

OVERVIEW

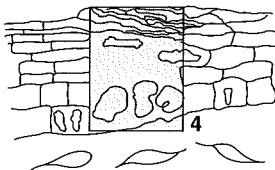
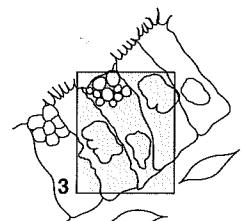
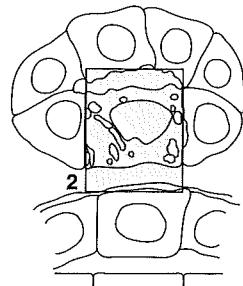
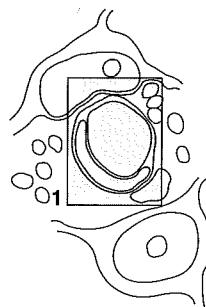
Epithelial tissue is composed of cells that work closely together as glands or as sheets that separate a lumen or space from underlying tissue. Internally, epithelial sheets line most surfaces, including the lumen of blood vessels (micrograph 1), kidney tubules (micrograph 2), and the gastrointestinal tract (micrograph 3). Externally, epithelium covers the entire body as the epidermis of skin (micrograph 4).

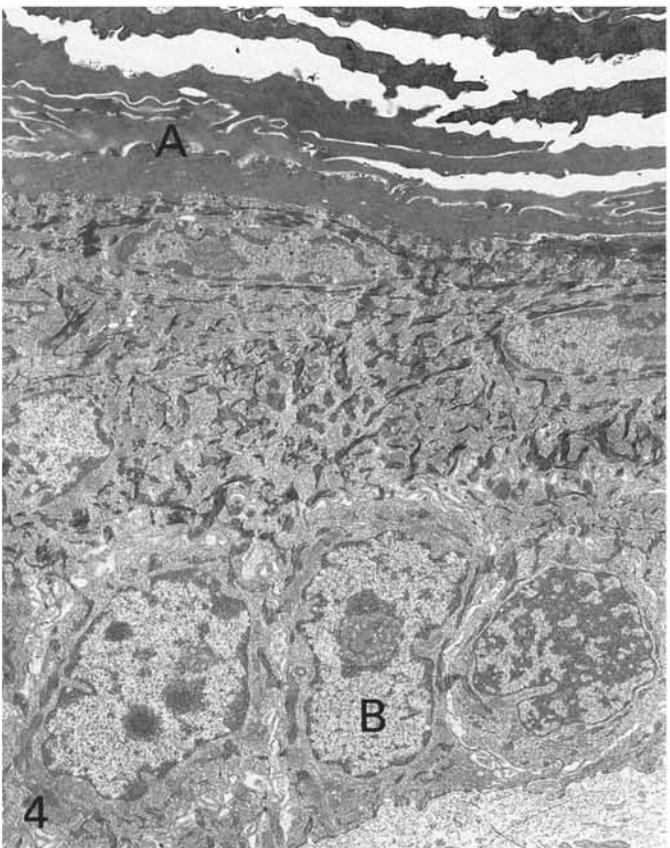
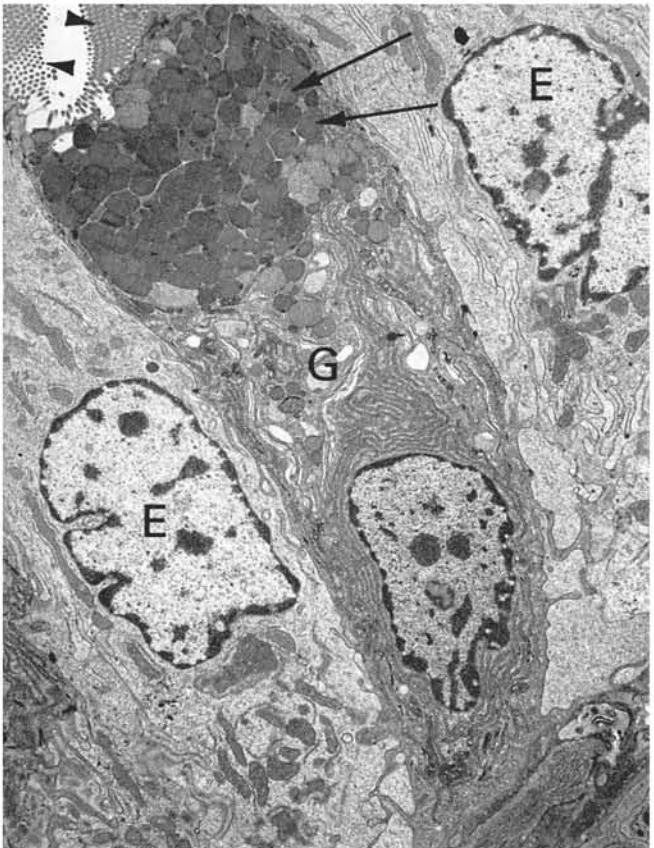
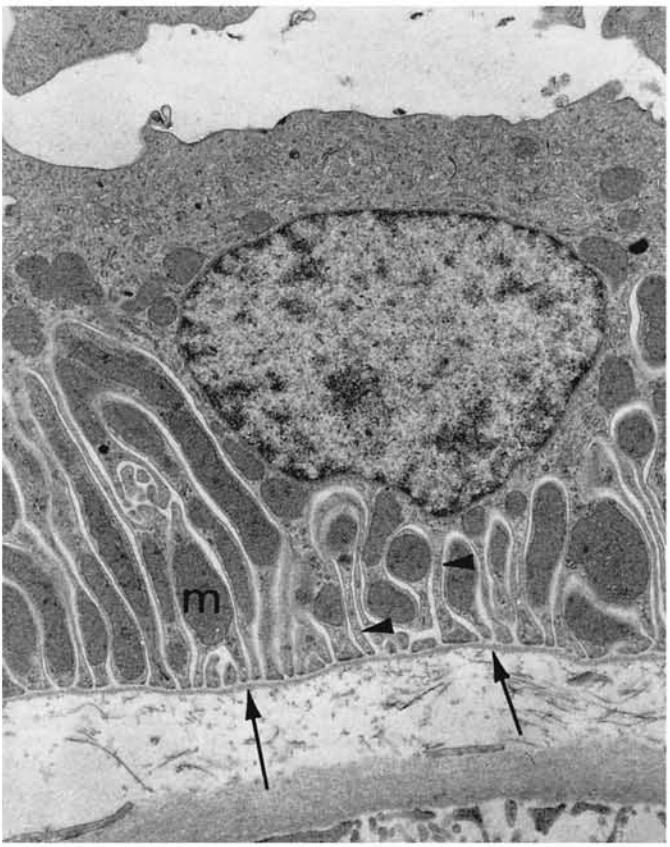
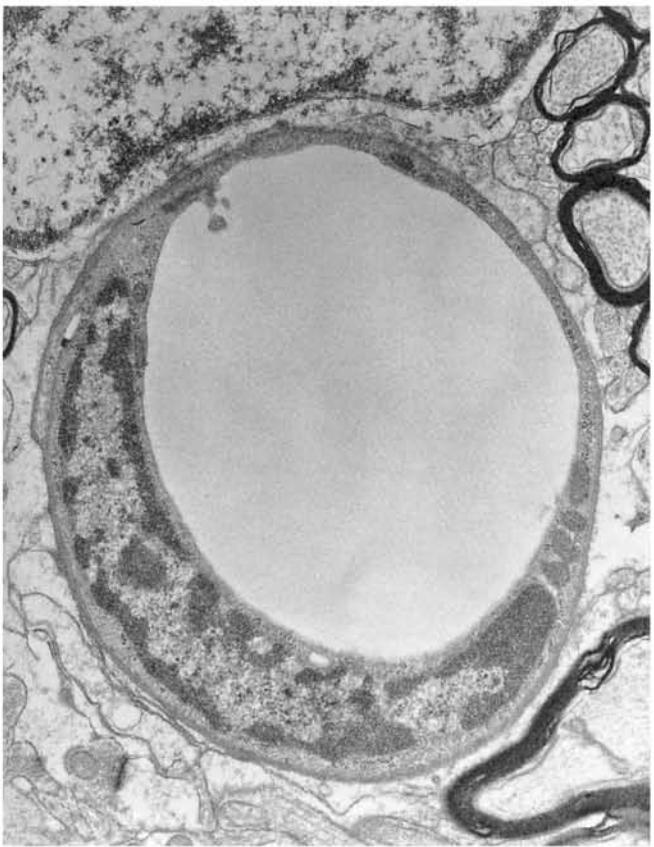
Epithelial sheets maintain a distinct **polarity** that relates to their function and morphology. In simple (single-layered) epithelium, which may be squamous, or flat (micrograph 1), cuboidal (micrograph 2), or columnar (micrograph 3), polarity is classically defined by distinctly different apical (adjacent to the lumen) and baso (abutting underlying tissue)-lateral (adjacent to neighboring cells) surfaces.

Apical specializations are best illustrated in the epithelium lining the intestine (micrograph 3). In goblet cells (G), granules (arrows) are concentrated close to the apical surface where they will release their contents; in enterocytes (E), microvilli (arrowheads) projecting from the apical surface increase the surface area for the absorption and digestion of nutrients. **Basolateral specializations** are most apparent in the distal tubule of the kidney (micrograph 2). Mitochondria (m) concentrated in the basal cytoplasm and the adjacent infolded basolateral membrane (arrowheads) reflect the active ion transport that occurs in this region. A well-defined basal lamina (arrows) attaches the cell to the underlying tissue.

In contrast to the examples above, polarity is not obvious in the ultrastructure of the simple squamous lining of the brain capillary (micrograph 1). The thinness of the lining reflects its primary function in rapid exchange of substances between blood and tissue. This apparent simplicity, however, is misleading, since this epithelium is specialized to function as a major barrier in the brain. Certain membrane proteins control mechanisms that exclude potentially harmful substances from crossing into the brain and interfering with neuron activity. Other membrane proteins regulate the supply of essential nutrients to this tissue. The selectivity of the barrier and transport processes depends upon the placement of these proteins in specific apical versus basolateral positions.

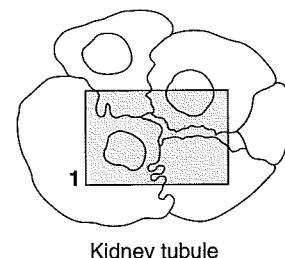
Whereas the polarity in simple epithelium refers to differences between parts of the same cell, in stratified epithelium it is often defined by differences between whole cells. In skin (micrograph 4) the basal cells (B) are undifferentiated and specialized for division whereas the apical cells (A) are highly differentiated “dead” packages of protein that, together with a lipid “mortar,” prevent water loss and penetration by environmental insults.



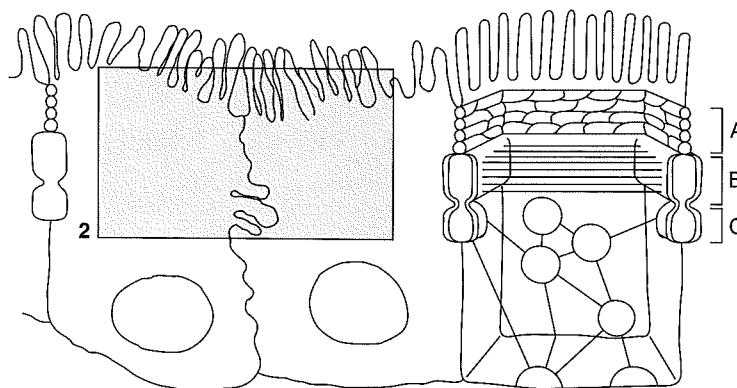


JUNCTIONAL COMPLEX

Epithelial cells that form sheets lining a lumen are typically joined together in their apical regions by **junctional complexes**. At low magnification, as in micrograph 1, these complexes appear as simple densities (arrows) at the boundary between adjacent cells. At the higher magnification shown in micrograph 2, it is obvious that a single complex is composed of individual junctions that have a distinct order with respect to the luminal surface: the zonula occludens, or tight junction (A), occupies the most apical position, then the zonula adherens (B), and next the macula adherens, or desmosome (C). Each junction has a unique role in coordinating the function of epithelial sheets.



