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IMMUNOLOGIC STRUCTURES AND FUNCTIONS OF THE GUT

J.-O. GEBBERS AND J. A. LAISSUE

SUMMARY

The intestine is richly populated with lymphoid tissue capable of initiating and effecting a wide variety of immunologic reactions. These reactions have consequences not only for the gut itself but for the body in general, and have established the importance of the *gut as an immunologic organ.*

Among the outer and inner surfaces of our body, the 200 to 300 m^2 of the gut contrast with the 2 m^2 of the skin, and the 80 m^2 of the lung. At the inner surface of the intestine, our organism contacts intimately bacteria, parasites, enzymes, toxins, a wide variety of dietary substances and their breakdown products.

The essential barrier against the permanent antigenic burden is the mucosa. Its integrity depends on the continual replication, maturation, and metabolism of its constituents. Additional defense functions are exerted by the mucus, lysozyme, phagocytes, other cells, humoral factors and biological response modifiers involved in inflammatory and immune reactions.

Some of these factors are being produced very close to the surface at which they act. The sum of the mechanical, humoral, cellular, immunologic and non-immunologic defense factors of the intestinal mucosa constitutes the *mucosal block.*

However, the block is not complete. Rather, a continuous antigenic uptake through the epithelial layer takes place. The specialized structures of Peyer's patches, solitary lymph follicles, appendix vermiformis and their associated epithelium allow a controlled *antigen uptake* (sampling). Because of the heavy antigenic load, the intestine can be described as the most important *immunologic contact organ* of our body. The antigens may give rise to local and systemic immune reactions with antibody production, *or* the suppression of systemic immunologic responses to ingested antigens (*«oral tolerance»*).

KEY WORDS: intestines – immunology

IMMUNOLOGISCHE STRUKTUREN UND FUNKTIONEN DES DARMES

Der Darm ist mit einem eigenen Immunsystem ausgestattet, das am Ort der Resorption die Aufnahme von Fremdmaterial kontrolliert, darüberhinaus aber auch wichtige systemische Schutzfunktionen ausübt. Die *Antigenaufnahme* im Darm kann zu Immunreaktionen mit entgegengesetzten Wirkungen führen: 1. zur Bildung von Antikörpern, vor allem der IgA-Klasse, die vom Epithel in das Lumen sezerniert werden, und 2. zur Unterdrückung der systemischen Immunreaktivität gegen oral aufgenommene Antigene («orale Toleranz»).

Das Darm-assoziierte Immunsystem ist das grösste unseres Körpers und kann unabhängig vom systemischen Immunsystem wirken. So bildet es zum Beispiel normalerweise sekretorische IgA-Antikörper gegen viele Dickdarmbakterien. In Kindern mit doppelläufiger Kolostomie induziert die Applikation von Poliomyelitis-Viren in das distale Kolon eine lokale spezifische Antikörper-Produktion, aber auch eine systemische IgM- und IgG-Reaktion. Bei Patienten mit Shigellen-Kolitis sind spezifische Antikörper sehr viel früher im Stuhl als im Serum nachweisbar. Diese Befunde führen zum Konzept des *Darms als Immunorgan.*

Abwehrmechanismen des Darms können unvollständig sein oder das Immunsystem kann überreagieren. Infektionen entstehen somit vermutlich infolge gestörter Abwehr und Auto- und Hyperimmunreaktionen infolge fehlerhafter Kontrollmechanismen. Komplexen, oft schädigenden Einflüssen stehen auch komplexe protektive Mechanismen gegenüber. Die funktionelle und strukturelle Integrität der *Mukosabarriere* ist hierbei sehr wichtig.

Hier sind einige Aspekte zur Antigenbelastung unseres Darms, zur Funktion und Orthologie der Mukosabarriere und ihres Immunsystems, zur Antigenaufnahme und dessen protektive Bedeutung für die sekretorische Immunität und die Toleranzinduktion zusammengefasst.

SCHLÜSSELWÖRTER: Darm – Immunsystem

MAIN FUNCTIONAL ASPECTS OF THE INTESTINAL MUCOSA

The *antigenic burden* of the gut is heavy. Bacteria, parasites, toxins, enzymes, and a host of dietary substances intimately contact the mammalian organism at the intestinal interface. There are many bacteria in the oral cavity and pharynx, but virtually none in the esophagus and stomach. In the intestine, the bacterial counts rise progressively from 10^2 to 10^3 organisms per ml in the proximal small bowel (*Dickmann* et al., 1976) to approximately 10^{12} bacteria per gram of the bowel contents in the rectum (Fig. 1) (*Hill* and *Drasar,* 1975). Because of a slow transit of intestinal contents, the colon is heavily exposed to bacterial and other antigenic substances (Fig. 2).

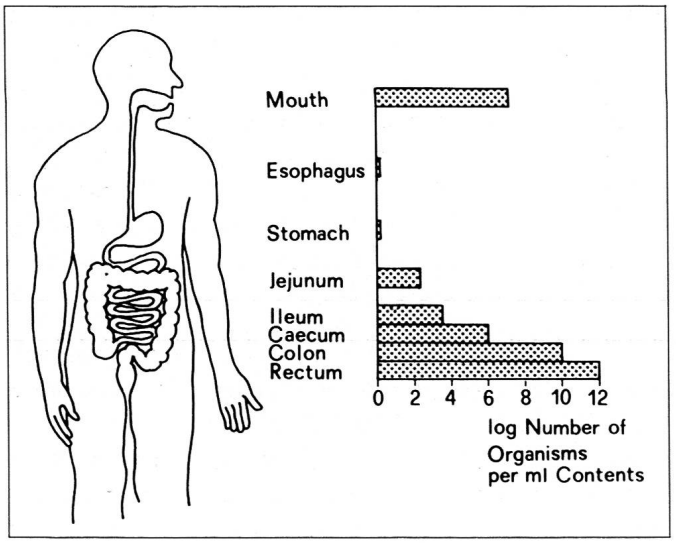

Fig. 1: Bacterial counts in different regions of the gastrointestinal tract in normal individuals.

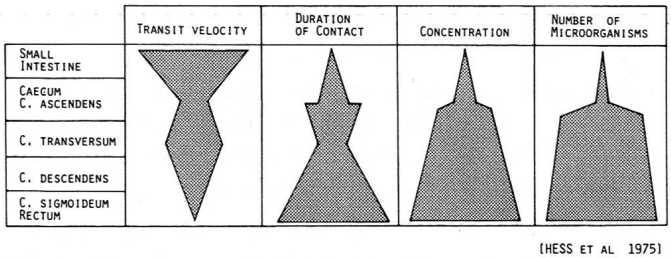

Fig. 2: Parameters of the transit of intestinal contents in different regions of the gut.

The essential *barrier against the permanent antigenic burden* is the mucosa. Although it prevents penetration of potentially noxious agents, it also allows exchange of substances between the gut lumen and the «milieu intérieur» of the body. The tunica mucosa with its rapid cell turnover, the mucus and lysozyme of Paneth cells are important defense mechanisms. The intestine is also equipped with an extensive local immune apparatus that functions fairly independently from the systemic immune mechanisms. The mechanical, humoral, cellular, immunologic, and non-immunologic defense factors in the intestinal mucosa constitute together the «mucosal block» (Fig. 3).

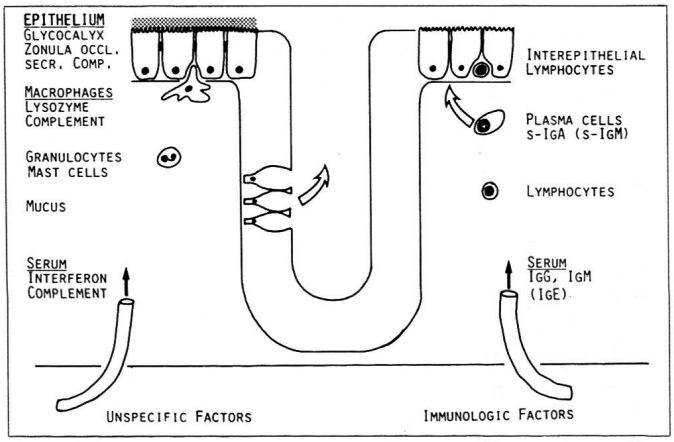

Fig. 3: The mucosal block as the sum of unspecific and immunologic barriers of the gut mucosa.

However, this block is not absolute. *Antigens are continuously taken up* through the epithelial layer. The resulting local or systemic immune reactions are twofold: Secretion of antibodies, mainly of IgA class, or suppression of systemic immunologic responses to ingested antigens («oral tolerance»). The specialized structures of Peyer's patches, solitary lymph follicles and appendix vermiformis allow a controlled uptake (sampling) of antigenic substances. Epithelial cells and their products are essential participants in both initial and final stages of reactivity to foreign materials. They play a role in antigen exclusion, transport of antigens from the lumen, bidirectional transport, degradation of antigens, antigen presentation, and antibody secretion (*Bockman* et al., 1983).

Mucins are complex hydrated gels composed of a variable group of glycoproteins. The physicochemical properties of the mucus secreted by the goblet cells (review: *Filipe,* 1979) are ideal for the task of covering, lubricating and protecting a constantly moving surface (*Nimmerfall* and *Rosenthaler,* 1980). The mucus interacts with other secretory products of the intestinal mucosa, such as lysozyme and immunoglobulin A (IgA; *Clamp,* 1980; Fig. 4).

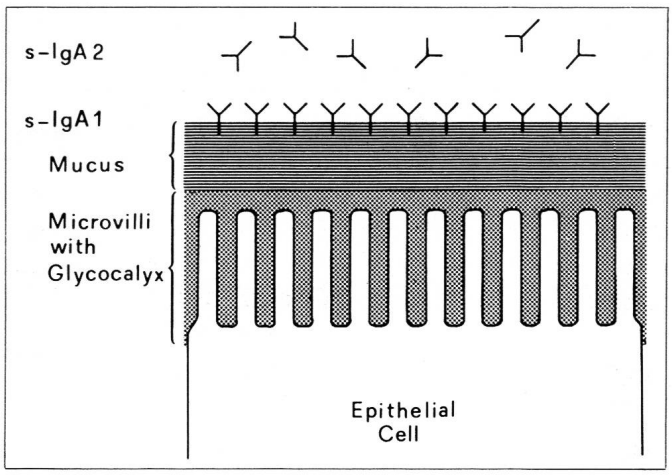

Fig. 4: Interaction of the intestinal mucus with secretory IgA (hypothesis).

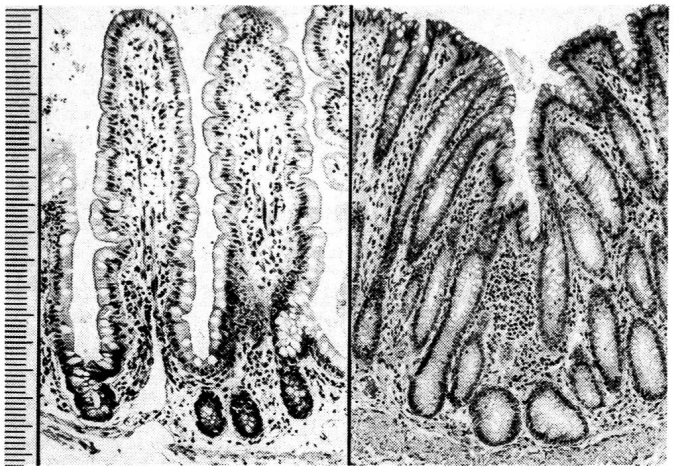

Fig. 5: Photomicrographs of the human intestinal mucosa. Left: Jejunal mucosa with a continuous sheet of simple epithelia which covers the connective tissue of the lamina propria. The crypts rest on the muscularis mucosae, the thin layer of smooth muscle that separates the mucosa from the submucosa below. Note that the crypts are less than one-third the length of the finger-shaped villi. Right: Colonic mucosa with long crypts of Lieberkühn around a transverse groove. The distance between two marks at the left figure margin is equivalent to 0.2 mm.

Immunologic events may influence the secretion of mucus (*Walker* et al., 1977; *Lake* et al., 1980; *Castro*, 1982).

