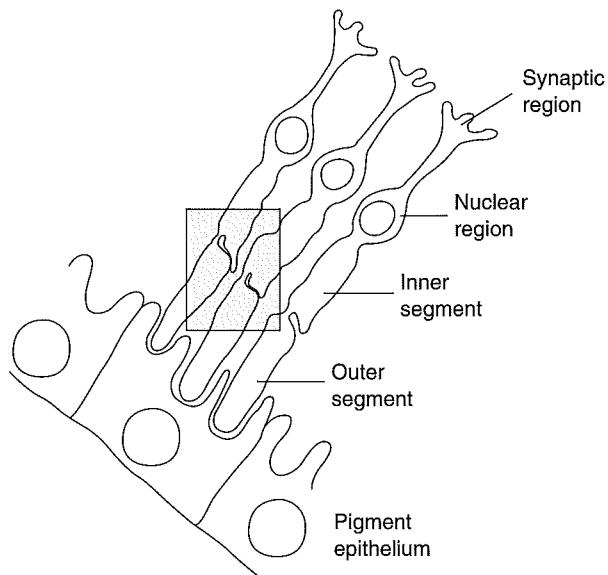


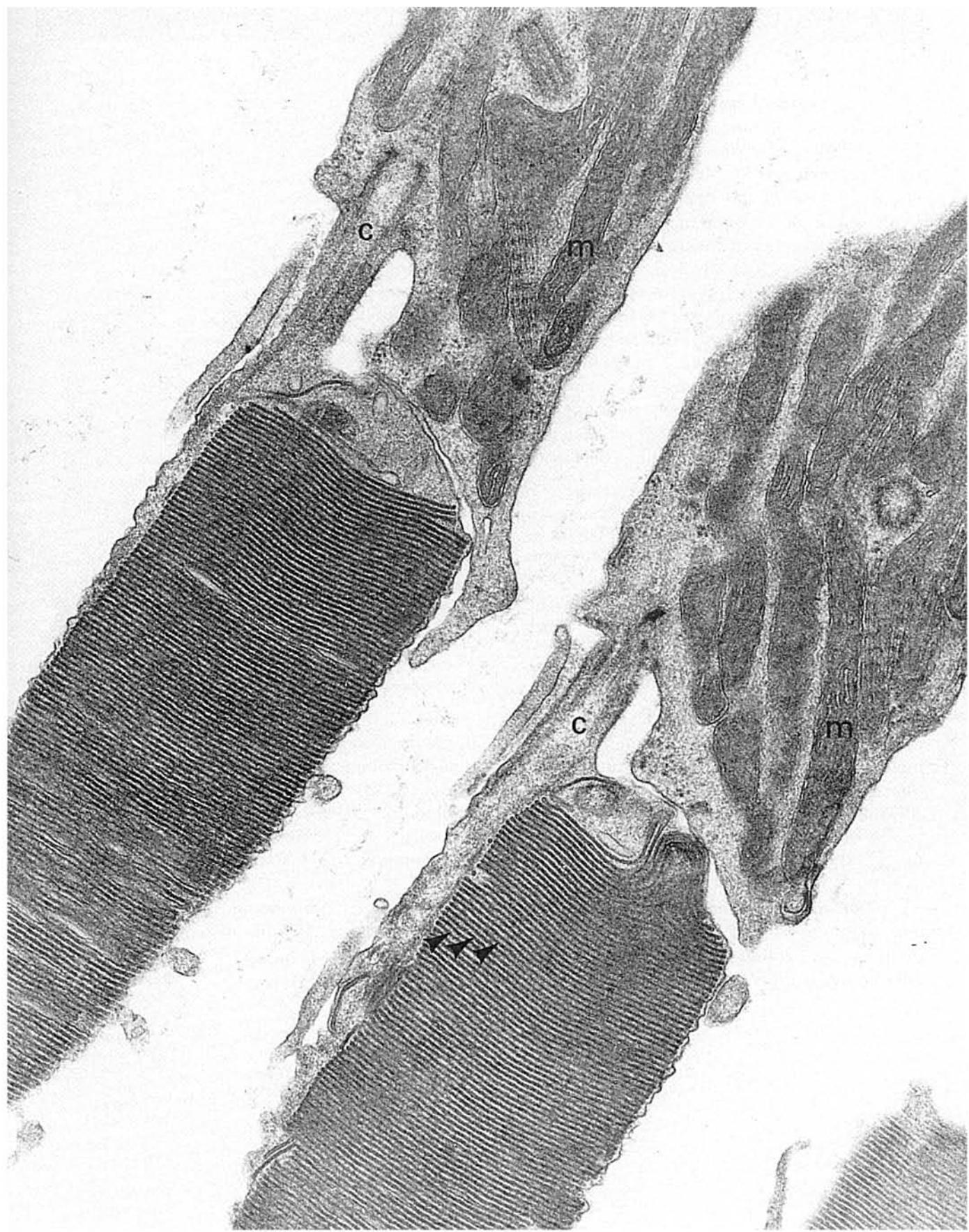
Photoreceptor cells, **rods and cones**, are concentrated in specific regions of the neural retina. Rods occupy the periphery and function in peripheral and night vision; cones are concentrated in the central fovea and function in the perception of detail and color. Both are elongated cells with a highly specialized polarity that includes, from basal to apical, a synaptic region, nuclear region, inner segment, and outer segment. Outer segments (closer to the outer surface of the eye) are connected to inner segments by a thin process containing a modified cilium (c, micrograph).

The **outer segments** are packed with layers of flattened membrane discs that are the sites of visual excitation. In rods (micrograph) the membranes form separate disclike sacs (arrowheads, micrograph) that are not connected to the outside plasma membrane except at the base near the cilium. Components of the disc membranes are synthesized in the inner segment and pass through the cytoplasmic bridge surrounding the cilium to the outer segment. The new membrane, formed in the outer segment near the cilium, is continually moved apically as other membrane is added. When discs reach the tip of the outer segment, they are phagocytosed by an adjacent layer of cells, the pigment epithelium.

**Visual pigments** are concentrated in the membranes of the outer segment. In both rods and cones, 11-*cis* retinal, a derivative of vitamin A, is the part of the pigment that is light sensitive. The 11-*cis* retinal is attached to a protein or opsin that is altered as a part of the cascade of visual excitation. All rods contain the visual pigment rhodopsin and respond to low-intensity light of several wavelengths. In contrast, there are three types of cones, each with a different opsin that responds preferentially to light of red, blue, or green wavelengths. At least 80% of rod and cone disc membrane proteins are opsins.

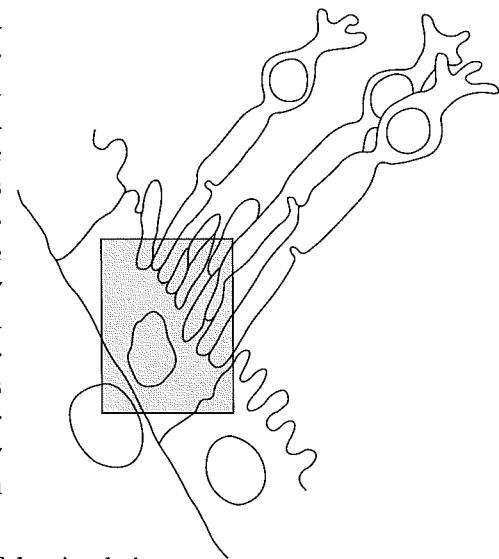
In the dark, rhodopsin is magenta. Light bleaches rhodopsin by changing the configuration of 11-*cis* retinal to all-*trans* retinal. During this conversion opsin undergoes a conformation change, which leads to an amplified cascade involving an intermediate protein, transducin, and cGMP phosphodiesterase. The cascade ends with a reduction in the level of cGMP and a subsequent closure of  $\text{Na}^+$  channels in the outer plasma membrane. The resulting hyperpolarization reduces the rate of release of neurotransmitter in the synaptic terminal part of the rod. This activates bipolar neurons in an adjacent layer and thus carries the excitation to the next level in the visual pathway. Energy requirements of the photoreceptor cells are met by mitochondria (m, micrograph) concentrated in the inner segment.





