addition of proline, the same rate of discharge could only be elicited by vibrations with larger amplitudes and higher frequencies (Watson and Hessinger 1994; Watson and Hudson 1994). Watson and Hessinger (1988) suggest that vibrations of this type may correspond to similar vibrations caused by small prey struggling to escape. Proline apparently counteracts the effects of NANA by depolymerizing the actin, which in turn results in the shortening of the hair bundles and accounts for the raising of their response frequency (Watson and Roberts 1994, 1995). Whether or not proline will turn out to be a metabolite responsible for modulating nematocyst discharge and GSH binding to the receptor in *Hydra* is a question that still needs to be addressed.

The intracellular events mediating the frequency response are also becoming clear. Watson and co-workers have shown that signal transduction, via receptors that bind NANA, use cAMP as a second messenger. By stimulating tentacles with nonvibrating probes coated with agar and bathing the sea anemones with specific activators of the various segments of the cAMP-production pathway (forskolin, dybutyryl cAMP, chlolera toxin), as well as an inhibitor of cAMP breakdown (caffeine), Watson and Hessinger (1992) were able to produce elongation of the hair bundles, which in turn resulted in the shift of discharge threshold to lower frequencies. Mire-Thibodeaux and Watson (1994*b*) have subsequently shown that NANA-induced hair-bundle elongation can be prevented by inhibiting protein kinase A, thereby by interfering with cAMP production.

With respect to mechanoreception, Thurm and colleagues have begun to analyze how the cnidocil apparatus of stenoteles in the hydrozoan polyp *Coryne tubulosa* initiates discharge as a response to mechanical stimulation. In *C. tubulosa* the nematocytes and sensory cells are located in clusters at the tips of the capitate tentacles. Thurm and co-workers have shown that receptor potentials are generated in the nearby nematocytes when the long cilium of a sensory cell or the cnidocil of another nematocyte is mechanically stimulated (Brinkmann 1994; Brinkmann et al. 1995; Oliver and Thurm 1996; Thurm et al. 1998; Holtmann and Thurm 2001*b*). In the hydrozoan polyp *Stauridiosarsia* sp., depolarizing membrane voltages could be recorded from the nematocyte when the cnidocil was deflected (Brinkman et al. 1996). The depolarization of the nematocyte is considered to control the exocytotic behavior of discharge in two ways: by causing the discharge of a proximate capsule by a high-threshold action potential in its nematocyte, and by the output of synaptic signals at the basolateral side of the nematocyte, which leads to slow excitatory postsynaptic potentials in other nematocytes of the same tentacle, suggesting that the nematocyte itself functions as a sensory cell (Brinkman et al. 1995). To date, no synaptic vesicles have been found within the nematocytes themselves (Holtmann and Thurm 2001*a*), and the situation may be similar to that suggested by Mackie et al. (1987) for the defensive nematocytes in the siphonophores *Apolemia uvaria* and *Cordagalma cordiformis*; these lack innervation and might therefore be responding to documented epithial impulses rather than behaving as independent effectors (Carré and Carré 1980). However, in *Staurosarsia* sp., Brinkman et al. (1995) argue that because there is no fixed ratio between the strength of the mechanical stimulus and the probability of nematocyst discharge or the size of the synaptic response, intermediate elements might participate in the generation of the excitatory postsynaptic potential (Brinkmann et al. 1995) (Figs. 15, 16).

Oliver and Thurm (1996) also investigated the electrical properties of the nematocytes of *Coryne* sp. and *Stauridiosarsia* sp. Using a piezoelectrically driven glass probe they deflected cilia of the nearby sensory nerve cell and recorded transient depolarizations of the impaled nematocyte some distance from the sensory cell. When the sensory cell was stimulated in the range of 0.5–1 Hz, the first 1–13 stimuli triggered excitatory postsynaptic potentials, after which the cell habituated. When the sensory cell was allowed to rest between stimuli for periods of 50–200 s, a deflection could again produce an excitatory postsynaptic potential in the nematocyte. The habituation is considered to be presynaptic, since stimulating another sensory cell also generates an excitatory postsynaptic potential. However, with stepwise deflections of the cilium of the sensory cell, lasting between 50 and 100 ms, no correlation between the angle of deflection and the amplitude of the response could be established, leaving open the question whether intermediate cells or mechanisms might not also be involved (Brinkmann et al. 1996). Thus, in spite of the early convincing arguments by Parker and others (Parker 1919; Parker and Van Alstyne 1932; Pantin 1942) that nematocysts were independent effectors, there is here a strong argument to indicate that neuronal or other electrical inputs to the nematocyte modulate nematocyst discharge.