EPITHELIUM

Structure

The mucosa of the intestine covers an area of about 200 to 300 m^2 (*Wilson,* 1962). This large *surface* warrants an optimal contact for absorption between nutrients and the mucosa. The plicae circulares (Kerckring's folds), the villi intestinales, the glandulae intestinales (crypts of Lieberkühn; Fig. 5), and the microvilli (Fig. 6) increase the inner surface of the otherwise smooth tubular small intestine by a factor of 600. The mucosa membrane of the colon has many transverse grooves at distances varying from 0.6 mm to 2 mm (Fig. 5). The villi of the small intestine, and the colonic «surface» epithelium absorb intestinal contents, whereas the crypts secrete various substances, and replace desquamated cells.

The *columnar villous and colonic «surface» epithelium* consists of principal cells (enterocytes) and few goblet cells. The polarity of the enterocytes is essential for transepithelial bidirectional transport. The basolateral surface takes up nutrients and also receives hormonal and other signals from the organism. Intercellular spaces in the basal parts of this epithelial layer are important for the absorptive and secretory functions of these cells.

The *brush (or striated) border* at the apical pole of the principal cell consists of 1.500 to 3.000 microvilli per cell (Fig. 6). These finger-like projections of the cell membrane increase the surface area of the mucosa by a factor of 15 to 25. The microvilli contain a cytoskeleton (*Matsudaira* and *Burgess,* 1982) with myosin, actin and tropomyosin (*Drenckhahn* and *Gröschel-Stewart,* 1980). They can move actively (*Rodewald* et al., 1976).

Filaments synthesized by the epithelium coat its microvillous and intermicrovillous membrane and radiate into the lumen. This *«glycocalyx»* or *«fuzzy coat»* consists of acid glycosoaminoglycans and glycoproteins (*Ito,* 1965). The glycocalyx probably increases the absorptive (and digestive?) surface and is an effective barrier to large particles, such as bacteria and fat droplets (Fig. 6; *Ito,* 1965).

The epithelial cells are connected by a *junctional complex* which consists of (a) the most apical zonula occludens (tight junction); (b) the zonula adherens (the underlying intermediate junction); and (c) the macula adherens (desmosomes). The tight junction is located at the base of the brush border (Fig. 6). It ties the epithelial cells together and seals epithelial interstices, acting as a diffusion barrier to large molecules, such as hemoglobin, and perhaps also to small molecules, and even to water. The intermediate junction and desmosomes probably tie the cells together.

The *crypt epithelium* is made up by five cell types: goblet cells (Fig. 7), differentiated and undifferentiated cells, enterochromaffin cells and, in the small intestine and the ap-

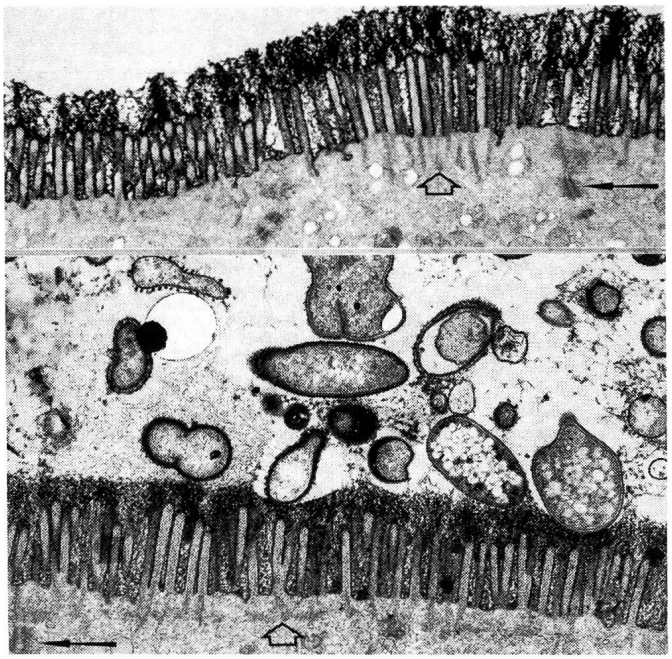

Fig. 6: Electron micrograph of human intestinal epithelia with microvilli representing finger-like projections of the apical cell membrane, whose area is markedly increased by them. Bundles of filaments within the microvilli extend the entire length of them and reach into the terminal web (open arrows). Thin filaments extend from this microvillous membrane into the lumen which constitute the glycocalyx («fuzzy coat»), a barrier which prevents bacterial contact to the microvillous membrane (bottom). The cell membranes of adjacent cells are joined together just below the surface by the junctional complex (arrows). Ruthenium red X 22.100.

pendix, the Paneth cells. The cytoplasmic granules of the goblet cells contain an acid mucus and usually aggregate in the apex («goblet»). All colonic goblet cells would occupy a volume equivalent to that of the exocrine pancreas.

Paneth cells secrete granules rich in lysozyme with marked bacteriolytic properties. Paneth cells may act as stationary phagocytes. They are capable of digesting Hexamita muris trophozoites or spiral microorganisms (*Erlandsen* and *Chase,* 1972 a, b) and may thus control the intestinal flora. There is a normal expression of *HLA-DR-like antigens* by human epithelial cells of the villi in the small intestine and by the epithelium of the colon in chronic inflammatory bowel disease (Fig. 8, *Scott* et al., 1980; *Chiba* et al., 1988). These membranebound glycoproteins are probably involved in antigen recognition and initiation of immune responses (*Bland,* 1988).

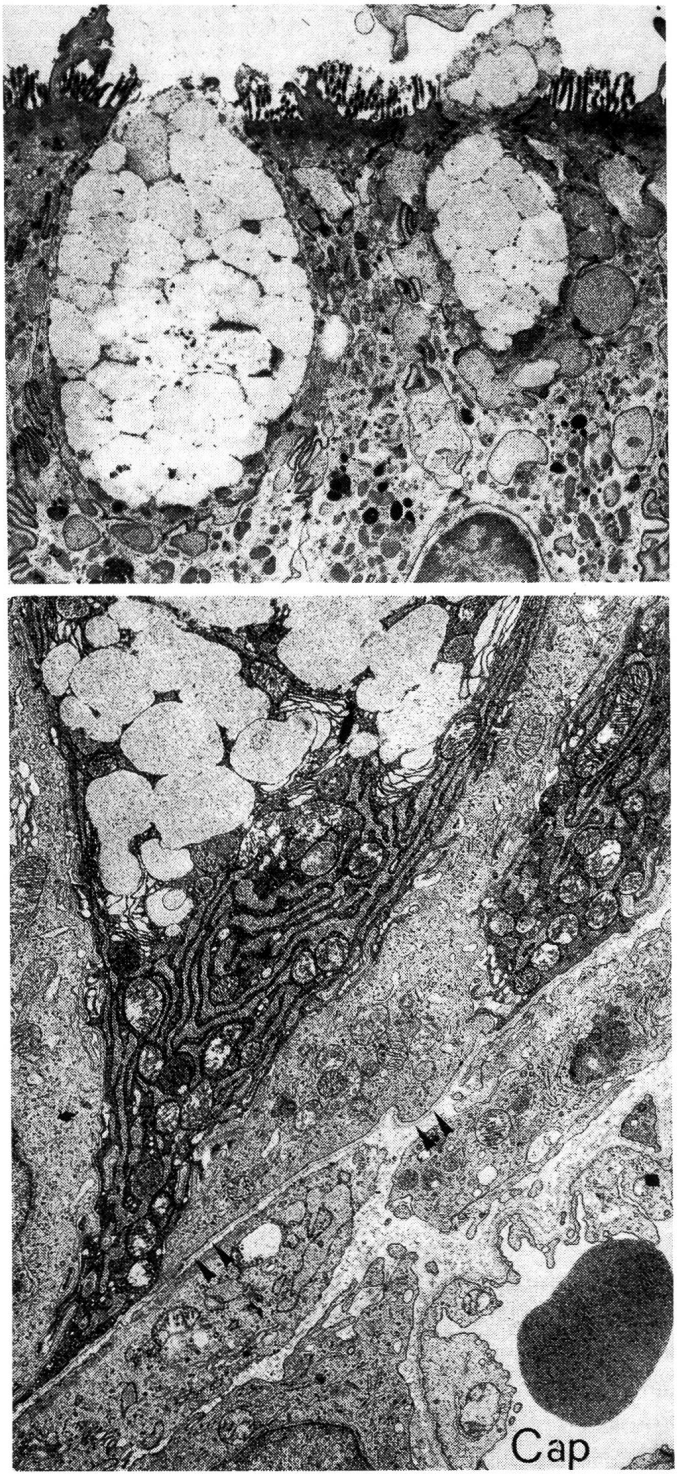

Fig. 7: Electron micrograph of human intestinal goblet cells with prominent basal and lateral rough endoplasmatic reticulum, extensive Golgi complex and apical mucus granules which are released into the intestinal lumen (top). Epithelial basement membrane (arrow heads). Blood capillary (Cap). X 6.350

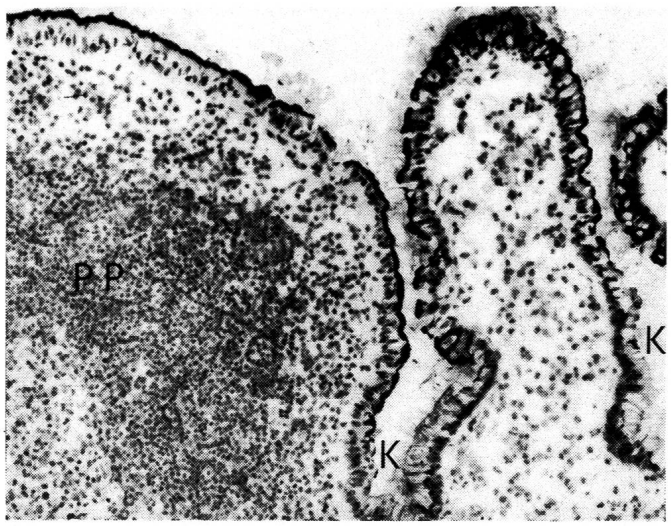

Fig. 8: Immunohistochemical demonstration of HLA-DR antigen on the epithelium of the human small intestine, namely on the follicle-associated epithelium of a Peyer's patch (PP), and on the villous epithelium but not on the crypt epithelium (K). Frozen section, alkaline phosphatase antin-alkaline phosphatase method, x220.

An organ-specific antigen, confined to goblet cells and intestinal glycocalyx (*Roche* et al., 1981), could be involved in autoimmune phenomena of certain chronic inflammatory conditions of the gastrointestinal tract. Circulating antibodies specific for antigens on the surfaces of or adjacent to colonic epithelia are present in up to 60% of patients with ulcerative colitis or granulomatous colitis (*Morbus Crohn;* review: *Gebbers,* 1981).

Kinetics, Functions

Proliferation and regeneration of epithelial cells take place in the deeper parts of the crypts. The different cell types originate from a pluripotent stem cell of the crypt base. The normal rate of cell production in the murine small intestine is about 10^8 cells per day (*Altmann* and *Enesco,* 1967; *Hagemann* et al., 1970). The rate of migration of the epithelial sheet over the villous surface ensures complete replacement of the intestinal lining in approximately 2 to 3 days. Similar estimates have been made in many of species. Renewal time in man has been estimated to be 4 to 6 days (*Weinstein,* 1974). A gradual morphological and functional differentiation occurs during the migration from the surface epithelium to the crypt base. An extrusion zone can be detected at the top of the villi.

Various *exogenous and endogenous regulatory factors* can influence the cell kinetics of the intestinal mucosa (Fig. 9).