## EYE: Pigment Epithelium, Overview

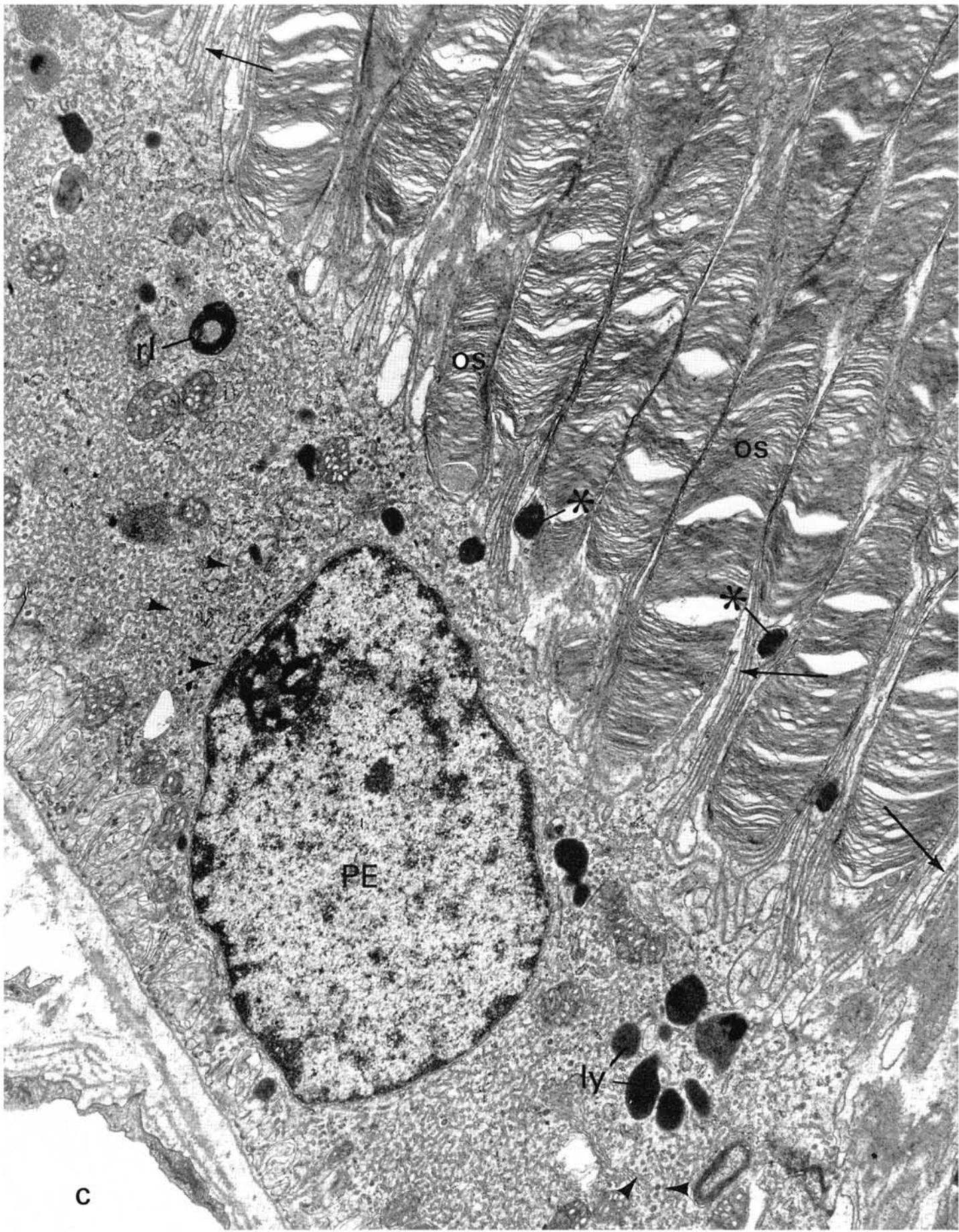
The **pigment epithelium** (PE, micrograph) consists of a single layer of cuboidal cells that extend narrow apical cytoplasmic processes (arrows, micrograph) around and between the outer segments (os, micrograph) of the photoreceptors. A major function of this epithelium is the phagocytosis of the outer segments. Phagosomes containing the outer segments fuse with lysosomes (ly, micrograph), where the process of digestion occurs. Occasionally lysosomes (\*, micrograph) are found within the fine pigment epithelium processes directly adjacent to the outer segments. Outer segments, digested in secondary lysosomes, leave residual lamellar structures (rl, micrograph). Phagocytosis of rod and cone outer segments varies diurnally, with rod phagocytosis occurring one half hour after the onset of light and cone phagocytosis occurring immediately after dark. It has been estimated that each pigment epithelium cell phagocytoses 2000–4000 discs daily.



The pigment epithelium is essential to the regeneration of the visual pigment and thus plays a major role in the completion of the visual cycle. The *all-trans* chromophore that results from photoisomerization in the outer segment membranes is continuously delivered to the pigment epithelium and converted back to the *11-cis* form by an isomerase located within the membranes (most likely the extensive smooth endoplasmic reticulum, arrowheads, micrograph) filling the pigment epithelium cytoplasm. *11-cis* retinal is then recycled back to the rods to be combined with opsin in newly formed membrane. The pigment epithelium also converts dietary vitamin A (*all-trans* retinol) to the *11-cis* form that is delivered to the photoreceptors. Night blindness is one outcome of vitamin A deficiency.

The retina has a **dual blood supply**. Capillaries (c, micrograph) of the choroid layer underlying the pigment epithelium supply the outer one third, including the rod and cone cells. Branches of the retinal artery course over the interior surface and supply the inner two thirds of the retina. In instances in which the neural retina detaches and loses the choroid blood supply, the retinal vessels become essential to survival of the photoreceptor cells. Retinal detachment in the fovea, where retinal arteries are absent, results in irreparable damage.

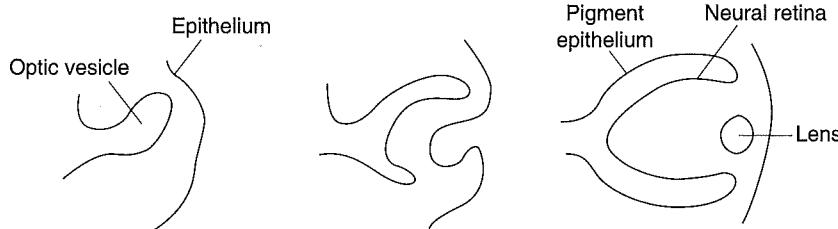
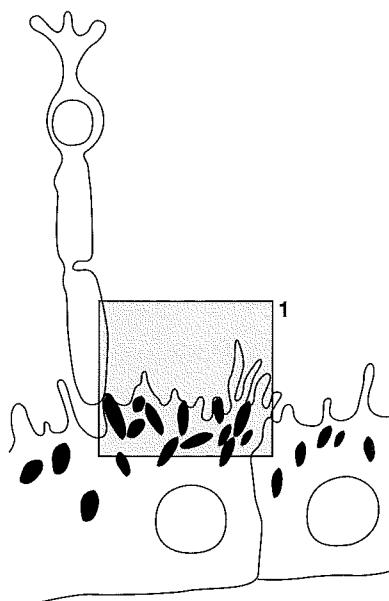
**Melanin granules** are an important component of pigment epithelium and act to absorb excess light to reduce interference and reflection. Melanin granules are present in the micrograph on page 387 but not in the facing micrograph from an albino rat.



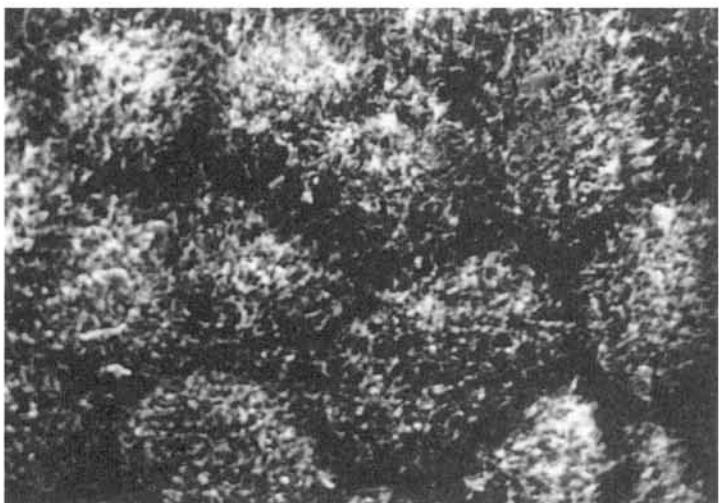
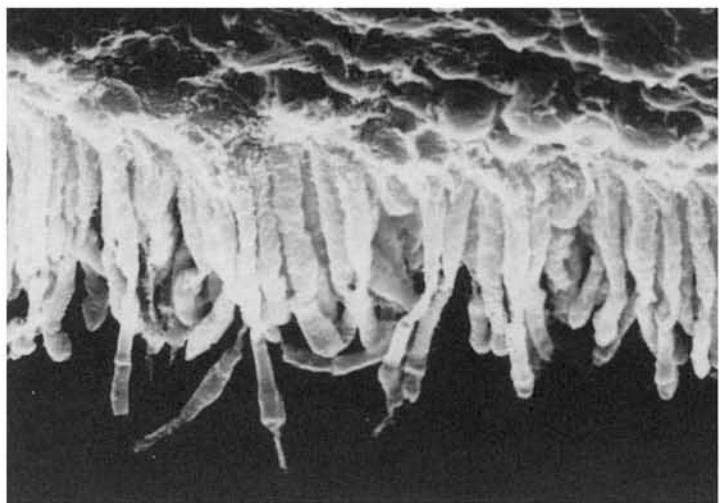
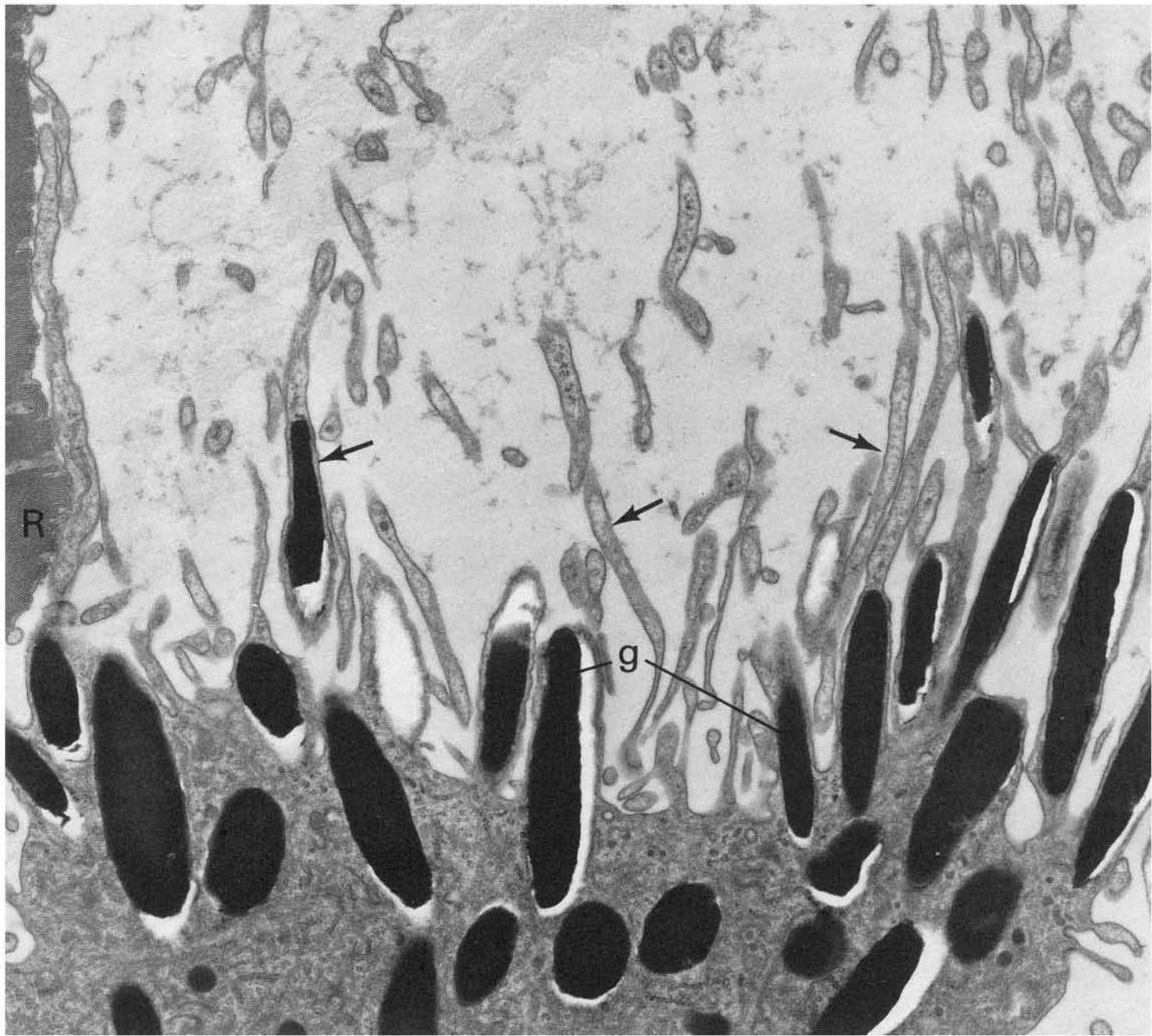
## EYE: Pigment Epithelium, Retinal Detachment