In this regard, Westfall et al. (1971*b*), Carré and Carré

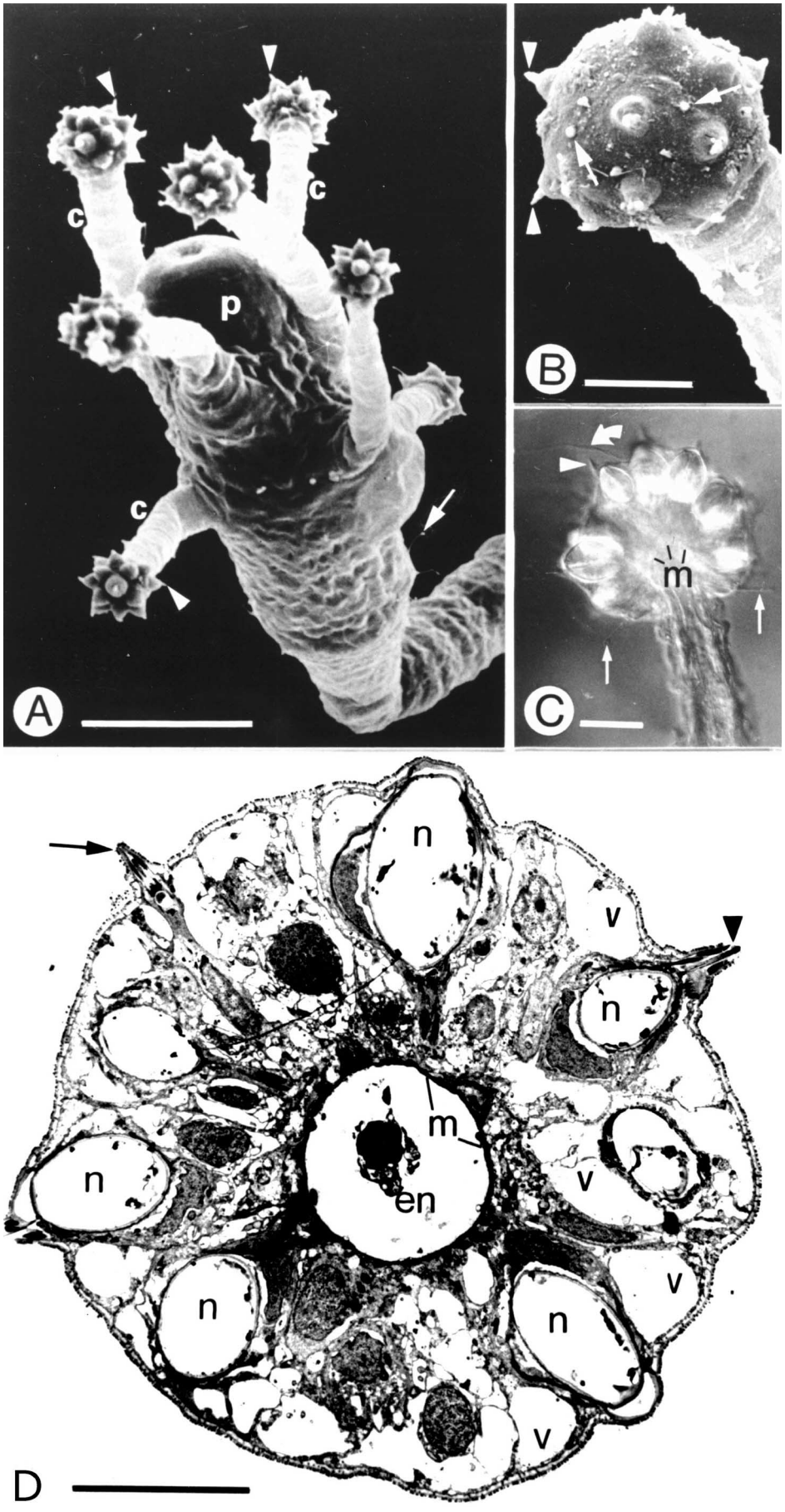


Fig. 16. (A) Isolated tentacular sphere of *Stauridiosarsia producta*, indicating placement of recording micropipettes and capillary pipette used to hold the specimen. *ca*, cnidocil apparatus; *cn*, cnidocyst; *cy*, stalk of nematocyte, including synapses; *mc*, capillary microelectrode; *pe*, pellicle; *sp*, stimulating glass probe. (B) Receptor potentials of a nematocyte generated by mechanical stimulation of the cnidocil. (C) An excitatory postsynaptic potential induced by mechanical stimulation of a distant nematocyte on the same tentacle. (From Brinkmann et al. 1996, reproduced with permission of J. Comp. Physiol. A, Vol. 178, © 1996 Springer-Verlag.)