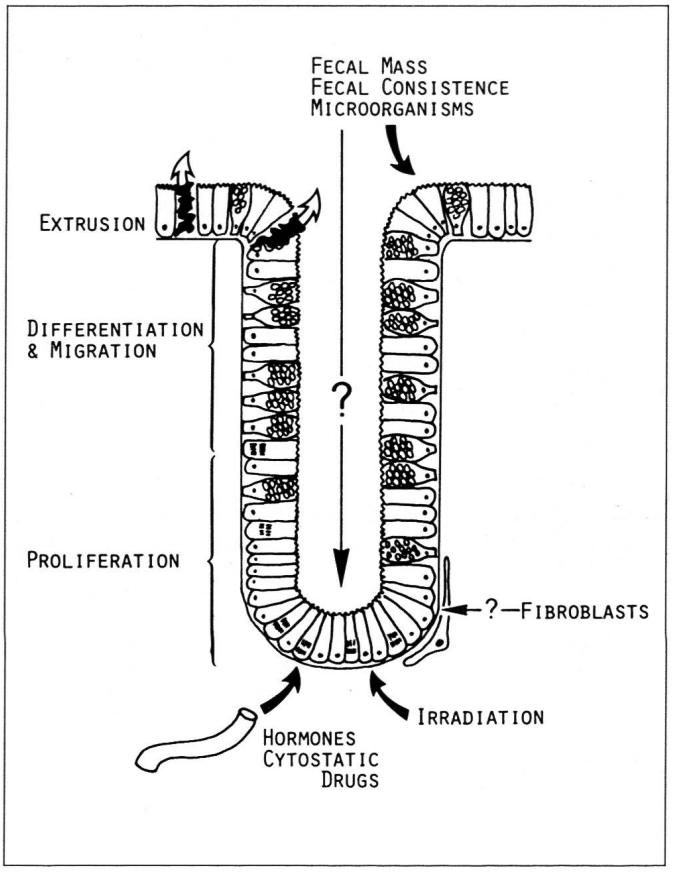

Fig. 9: Factors influencing the epithelial cell kinetics of the intestinal mucosa.

Different *trophic factors* control mucosal growth and atrophy (review: *Diamond* and *Karasov,* 1983). Pregnancy and lactation, both associated with increased caloric requirement and food intake, result in an increased absorptive area in hamsters: Intestinal length, villus height, and mucosal area increase. The intestine responds in a similar way to diabetes mellitus, to increased feeding rates (hyperphagia), and to surgical resection of diseased intestinal segments. In contrast, starvation leads to mucosal atrophy and decreased absorption rates. These effects are not abolished by parenteral nourishment. Much of the trophic response of the intestinal mucosa appears to result from direct effects of luminal contents on the enterocytes. Indirect effects are mediated by hormones, e. g. gastrin, glucagon, enteroglucagon, cholecystokinin, secretin, insulin and prolactin, by pancreatic and biliary secretion, and possibly by nerves (*Diamond* and *Karasov,* 1983).

The epithelial life cycle is significantly shaped by the *microbial status of the intestine.* There are striking differences between the intestine of *germ-free and conventional ani-*

mals. The wall of the small intestine of germ-free animals of many species is thinner and less well hydrated than in conventional counterparts (*Thompson* and *Trexler,* 1971). The intestinal villi of germ-free animals are more slender and longer than those of conventional animals, the epithelia more uniform (*Abrams* et al., 1963), and the total surface area is reduced by about 10 to 30%. In the absence of the bacterial flora the renewal of the epithelium is markedly retarded (*Abrams* et al., 1963). The mitotic index of crypt cells is lower in germ-free than in conventional animals, the generation cycle prolonged, and the pool of proliferating cells smaller. The transit time of epithelial cells moving along the villus is also prolonged in germ-free animals. Germfree animals have fewer lymphocytes, particularly of intraepithelial lymphocytes, plasma cells (particularly IgA-cells; *Crabbe* et al., 1968) in the lamina propria of the gut than conventional animals (*Abrams* et al., 1963). The development of Peyer's patches also depends on the microbial status of the host.

The normal flora may reduce several *absorptive functions* of the gut (*Ford* and *Coates,* 1971; *Reddy* et al., 1969).

THE IMPERFECT BARRIER: ANTIGEN UPTAKE

Most potential food antigens are broken down before absorption. The bulk of luminal contents flows through the center of the gut. Thus, most potential antigens in the gut lumen never reach the mucosa. However, a permanent uptake of macromolecules, mostly derived from food and from the gut flora, takes place. Although this amount of antigens is proportionately small, it may initiate immune responses. The HLA-DR-like antigens expressed by the human gut epithelia (Fig. 8) may play a role for the presentation of foreign antigens to the local immune system by the epithelial cells (*Bjerke* and *Brandtzaeg,* 1988; *Bland,* 1988; *Natali* et al., 1981; *Scott* et al., 1980).

The *uptake of intestinal contents* has also been studied by use of particles. Ingested latex (*LeFevre* et al., 1978) or carbon particles (*Joel* et al., 1978) gradually accumulate in the lymphatic follicles of Peyer's patches. Later, these particles appear in draining lymph nodes and lymphoid collections elsewhere in the body. Large molecules and particulate matter travel across the apical epithelium to the baso-lateral interepithelial space, then across the gaps in the intestinal epithelial basement membrane. The macromolecules may be taken up by local macrophages. They gain access to local lymph nodes or directly to the blood capillaries. The *macromolecules may penetrate through* I) the lamina epithelialis at particular sites (see below); II) intercellular tight junctions because of cellular breakdown. This may occur in malnutrition or under the influence of alcohol; III) and at the tip of the villi through the major cellular extrusion zones. The extent to which particulate matter crosses the villous epithelium is not well-known. Starch particles (*Volkheimer* and *Schulz,* 1968) and even asbestos (*Cook* and *Olson,* 1979) may cross the intestinal epithelium, reach the systemic circulation and appear in the urine.

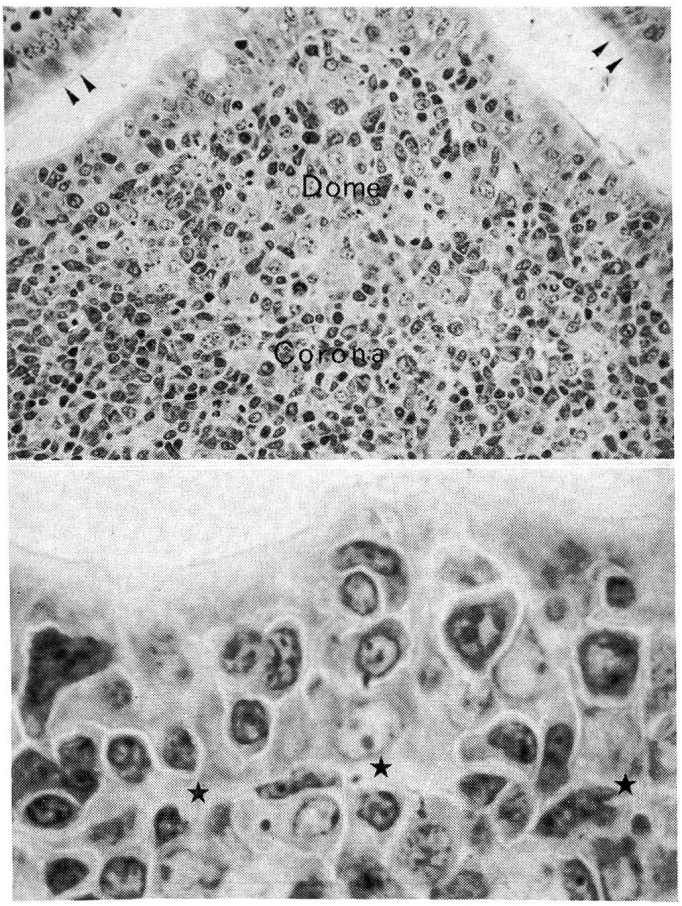

Fig. 10: Photomicrographs of the follicle-associated epithelium covering the dome area of a murine Peyer's patch. Top: The nuclei of the follicle-associated epithelium can be seen in various levels, whereas nuclei of the villous epithelium (arrow heads) are typically located at the base of the cells. Dome area with lymphocytes, macrophages, and some plasma cells. Bottom: Higher magnification showing many intraepithelial lymphocytes. Epithelial basement membrane (asterisks). Semithin sections, toluidine blue, Top: X 520; bottom: X 890.

The *main site for the uptake of macromolecules* is the epithelium overlying aggregated (Peyer's patches, appendix vermiformis) or solitary lymphatic follicles (Fig. 10). The

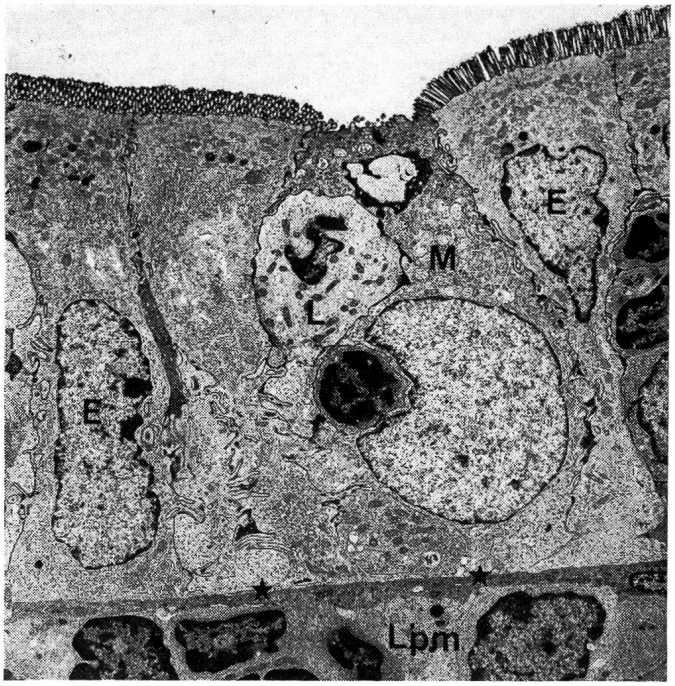

Fig. 11: Electron micrograph of M (membranous) cells (M) with short and irregular microvilli in the follicle-associated epithelium of a murine Peyer's patch. Underneath the M cell are intraepithelial lymphocytes (L) associated with the M cells. X 8.300.

follicle-associated epithelium has a sheet of columnar epithelial cells with interspersed *«membranous» (M) epithelial cells* (*Owen* and *Jones,* 1974; *Owen,* 1977). The surface membrane of these M cells has not microvilli, but many small projecting folds, microfolds (Fig. 11, 12). They contain few if any lysosomes (*Owen* et al., 1981). The M cells attach to regular absorptive cells by tight junctions and form a lattice work with many interstitial intraepithelial lymphocytes. M cells are instrumental for the transepithelial transport of potentially antigenic material, such as horseradish peroxidase (*Owen,* 1977; *Ducroc* et al., 1983; *Keljo* and *Hamilton,* 1983) or carbon particles (*Joel* et al., 1978; Fig. 12). The M cell is an ideal gateway for the presentation of enteric antigens to the cells of the immune system. A similar mechanism exists in the bronchus-associated lymphatic tissue and in the bursa of the chicken cloaca (*Bienenstock* et al., 1976). Human M cells have been demonstrated in the appendix vermiformis (*Bockman* and *Cooper,* 1975) and in Peyer's patches (*Owen* and *Jones,* 1974). Many, if not all, M cells probably derive from undifferentiated crypt cells (*Bye* et al., 1984).

Other absorptive cells may take up small particles by pinocytosis and shuttle them into phagolysosomes, where they are degraded and destroyed (antigen degradation). In experiments with isolated intestinal loops, certain antigens elicit specific secretory antibody only when introduced into loops containing Peyer's patches (*Cebra* et al., 1977). The function of solitary lymphatic follicles may be similar to that of Peyer's patches (*Keren* et al., 1978).

Are M cells channels for infection? The follicle-associated epithelium, in particular the M cell, is a weak link in the mucosal barrier (Fig. 13, 14). The M cells are not common sites of microbial penetration (*Owen* and *Nemanic,* 1978). However, they may endocytize noninvasive Vibrio cholerae in the rabbit (*Owen* et al., 1982). M cells provide specific routes of entry for reoviruses from the intestinal tract into the systemic circulation (*Wolf* et al., 1981; 1983). The protozoan Giardia lamblia penetrates through gaps in the Peyer's patch epithelium (*Owen,* 1982). The gaps may be due to rupture of M cells distended by intraepithelial lymphocytes. In Crohn's disease, ulcerations in the vicinity of M cells in Peyer's patches in an otherwise apparently unaffected intestinal epithelium suggest that penetration of an unknown antigen may result in a harmful hyperstimulation of the local immune system and to harmful effects (*Gebbers* and *Otto,* 1981; 1985).