Micrograph 1 depicts a **pigment epithelium** cell in which **melanin granules** (g) pack the apical cytoplasm and the fine extensions (arrows) that normally surround the rod outer segments. In this preparation only a single rod outer segment (R) is found in the vicinity of the epithelium. Photoreceptor outer segments and pigment epithelium frequently separate during tissue preparation. Such separation is dramatically illustrated in scanning electron micrographs 2 and 3, in which the outer segments were left dangling free (micrograph 2) and pigment epithelium processes extend out, released from their attachment to the outer segments (micrograph 3).

In vivo, a tight association between the pigment epithelium and photoreceptor cells is essential for vision to occur; rhodopsin is not regenerated if close contact is not maintained. This association, as necessary as it is, is the most tenuous in the eye. During the development of the eye the pigment epithelium and the neural layers of the retina originate from separate regions of the optic vesicle. Even though the apical regions of the two layers come together as the optic cup forms, they do not appear to attach via junctions; they are held together by the pigment epithelium cellular processes that project out and wrap around the outer segments.



**Retinal detachment** occurs in 1 out of 15,000 persons as a result of aging, metabolic disorders, trauma, or vascular disease. In certain instances operations can be performed to approximate the two layers, and, using laser surgery, weld the tissues together.



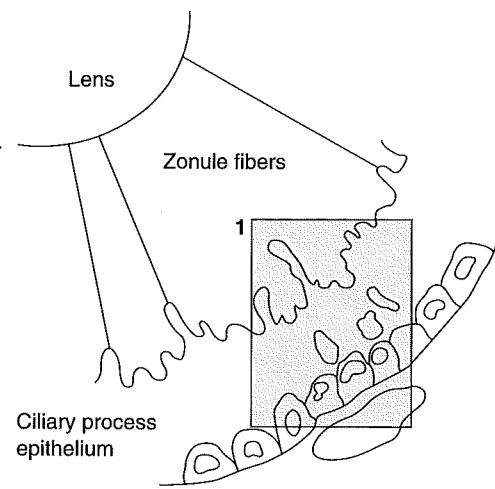
## EYE: Ciliary Processes

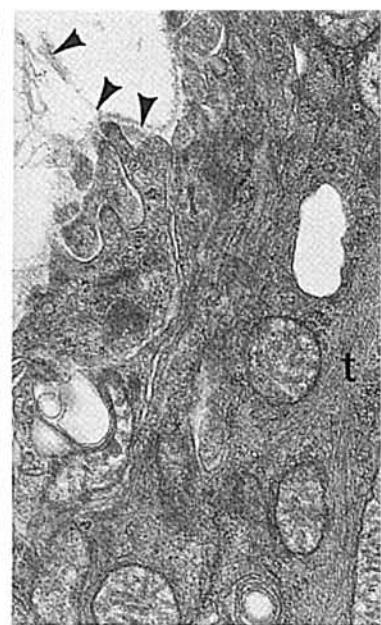
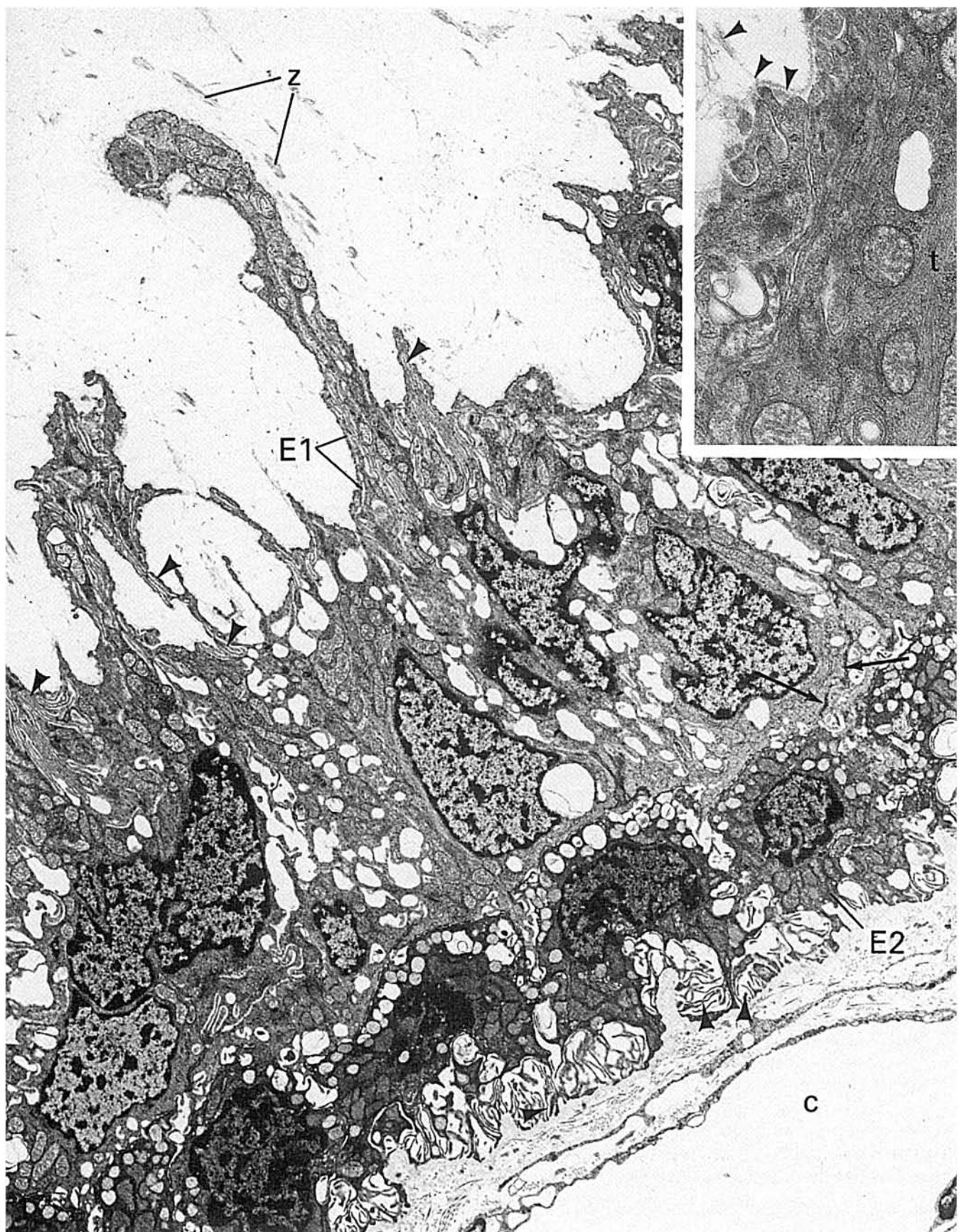
**Ciliary processes** are ridgelike extensions that project from the ciliary body toward the lens. The processes are covered by a two-layered epithelium (E1 and E2, micrograph 1) whose apical surfaces face one another. The inner layer of this epithelium is continuous with the neural retina in the back of the eye, the outer layer with the nonneural pigment epithelium. Normally the outer layer (E2, micrograph 1) of the ciliary epithelium is pigmented, as in the pigment epithelium of the retina. Micrograph 1, however, was taken from an albino rat.