Kidney tubule

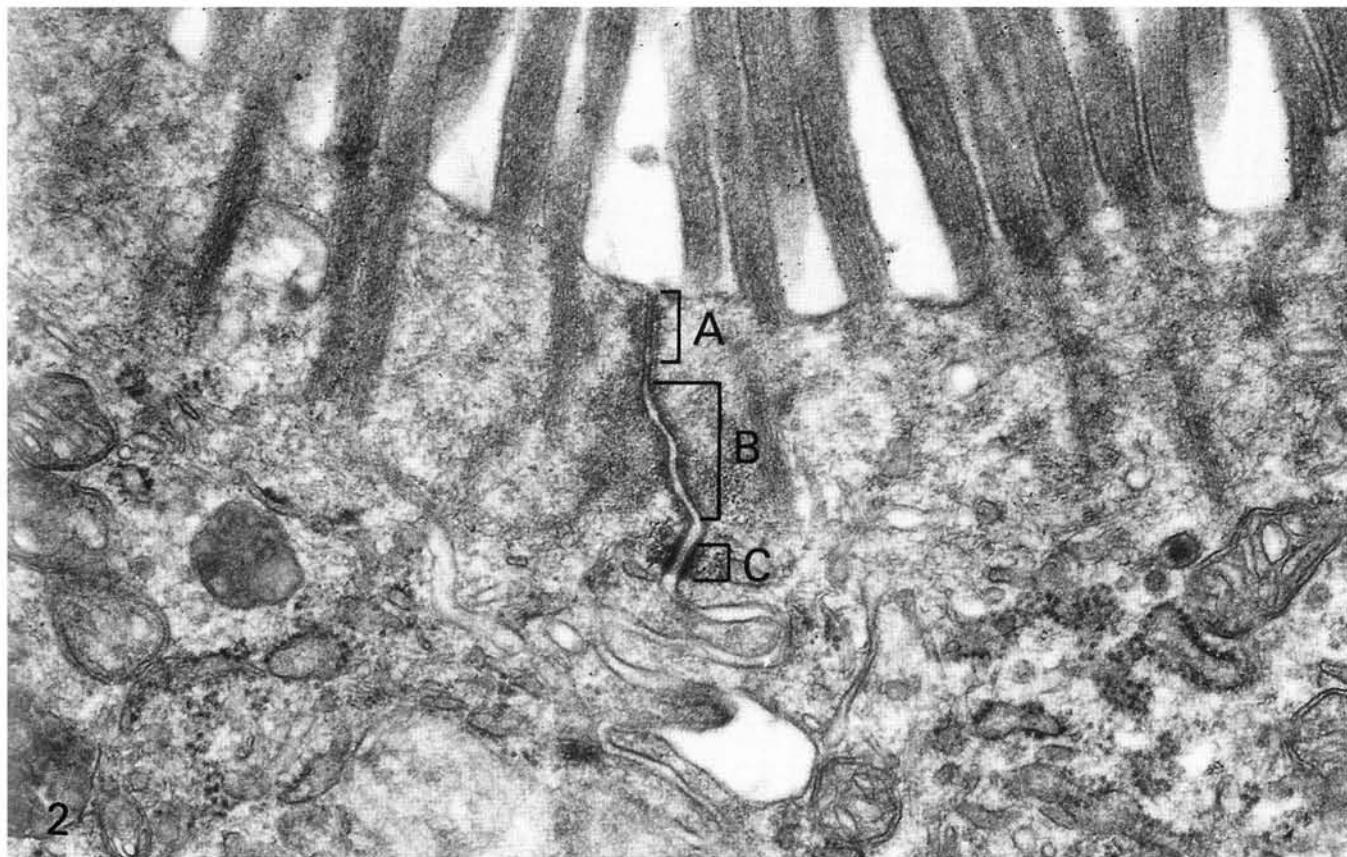
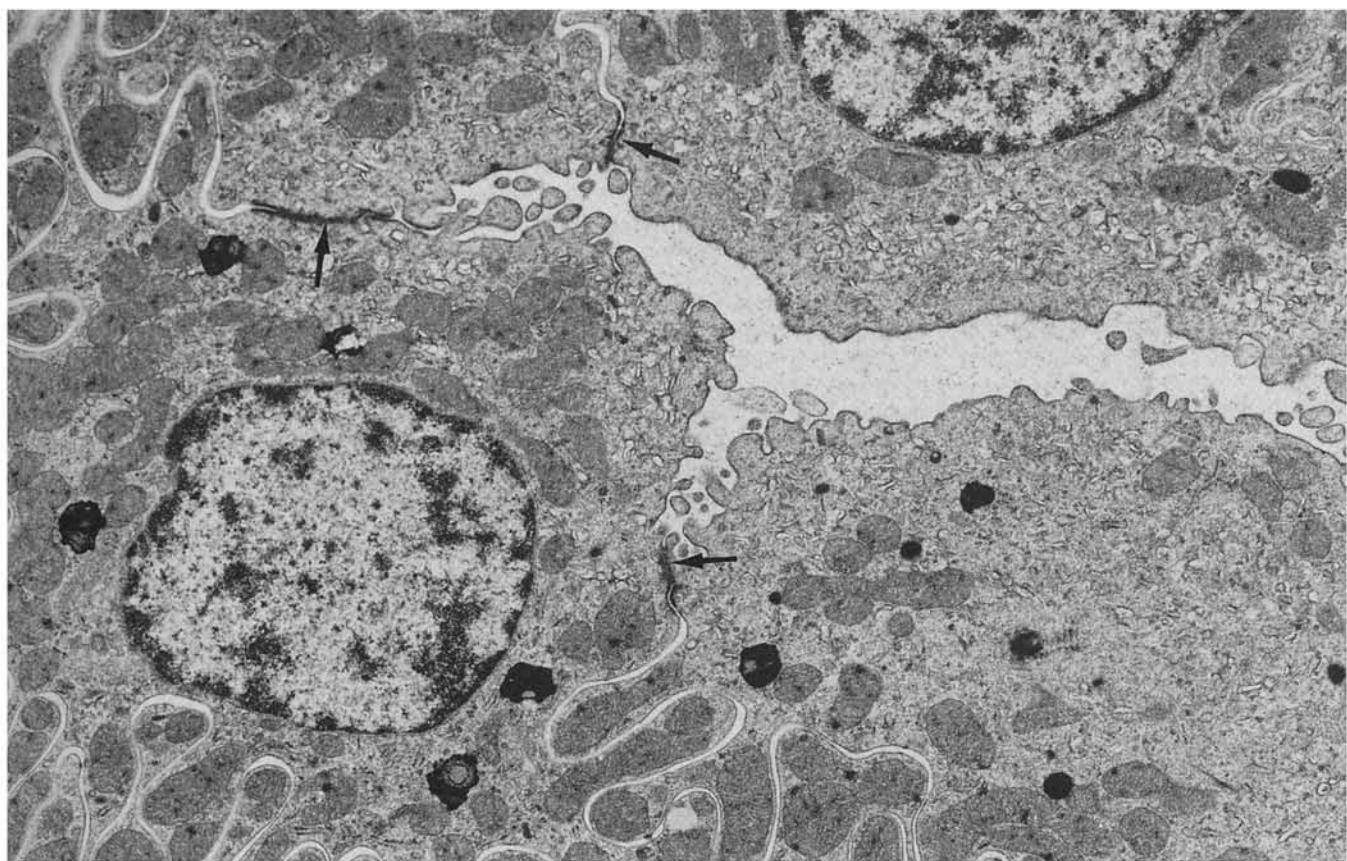


The **zonula occludens** (A) maintains polarity and controls the movement of substances across epithelial barriers. The membranes of adjacent cells come together at regular intervals to seal the two cells together. These areas of contact are actually anastomosing strips that continue around the entire circumference of the cell.

The **zonula adherens** (B), like the zonula occludens, is a beltlike junction that surrounds the entire cell. Actin filaments associated with this junction are part of an extensive network concentrated in the microvilli and apical cytoplasm. The actin–zonula adherens complex is important in contraction of the apical surface during morphogenesis and differentiation. Vinculin and α -actinin, found in focal adhesion plaques and the contractile unit of muscle, have been localized in the dense plaques of the zonula adherens.

The **macula adherens** (C) is a spotlike junction. Associated intermediate filaments extend from one spot to another on lateral and basal cell surfaces.

In contrast to the tight association of cell membranes in the zonula occludens, adjacent cell membranes of adherens junctions appear separated by a relatively wide extracellular space. In both the zonula adherens and macula adherens this space contains densities (particularly obvious in the desmosome in micrograph 2) composed of the glycosylated portions of membrane proteins of the cadherin family. The “interlocking” of these proteins provides cell-to-cell adherence. On the cytoplasmic side of each adherens junction other proteins form dense plaques into which the cytoskeletal elements insert, actin into the zonula adherens and intermediate-sized filaments into the macula adherens.



ZONULA OCCLUDENS (TIGHT JUNCTION)

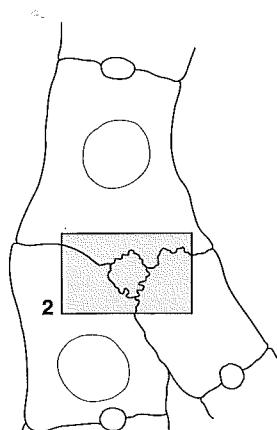
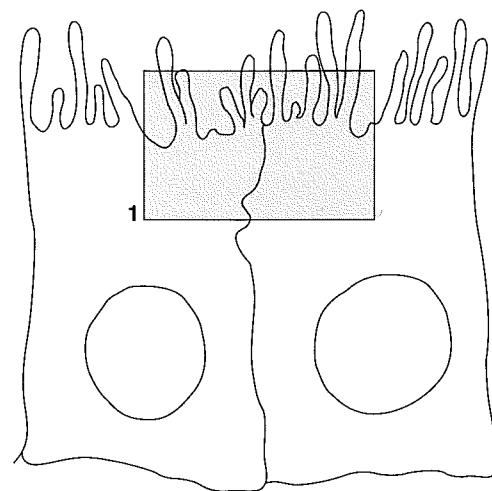
Two components of the junctional complex, the zonula occludens (ZO) and zonula adherens (ZA), are evident in micrograph 1. In the **zonula occludens**, the regions where the membranes of adjoining cells seem to fuse are visible. These areas of fusion regulate two types of movement between the lumen and underlying tissue, paracellular (between cells) and transcellular (through cells).