The uptake of antigens is age-dependent. In the premature infants, more alimentary antigens appear to be absorbed than in older infants and in adults. In pigs, calves and some small animals (rodents), specific or non-specific, energy dependent transport systems mediate the uptake of macromolecules by columnar epithelia during the postnatal period. Some animals, e. g. calves, pig etc., are agammaglobulinemic at birth and obtain their first antibodies passively through a Fc receptor-associated postnatal uptake. Antigen-IgG complexes traverse the gut epithelium of neonatal rats, a capacity formerly attributed only to maternal antibodies (*Abrahamson* et al., 1979). A selective transport of IgG-antigen complexes across the intestine may influence the development of systemic immunity and tolerance in the newborn. The factors which govern *«closure»* of the intestinal transport system are not completely understood. Hormonal factors are involved; cortisone may accelerate the closure (*Morris* and *Morris,* 1976). In fact, significantly less bovine serum albumin fed to infant rabbits remaines antigenically intact in the serum of breast-fed rabbits than in bottle-fed animals (*Udall* and *Walker,* 1982). Antibodies present in the breast milk may limit the uptake of macromolecules.

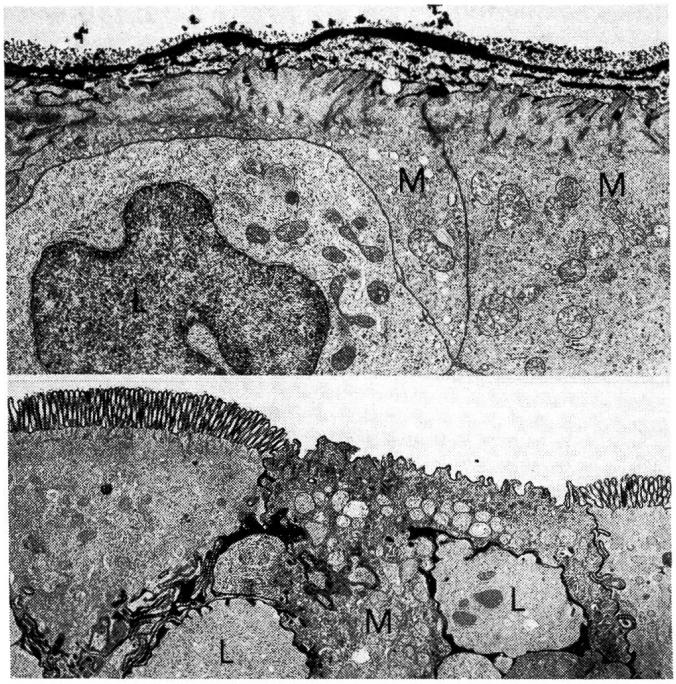

Fig. 12: Electronmicrographs of murine M cells after intraluminal instillation and sequential uptake of horseradish peroxidase (black reaction products). Top: 10 min after instillation, the reaction products cover the microvilli of the M cells and is seen in intermicrovillous pits. Note the numerous «empty» cytoplasmic vacuoles of the M cells. Bottom: One hour after instillation, the reaction products are seen in some cytoplasmic vesicles of the M cell (M) and in the epithelial interstices around lymphocytes (L). 3.3'-diaminobenzidine tetrachloride, H_2O_2. Top: X 11.400; bottom: X 8.100.

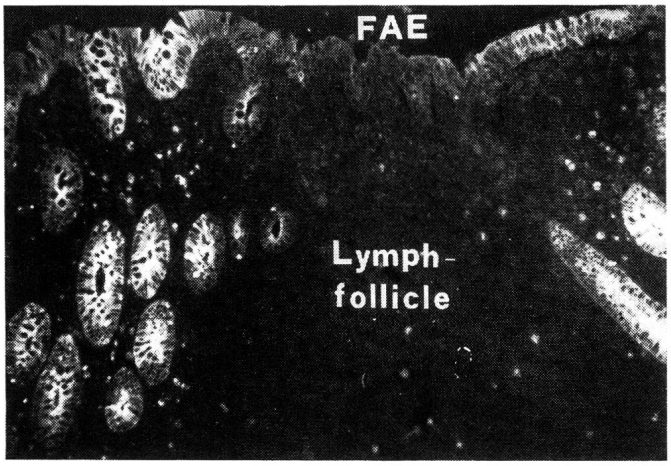

Fig. 13: Immunohistochemical demonstration of secretory IgA in the crypt and surface epithelium of the human colon. Note the absence of sIgA in the follicle associated epithelium (FAE). Indirect immunofluorescence, X 220.

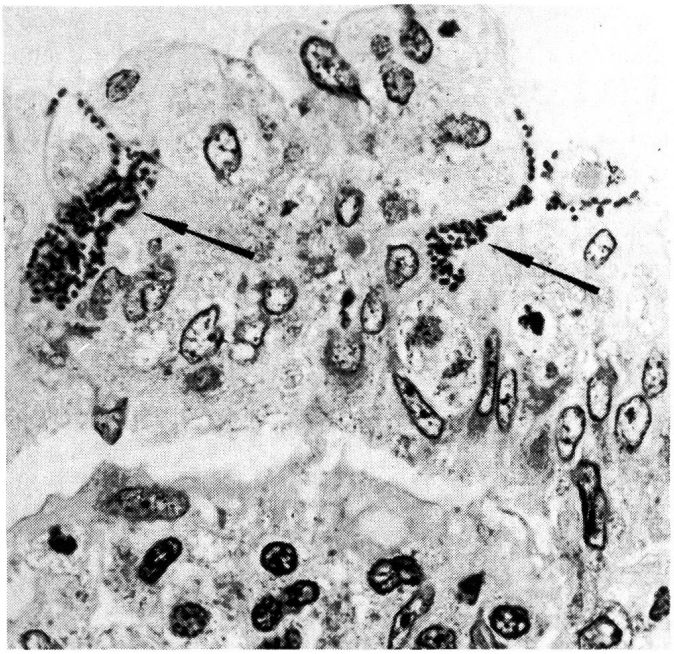

Fig. 14: Photomicrograph. Follicle-associated epithelium with bacteria in the human appendix vermiformis. Semithin section, Giemsa. X 750.

Studies on the intestinal uptake of 1.8 μm particles in young (24 days) and aged (18 months) mice indicated that aged mice exhibited significant more particle accumulation in Peyer's patches than young mice (*LeFevre* et al., 1989).

IgA-class antibodies present in the mucosa or at its surface *reduce antigen absorption* (*Lim* and *Rowley,* 1982; *Swarbrick* et al., 1979; *Walker* and *Isselbacher,* 1977). Persons suffering from a selective IgA deficiency absorb more antigens, and hence develop greater immune responses against dietary antigens than normal adults (*Cunningham-Rundles* et al., 1978). The mechanisms are poorly understood. Antigen complexed with IgA and trapped at the enterocyte surface might be more susceptible to degradation by pancreatic enzymes (*Bienenstock* and *Befus,* 1983).

The transport is bidirectional: The intestinal epithelium is able to excrete substances of high molecular weight into the intestinal lumen (Fig. 15). Three routes exist within the villus: between the cells, through the cells, or at the cell extrusion zone (*Dobbins,* 1975). Since both albumin and peroxidase can be taken up at the lateral membrane of the epithelial cell, presumably by pinocytosis, analogous substances of high molecular weight might be excreted via the same route or by extrusion together with epithelial cells. The follicle-associated epithelium thus efficiently transports macromolecules in both directions (*Bockmann* and

Stevens, 1977). Tubular vesicles within the enterocyte mediate the transport of macromolecules (*Rodewald*, 1980).

MUCOSAL LAMINA PROPRIA

The mucosal epithelium is intimately associated with an equally dynamic *mesenchymal component,* the lamina propria. Stromal cells, fibroblasts in particular, are closely involved in epithelial differentiation during normal development, and in maintaining the differentiated phenotype of epithelial cells in adult tissues (*Durnberger* et al., 1978; *McLoughlin,* 1961; *Ozzello,* 1970). Fibroblasts adjacent to the intestinal epithelium accompany the migrating epithelium from the crypt to villus (*Marsh* and *Trier,* 1974).

The plasma cells, lymphocytes, macrophages, eosinophilic granulocytes, mast cells, the solitary and the aggregated lymphatic follicles constitute a *diffuse lymphoid organ* that belongs to the intestinal immune system (Table).

Lymphocytes are often found in the interstitial spaces of the epithelium (Fig. 15, 16). The epithelium contains as many lymphocytes as does the spleen. *Intraepithelial lymphocytes* are functionally competent cells, and not merely senescent cells (*Arnaud-Battandier* et al., 1978). In mice, the intraepithelial lymphocytes are mainly T cells (*Guy-Grand* et al., 1978). In the human intestinal mucosa, most intraepithelial lymphocytes appear to be T cells capable of cytotoxic or suppressor functions. Their secretion products (lymphokines) may have several effects on the epithelium (*Castro,* 1982). Intraepithelial lymphocytes and spleen cells, but not bone marrow cells, are able to secrete a factor capable of inducing Ia antigen expression on rat intestinal epithelia *in vitro* (*Cerf-Bensussan* et al., 1984). Possibly, the lymphocytes migrate into the crypt epithelium and reach the surface epithelium while being activated (Fig. 17). T-lymphocytes returning to the lamina propria of the bowel may suppress IgG-production, while they stimulate IgA-synthesis by mucosal cells (*Elson* et al., 1979; *Swarbrick* et al., 1979; *Brandtzaeg* et al., 1988).

Table

Intestinal immune system in man Cellular and structural elements
Lymphocytes in: epithelium, lamina propria, follicles Plasma cells Macrophages, mast cells, granulocytes
Solitary lymph follicles Peyer's patches Appendix vermiformis Mesenteric lymph nodes

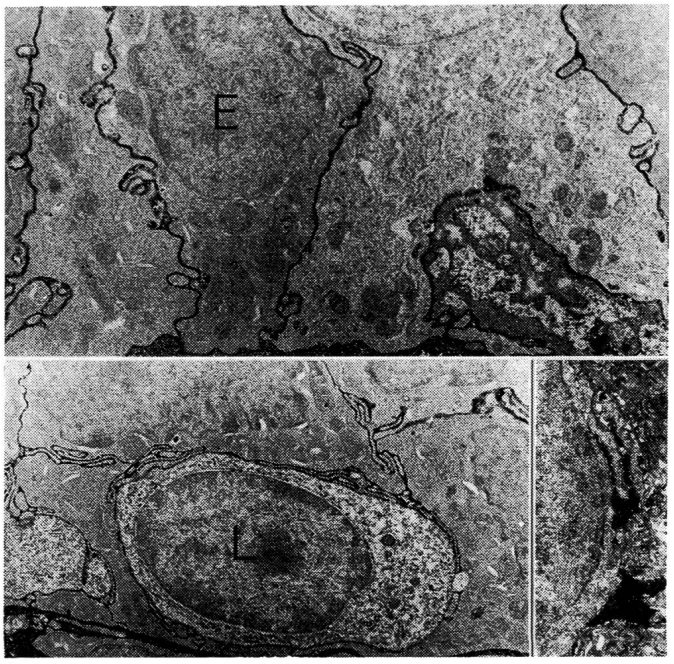

Fig. 15: Electron micrographs. Experiment demonstrating the bidirectional transport in the murine gut epithelium. Thirty minutes after the intravenous application of horseradish peroxidase the black reaction products can be seen in the lamina propria and in the epithelial interstices of the jejunum (top) and of the colon (bottom). E = enterocyte. L = intraepithelial lymphocyte.
3.3'-diaminobenzidine tetrachloride, H_2O_2. X 10.800 Inset: Intraepithelial lymphocyte with reaction products. X 17.800.