A primary function of the ciliary epithelium is the secretion of the **aqueous humor**, a fluid that fills the posterior and anterior chambers of the eye. Aqueous humor originates from the plasma circulating in the underlying stromal capillaries (c, micrograph 1). Components are selectively moved across the epithelium from the stroma to the posterior chamber. The selectivity is maintained to a large degree by tight junctions that are a part of apical junctional complexes (arrows, micrograph 1) between cells of the inner epithelial layer (E1, micrograph 1). The ultrastructure of the epithelium reflects its role in active transport. Mitochondria provide the energy, and extensive infoldings (arrowheads, micrograph 1) on both basal surfaces provide the increased surface area needed to effect transport. The two layers of epithelial cells cooperate to (1) transport glucose, the energy source of the avascular lens and cornea, (2) transport and concentrate ascorbic acid, an important detoxicant for radicals formed during UV damage, and (3) exclude most proteins, an important part of the mechanism of protection from foreign antigens. Proteins that leave the underlying fenestrated capillaries with relative ease are blocked in their transit at the tight junctions.

Aqueous humor is a circulating fluid. The rate of production and the removal are balanced to maintain an intraocular pressure that is essential to maintaining the mechanical stability and optical properties of the eye. The fluid produced by the ciliary processes passes to the posterior and then anterior chambers and is finally absorbed into the canal of Schlemm and scleral veins in the limbus region (where the sclera and cornea meet). Any disturbance in this flow that causes increased pressure (glaucoma) can reduce and even irreversibly affect sight.

The ciliary processes also play an important mechanical role as the site of attachment of the lens to the ciliary body. **Zonule fibers** (z, micrograph 1) extend from the basal lamina of the inner epithelial layer to the lens capsule. The association of zonule fibers with this basal lamina is illustrated particularly well in the inset (arrowheads). The zonule fibers, similar in composition to elastic fibers, along with the smooth muscle of the ciliary body, control changes in the shape of the lens and thus its focal length. Zonule fibers are taut and the epithelial layers are stretched toward the lens (micrograph 1) when the smooth muscle is relaxed. The tension pulls the lens into an ellipsoid shape for far vision. When the ciliary muscles contract, the ciliary processes move closer to the lens and the tension on the epithelial cells, zonule fibers, and lens is reduced. The lens takes on the more spherical shape necessary for near vision. The cytoplasm of the inner epithelial layer is packed with tonofilaments (t, inset) that maintain the integrity of these cells as they relax and stretch with accommodation.





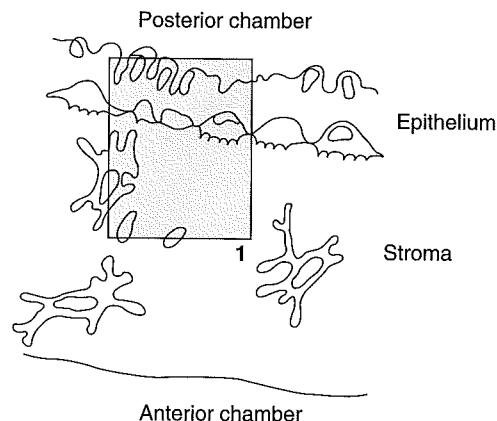
The iris rests on the anterior lens surface and separates the posterior from the anterior chamber of the eye. The surface of the iris facing the anterior chamber is lined by a discontinuous layer of fibroblastlike cells while the surface facing the posterior chamber is lined by two layers of epithelial cells (E1 and E2, micrograph 1) that are continuous with the epithelium of the ciliary process. As in the ciliary process, the epithelial cells in the iris are positioned with their apical surfaces attached and one basal surface adjacent to the aqueous humor, the other adjacent to a connective tissue stroma. Unlike the ciliary process, the epithelial cells of the iris are not involved in the production of aqueous humor and do not possess the characteristic basal infoldings associated with ion movement and secretion.

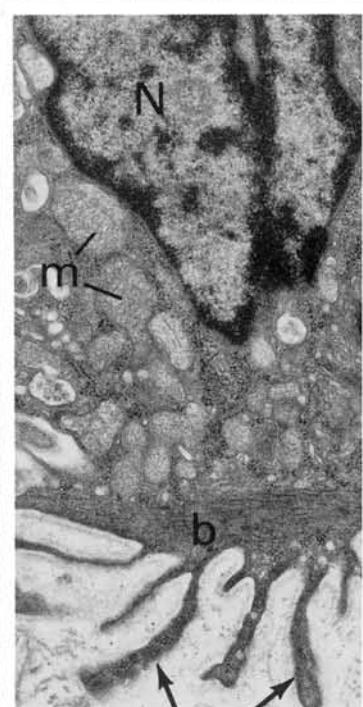
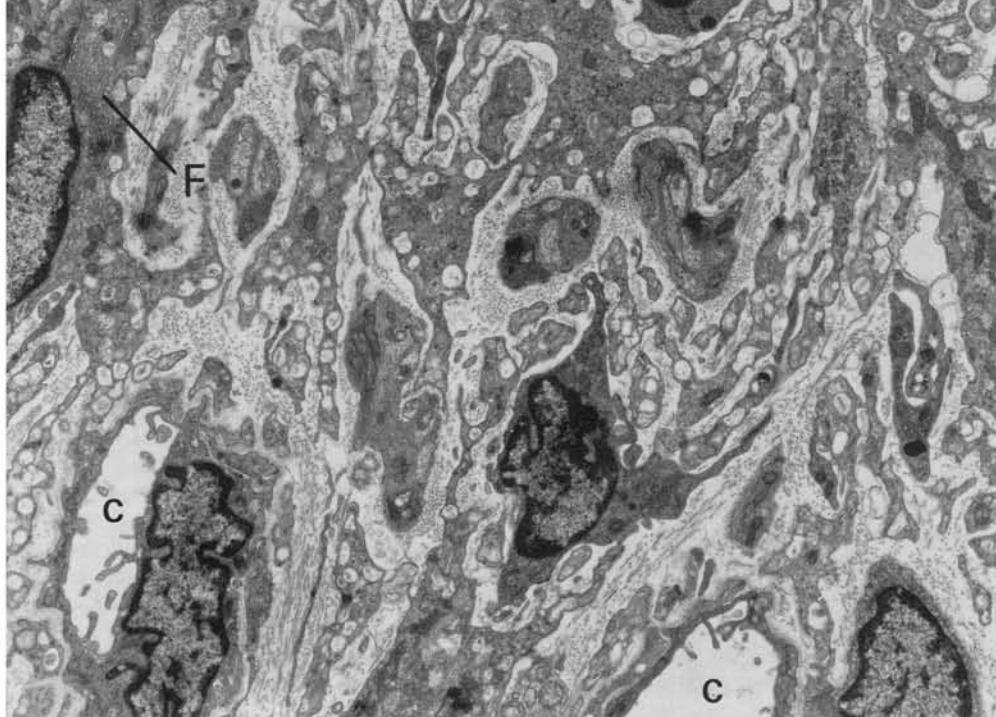
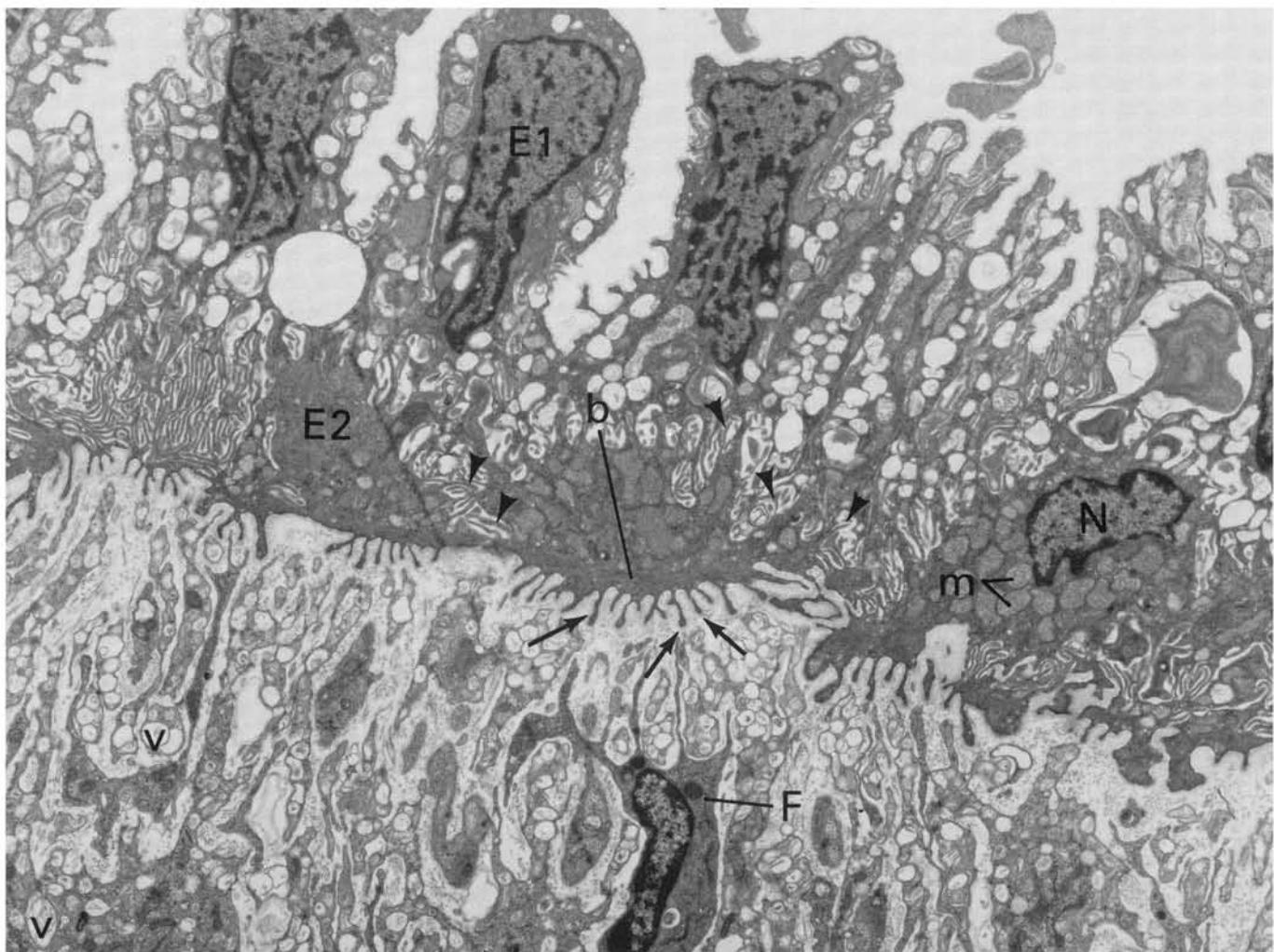
The layer of epithelial cells adjacent to the stroma (E2, micrograph 1) consists of myoepithelial cells that comprise the **dilator muscle** of the iris. These cells have a unique layered organization evident in both micrograph 1 and the inset: (1) a region containing the nucleus (N) and surrounding mitochondria (m) that controls the synthetic and metabolic activities; (2) an underlying band (b) of highly organized filaments that effect contraction; (3) basal interdigitations (arrows) with the stoma that increase the surface area of attachment so critical during the frequent contraction/relaxation cycles. Contraction of the radially oriented filaments opens the iris diaphragm, increasing pupil size. Lateral interdigitations (arrowheads, micrograph 1) between cells accommodate the shape changes associated with this movement.