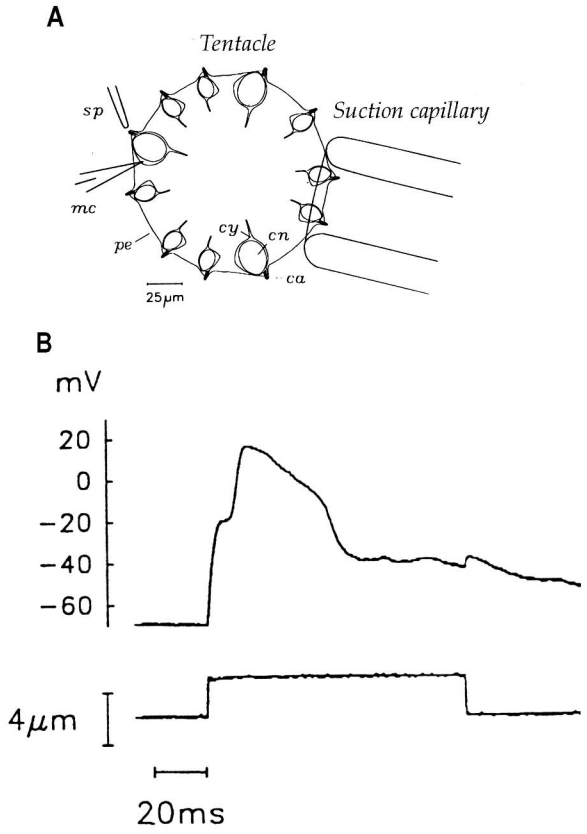
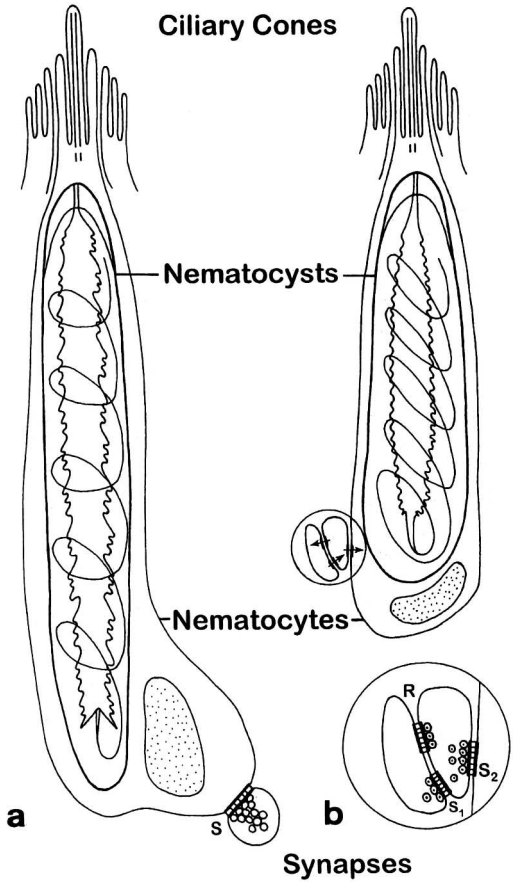


Fig. 17. Synapses on two types of nematocytes of the sea anemone *Aiptasia pallida*. (*a*) Clear vesicles in a nerve synapsing onto a p-mastigophore. (*b*) Dense-core vesicles in two nerves, one of which synapses onto the basitrichous isorhiza and makes a reciprocal synapse with the other. (From Westfall et al. 1998, J. Morphol., Vol. 238, copyright © 1998, Wiley–Liss Inc., reproduced with permission of John Wiley & Sons, Inc.)