Recent investigation of the T-cell receptors particularly of the intraepithelial lymphocytes and their relationship to the epithelium have led to new concepts of their function. The expression of CD8 on γ/δ-intraepithelial lymphocytes strongly suggests that these cells will be specific for class I MHC molecules, as CD8 expression is associated with class I MHC recognition, and isolated CD8 binds class I MHC molecules. The γ/δ T-cell recognition of autologous class IB MHC molecules expressed by epithelial-cells under conditions of stress might be an effective if seemingly primitive means of epithelial defense. This recognition event should lead to killing of the epithelial cell (Fig. 16, *Goodman* and *Lefrancoise,* 1988). This form of defense at the immunological frontiers, outside the epithelial base-

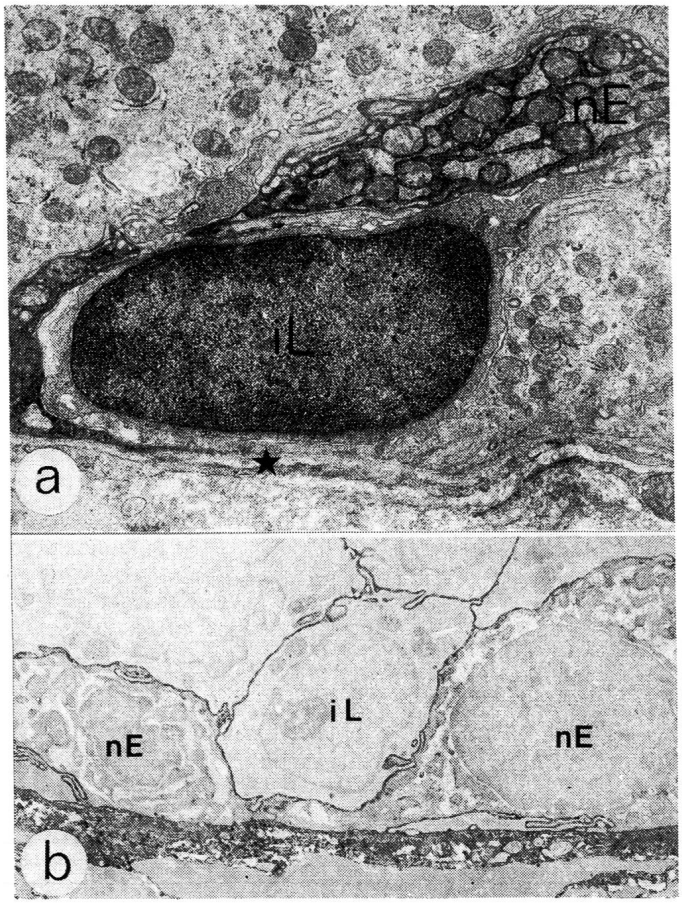

Fig. 16: Electron micrographs of the colonic mucosa in ulcerative colitis: Intraepithelial lymphocytes (iL) typically situated near the epithelial basement membrane (*) adjacent to necrotic epithelial cells (nE). The interstitial space is «stained» in vitro by exogenous peroxidase. a: X 18 000, b: 15 800

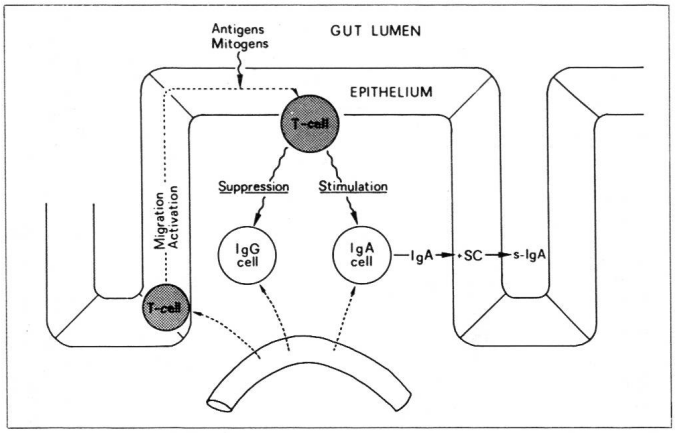

Fig. 17: Migratory pathway and functions of the intraepithelial lymphocytes of the intestine (hypothesis).

ment membranes, could be highly effective. Epithelia that lose a cell or two rapidly cover such lesions by migration of healthy cells into open area. As long as an infected or a transformed cell is killed before spread across the basement membrane can occur, neither infection nor malignancy can ensue (*Janeway,* 1988). It is tempting to speculate that this present-day frontier is also the site in which cell-mediated immunity originated, and that this «new» component of the immune system is actually the oldest.

There are many *T and B lymphocytes* in different states of activation distributed *in the lamina propria.* Most of the T cells have surface characteristics of helper or inducer cells.

About 90% of the intestinal *plasma cells* normally produce and secrete dimeric IgA (Fig. 18). Upon secretion, IgA penetrates into the epithelia, where it is bound to the secretory component and extruded as *secretory IgA.* The *secretory component* is synthesized by epithelial cells. It protects the IgA-molecules in the gut lumen against degradation by enzymes and toxins (*Brandtzaeg,* 1983; *Brandtzaeg* and *Prydz,* 1984).

The *migrational pathways of enteric immunocytes* are intricate. The intestinal IgA-cells are primed in the *Peyer's* patches, possibly to some extent also in the solitary lymphatic follicles. The maturing cells migrate into the thoracic duct via the mesenteric lymph nodes (Fig. 19). Having reached the systemic circulation, they return to the gut mucosa as IgA-secreting plasma cells or their immediate precursors (*Hall,* 1979; *Bienenstock* and *Befus,* 1980). This journey from the gut-associated lymphoid tissue back to the gut lamina propria takes about 4 to 6 days (*Hall,* 1979). However, many of the mature IgA-precursor cells may also home to the connective tissue of other secretory structures such as mammary glands, salivary glands, bronchial tissue and of the genitourinary tract and constitute «a common mucosal immune system» (*Bienenstock* et al., 1978).

The tissue specific homing of blood-borne lymphocytes is regulated by interactions with the endothelium of specialized venules in organized lymph nodes and mucosal lymphoid tissues. Recently, a «vascular addressin» in the mouse has been identified as a tissue-specific endothelial-adhesion molecule for lymphocytes, and it has been concluded that it could regulate lymphocyte traffic into the mucosal tissues by mediating attachment of blood-borne cells to the endothelium (*Nakache* et al., 1989).

Clusters of *macrophages* with morphological signs of increased activity are found under the surface epithelium (Fig. 20). There are no macrophages within the epithelial layer. However, cytoplasmatic extensions often reach into

Fig. 18: Immunohystochemical demonstration of IgA in the human colonic mucosa in numerous plasma cells of the lamina propria, and in the epithelium. Indirect immunofluorescence, X 330

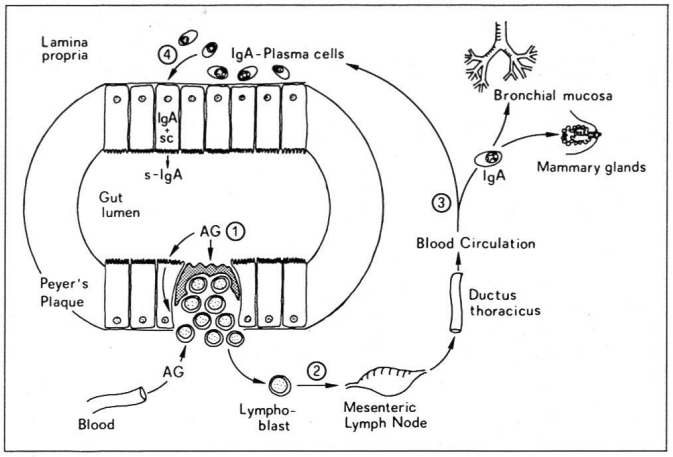

Fig. 19: Stimulation and circulation of intestinal IgA cells.
1. Uptake of luminal antigen (AG) through the dome-epithelium of *Peyer's* patches.
2. Migratory pathway of maturing lymphoblasts through mesenteric lymph node, and thoracic duct into the systemic circulation.
3. IgA cells or their immediate precursors home to the gut mucosa (and to mammary glands or bronchial mucosa) where they secrete IgA in response to antigenic stimulation (4).

the epithelial interstices where they contact intraepithelial lymphocytes. This could express a functional interaction. Ingested carbon particles cross the epithelium of Peyer's patches in mice and appear in subepithelial macrophages (*Joel* et al., 1978). Later, carbon-laden macrophages were present in all areas of Peyer's patches. Approximately eight days elapsed between gavage and appearance of carbon-laden macrophages in germinal centers. Carbon was evident in Peyer's patches and mesenteric lymph nodes four months after cessation of carbon ingestion. The mobility of macrophages was thought to play a role in this distribution. Solitary lymphatic follicles along the intestine handled the carbon in a manner similar to the follicles aggregated in Peyer's patches. Through phagocytosis, interaction with lymphocytes, production of lysozyme and other substances, macrophages contribute to the intestinal mucosal block.

GUT-ASSOCIATED LYMPHOID TISSUE (GALT)

The *Galt* consists of distinct aggregates of lymphoid cells located in the intestinal mucosa and submucosa, in Peyer's patches, appendix vermiformis, solitary lymphatic follicles, and of the mesenteric lymph nodes. Together with the diffusely scattered mucosal lymphocytes and plasma cells, the *Galt* forms the intestinal immune system (table). *Peyer's patches* occur in the antimesenteric part of the whole mammalian small intestine (*Peyer*, 1677). They are white, oval to rectangular, slightly raised aggregates of at least five lymphatic follicles of variable size (maximum length: 28 cm; *Cornes,* 1965). Peyer's patches are usually larger and more abundant in the ileum, but they do occur in the duodenum and jejunum as well.

In humans, the number of patches and follicles *changes with age.* The average number of patches increases from about sixty at 24 to 29 weeks of gestation to about 240 at the age of 12 to 14 years, and it decreases to about 100 in persons of more than seventy years of age (*Cornes,* 1965).

Histologically, the nuclei of the flat follicle-associated epi-

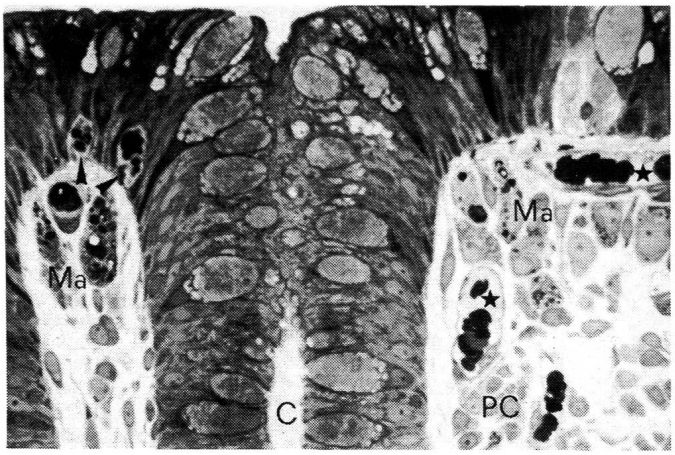

Fig. 20: Photomicrograph of the upper parts of the human colonic mucosa. Subepithelial macrophage clusters (Ma), cytoplasmic projections of macrophages into the epithelial interstice (arrow heads), and plasma cell cluster (PC). * = capillary, C = crypt. Semithin section, toluidin blue. X 660.

thelium are located at various distances from the basement membrane, whereas those of the villous epithelium are located at the base of the cells (Fig. 10). The follicle-associated epithelium has few goblet cells, contains specialized M cells and many lymphocytes (Fig. 10–12). The typical lymphatic follicle, situated below the associated epithelium, contains three zones (Fig. 10, 21): I) A *dome region* with an associated corona is located immediately beneath the epithelium. The dome contains many large or medium-sized lymphocytes, few small lymphocytes and plasma cells, and many macrophages that contain debris, lipofuscin-like material and, in certain species, bacterial remnants. The corona surrounds II) a large *germinal center* and separates the follicle from the surrounding interfollicular area. The structure of the germinal center (*Sminia* et al., 1982) and its proliferative activity (*Faulk* et al., 1971) resemble to that of germinal centers in other lymphoid organs. III) The *thymus-dependent area* because it contains mainly small T lymphocytes clustered between large follicles (*Joel* et al., 1972; Fig. 21). In addition, there are Ia-positive, interdigitating cells (*Sminia* et al., 1982), and many venules with a tall endothelium. They correspond to the postcapillary venules in lymph nodes, important sites for the migration of lymphocytes into tissues. *Plasma cells* are mainly present in the dome region and within the dome epithelium (Fig. 10).