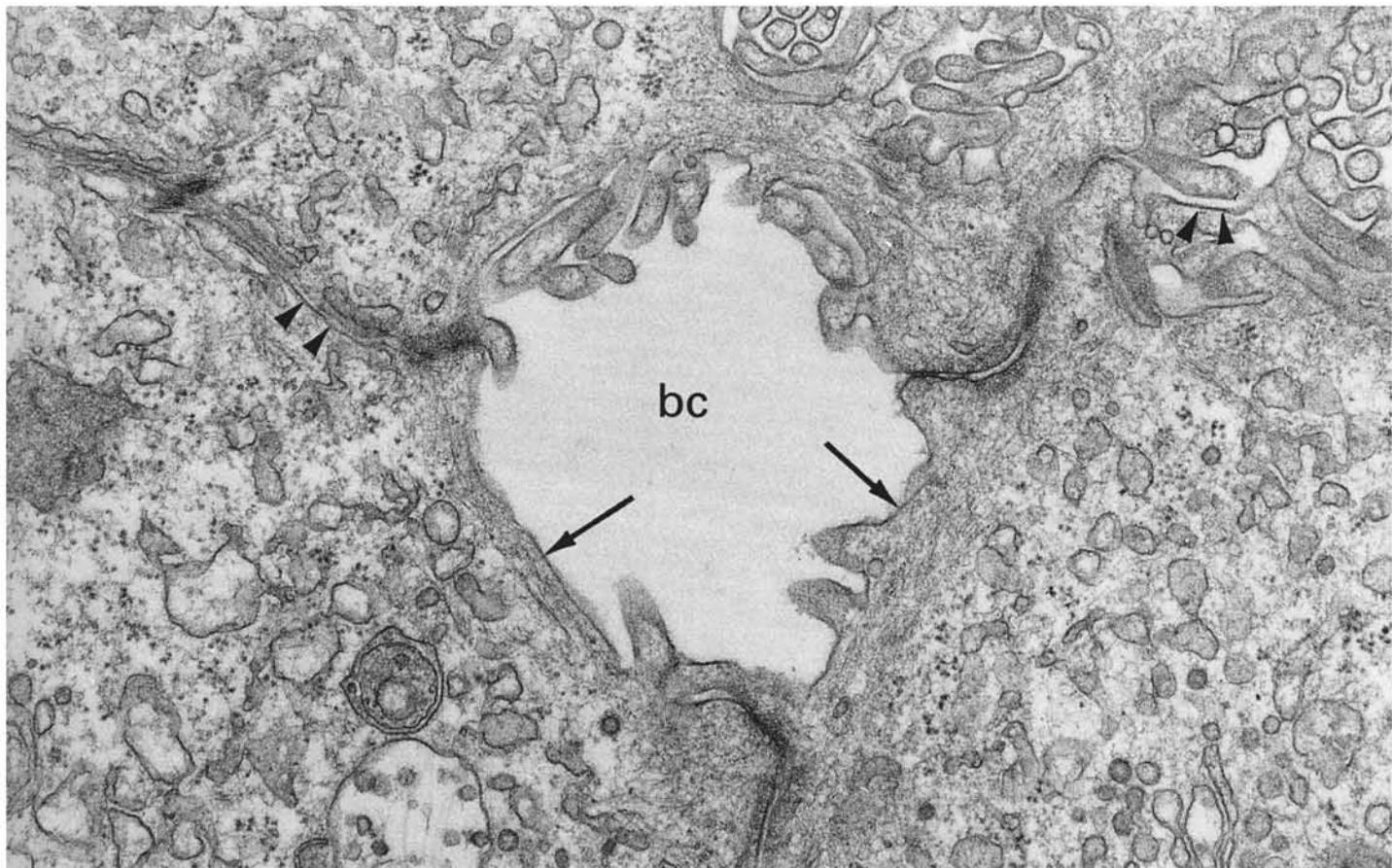
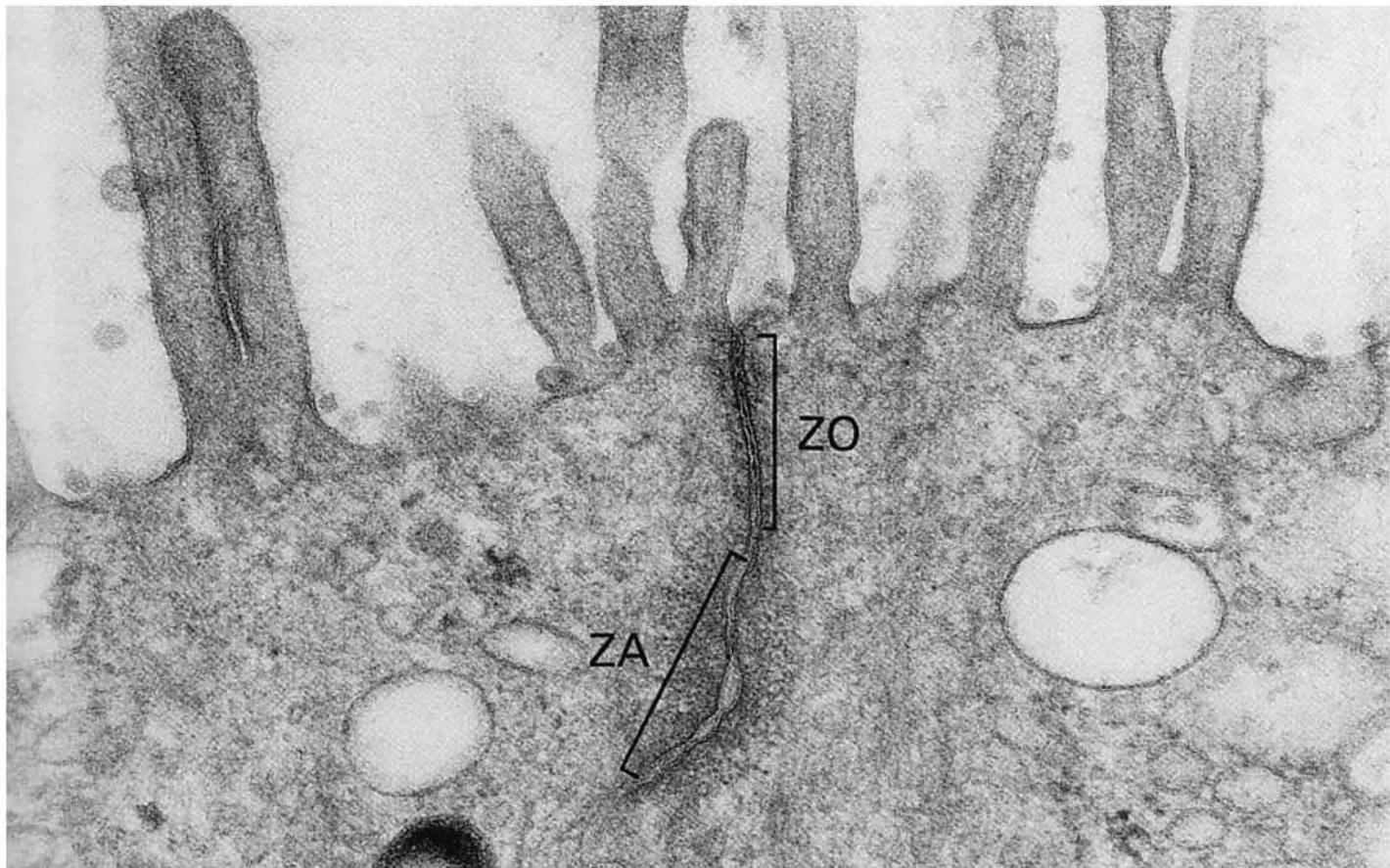
- **Paracellular movement:** Zonula occludens completely prevent the paracellular movement of macromolecules and polar molecules, and they restrict, to varying degrees, the movement of ions and small nonpolar molecules. Paracellular transport through tight junctions at different locations can vary from very leaky (electrical resistance as low as $5 \Omega \cdot \text{cm}^2$) to very selective ($2000 \Omega \cdot \text{cm}^2$). The degree of resistance has been correlated with the number of fusion areas that encircle the cell parallel to the surface.

- **Transcellular movement:** Certain membrane channels, enzymes, and receptors are localized in either the apical or basolateral cell membrane. Such restricted placement is essential to the localization of surface events adjacent to different environments (e.g., lumen vs. underlying connective tissue) and to the transport of molecules across cells. Tight junctions appear to contribute to the maintenance of this polarity by preventing (or restricting) the mixing of proteins and lipids between the apical and basolateral membranes.

In micrograph 2, the apical surfaces of three liver cells, joined via junctional complexes, define a bile canalculus (bc). The formation of bile, the exocrine product of the liver, depends upon both transcellular and paracellular events. Bile acids, cholesterol derivatives important in the emulsification of fats, are transported vectorially from the blood to the bile canaliculi. This transcellular transport depends upon the segregation of different proteins to the apical (arrows) and basolateral domains (arrowheads: lateral cell surface). Once the bile acids are secreted into the canalicular lumen, an osmotic gradient is created that draws ions and water into bile through the tight junctions via the paracellular pathway. Most of the sodium content of bile is derived in this way.

Tight-junction permeability is altered in response to diverse events. It has been suggested that actin filaments associate with proteins (ZO-1) unique to tight junctions and participate in adjusting permeability. Densities adjacent to these junctions may represent cytoskeletal elements.



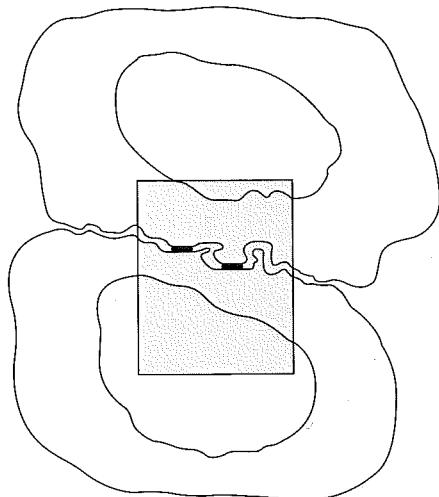


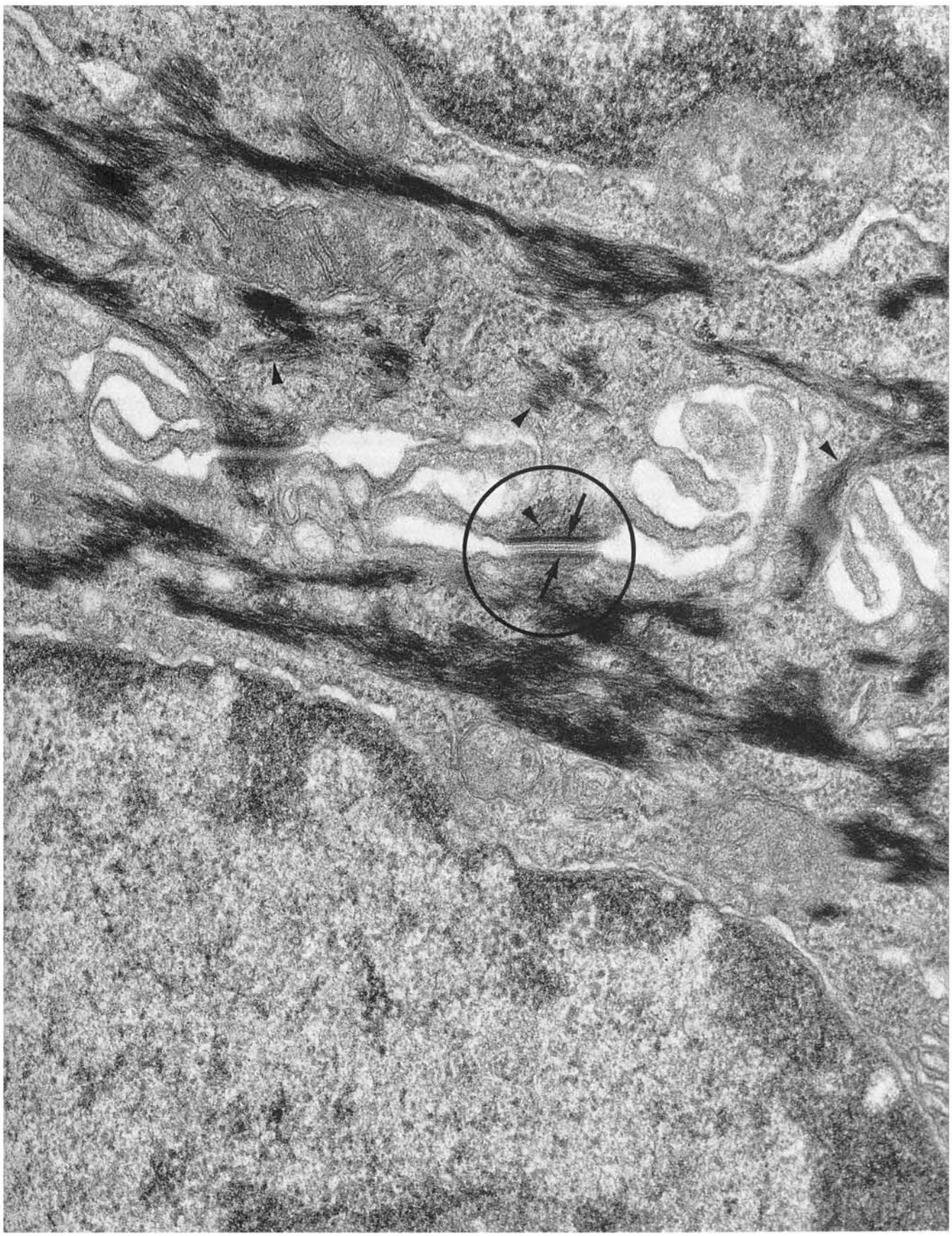
MACULA ADHERENS (DESMOSOME)