(1980), Hufnagel and Kass-Simon (1988), and Westfall (1988, 1998) have presented ultrastructural evidence of nerves synapsing onto nematocytes. In *Apiptasia pallida*, Westfall and colleagues (1998, 1999) present striking and detailed electron micrographs showing synapses on mastigophore and basitrich nematocytes, nematoblasts, and spiroctyes. The synapses contain either dense-core or clear synaptic vesicles, suggesting the presence of at least two types of neurotransmitter (Fig. 17). The authors call attention to the fact that different types of nematocytes are innervated by neurons containing different types of synaptic vesicles and suggest that because sequential as well as reciprocal neuro-neuronal synapses exist in the neurons that ultimately synapse onto the nematocytes and spirocytes, neuronal modulation of nematocyst discharge may be complex and involve both sensory and ganglion cells. In the siphonophores *A. uvaria* and *C. cordiformis*, nematocytes used for feeding and predation possess synaptic innervation (Carré and Carré 1980).

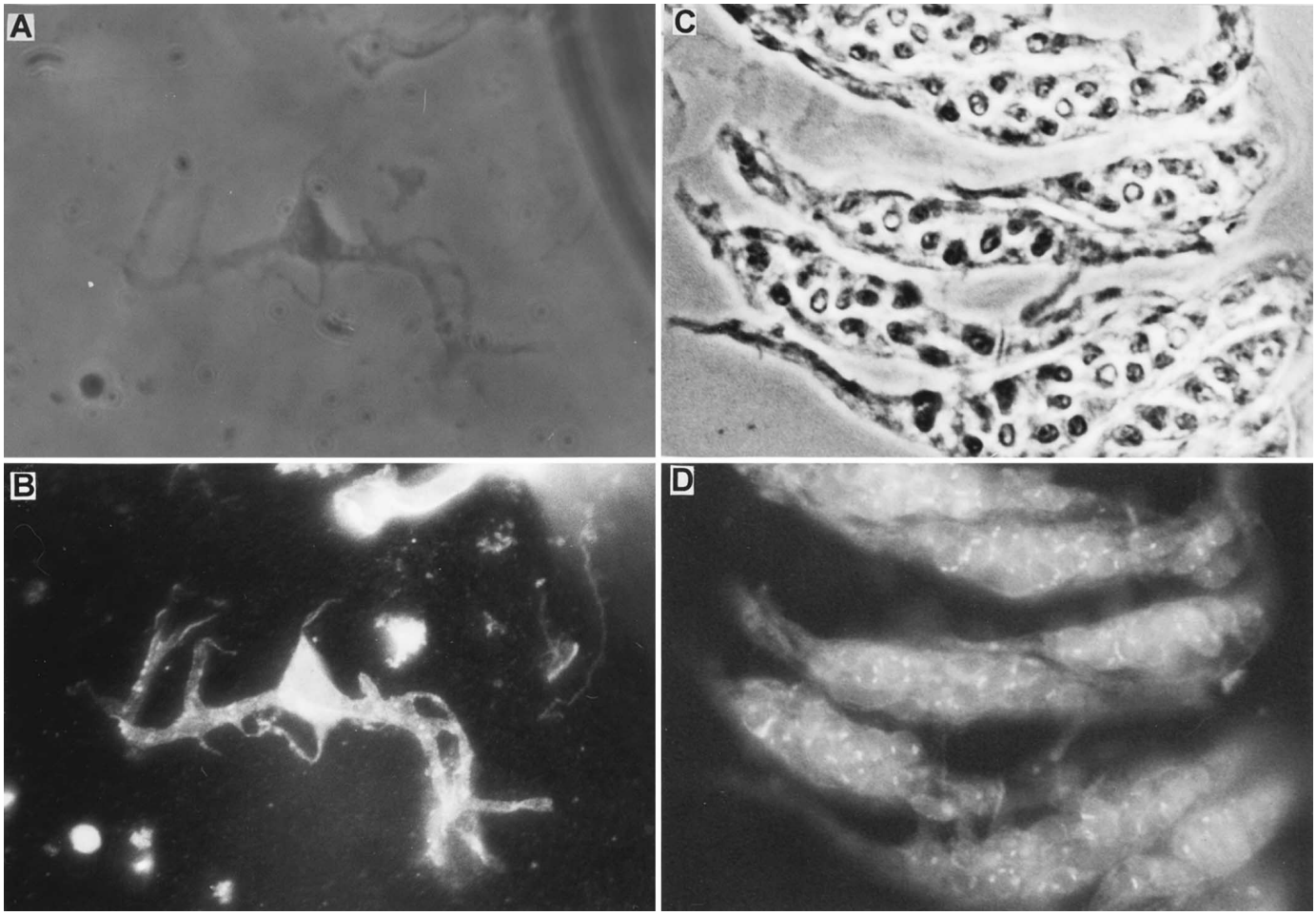
On the basis of behavioral data (Ewer 1947; Ross and Sutton 1964; Slautterback 1967; Kass-Simon 1988), arguments have been made (Kass-Simon 1988) that at least inhibitory innervation is necessary to selectively prevent nematocyst discharge, say, for example, during locomotion or tentacle bending in *Hydra*.