The dilator myoepithelial cells attach to the stromal sphincter muscle that circles the pupillary margin. Contraction of the dilator and sphincter is controlled primarily by autonomic nervous innervation. A sympathetic release in response to a number of factors, including changes in the amount of light, fear, or pain, results in dilator contraction and pupil enlargement.

Pupil size is adjusted frequently to ensure the greatest degree of visual acuity and depth of focus. Other structures within the iris also function to improve visual acuity. Typically, pigment in both epithelial layers and stromal melanocytes absorbs stray light that would otherwise create aberrations. Vision is poor in the absence of pigment, as in the albino condition (micrograph 1).

The stroma of the iris contains fibroblasts (F, micrograph 1) that have numerous fine processes. The vacuolelike structures (v, micrograph 1) that appear to be within these cells actually represent extracellular regions between these processes. Capillaries (c, micrograph 1) sitting among the fibroblasts are lined by nonfenestrated endothelium. The endothelium acts as a barrier in one direction, preventing the movement of most molecules from blood to stroma, while facilitating movement in the opposite direction. These permeability characteristics enable these vessels to act as “sinks” to remove large molecules that reach the aqueous humor and could interfere with visual acuity. The structure of stromal iris capillaries contrasts with the highly permeable fenestrated lining of the vessels in the ciliary processes.





## EYE: Lens

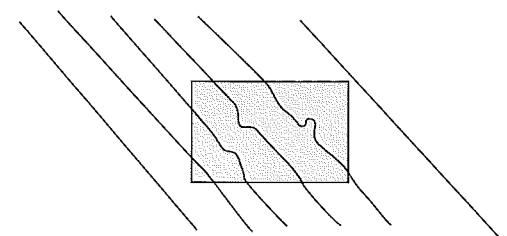
The lens and the cornea are the major refractive organs in the eye. The lens has less refractive power than the cornea, but it has the unique ability to change shape and thus change focal length. The lens is entirely cellular and its refractivity and transparency are characteristics of the special composition and arrangement of these cells.

The **lens** consists of a single type of epithelial cell in different stages of differentiation. The epithelial cells continue to grow and develop throughout life. Stem cells form a single cuboidal layer over the anterior lens surface. At the lateral periphery of the lens they divide and begin to elongate and differentiate into **lens fibers** as they move to the lens interior. The fibrous nature of the lens is evident in low-magnification scanning electron micrograph 1, in which the elastic capsule (c) of the lens has peeled back, revealing the fibers (f). Lens fibers (micrograph 2) are mature cells that have lost their organelles, including nuclei, and are packed with soluble structural proteins called crystallins. The age-related decrease in the ability of the lens to accommodate for near vision is, in part, related to the accumulation of more lens fibers, but it is due primarily to decreased elasticity of the capsule.

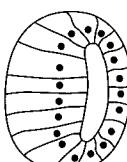
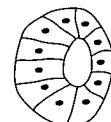
Mature lens fibers are tightly packed and join with one another via knob-and socketlike associations (k, micrograph 2). These elaborate cell interdigitations maintain the lens organization during shape changes associated with accommodation. In addition, close packing of cells prevents excess light scattering and facilitates communication between adjacent cells.

**Aqueous humor** bathes the avascular lens, providing the energy source, glucose, and collecting ions and water removed from the lens. **Gap junctions** (arrowheads, micrograph 2), which occupy an extensive portion of the lens fiber surface, provide the only means for transport of glucose and ions from one cell to the next to maintain the functioning of cells isolated in the lens interior.

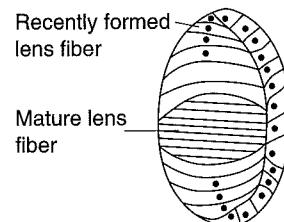
An important role of glucose is to provide energy to maintain crystallins in a reduced form, thus preventing aggregation. Glucose also provides energy for the operation of an  $\text{Na}^+\text{K}^+$ -ATPase, a major cell membrane protein. This ion pump maintains a net ion concentration that draws water out of the cells, thus preventing osmotic swelling within the lens. Since crystallin aggregation and osmotic swelling are the two major causes of cataracts (lens opacity), it is clear how the communication via gap junctions is critical to vision. It has been shown that gap junctions in the lens change with age, as does the incidence of cataracts.