Desmosomes are common in skin (micrograph), where they are important in maintaining the integrity of an epithelium subjected to continual abrasion and distortion. In the encircled desmosome, characteristic components are particularly well illustrated: (1) the **dense line** bisecting the intercellular space where the glycosylated portions of integral membrane proteins meet; (2) the **dense plaque** (arrows) of concentrated proteins (including nonglycosylated membrane proteins) on the cytoplasmic side; and (3) **intermediate filaments** (arrowheads).

Desmosomes are not effective individually, but rather depend upon their association with other desmosomes in order to function. Stress applied to any one desmosome is rapidly distributed to others by the intermediate filaments (keratin tonofilaments in epithelium), which course within the cell from one desmosome to another.

Each of the desmosomal proteins plays an important part in the adhesive complex. Autoimmune disorders occur that affect desmosomal intercellular linking proteins (desmoglea) and plaque proteins (desmoplakins). In these diseases, bound antibodies interfere with cell-to-cell adherence, resulting in many cases in a group of diseases, epidermolysis bullosa, characterized by blistering that is potentially lethal.



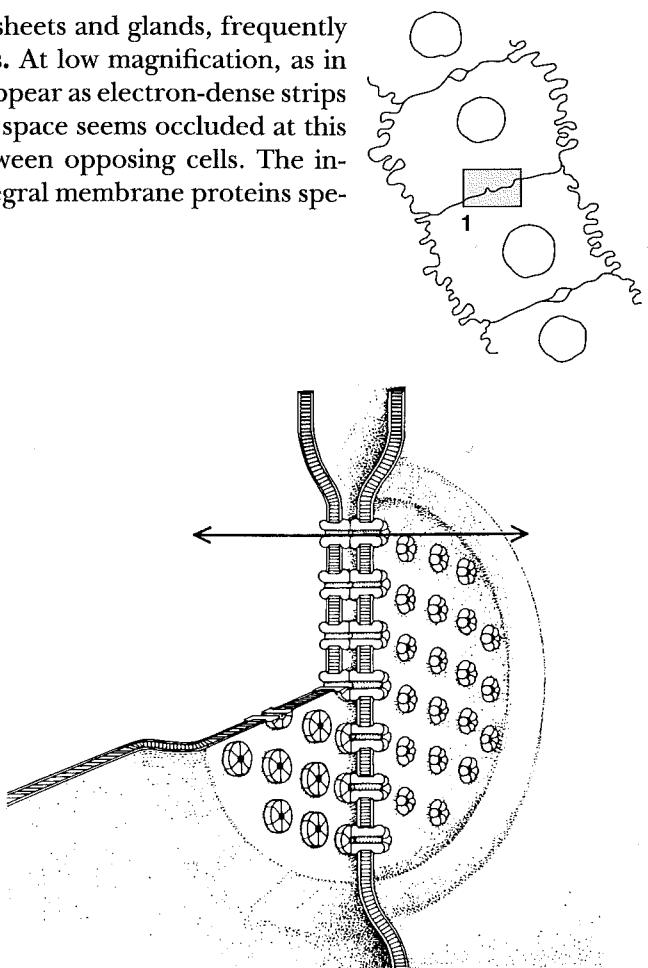


GAP JUNCTION

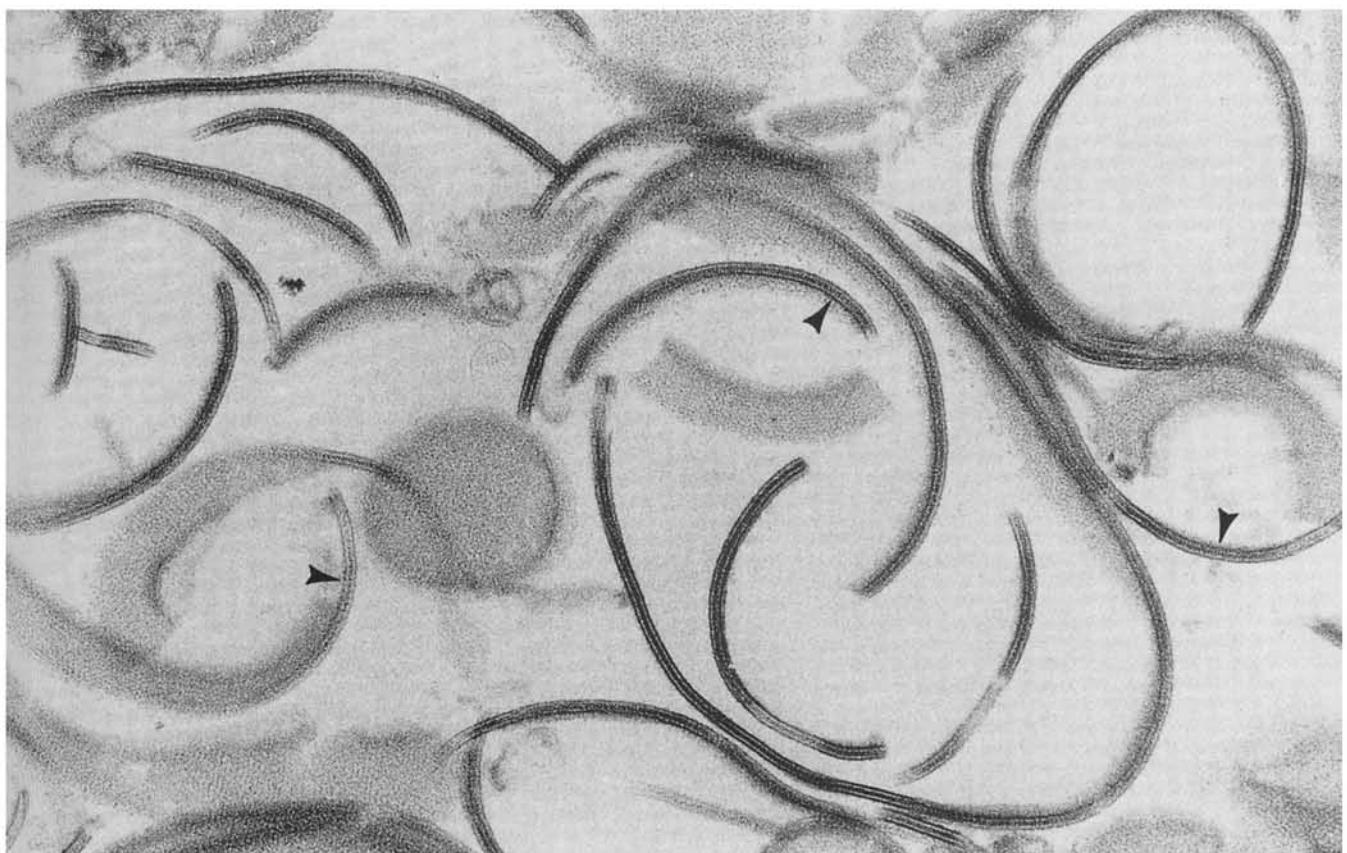
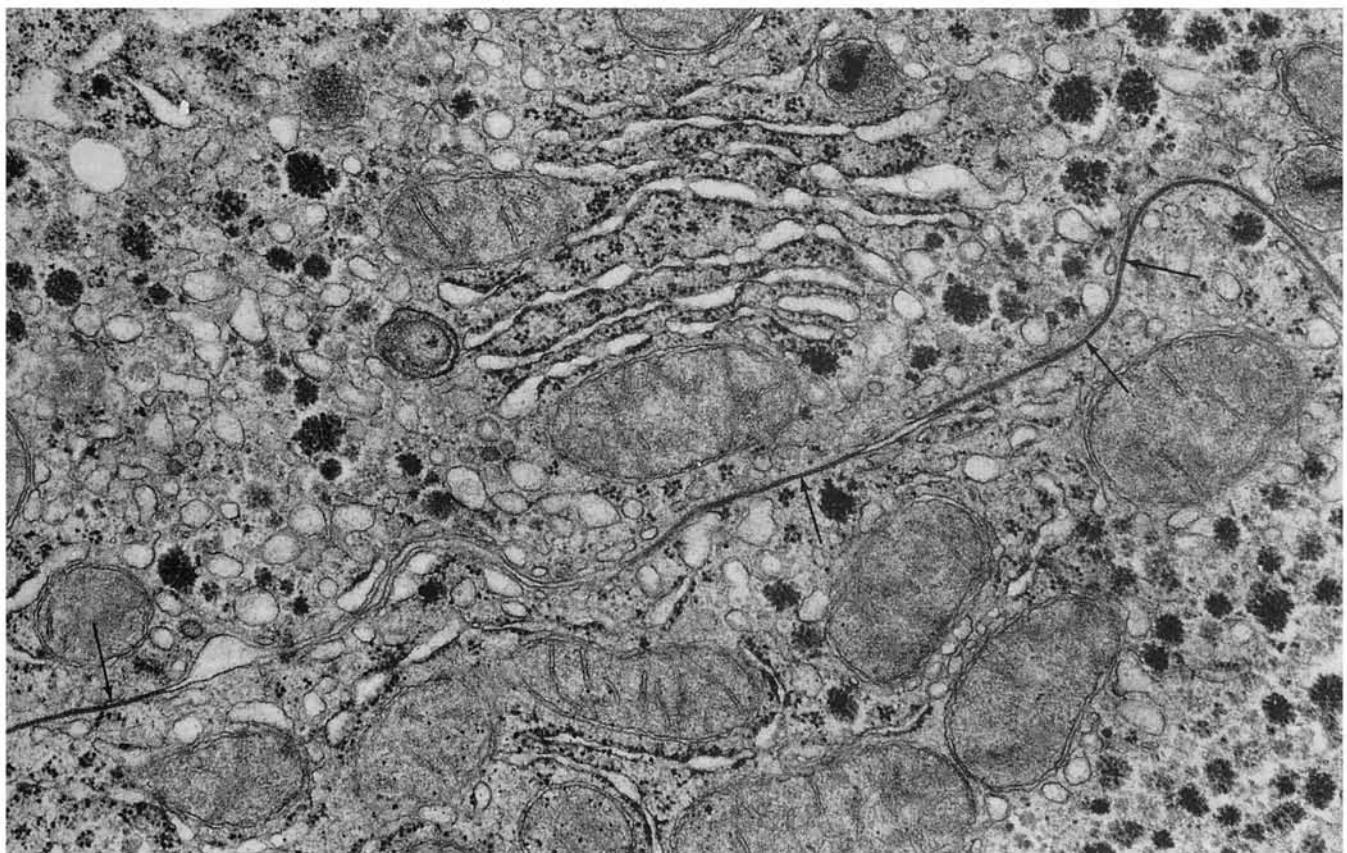
Cells in close contact, such as in epithelial sheets and glands, frequently communicate with one another via **gap junctions**. At low magnification, as in micrograph 1 of liver hepatocytes, gap junctions appear as electron-dense strips (arrows) between adjacent cells. The intercellular space seems occluded at this magnification, but in fact there is 2-nm gap between opposing cells. The increased electron density is an accumulation of integral membrane proteins specialized as channels between these two cells.