Recent pharmacological and immunohistochemical evidence supports the contention that nerves modulate discharge in many if not all cases. Thus, Lawonn and Thurm (1994) have shown that the dopamine D2 antagonist spiperone removes post-feeding inhibition of stenoteles in *Hydra*, and its agonist, quinpirole, prevents recovery from inhibition, even after 8 days of starvation. Several studies indicate that nerves and receptors specific for acetylcholine, serotonin, epinephrine (Welsh 1960; Lentz and Barnett 1961, l962; Wood and Lentz 1964), and glutamate (Hufnagel et al. 1993, 1997; Hufnagel and Kass-Simon 1995) are associated with nematocytes and spirocytes (Westfall et al. 2000), and give strong support for excitatory and inhibitory neuronal control or modulation of nematocyst discharge (Fig. 18).

Summary and conclusion

The unique ability of nematocysts to function as specific, energy-efficient weapons of feeding and defense can be attributed to the development of intricate internal structures

Fig. 18. (A and B) Anti-glutamate antibody fluorescence in the varicosities and cell body of a sensory cell dissociated from the battery-cell complexes of tentacles in *H. attenuata*. Similar sensory cells have been observed in intimate association with nematocytes. (A) Phase-contrast image. (B) Cells stained with polyclonal anti-glutamate antibody. 1600×. (C and D) Localization of glutamate kainate / α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors (GR2/3) on numerous nematocytes of several dissociated battery-cell complexes. (C) Phase-contrast image. (D) Cell stained with anti-GluR2/3 antibody. 540×. (Photographs courtesy of L.A. Hufnagel and G. Kass-Simon.)



that store the latent forces responsible for the ensnarement of prey and the delivery of packaged toxins. Although the processes by which the nematocyte–nematocyst complex finds its final, and perhaps predetermined, location in the animal have been extensively described, the nature of the cellular and molecular mechanisms governing its migration and patterned docking have hardly been formulated, let alone definitively analyzed. Conjectures that patterned docking is dependent upon an external informational signal, as has been suggested for some hydrozoans, or is entirely a result of self-assembly, as may exist in siphonophores, are equally credible, but far from conclusively demonstrated.

In contrast, the chemical and physical mechanisms controlling nematocyst behavior have begun to be identified. Explosive forces appear to result from the release of intrinsic energy stored in the coiled thread during development, as well as from osmotically induced changes in intracapsular hydrostatic pressure (resultant upon an increase of intracapsular free calcium), which apparently require the presence of the surrounding nematocyte. In those cases that have been studied, specific molecules binding to adjacent cells appear to be able to alter the frequency response to mechanical stimulation of the nematocyte to coincide with the swimming frequencies of prey animals; the shift in response frequency depends upon a change in the length of the sensory hairs in adjacent cells. However, more cases will have to be studied before the question of whether or not chemical receptor sites are present also on the cnidocil of the nematocyte can be definitively decided. Similarly, the receptors and mechanisms that govern the inhibition of discharge by other food-derived molecules have yet to be identified and described. Electrophysiological studies support the hypothesis that mechanical, chemical, and electrical stimuli, ultimately causing calcium influx into the nematocyte, mediate the exocytotic event of discharge. Detailed hypotheses of how that might happen have yet to be formulated. Nonetheless, accumulating anatomical, behavioral, and electrophysiological evidence indicates that nematocyst discharge is modulated, in many if not all cases, by excitatory and inhibitory nerves impinging upon the nematocyte.

Thus, although it cannot yet be said that a comprehensive picture of the molecular physiology of nematocyst behavior and development exists, and despite the many questions that

remain, the outline that has so far been drawn has yielded significant insights; its concepts and approaches impart to future studies their context and direction.

Acknowledgements

We thank Sherrell Hooper for assiduous library research and D.A. Nash for critically reading the manuscript.

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