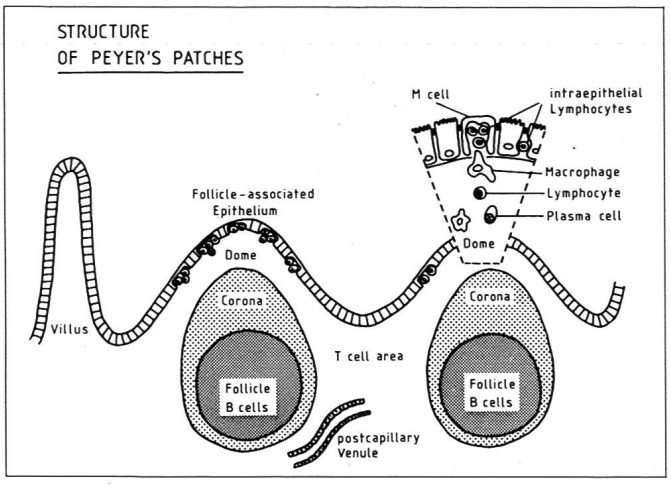

Fig. 21: Structure of Peyer's patches (see text).

Solitary lymphatic follicles abound throughout the intestinal tract, particularly in the colon and rectum, with an average of 3 to 4 follicles per square centimeter in the large intestine (*Dukes* and *Bussey,* 1926). They have a diameter of 0.5 to 1.0 mm (Fig. 22). A germinal center may be present. The associated epithelium contains M cells (*Rosner* and *Keren,* 1984). Solitary lymphatic follicles are presumably structural and possibly functional equivalents of Peyer's patches (*McDermott* et al., 1980; *Keren* et al., 1978; *Rosner* and *Keren,* 1984).

Mesenteric lymph nodes receive the lymph from the small and large intestine in humans. The lymphatics run along the mesenteric arteries. Mesenteric lymph nodes have many lymphoblasts precommitted to IgA synthesis (*McWilliams* et al., 1977).

The *appendix vermiformis* of man is a blind tubular protrusion of the cecum that measures 5 to 10 mm wide and 2 to

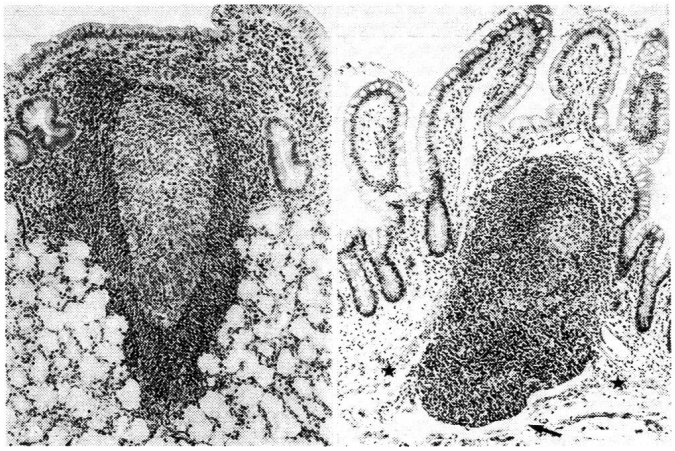

Fig. 22: Photomicrographs of solitary lymphatic follicles with germinal centers and lymph sinus (arrow) in the human intestinal mucosa (lamina muscularis mucosae with asterisks). Left: Duodenum. Right: Ileum. X 120.

20 cm long. It has mostly been regarded as a purely vestigial organ. This assumption is based on its small size and lack of digestive function. This is in contrast to the enormous cecum and appendix of the rabbit or of small rodents, where cellulose is broken down into carbohydrates by bacterial action. However, *Berry* (1900) found that the lymphoid tissue of the large intestine tends to aggregate in a specially differentiated part of the cecum, the vermiform appendix, as a species ascends on the scale of vertebrates. In primate *phylogenesis,* the length of the appendix progressively increases as the cecum shrinks in relation to the total colon length. An appendix began to develop in certain Old World Monkeys and grew to full size in anthropoid apes; far from being a vestigial organ, its progressive enlargement during primate phylogenesis suggests a functional role (*Scott,* 1980).

The *structure* – and probably the function – of the lymphatic follicles in the appendix, and of their associated epithelium, are similar to those of Peyer's patch (Fig. 10–14). The *appendix of the newborn* contains very few small lymphatic follicles without germinal centers (Fig. 23). Mature plasma cells are absent. The epithelial cells contain secretory component but no IgA. Germinal centers are not detected until the 4th week of postnatal life. Mature plasma cells appear earlier than germinal centers, and contain mainly IgM and IgA (Fig. 24).

There are signs of IgM secretion through the epithelium in the first two months. Thereafter, the number of IgM cells decreases while that of IgG cells increases (Fig. 24). Thus, the distribution of the main plasma cell classes in the *adult appendix vermiformis* differs from that in the other intestinal mucosa by a higher proportion of IgG (35 to 40%) and a constant proportion of IgE (2 to 3%), while IgA cells constitute 50 to 60%, and IgM cells about 10% of the plasma cell population, respectively (Fig. 24). Mucosal volume, plasma

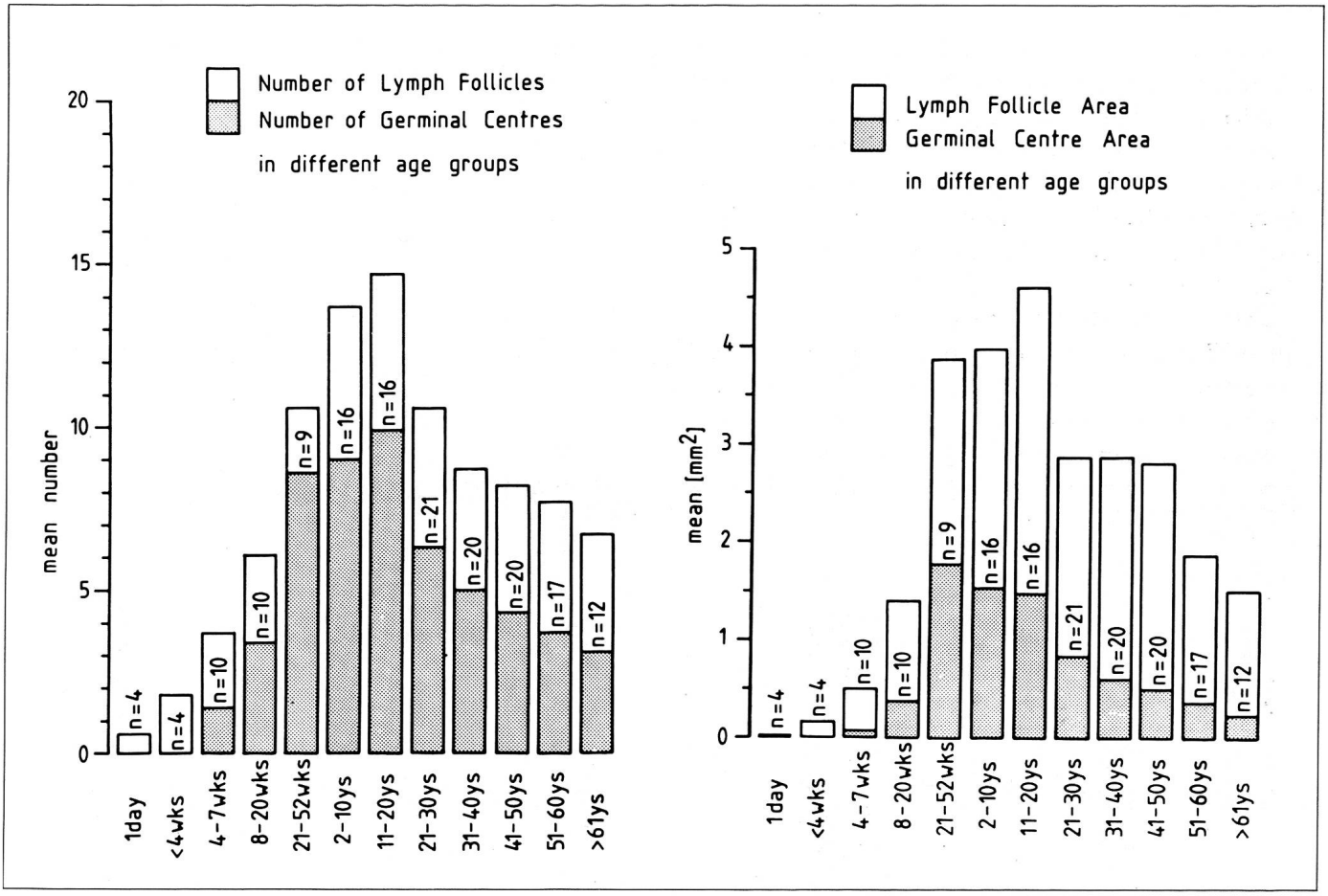

Fig. 23: The lymphatic parenchyma of the human appendix vermiformis.
Left: Number of lymphatic follicles and germinal centers per cross section (mean values) versus age.
Right: Areas of lymphatic follicles and germinal centers per cross section (mean values) versus age.

cell density, number and size of lymphatic follicles and germinal centers remain nearly constant until the old age (Fig. 23). Nor does the average number of solitary lymphatic follicles in the intestine of humans obviously decrease in old age (*Dukes* and *Bussey,* 1926). These findings contrast with the reduction of the peripheral lymphoid tissue in other organs in aging individuals. The *Galt* system may thus differ from its systemic counterpart.

REFERENCES

Abrahamson D. R., Powers A., Rodewald R. (1979): Intestinal absorption of immune complexes by neonatal rats: A route of antigen transfer from mother to young. Science *206*, 567–569. – *Abrams G. D., Bauer H., Sprinz H.* (1963): Influence of the normal flora on mucosal morphology and cellular renewal in the ileum. A comparition of germfree and conventional mice. Lab. Invest. *12*, 355–363. – *Altmann G. G., Enesco M.* (1967): Cell number as a measure of distribution and renewal of epithelial cells in the small intestine of growing and adult rats. Am. J. Anat. *121*, 319–324. – *Arnaud-Battandier F., Bundy B. M., O'Neill M., Bienenstock J., Nelson D.L.* (1978): Cytotoxic activities of gut mucosal lymphoid cells in guinea pigs. J. Immunol. *121*, 1059–1065. – *Berry R. J. A.* (1900): The true caecal apex, or the vermiform appedix: Its minute and comparative anatomy. J. Anat. Physiol. *35*, 83–98. – *Bhalla D. K., Owen R. L.* (1982): Cell renewal and migration in lymphoid follicles of Peyer's patches and cecum – an autoradiographic study in mice. Gastroenterology *82*, 232–242. – *Bienenstock J., Johnston N.* (1976): A morphologic study of rabbit bronchial lymphoid aggregates and lymphoepithelium. Lab. Invest. *35*, 343–351. – *Bienenstock J., Befus A. D.* (1980): Mucosal immunology. A review. Immunology *41*, 249–270. – *Bienenstock J., Befus A. D.* (1983): Some thoughts on the biologic role of immunoglobulin A. Gastroenterology *84*, 178–185. – *Bienenstock J., McDermott M. R., Befus A. D., O'Neill M.* (1978): A common mucosal immunologic system involving the bronchus, breast and bowel. In: *J. R.*