Gap junctions isolated from hepatocytes are shown in micrograph 2 (courtesy of Dr. E. Gogol). At this increased resolution, dark bands bridging the intercellular gap can be seen (areas at arrowheads). These bands are protein channels, **connexons**, that consist of a central pore of 1.5 nm, surrounded by six identical polypeptide subunits, connexins. A connexon spanning one membrane binds to another from the adjacent membrane to form a continuous channel.

Small molecules and ions (but not macromolecules) can readily pass from one cell to another through an open connexon pore. Increased concentration of calcium or hydrogen ions causes tilting and sliding of the connexon subunits to effectively close the pore and stop communication. The ability of cells to control communication may be important in a number of different ways, for example, (1) as a protective mechanism following the death of adjacent cells and (2) as an essential step during differentiation and the acquisition of unique properties.



From L. A. Staehelin and B. E. Hull, *Sci. Amer.* 238: 150
(May 1978).



APICAL SPECIALIZATIONS: Cilia

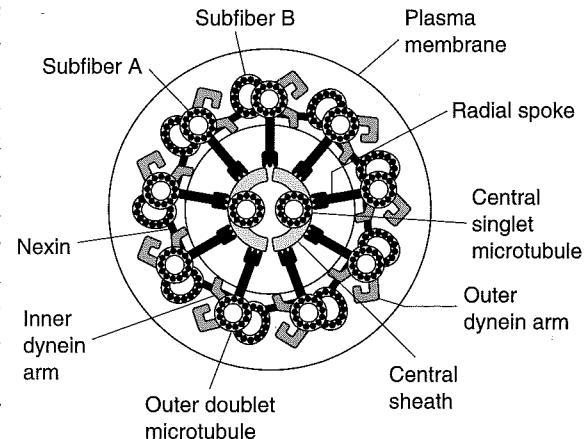
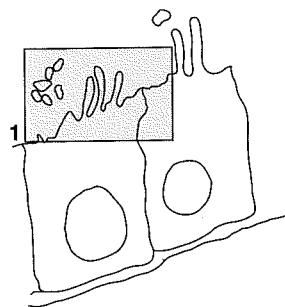
Cilia, 3 to 4 μm in length, project from the apical surface of certain epithelial cells and function in the coordinated movement of luminal contents. They are easily identified in longitudinal section (micrograph 1) by characteristic bands of microtubules (arrows) that extend from basal bodies (b) in the apical cytoplasm.

In cross section (micrograph 2) the core of each cilium is seen to contain precisely arranged microtubules, the **axoneme**, composed of one central unit containing two complete microtubules and nine peripherally distributed doublets. Each doublet consists of one complete tubule (subfiber A) attached to an incomplete tubule (subfiber B). Dynein side arms (arrows, micrograph 2) project from the A tubule of each doublet.

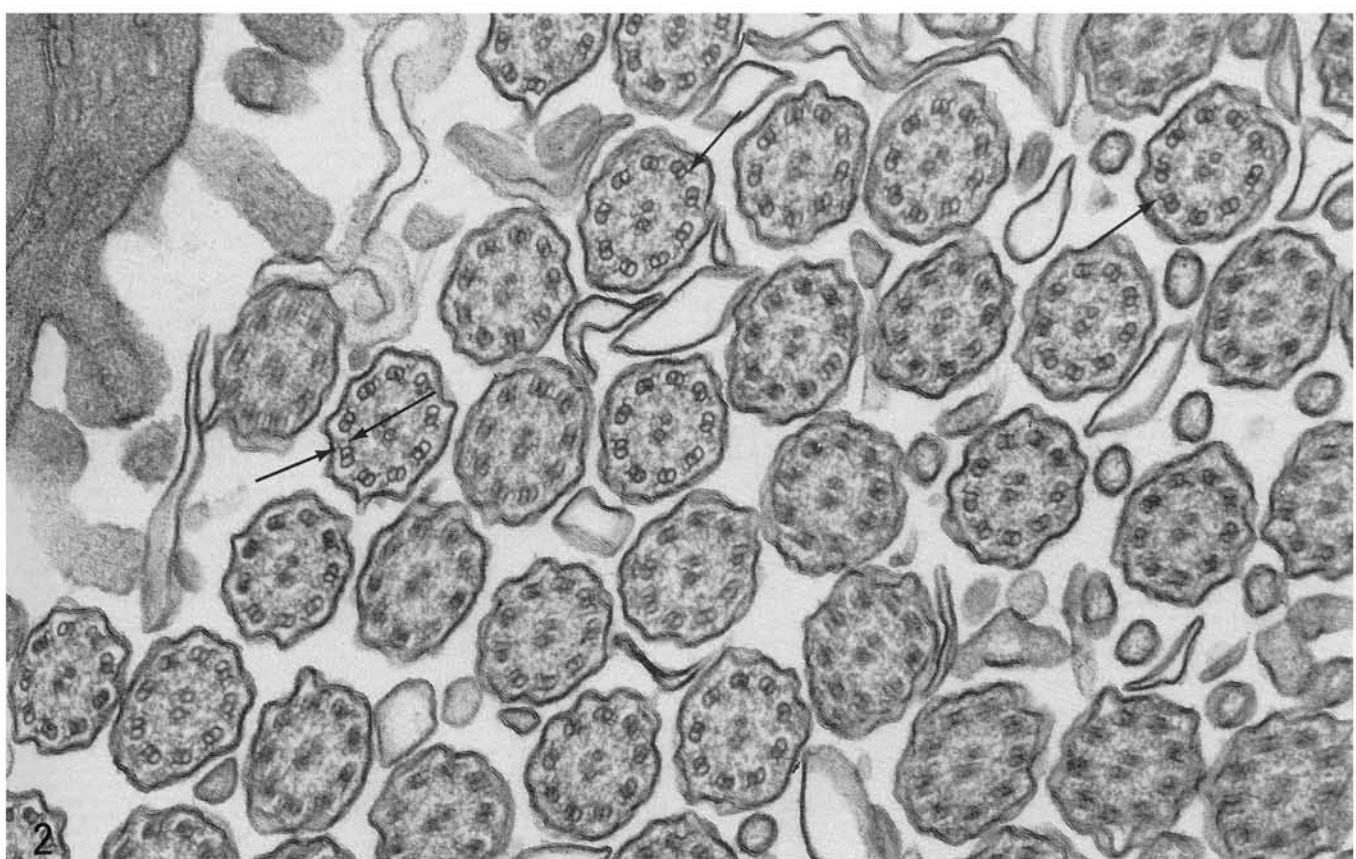
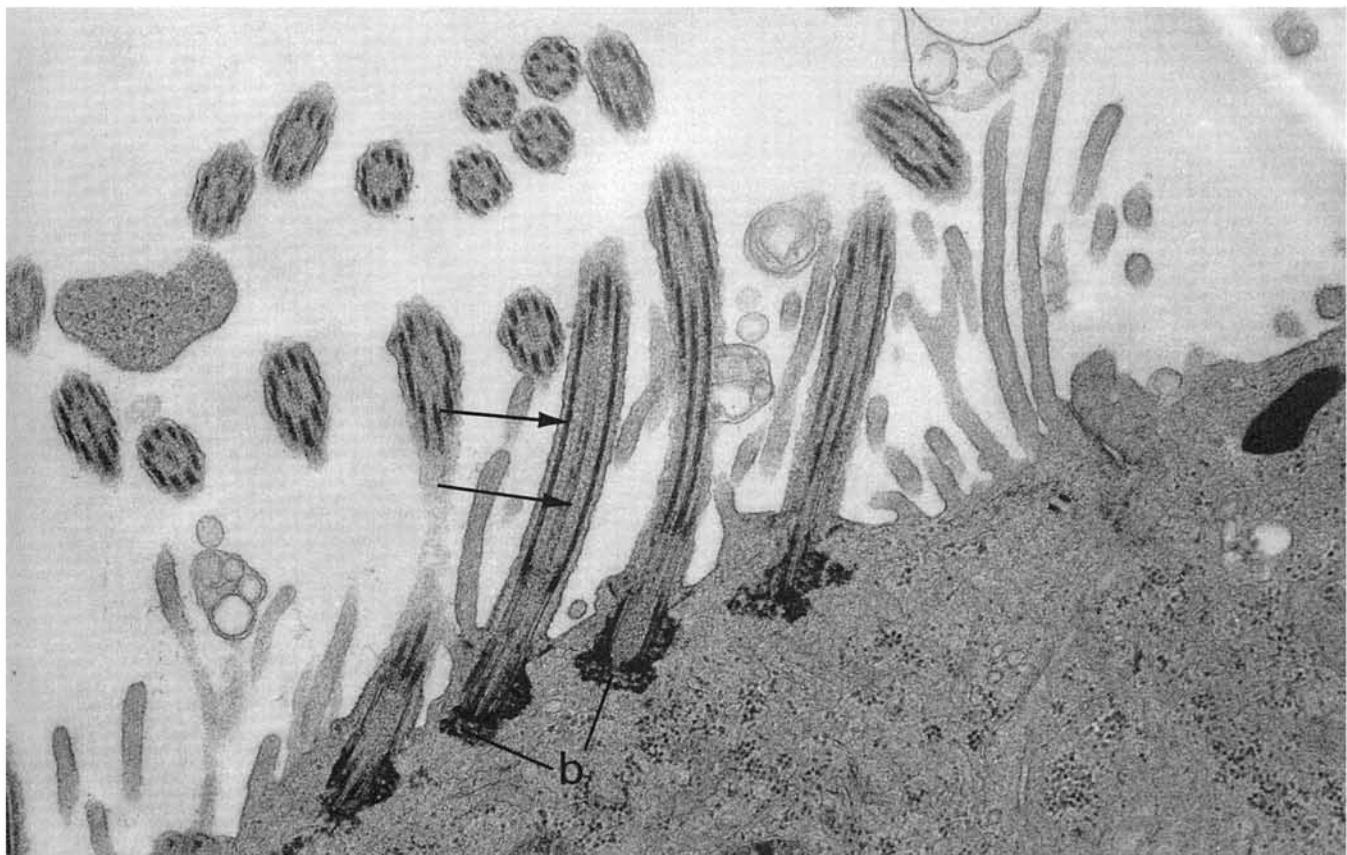
Each cilium moves with a rapid forward effective stroke and a slower whiplike recovery stroke. Movement is initiated by chemical (e.g., neurotransmitters, hormones) or mechanical factors. It is propagated within sheets of cells via gap junctions. Thousands of cilia covering an epithelial sheet move in a given direction slightly out of phase with each other to create a wavelike pattern. This ciliary beating involves the controlled attachment and detachment of the **dynein side arms** to the facing B tubule such that each doublet “walks” along an adjacent doublet. Dynein, like the myosin head, is an ATPase, and the hydrolysis of ATP provides the force for the shearing between doublets. Evidence suggests that the outer dynein arm controls the final sliding velocity whereas the inner arm may initiate the sliding.