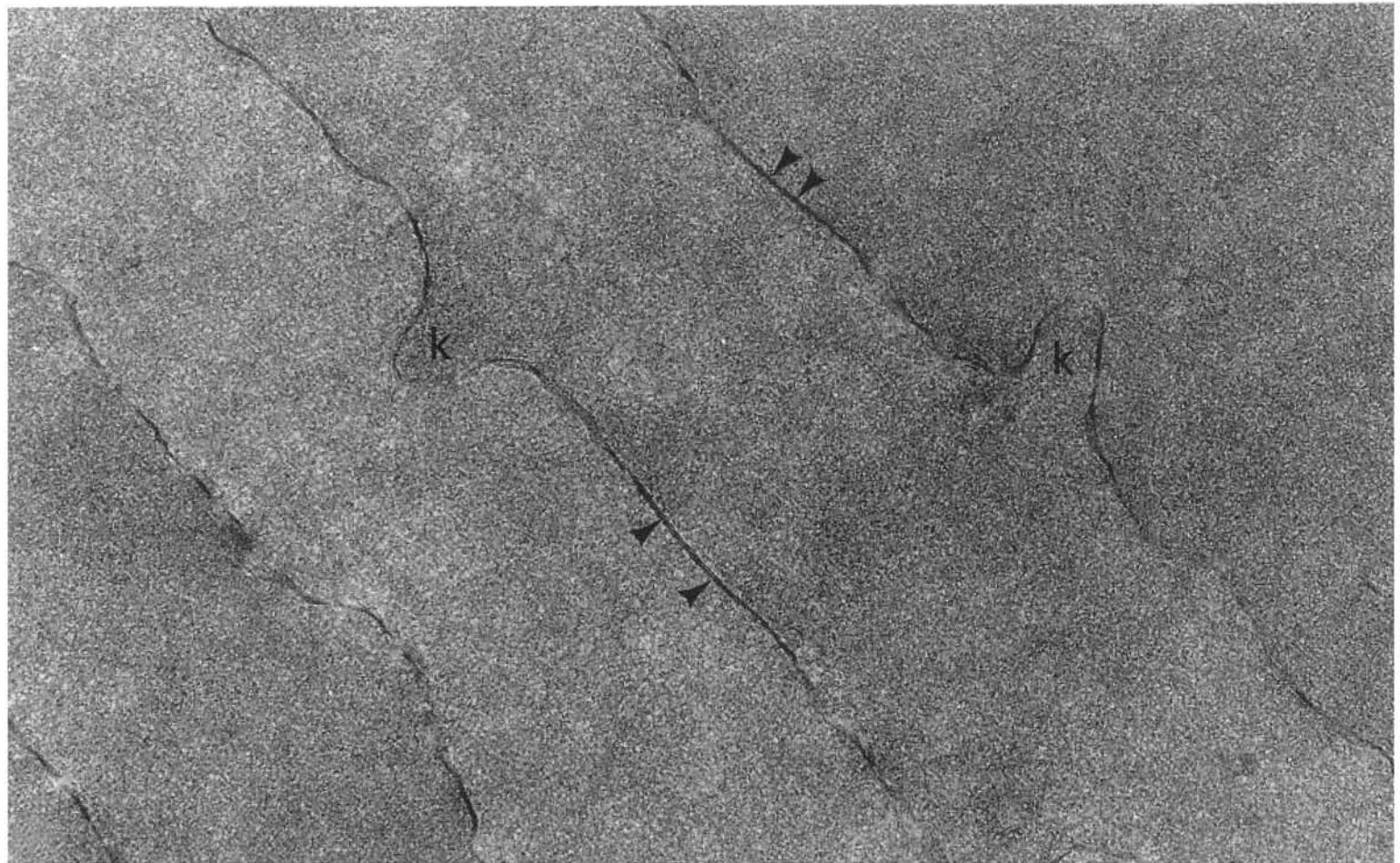
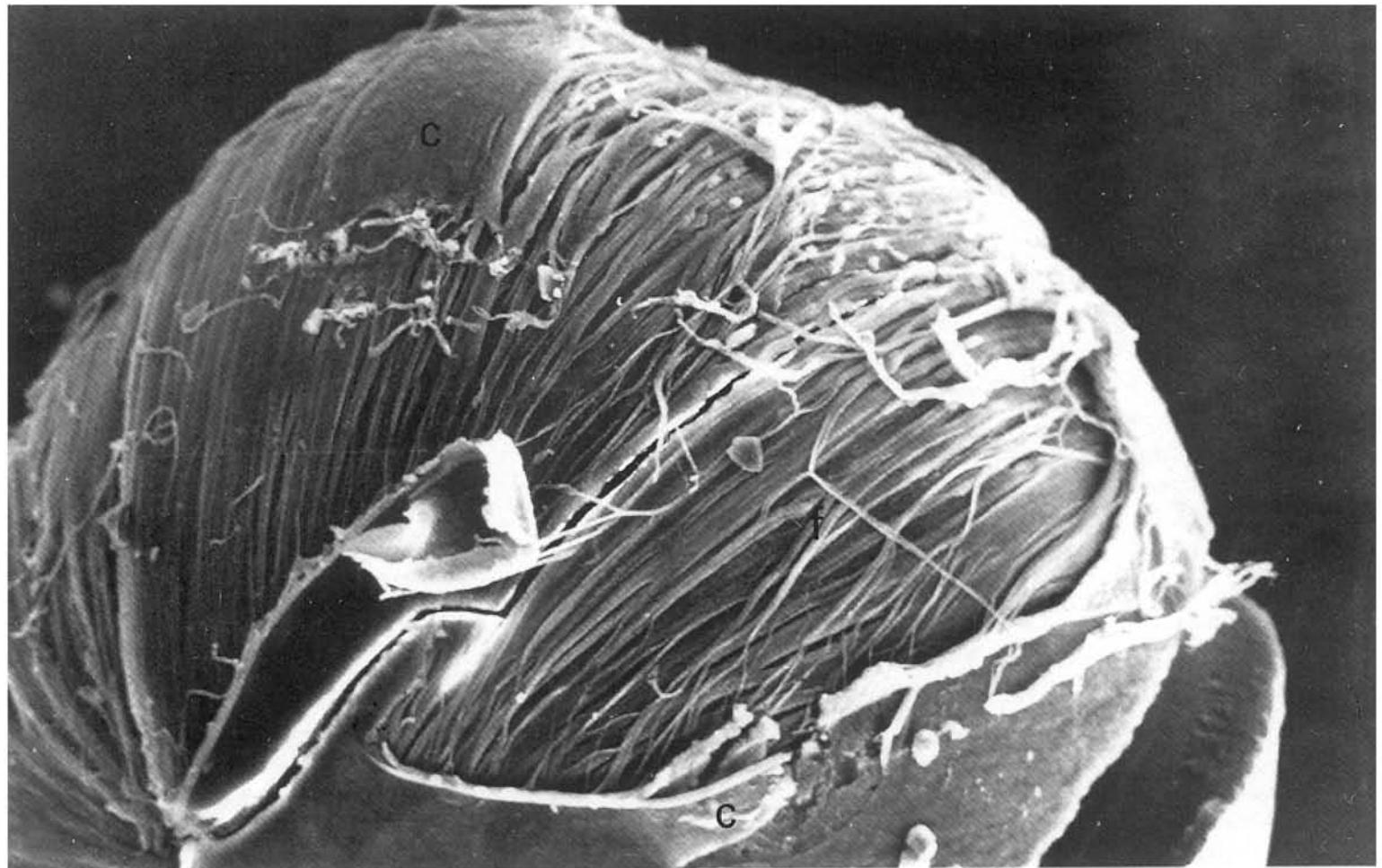
Embryonic lens



Adult lens



Modified from B. Alberts et al., *Molecular Biology of the Cell*, Garland, New York, 1989.

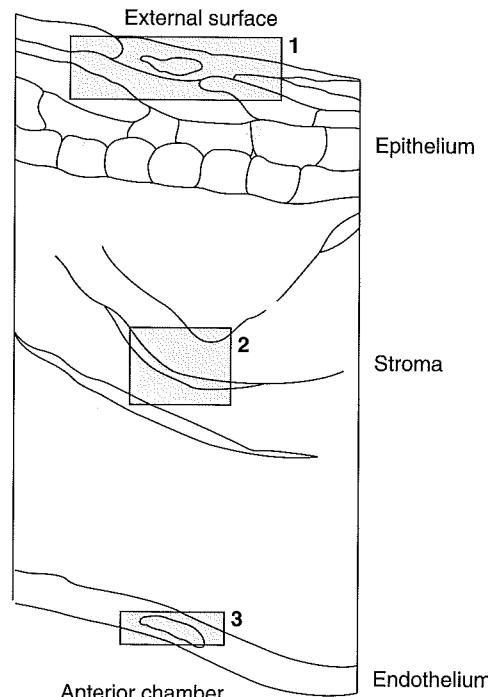


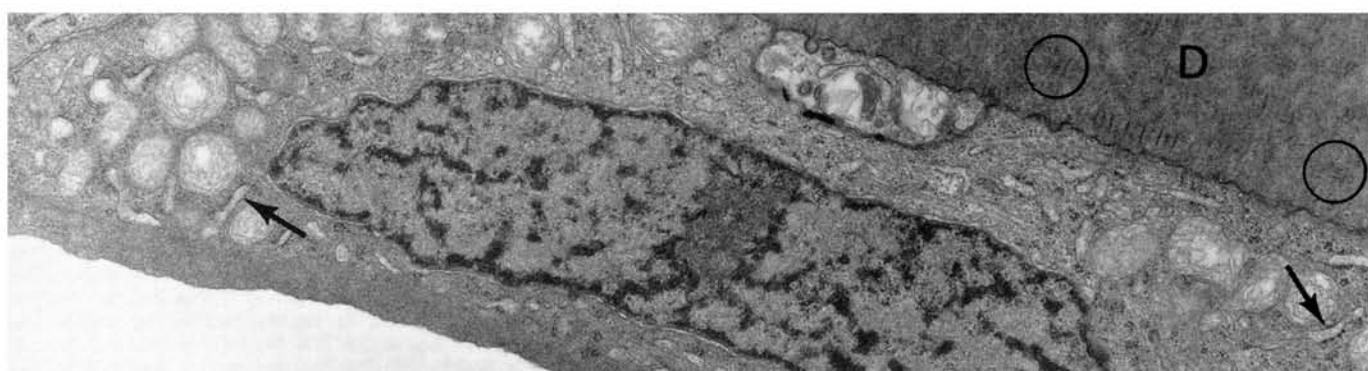
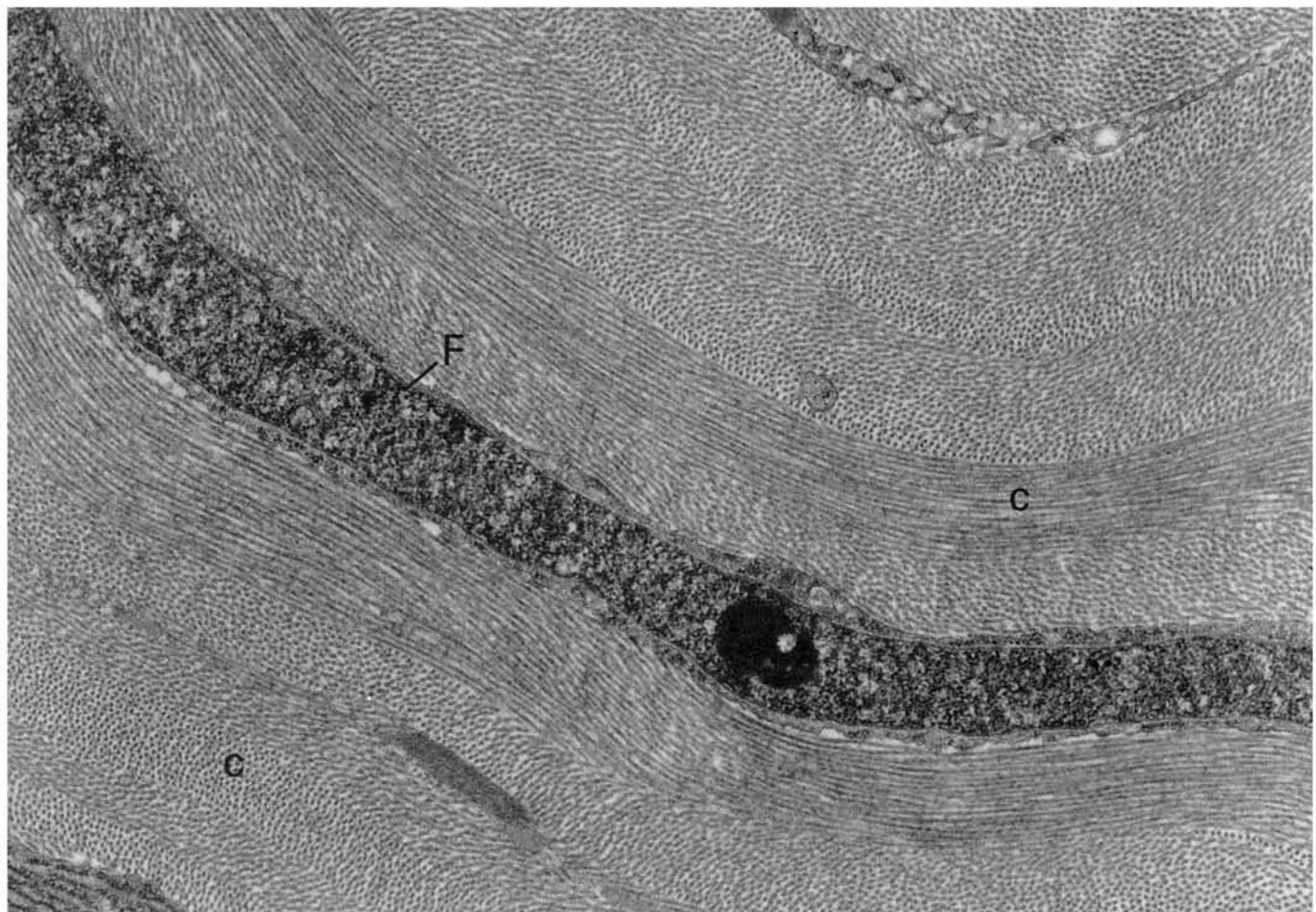
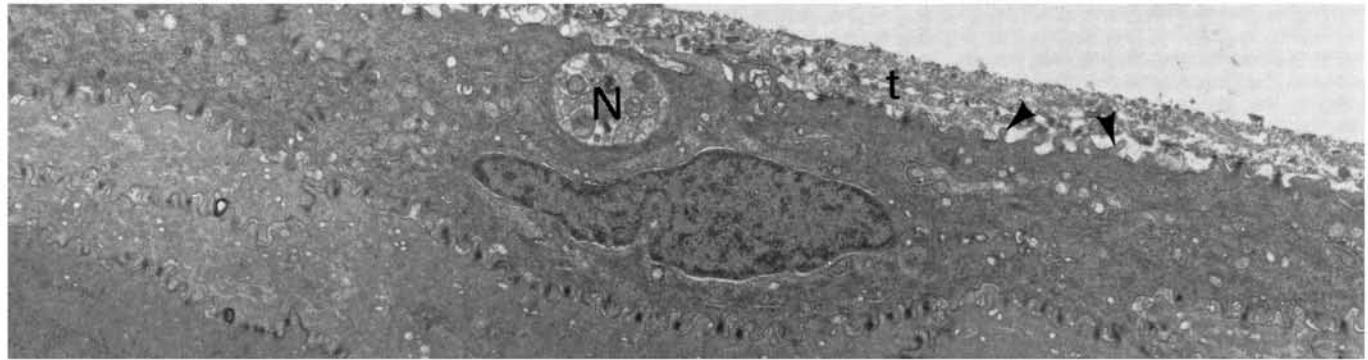
The cornea is a fixed-focal-length lens and, as such, its most important characteristics are transparency and refractive ability. The overall smooth, spherical shape of the cornea is maintained in large part by the pressure exerted by the aqueous humor on the inner surface. The finer aspects of maintaining shape and transparency are dependent upon the specific organization within each corneal region. The cornea is similar to the lens in being avascular, but, unlike the lens, it is rich in extracellular matrix.