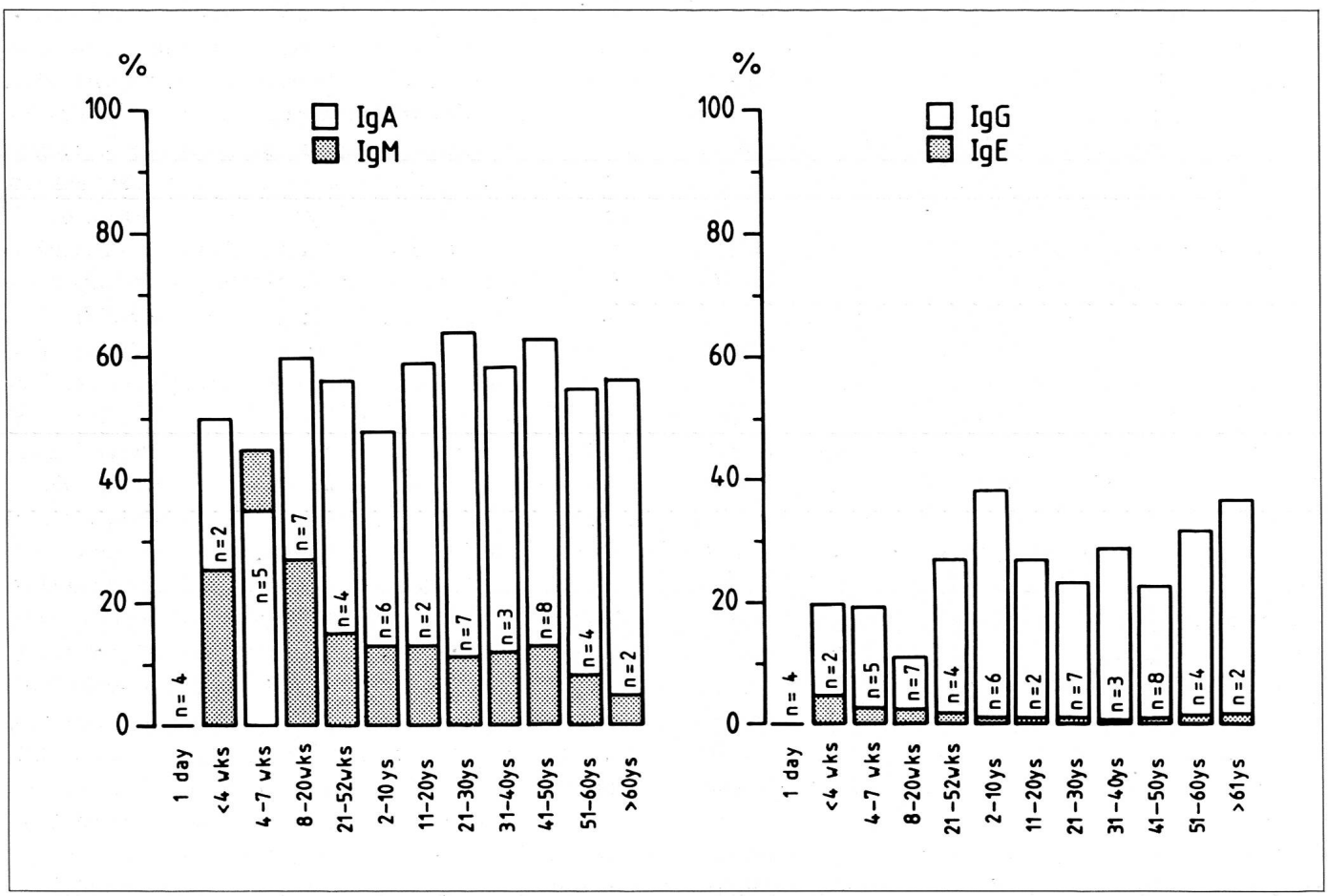

Fig. 24: The lymphatic parenchyma of the human appendix vermiformis: Distribution of the main immunoglobulin classes of the mucosal plasma cells versus age.

McGhee, J. Mestecky, J. L. Babb (edit.) Secretory Immunity and Infection. pp *53–66*. Plenum Press, New York. – *Bjerke K., Brandtzaeg P.* (1988): Lack of relation between expression of HLA-DR and secretory component (SC) in follicle-associated epithelium of human Peyer's patches. Clin. exp. Immunol. *71*, 502–507. – *Bland P.* (1988): MHC class II expression by the gut epithelium. Immunol. today *9*, 174–178. – *Bockman D. E., Cooper M. D.* (1975): Early lymphoepithelial relationships in the human appendix. A combined light-and electron-microscopic study. Gastroenterology *68*, 1160–1168. – *Bockman D. E., Boydston W. R., Beezhold D. H.* (1983): The role of epithelial cells in gut-associated immune reactivity. In: McGhee J. R., Mestecky J. (eds) The Secretory Immune System. Ann. New York Acad. Sci. *409*, 129–144. – *Bockman D. E., Stevens W.* (1977): Gut-associated lymphoid tissue: Bidirectional transport of tracer by specialized epithelial cells associated with lymphoid follicles. J. Reticuloendothel. Soc. *21*, 245–254. – *Brandtzaeg P.* (1983): Immunohistochemical characterization of intracellular J-chain and binding site for secretory component (SC) in human immunoglobulin (Ig)-producing cells. Mol. Immunol. *20*, 941–966. – *Brandtzaeg P., Prydz H.* (1984): Direct evidence for an integrated function of J- chain and secretory component in epithelial transport of immunoglobulins. Nature *311*, 71–73. – *Brandtzaeg P., Sollid L. M., Thrane P. S., Kvale D., Bjerke K., Scott H., Kett K., Rognum T. O.* (1988): Progress report: Lymphoepithelial interaction in the mucosal immune system. Gut *29*, 1116–1130. – *Bye W. A., Allan C. H., Trier J. S.* (1984): Structure, distribution, and origin of M cells in peyer's patches of mouse ileum. Gastroenterology *86*, 789–801. – *Castro G. A.* (1982): Immunological regulation of epithelial function. Am. J. Physiol. *243*, G321–G329. – *Chiba M., Iizuka M., Masamune O.* (1988): Ubiquitous expression of HLA-DR antigens on human small intestinal epithelium. Gastroent. Jap. *23*, 109–116. – *Cebra J. J., Kamat R., Gearhart P., Robertson S. M., Tseng J.* (1977): The secretory IgA system of the gut. Ciba Foundation Symposium 46 (new series). pp *5–28* Elsevier, Excerpta Medica, North Holland, Amsterdam - Oxford - New York. – *Cerf-Benussan N., Quaroni A., Kurnick J. T., Bhan A. K.* (1984): Intraepithelial lymphocytes modulate Ia expression by intestinal epithelial cells. J. Immunol. *132*, 2244–2252. – *Clamp J. R.* (1980): Gastrointestinal mucus. In: *R. Wright* (ed) Recent Advances in Gastrointestinal Pathology. pp *47–58*. Saunders, London - Philadelphia - Toronto. – *Cook P. M., Olson G. F.* (1979): Ingested mineral fibers: Elimination in human urine. Science *204*, 195–198. – *Cornes J. S.* (1965): Number, size, and distribution of Peyer's patches in the human small intestine. I. The development of Peyer's patches. Gut *6*, 225–229. – *Crabbé P. A., Bazin H., Eyssen H., Heremans J. F.* (1968): The normal microbial flora as a major stimulus for proliferation of plasma cells synthesizing IgA in the gut. The germfree intestinal tract. Intern. Arch. Allergy. *34*, 362–368. – *Crane R. K.* (1975): A digestive-absorptive surface as illustrated by the intestinal cell brush border. Trans. Amer. Micros. Soc. *94*, 529–544. – *Cunningham-Rundles C., Brandeis W. E., Good R. A., Day N. K.* (1978): Milk precipitins, circulating immune complexes, and IgA deficiency. Proc. Nat. Acad. Sci. USA *75*, 3387–3389. – *Diamond J. M., Karasov W. H.* (1983): Trophic control of the intestinal mucosa. Nature *304*, 18. – *Dickman M. O., Chappelka A. R., Schaedler R. W.* (1976): The microbial ecology of the upper small bowel. Am. J. Gastroent. *65*, 57–62. – *Dobbins W. O.* (1975): Human intestinal epithelium as a biological membrane. In: Trump B. F., Arstila A. U. (eds) Pathobiology of Cell Membranes. pp 441–442. Academic Press New York, San Francisco, London. – *Drenckhahn D., Gröschel-Stewart U.* (1980): Localization of myosin, actin, and tropomyosin in rat intestinal epithelium: Immunohistochemical studies at the light and electron microscopic levels. J. Cell Biol. *86*, 475–482. – *Ducroc R., Heyman M., Beaufrere B., Morgat J. L., Desjeux J. F.* (1983): Horseradish peroxidase transport across rabbit jejunum and Peyer's patches in vitro. Am. J. Physiol. *245*, G54–G58. – *Dukes C., Bussey H. J. R.* (1926): The number of lymphoid follicles of the human large intestine. J. Pathol. Bacteriol. *29*, 111–117. – *Durnberger H., Heuberger B., Schwartz P.* (1978): Mesenchyme mediated effect of testosterone on embryonic mammary epithelium. Cancer Res. *38*, 4066–4070. – *Elson C. O., Heck J. A., Strober W.* (1979): T-cell regulation of murine IgA synthesis. J. Exp. Med. *149*, 632–643. – *Erlandsen S. L., Chase D. G.* (1972a): Paneth cell function: Phagocytosis and intracellular digestion of intestinal microorganisms. I. Hexamita muris. J. Ultrastruct. Res. *41*, 296–318. – *Erlandsen S. L., Chase D. G.* (1972b): Paneth cell function: Phagocytosis and intracellular digestion of intestinal microorganisms: II. Spiral microorganism. J. Ultrastruct. Res. *41*, 319–333. – *Faulk P. W., McCormick J. N., Goodman J. R., Yoffey J. M., Fudenberg H. H.* (1971): Peyer's patches: Morphological studies. Cell. Immunol. *1*, 500–520. – *Filipe M. I.* (1979): Mucins in the human gastrointestinal epithelium: A review. Invest. Cell. Pathol. *2*, 195–216. – *Ford D. J., Coates M. E.* (1971): Absorption of glucose and vitamins of the B complex by germfree and conventional chicks. Proc. Nutr. Soc. *30*, 10A. – *Gebbers J.-O.* (1981): Colitis ulcerosa: Immun- und Ul-