A sliding movement is converted to bending since all doublets are anchored to the basal body. Accessory proteins within the axoneme, such as the radial spokes that extend from the A tubules, nexin elastic filaments that attach adjacent doublets, and an inner sheath surrounding the central pair of microtubules, are important in stabilizing the complex to provide coordinated movement within each cilium.

Defects in cilia have profound effects during development and in the respiratory and reproductive systems in which their action is most vital to organ function. Congenital abnormalities (Kartagener's syndrome) and acquired abnormalities (particularly in the respiratory system exposed to environmental hazards) can lead to immotile cilia or altered beat frequency. Even though ultrastructure does not always reflect malfunction, deficiencies in cilia are frequently associated with absent or altered dynein side arms.



Modified from L. Stryer, *Biochemistry*, 3rd Ed., Freeman, New York, 1988.

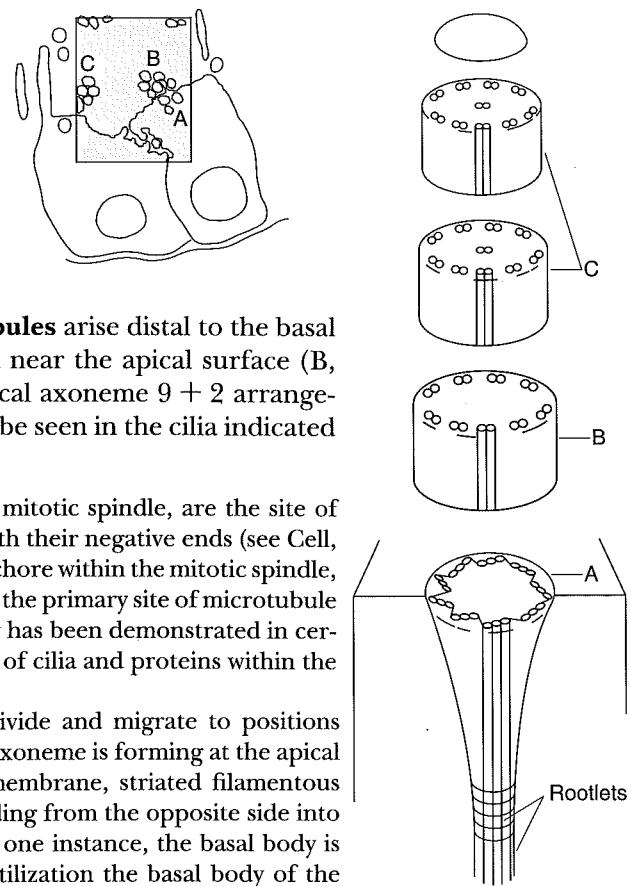


APICAL SPECIALIZATIONS: Cilia, Basal Body

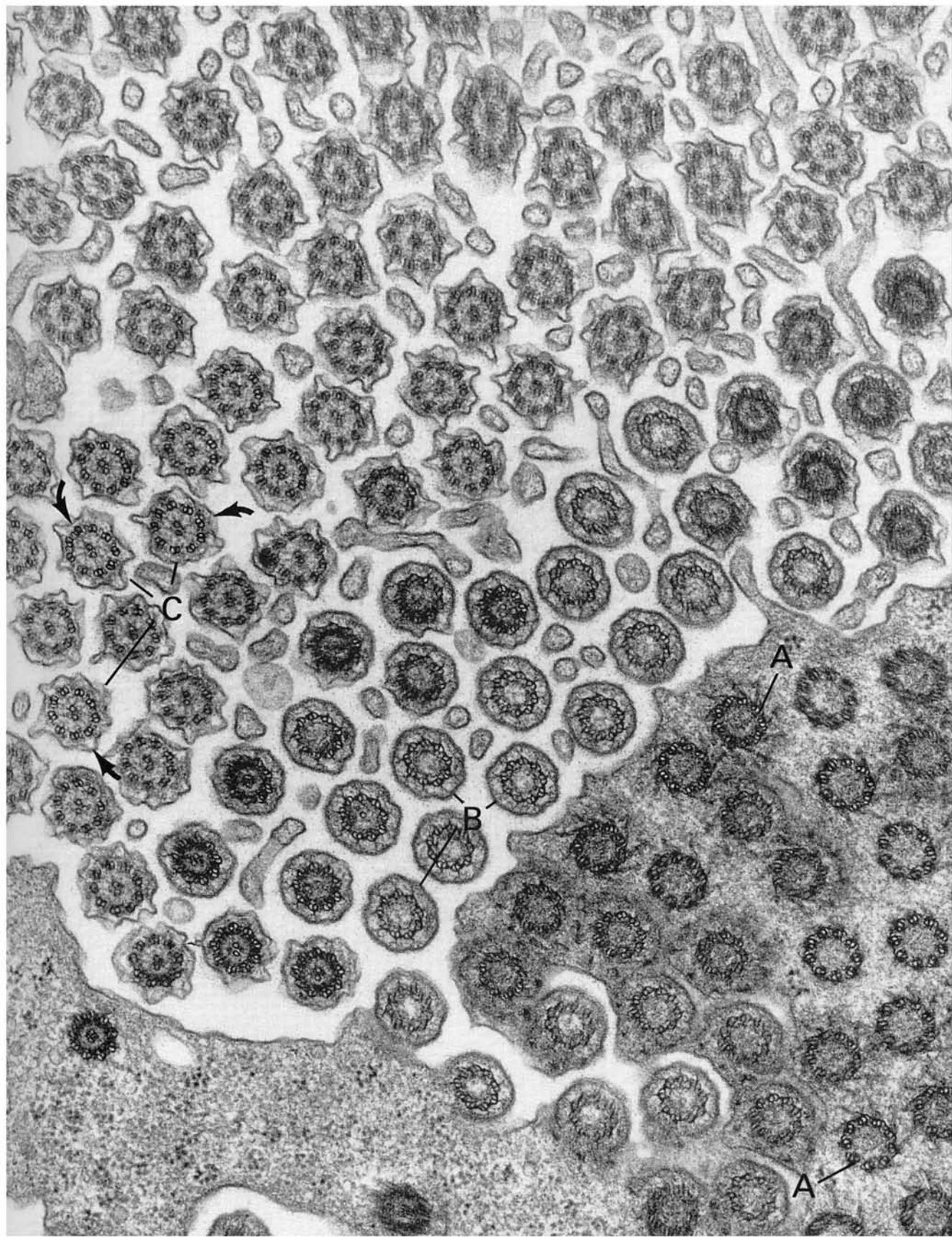
The micrograph depicts the apical surface of an epithelial cell and cross sections of cilia at various distances distal to the apical cytoplasm. Cilia develop from **basal bodies** (A, micrograph) in the apical cytoplasm. Basal bodies originate from and have a substructure similar to that of centrioles, with nine peripheral microtubule triplets. The two inner microtubules of each triplet in a basal body act as templates for the growth of the **outer doublets** in the cilium. The **central microtubules** arise distal to the basal body and are not present in cross sections of cilia near the apical surface (B, micrograph). In more distal cross sections the typical axoneme $9 + 2$ arrangement is evident (C, micrograph). Radial spokes can be seen in the cilia indicated by curved arrows.

Basal bodies, like the centriole region of the mitotic spindle, are the site of nucleation of microtubules and are associated with their negative ends (see Cell, pages 34, 36). The tip of each cilium, like a kinetochore within the mitotic spindle, is the positive end region of the microtubules and the primary site of microtubule assembly and disassembly. A degree of homology has been demonstrated in certain species between proteins that "cap" the tips of cilia and proteins within the kinetochore.

Basal bodies develop from centrioles that divide and migrate to positions directly under the apical cell membrane. As the axoneme is forming at the apical region of the basal body adjacent to the cell membrane, striated filamentous rootlets (not seen on the micrograph) are extending from the opposite side into the cytoplasm to anchor each cilium. In at least one instance, the basal body is known to return to a centriole function. At fertilization the basal body of the sperm flagellum develops into the centrioles of the mitotic spindle of embryo cleavage.



Modified from J. A. G.
Rhodin, *Histology, a Text
and Atlas*, Oxford University
Press, New York, 1974.

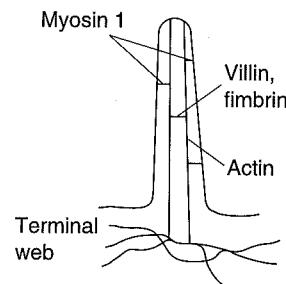
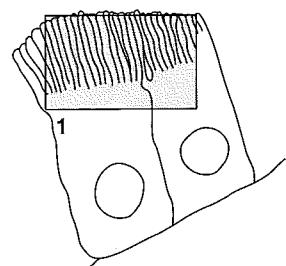