The **stratified squamous epithelium** (micrograph 1) on the outer corneal surface is not keratinized (conserving image quality) and yet is exposed to many different types of insults. The epithelial cells have a short turnover time of seven days, and are covered by a protective tear film (t, micrograph 1) that can be as thick as 7 microns. This film, secreted by the epithelium itself, lacrimal glands, and goblet cells in the conjunctiva, is held in place by microvilli (arrowheads, micrograph 1) on the apical surface of the upper cell layer. The epithelium is richly innervated with free nerve endings (N, micrograph 1), which function in the blinking reflex that cleanses and spreads the fluid layer evenly across the corneal surface.

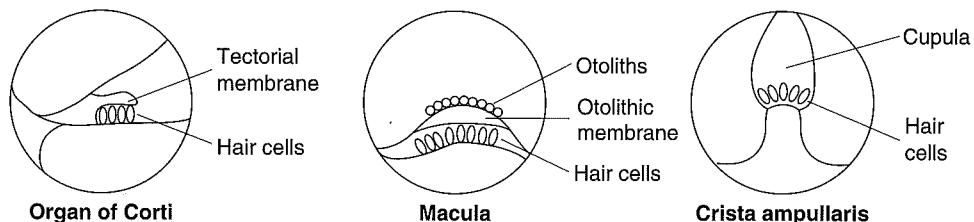
The **simple squamous endothelium** (micrograph 3) lining the inner corneal surface is the site of transport between the aqueous humor and corneal stroma. Ions and water are moved across this layer out of the cornea, preventing edema, and glucose, the energy source for all corneal cells, is moved into the cornea. The rough endoplasmic reticulum (arrows, micrograph 3) synthesizes the membrane pumps and channels important to this movement, and is also responsible for the synthesis of the unique endothelial basement membrane, **Descemet's membrane** (D, micrograph 3). The characteristic ladderlike structures (circles, micrograph 3) are cross-sectional views of a latticelike network of Type VIII collagen. This thick basement membrane is one of the few regions that contains a high concentration of this relatively rare type of collagen.

A dense collagen **stroma** (micrograph 2) that occupies 90% of the cornea is sandwiched between the surface epithelium and the inner endothelial layer. Fibroblasts (F, micrograph 2) extend processes to distant neighboring cells to form an interconnected network. The Type I collagen fibrils (c, micrograph 2), synthesized by the fibroblasts, have a small, uniform diameter and are tightly packed and evenly spaced. A fibril diameter less than one-half the wavelength of light and the similarity between the refractive index of the fibrils and the intervening ground substance are the most critical aspects of structure needed to maintain transparency. The larger aspect of organization, the alternating layers of collagen, which in certain regions appear to be at right angles, functions in providing the strength needed to maintain shape.

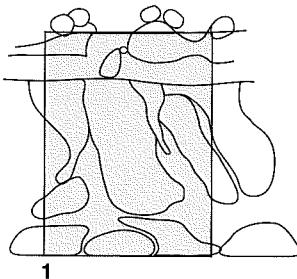




The sensory regions for hearing (organ of Corti in the cochlea) and equilibrium (macula in the utricle and saccule, for linear acceleration; crista ampullaris in semicircular canals, for angular acceleration) are localized in the inner ear. In each region, **sensory cells** convert a mechanical displacement into a nerve impulse. Bending of a **hair bundle** that projects from the sensory cell apical surface affects the rate of neurotransmitter release at synapses on the basolateral surface. Dendrites of the eighth cranial nerve carry the impulse to the CNS. Hair bundles are tightly associated with an overlying structure (tectorial membrane, otolithic membrane, or cupula) that helps regulate hair bundle displacement.