trastrukturpathologie. Thieme, Stuttgart - New York. – *Gebbers J.-O., Otto H. F.* (1973): Das Membranverhalten der interepithelialen Lymphocyten des Darmes. Eine elektronenmikroskopische Untersuchung an Ruthenium-Rot gefärbtem Gewebe. Virchows Arch. A *361*, 175–184. – *Gebbers J.-O., Otto H. F.* (1981): Immuno- and ultracytochemical observations in Crohn's disease. pp 136–145. In: Pena A. S., Weterman I. T., Booth C. C., Strober W. (eds) Recent Advances in Crohn's Disease. Martinus Nijhoff, The Hague, Boston, London. – *Gebbers J.-O., Otto H. F.* (1985): Alterations of the intestinal mucosal block in ulcerative colitis and Crohn's disease – immunological and ultrastructural findings, and considerations of the pathogenesis. Klin. Pädiat. *197*, 341–348. – *Goodman T., Lefrancois L.* (1988): Expression of the γ-δ T-cell receptor on intestinal CD8+ intraepithelial lymphocytes. Nature *333*, 855–857. – *Guy-Grand D., Groscelli C., Vassalli P.* (1978): The mouse gut T lymphocyte. A novel type of T cell. Nature, origin, and traffic in mice in normal and graft-versus-host conditions. J. Exp. Med. *148*, 1661–1677. – *Hagemann R. F., Sigdestad C. P., Lesher S.* (1970): A quantitative description of the intestinal epithelium of the mouse. Am. J. Anat. *129*, 41–49. – *Hall J.* (1979): Lymphocyte recirculation and the gut: The cellular basis of humoral immunity in the intestine. Blood Cells *5*, 479–492. – *Hess M. W., Zimmermann A., Brun del Re G., Cottier H.* (1975): Immunologische Aspekte gastrointestinaler Neoplasien. Schweiz. Med. Wochenschr. *105*, 570–575. – *Hill M. J., Drasar B. S.* (1975): The normal colonic bacterial flora. Gut *16*, 318–323. – *Ito S.* (1965): The enteric surface coat on cat intestinal microvilli. J. Cell Biol. *27*, 475–491. – *Janeway C. A.* (1988): Frontiers of the immune system. Nature *333*, 804–806. – *Joel D. D., Hess M. W., Cottier H.* (1972): Magnitude and pattern of thymic lymphocyte migration in neonatal mice. J. Exp. Med. *135*, 907–923. – *Joel D. D., Laissue J. A., LeFevre M. E.* (1978): Distribution and fate of ingested carbon particles in mice. J. Reticuloendothel. Soc. *24*, 477–487. – *Keljo D. J., Hamilton J. R.* (1983): Quantitative determination of macromolecular transport rate across intestinal Peyer's patches. Am. J. Physiol. *244*, G637–G644. – *Keren D. F., Holt P. S., Collins H. H., Gemski P., Formal S. B.* (1978): The role of Peyer's patches in the local immune response of rabbit ileum to live bacteria. J. Immunol. *120*, 1892–1896. – *Lake A. M., Bloch K. J., Sinclair K. J., Walker W. A.* (1980): Anaphylactic release of intestinal goblet cell mucus. Immunology *39*, 1–6. – *LeFevre M. E., Vanderhoff J. W., Laissue J. A., Joel D. D.* (1978): Accumulation of 2-μm latex particles in mouse Peyer's patches during chronic latex feeding. Experientia *34*, 120–122. – *LeFevre M. E., Boccio A. M., Joel D. D.* (1989): Intestinal uptake of fluorescent microspheres in young and aged mice. Proc. Soc. Exp. Biol. Med. *190*, 23–26. – *Lim P. L., Rowley D.* (1982): The effect of antibody on the intestinal absorption of macromolecules and on intestinal permeability in adult mice. Int. Arch. Allergy Appl. Immun. *68*, 41–46. – *Marsh M. N., Trier J. S.* (1974): Morphology and cellular proliferation of subepithelial fibroblasts in adult mouse jejunum. II. Radioautographic studies. Gastroenterology *67*, 636–642. – *Matsudaira P. T., Burgess D. R.* (1982): Organization of the cross-filaments in intestinal microvilli. J. Cell Biol. *92*, 657–664. – *McDermott M. R., O'Neill M. J., Bienenstock J.* (1980): Selective localization of lymphoblasts prepared from guinea pig intestinal lamina propria. Cell. Immunol. *51*, 345–348. – *McLoughlin C. B.* (1961): The importance of mesenchymal factors in the differentiation of the chick epidermis. II. Modification of the epidermal differentiation by contact with different types of mesenchyme. J. Embryol. Exp. Morphol. *9*, 385–409. – *McWilliams M., Phillips-Quagliata J. M., Lamm M. E.* (1977): Mesenteric lymph node B lymphoblasts which home to the small intestine are precommitted to IgA synthesis. J. Exp. Med. *145*, 866–872. – *Morris B., Morris R.* (1976): The effects of corticosterone and cortisone on the uptake of polyvinyl pyrrolidone and the transmission of immunoglobulin G by the small intestine in young rats. J. Physiol. *254*, 389–403. – *Nakache M., Berg E. L., Streeter P. R., Butcher E.* (1989): The mucosal vascular addressin is a tissue-specific endothelial cell adhesion molecule for circulating lymphocytes. Nature *337*, 179–181. – *Natali P. G., DeMartino C., Quaranta V., Nicotra M. R., Frezza F., Pellegrino M. A., Ferrone S.* (1981): Expression of Ia-like antigens in normal human nonlymphoid tissues. Transplantation *31*, 75–78. – *Nimmerfall F., Rosenthaler J.* (1980): Significance of the goblet-cell mucin layer, the outermost luminal barrier to passage through the gut wall. Biochem. Biophysic. Res. Commun. *94*, 960–966. – *Owen R. L.* (1977): Sequential uptake of horseradish peroxidase of lymphoid follicle epithelium of Peyer's patches in the normal unobstructed mouse intestine. Gastroenterology *72*, 440–451. – *Owen R. L.* (1982): Macrophage function in Peyer's patch epithelium. Adv. Exp. Med. Biol. *149*, 507–513. – *Owen R. L., Jones A. L.* (1974): Epithelial cell specialization within human Peyer's patches: An ultrastructural study of intestinal lymphoid follicles. Gastroenterology *66*, 189–203. – *Owen R. L., Nemanic P.* (1978): Antigen processing structures of the mammalian intestinal tract: A Sem study of lymphoepithelial organs. Sem II: 367–378. –

Owen R. L., Apple R. T., Bhalla D. K. (1981): Cytochemical identification and morphometric analysis of lysosomes in M cells and adjacent columnar cells of rat Peyer's patches (abstr.). Gastroenterology *80*, 1246. – *Owen R. L., Pierce N. F., Apple R. T., Cray W. C.* (1982): Phagocytosis and transport by M cells of intact Vibrio cholerae into rabbit Peyer's patch follicles (abstr.). J. Cell Biol. *95*, 446a. – *Peyer J. C.* (1677): Exercitatio anatomico-medica de Glandulis intestinorum. Schaffhausen, Switzerland. – *Reddy B. S., Pleasants J. R., Wostmann B. S.* (1969): Effects of intestinal microflora on calcium, phosphorus, and magnesium metabolism in rats. J. Nutr. *99*, 353–359. – *Richman L. K., Graeff A. S., Strober W.* (1981): Antigen presentation by macrophage-enriched cells from the mouse Peyer's patch. Cell. Immunol. *62*, 110–118. – *Roche J. K., Cook S. L., Day E. D.* (1981): Goblet cell glycoprotein: An organ-specific antigen for gut. Isolation, tissue localization and immune response. Immunology *44*, 799–810. – *Rodewald R.* (1980): Distribution of immunoglobulin G receptors in the small intestine of the young rat. J. Cell Biol. *85*, 18–32. – *Rodewald R., Newman S. B., Karnovsky M. J.* (1976): Contraction of isolated brush borders from the intestinal epithelium. J. Cell Biol. *70*, 541–554.– *Rosner A. J., Keren D. F.* (1984): Demonstration of M cells in the specialized follicle-associated epithelium overlying isolated lymphoid follicles in the gut. J. Leukocyte Biol. *35*, 397–404. – *Scott G. B. D.* (1980): The primate caecum and appendix vermiformis: a comparative study. J. Anat. *131*, 549–563. – *Scott H., Solheim B. G., Brandtzaeg P., Thorsby E.* (1980): HLA-DR-like antigens in the epithelium of the human small intestine. Scand. J. Immunol. *12*, 77–82. – *Sminia T., Janse E. M., Wilders M. M.* (1982): Antigen-trapping cells in Peyer's patches of the rat. Scand. J. Immunol. *16*, 481–485. – *Swarbrick E. T., Stokes C. R., Soothill J. F.* (1979): Absorption of antigens after oral immunisation and the simultanous induction of specific tolerance. Gut *20*, 121–125. – *Szewczuk M. R., Campbell R. J., Jung L. K.* (1981): Lack of age-associated immune dysfunction in mucosal-associated lymph nodes. J. Immunol. *126*, 2200–2204. – *Thompson G. R., Trexler P. C.* (1971): Gastrointestinal structure and function in germfree or gnotobiotic animals. Gut *12*, 230–239. – *Udall J. N., Walker W. A.* (1982): The physiologic and pathologic basis for the transport of macromolecules across the intestinal tract. J. Pediatr. Gastroenterol. Nutr. *1*, 295–301. – *Volkheimer G., Schulz F. H.* (1968): The phenomenon of persorption. Digestion *1*, 213–218. – *Walker W. A., Wu M., Bloch K. J.* (1977): Stimulation by immune complexes of mucus release from goblet cells of the rat small intestine. Science *197*, 370–371. – *Weinstein W. M.* (1974): Epithelial cell renewal of the small intestinal mucosa. Med. Clin. North Am. *58*, 1375–1382. – *Wilson T. H.* (1962): Intestinal Absorption. Saunders, Philadelphia – London – Toronto. – *Wolf J. L., Rubin D. H., Finberg R., Kauffman R. S., Sharpe A. H., Trier J. S., Fields B. N.* (1981): Intestinal M cells: A pathway for entry of reovirus into the host. Science *212*, 471–472. – *Wolf J. L., Kauffman R. S., Finberg R., Dambrauskas R., Fields B. N., Trier J. S.* (1983): Determinations of reovirus interaction with the intestinal M cells and absorptive cells of murine intestine. Gastroenterology *85*, 291–300.

Les structures et fonctions immunologiques de l'intestin

L'intestin est richement doté de tissu lymphoïde capable d'initier et d'effectuer une multitude de réactions immunologiques. La répercussion de ces réactions dans tout le corps ont permis de mettre en évidence *l'intestin en tant qu'organe immunologique à part entière.*

En comparant les différentes surfaces du corps humain, les 200 à 300 m^2 de l'intestin contrastent singulièrement avec 2 m^2 pour la peau et 80 m^2 pour les poumons. La surface muqueuse intestinale met le corps en contact étroit avec des bactéries, parasites, enzymes, toxines, une vaste variété de substances alimentaires et leur produits de dégradation.

La muqueuse représente la barrière essentielle aux agressions permanentes des antigènes. L'intégrité de sa fonction dépend d'un renouvellement cellulaire constant et du métabolisme de ses structues. Une fonction de défense supplémentaire est offerte à l'aide de mucus, lysozymes, phagocytes, différentes cellules, facteurs endocriniens et modulateurs biologiques participant aux réactions inflammatoires et immunologiques.

Certains de ces facteurs sont produits à proximité de leur lieu d'action. L'ensemble des facteurs de défense mécaniques, endocriniens, immunologiques et non-immunologique de la muqueuse intestinale constitue la *barrière muqueuse.*

Cependant, cette barrière n'est pas complète. Plutôt, une adsorption antigénique a lieu à travers la couche épithéliale. Les structures spécialisées des plaques de Peyer, des follicules lymphoïde solitaires, de l'appendix vermiformis et leur épithélium permettent une *adsorption antigénique* contrôlée (sampling). En raison de son importante exposition aux antigènes, l'intestin est considéré comme *l'organe immunologique de contact* le plus important du corps humain. Les antigènes peuvent induire des réactions immu-

nologiques locales et systémiques, avec production d'anticorps; *par contre,* ils peuvent également diminuer la réponse immunologique systémique à l'égard d'antigènes ingérés (*«oral tolerance»*).

Strutture immunologiche e funzioni dell'intestino

L'intestino abbonda di tessuto linfoide in grado di iniziare ed esercitare una vasta gamma di reazioni immunologiche. Questo reazioni hanno conseguenze non solo per l'intestino stesso, ma per l'organismo in generale, da cui i'importanza dell'*intstino quale organo immunologico.*
Fra le superfici esterne ed interne del nostro corpo, l'intestino con i suoi 200–300 m^2 spicca rispetto ai 2 m^2 della pelle e agli 80 m^2 dei polmoni. Mediante la superficie interna dell'intestino il nostro organismo entra in stretto contatto con batteri, parassiti, enzimi, tossine e una grande quantità di sostanze alimentari con i rispettivi prodotti metabolici. La barriera essenziale contro la continua sollecitazione antigenica é rappresentata dalla mucosa. La sua integrità dipende dalla continua replicazione, maturazione e dal metabolismo dei suoi elementi costitutivi.
Funzioni difensive supplementari vengono esercitate dal muco, da lisozimi, da fagociti e altre cellule, da fattori umorali e modificatori di risposte biologiche coinvolti in reazioni di tipo infiammatorio e immunitario.
Alcuni di questi fattori vengono prodotti molto vicino alla superficie sulla quale agiscono. La somma dei fattori difensivi di tipo meccanico, umorale, cellulare, immunologico (e non) della mucosa intestinale costituice una *barriera.*
Il blocco però non é completo. Infatti ci é una continua assimilazione di antigeni attraverso gli strati epiteliali. Strutture quali le piastre di Peyer, i follicoli linfatici solitari, l'appendice vermiforme con l'epitelio bro associato permettono un'*assimilazione antigenica* controllata.
A causa del grosse carico di antigeni, l'intestino può essere descritto come *l'organo immunologico di contatto* più importante del nostro organismo. Gli antigeni possono innescare reazioni immunologiche locali e sistemiche con produzione di anticorpi, oppure sopprimere le risposte immunologiche sistemiche in risposta ad antigeni ingeriti («toleranza orale»).

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