APICAL SPECIALIZATIONS: Microvilli

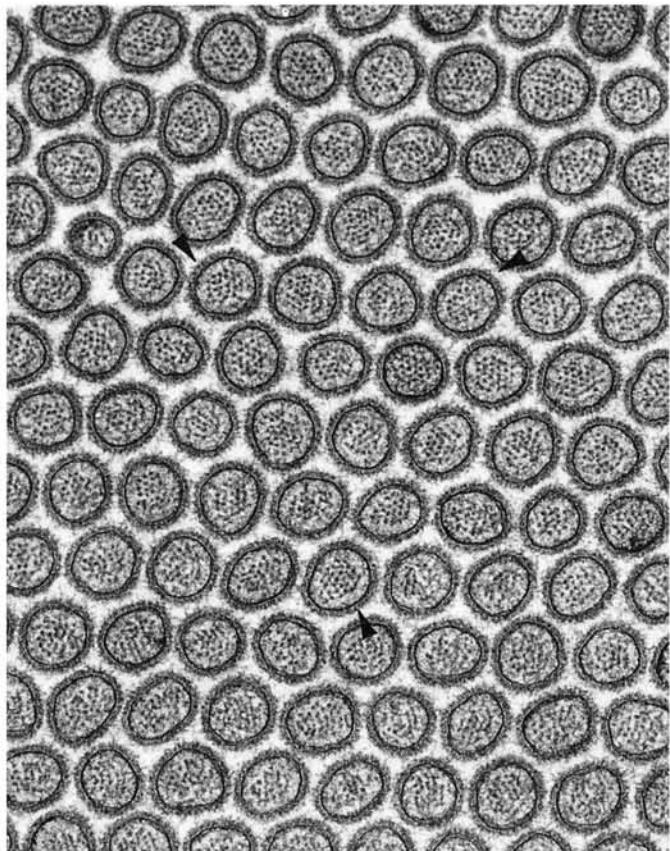
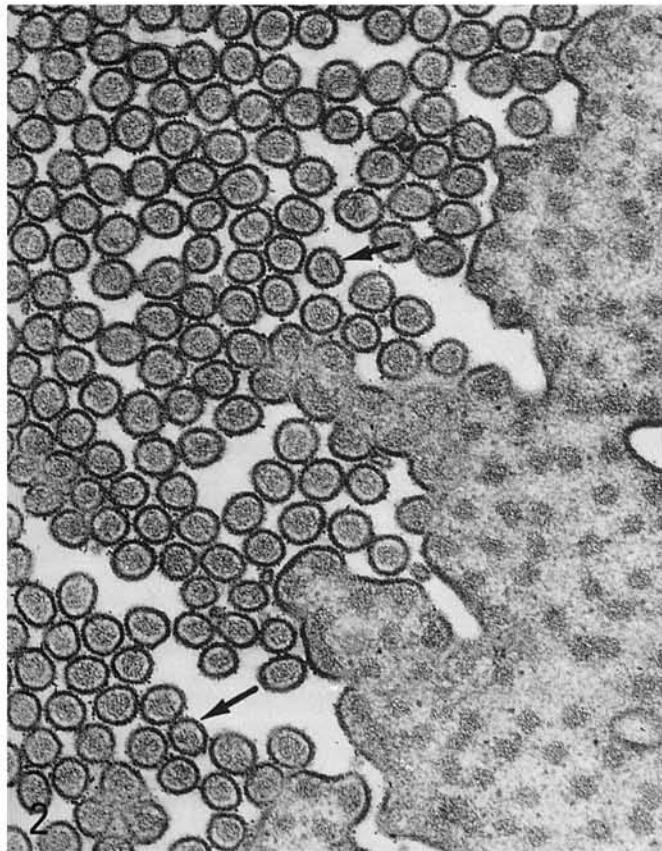
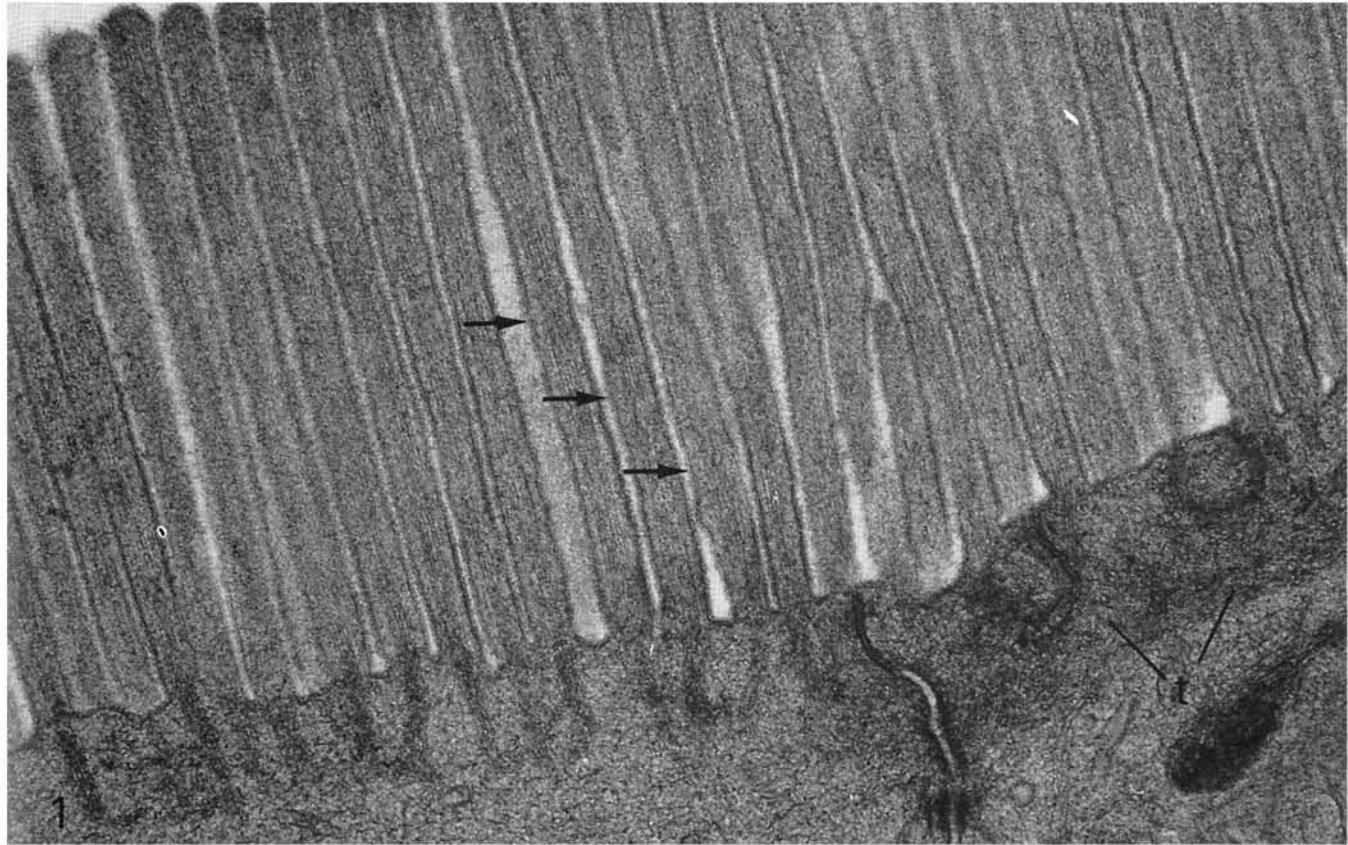
Microvilli (seen in longitudinal section in micrograph 1 and cross section in micrographs 2 and 3) are relatively short ($1 \mu\text{m}$) surface projections that increase the apical surface area of the cell. Each microvillus (arrows, micrographs 1 and 2) has a core of actin filaments that extend into the apical cytoplasm to form a terminal web (t, micrograph 1). Actin filaments of the terminal web cross-link to form an extensive network throughout the apical region. This network, anchored at the lateral surfaces into the zonula adherens, stabilizes the microvilli and enables the apical surface to act as a unit.

Other microvillar proteins bind actin microfilaments together (villin, fimbrin) and to the cell membrane (myosin 1). This assembly of proteins provides additional strength and rigidity for microvilli. In addition, the myosin 1 has ATPase activity and binds to actin in an ATP-reversible manner. This activity may facilitate a type of membrane movement.

The section of microvilli in micrograph 3 illustrates the internal, regularly arranged actin filaments (seen as dots in cross section) and an external “fuzzy coat” (arrowheads), the **glycocalyx**. The glycocalyx consists of the carbohydrate side chains of membrane proteins and lipids that extend beyond the lipid bilayer. Even though present on all apical surfaces, the glycocalyx is most pronounced on cells lining the small intestine, where it can reach a thickness of $0.5 \mu\text{m}$. This reflects a unique specialization of the intestinal surface in digestion. The final steps in the breakdown of proteins and carbohydrates are carried out directly on the cell surface by enzymes that are integral membrane proteins and a part of the glycocalyx.



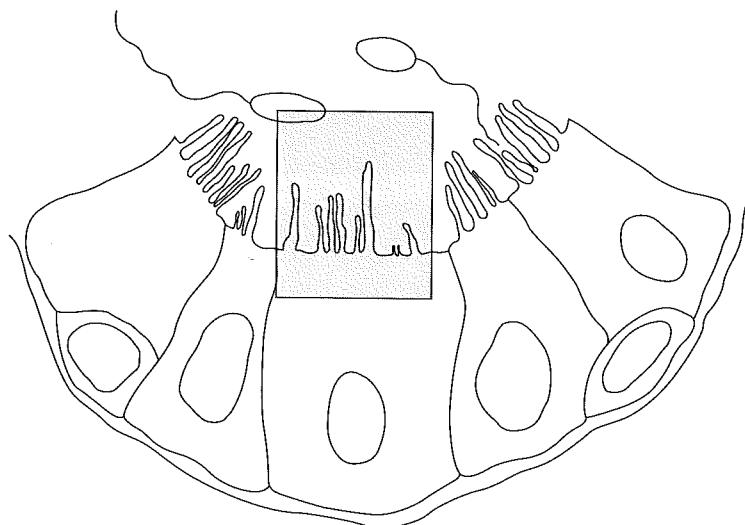
Modified from J. Darnell et al., *Molecular Cell Biology*, Scientific American Books, New York, 1986.

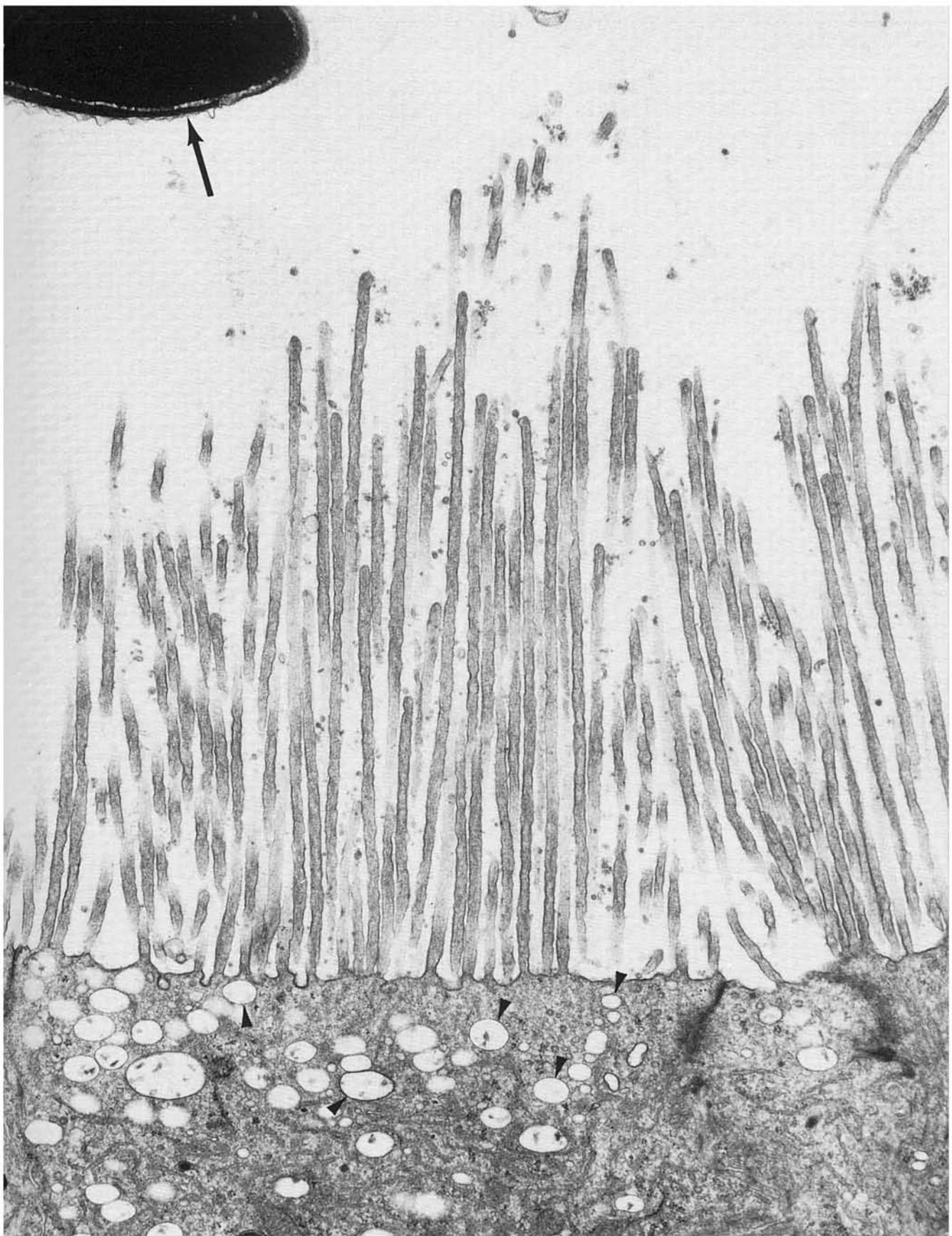


APICAL SPECIALIZATIONS: Stereocilia

The apical surface of a few cell types (such as the epididymal epithelial cell shown here) contains extremely long microvilli. The supportive filamentous core of actin is less well developed in these projections than it is in the shorter, more typical microvilli of the intestinal lining cells. The reduced cytoskeletal support and their long length contribute to a greater flexibility, leading to a resemblance to cilia at the light-microscope level. These microvilli are referred to as **stereocilia**, even though their **actin core** structure is very different from the microtubule core of true cilia.