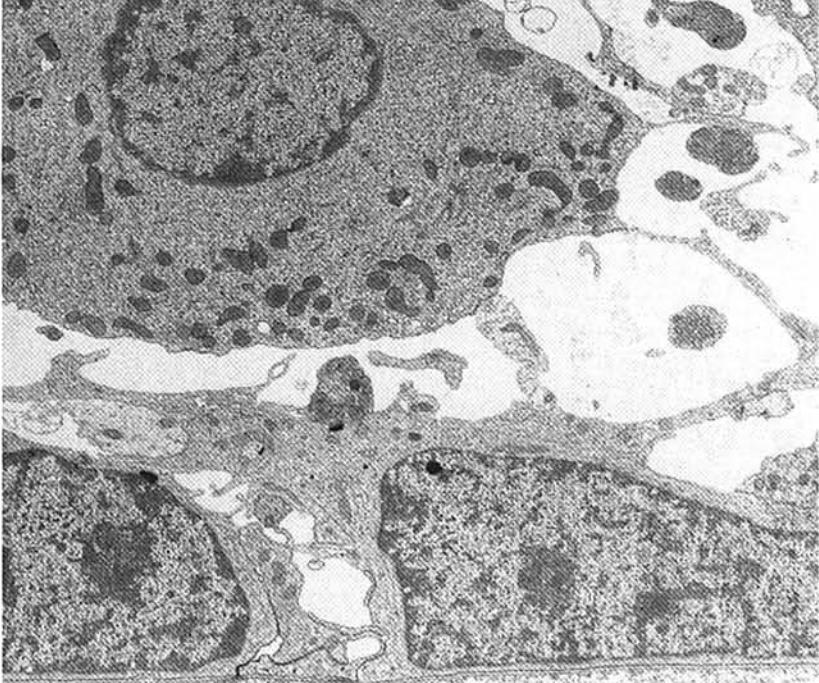
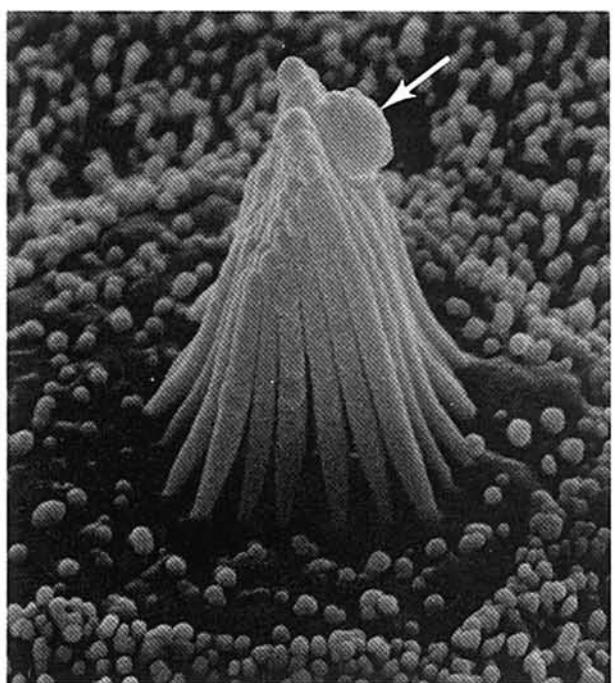
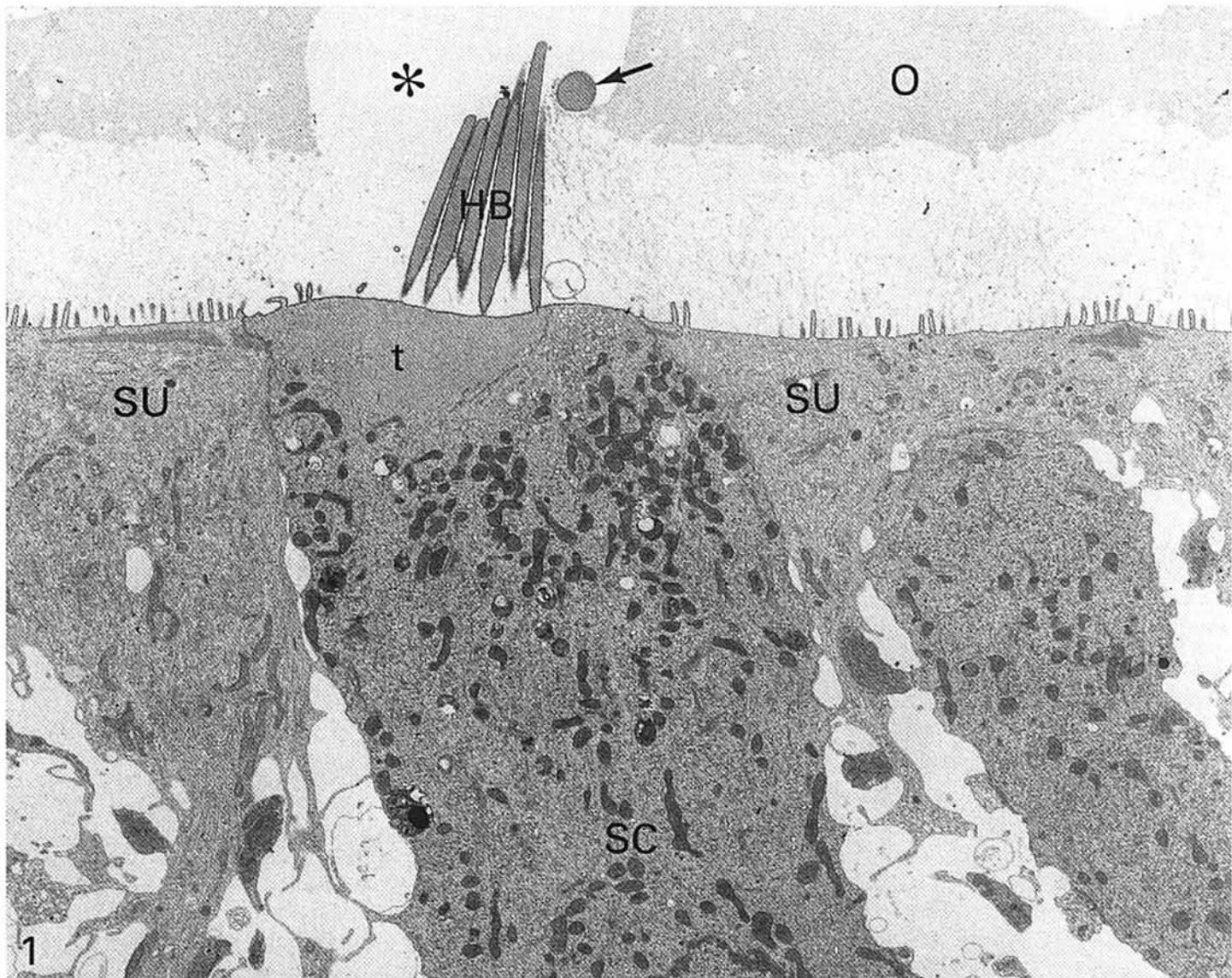
The structure of sensory cells (SC, micrograph 1) is very similar within different classes of vertebrates. A hair bundle (HB, micrograph 1) projects from the sensory cell apical surface in the bullfrog sacculus (micrographs, courtesy of Dr. A. J. Hudspeth and Dr. R. A. Jacobs), as it does in humans. This bundle consists of many **stereocilia** and a single, nonmotile **kinocilium** (arrows, micrograph 1 and inset: apical swelling of kinocilium). The stereocilia increase in length toward the kinocilium (inset). The hair bundle, a stiff unit with individual components attached to one another, is able to pivot at the tapered ends connected to the apical surface. Stability is provided by actin filaments within the stereocilia that extend into the apical cytoplasm to form an unusually dense terminal web (t, micrograph 1). Minute displacements of the bundle toward the kinocilium activate the sensory cells by opening ion channels at the tips of the stereocilia. Cations (primary  $K^+$ ) enter and the membrane is depolarized. Bending away from the kinocilium closes channels (including those open at rest), thus hyperpolarizing the membrane.



Hair cells are surrounded by **supporting cells** (SU, micrograph 1) that contain microvilli dwarfed in size by the stereocilia of the hair bundle. Supporting cells are tightly attached to hair cells, and zonula occludens junctions effectively separate **endolymph** (bathing the apical surface with a high  $K^+$  concentration) from **perilymph** (surrounding the basolateral surface with a high  $Na^+$  concentration).

In the saccule (and utricle) an **otolithic membrane** (O, micrograph 1) overlies the sensory region or macula, except directly over the hair bundle (\*, micrograph 1). The hair bundle, particularly the kinocilium, is attached laterally to the otolithic membrane. Embedded in this membrane are calcium-containing **otoliths** (not seen in micrograph 1 or inset) of a high specific gravity. Movement of the sensory cells, with head movement, relative to the more stationary otoliths bends the hair bundle.

The mechanical stimulus in the cochlea is **fluid movement**. The amplitude and frequency of waves encode loudness and pitch. In each inner ear sensory region the signal is transduced by sensory cells with essentially the same structure and function.



## OLFACTORY EPITHELIUM

The **olfactory epithelium** is highly specialized to detect small stereochemical differences between odoriferous molecules in extremely low concentrations (parts per trillion). The sensory receptors that accomplish this are **bipolar neurons** whose cell bodies occupy a distinct layer within this pseudostratified epithelium. Axons extend into the underlying connective tissue to the olfactory bulb in the central nervous system (CNS); dendrites project apically and expand to form **olfactory vesicles** (OV, micrograph) on the epithelial surface. Each vesicle contains the basal bodies (b, micrograph) of 5–20 nonmotile cilia that project into the nasal cavity and rest in the overlying secretion.

With a 9 + 2 microtubule arrangement, the proximal regions of the cilia have the general appearance of true cilia. However, dynein side arms, the ciliary “motors,” are lacking. As the cilia taper distally, the axoneme is reduced to a few microtubules (circles, micrograph). The large surface area of membrane covering the cilia is the site of the sensory receptors and ion channels associated with the primary excitation. Binding of odoriferous substances to the receptors initiates a cascade of events that opens  $\text{Na}^+/\text{K}^+$  channels, leading to changes in membrane potential. Changes in potential over the cilia surface are summed and an action potential generated in the axon. A single olfactory neuron responds to more than one but not to all odors. To distinguish the more than 10,000 odors, patterns of neuronal activity are transferred to the brain, where processing occurs.

Each olfactory dendrite is wrapped by and attached to surrounding **supporting cells**. Junctions (arrowheads, micrograph) are frequently seen binding these two cell types together; the olfactory neurons (N, micrograph), recognized by the prominent cytoskeleton of microtubules, are easily distinguished from the supporting cells (S, micrograph). In addition to providing support and a unique environment for the olfactory dendrite, the supporting cells have a direct, essential role in the process of olfaction. The prominent smooth ER (arrows, micrograph) contains the enzymes that remove excess odorous molecules and inactivate them, terminating the sensory signal and thus maintaining the sensitivity of the system. The enzymes, a P-450 detoxifying complex similar to that found in other cells (see Cell, page 22), metabolize the odorants and release the products into the blood.

Both the olfactory neurons and the supporting cells are replaced regularly by the division and differentiation of **basal cells**. Olfactory neurons are the only neurons in the body that are replaced, and the olfactory region is the only site where neurons are directly exposed to an external environment. The nasal cavity is a turbulent area where neurons are easily damaged. As each neuron is replaced, the axon must grow, enter the olfactory bulb, and establish new synapses with CNS neurons. Other axons in the peripheral nervous system are known to regenerate; however, they do not continue to grow after they enter the CNS. The ability of olfactory axons to grow in the CNS is attributed to unique glial cells that wrap the unmyelinated axons from the olfactory epithelium to their region of synapse in the olfactory bulb. These glial cells, which originate from the epithelial basal cells, have characteristics of both Schwann cells and astrocytes.