In the epididymis, fluid absorption by the epithelium creates a current that is essential to the transport of sperm. Both the increased surface area provided by the stereocilia and the vesicles (arrowheads) in the apical cytoplasm reflect this function. Epididymal cells also contribute unique proteins to the luminal fluid, some of which associate with sperm (arrow indicates a sperm head) and may be important in the development of the ability of sperm to fertilize ova. It is possible that the increased cell surface provided by the stereocilia is also significant in this secretory process.





APICAL SPECIALIZATIONS: Transitional Epithelium

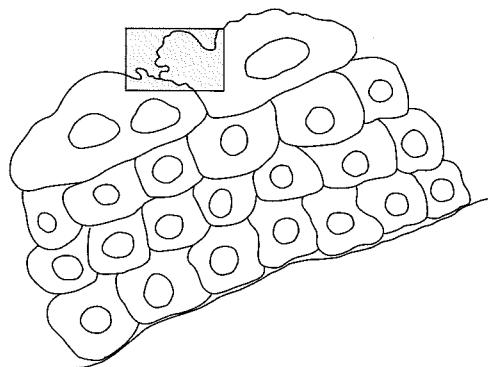
Transitional epithelium, found only in the urinary tract, is a stratified epithelium in which the apical cells change shape from cuboidal to squamous, depending on the degree of distention. In addition to a junctional complex typical of many epithelia, the surface cells of this epithelium possess a thick glycocalyx, abundant tonofilaments, characteristic membrane vesicles, and scallops along the luminal surface.

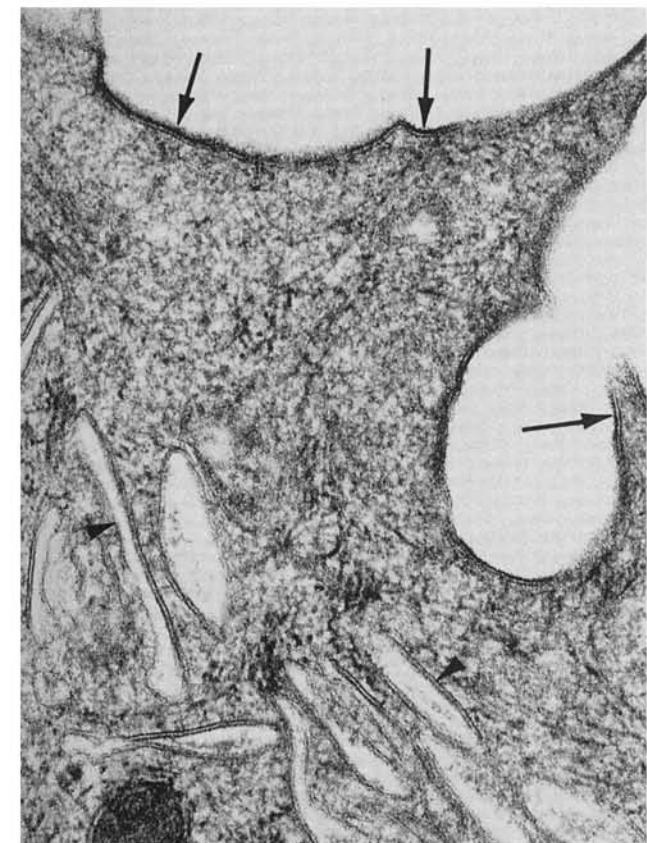
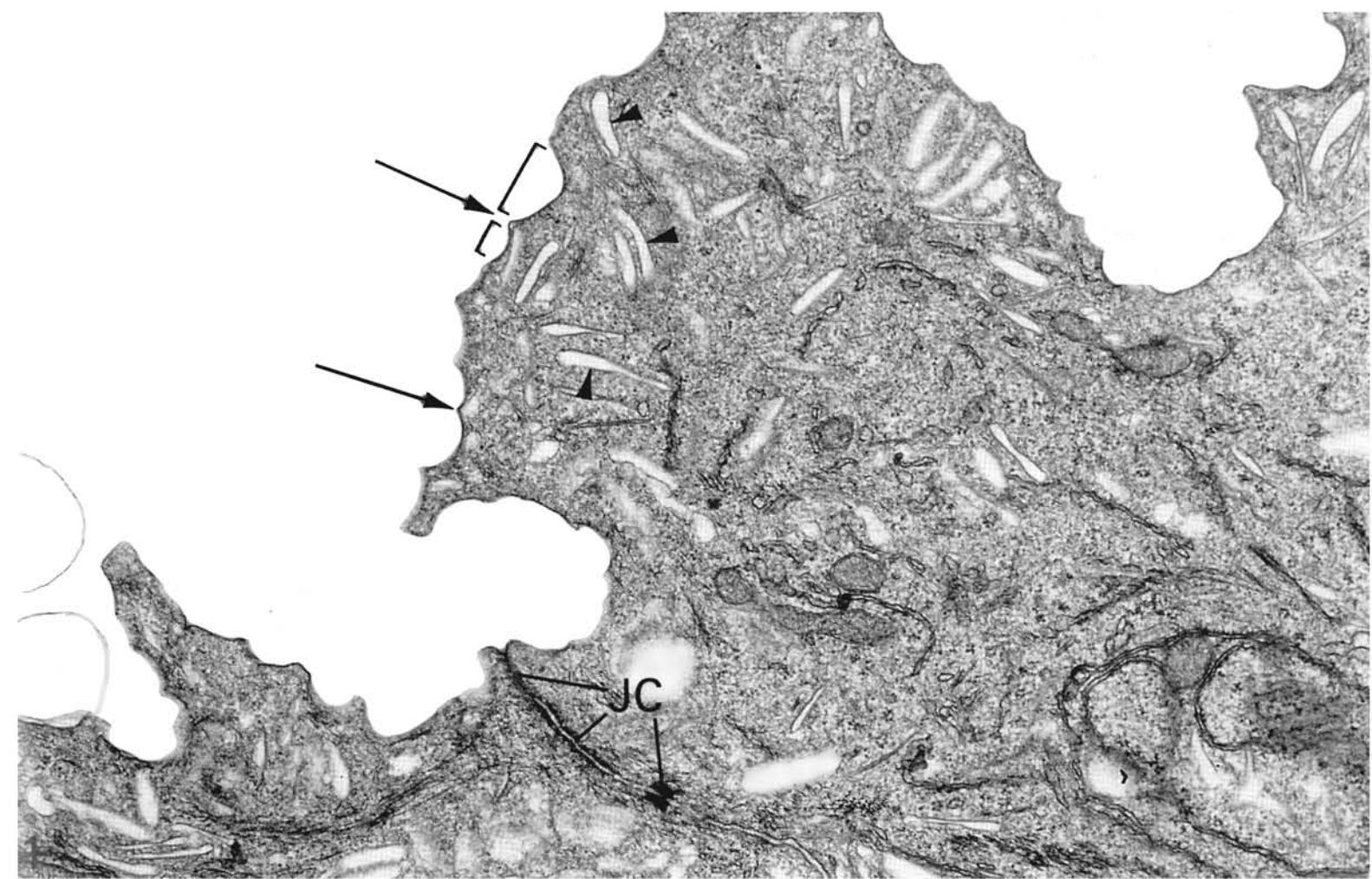
The ultrastructure of the apical cell layer of this stratified epithelium reflects its two major functions.

1. It is a **permeability barrier**: Tight junctions of the junctional complexes (JC, micrograph 1) between these cells prevent the paracellular movement of ions and water between the lumen and intercellular regions. This barrier maintains the hypertonicity of urine, which in turn is essential to overall ion and water balance. The thick **glycocalyx** (arrows, micrograph 2) plays a significant role in preventing bacterial infection and is commonly referred to as the “antiadherence factor.” It is not known whether it also contributes to the protection of the surface epithelium from the caustic urine.

2. It plays a role in the **adjustment of surface area**: Division of the apical membrane of each surface cell into rigid, concave **plaque regions** (brackets, micrograph 1) containing densely packed particles, separated by **interplaque regions** (arrows, micrograph 1) devoid of these particles, gives the surface a scalloped appearance. Plaques, hinged at interplaque regions, provide for an efficient, orderly means of surface folding and unfolding when the urinary tract lining accommodates different volumes of urine. **Vesicles** (arrowheads, micrographs 1 and 2) found near the apical surface represent either sections through folds or compartments that have pinched off to form separate entities during relaxation of the epithelium.

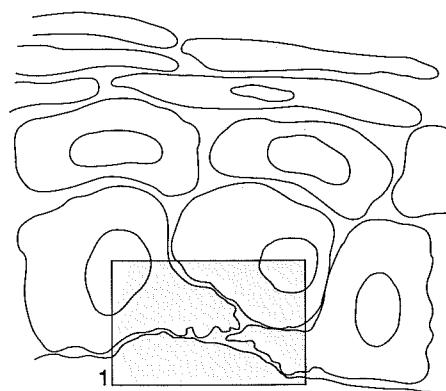
Tonofilaments (curved arrows, micrograph 3) provide strength to maintain the integrity of the transitional epithelium during the distortion associated with stretching and relaxing. These filaments associate with both the plaque proteins and desmosomes.





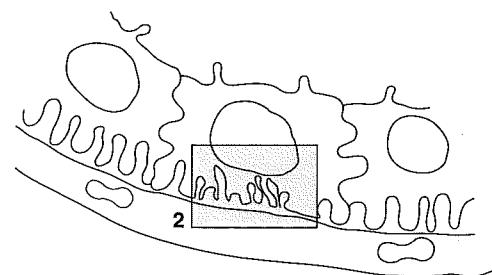
BASAL SPECIALIZATIONS

An electron-dense band, the **basal lamina**, or lamina densa (arrows, micrograph 1), follows the contours of the basal surface of epithelial sheets. The basal lamina is the site where epithelial cells attach to the extracellular matrix. Its functions are diverse, some a direct property of the structure itself (e.g., permeability barrier, neurotransmitter breakdown) and others expressed as effects on associated cells (e.g., induction of differentiation, including polarity). In many instances (as in micrograph 1) the basal lamina is associated with a connective tissue layer of fine reticular collagen fibers (arrowheads) that is referred to as the **reticular lamina**. The basal and reticular laminas are visible as a single structure, the **basement membrane**, at the light-microscope level.



The basal lamina is composed of over 100 different polypeptides. Type IV collagen, laminin, fibronectin and heparan (and heparin) sulfate proteoglycan are the most abundant. These proteins are also present in the space (**lamina rara**) between the cell and the basal lamina but are generally less abundant in this region. They bind to one another, to the epithelial cells, and to the underlying connective tissue to form complex patterns. Integrins, membrane proteins specialized for adhesion, mediate many of the signals from matrix to cell. Fibronectin extends from integrin receptors on the basal cell surface through the basal lamina to bind to reticular lamina collagen. Laminin and fibronectin have a particularly strong affinity for tumor cells and appear to facilitate the escape of cancerous cells across the basal lamina into the surrounding tissue.

In regions where a major function of the epithelial cell is directed toward secreting into or absorbing substances from the blood, the epithelial basal lamina fuses with the basal lamina of the capillary lining. This brings the epithelial cell close to the blood supply to facilitate exchange. In micrograph 2 the basal laminas of a kidney proximal tubule epithelial cell (Ep) and a capillary endothelial cell (E) appear fused except at one location (arrow) where two separate laminas can be seen. In the kidney tubule shown here, the basolateral surface is specialized, with infoldings (arrowheads) and mitochondria (m) to accommodate an ion pump that retrieves 60 to 70% of the Na^+ lost in the initial filtration process.



Hemidesmosomes (white arrows, micrograph 1) are frequently found on the basal surface of epithelial cells. Their ultrastructure resembles half of a desmosome; however, their protein composition is unique. Tonofilaments insert on the cytoplasmic side. Other proteins project extracellularly, (circle), bridge the lamina rara, and appear to insert into the basal lamina.

