Functional Histology of Appendix

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Summary. The appendix is a prominent example of gut associated lymphoepithelial tissue, whose function is to react to the wide variety of antigens present in the gastrointestinal tract. It is composed of a large number of repeating units, the lymphoid follicles, each of which is divided into an apical dome, a large basal nodule with a germinal center, and laterally extending thymus dependent areas. The dome epithelium consists mainly of columnar absorptive cells and of specialized follicle associated epithelial (FAE) cells which are efficient at transporting material from the lumen to the underlying lymphoid tissue, and may also transport macromolecules from the lymphoid follicle into the lumen. The dome epithelium normally has large numbers of lymphocytes within it, as well as smaller numbers of macrophages and plasma cells. Macrophages, and perhaps FAE cells, are capable of processing and presenting antigens to reactive lymphocytes. Lymphocyte proliferation and differentiation in response to antigenic stimulation begins in the lymphoid follicles, but most of the lymphocytes leave by the lymphatics, migrate through lymph nodes and spleen, frequently to complete differentiation into IgA-secreting plasma cells in the lamina propria of mucosal surfaces. Normal function of appendix probably helps suppress potentially destructive humoral antibody responses while promoting local immunity.

The gastrointestinal tract is subjected to continual stimulation by large quantities of antigens, including food antigens, microorganisms, and by-products of microorganisms. The tissue which responds to these antigens ranges from diffuse lymphoid tissue distributed throughout the lamina propria, through solitary follicles (or nodules), to highly organized accumulations of follicles such as those which comprise Peyer’s patches and appendix. Each lymphoid follicle, whether it occurs singly or in a group, has a special association with the gastrointestinal epithelium which separates it from the lumen. Invasion of the overlying epithelium by lymphoid cells produces a so-called lymphoepithelium. The structures which respond to gastrointestinal antigens, including both lymphoid cells and epithelial cells, are referred to collectively as gut-associated lymphoepithelial tissue, or GALT.

The quantity, location, and organization of GALT varies among species. The bursa of Fabricius in birds, the cecal tonsils in mice, and the Payer’s patches in rats present differences, but they also display some striking similarities in structure which reflect similar functional capabilities.

The appendix is an example of GALT which is prominent in man. The appendix reaches its greatest relative size and organization, however, in the rabbit. The rabbit appendix therefore has served as an experimental model in numerous studies. The
The purpose of the present paper is to review the significant features of appendiceal histology from studies in humans and rabbits and to correlate these features with the functional capabilities of GALT. It is hoped thereby to provide a clear unified picture of our current level of understanding of the function of appendix in responding to gastrointestinal antigens and maintaining health in the face of this continual bombardment.

**ORIENTATION OF APPENDIX**

The appendix of adult rabbits is remarkable in its size and in its degree of organization. It has the diameter of small intestine but its wall is composed mainly of lymphoid follicles. The appendix is 7–10 cm long, the average thickness of the wall is 3.2 mm, and the average weight is 6.9 g (ENTICKNAP, 1953). Each lymphoid follicle is approximately 0.5 mm in diameter, with its base abutting the muscularis externa and its apical or luminal pole shaped like a dome and covered with epithelium. The lining of the lumen of the adult appendix is a relatively smooth mucosal surface. The arrangement is demonstrated well by scanning electron microscopy (FUJITA et al., 1971; BOCKMAN and BOYDSTON, 1983). There are no villi. At approximately 0.5 mm intervals, there are stomata leading to recesses, or moats, surrounding the domes of follicles (Fig.

![Fig. 1. Scanning electron micrograph of the mucosal surface of adult rabbit appendix. The central portions of the domes (D) which form the luminal pole of each lymphoid follicle are visible through stomata in the mucosal surface. The stippled appearance of the intervening mucosal surface is due to the openings of crypts of Lieberkühn. ×50. (Reprinted with permission from Scanning Electron Microscopy/1982).](image-url)
1) The central portion of domes is visible through the stomata. Intestinal crypts also open into the lumen, and their small orifices dot the mucosal surface between stomata (Fig. 2).

The mucosa forms a cupola over each dome (Fig. 3). The interval between dome epithelium and epithelium of the cupola is the moat which is continuous with the appendiceal lumen through the stomata. The three-dimensional arrangement of the interval between dome and cupola is like an inverted cup. The extension of the space through the stoma would form an attached stem. This arrangement led JOLLY (1923) to call the space “Le Chalice.”

Each lymphoid follicle has a basal enlargement, the basal nodule, which has a germinal center in its middle area (Fig. 3). Basal nodules from adjacent follicles appose each other, but are separated by thin trabeculae. Lateral extensions of lymphoid cells from the base of domes join adjacent follicles as “ailerons” (JOLLY, 1923) or thymus dependent areas (WAKSMAN et al., 1973). In the thymus dependent areas, postcapillary venules with high endothelium are prominent.

Extensive lymphatic sinuses surround the lower (basal nodule) portions of the lymphoid follicles. The extent of these sinuses is not evident after routine histological preparation. Consequently, their presence has not been recognized by many investigators.

Fig. 2. Scanning electron micrograph of the mucosal surface of adult rabbit appendix. The dome epithelium, as viewed at this magnification through the stoma, is heterogeneous. The cells which appear lighter in this micrograph are specialized follicle associated epithelial (FAE) cells. The openings of crypts of Lieberkühn are indicated by arrows. × 450. (Reprinted with permission from Scanning Electron Microscopy/1982).
Crabb and Kelsall (1940) demonstrated the lymphatics by injecting India ink beneath the serosa of the appendix, then observing its distribution in histological sections. Their drawings from sections cut in different planes showed vast accumulation around the lower portions of follicles, penetration into the follicles, primarily in the upper portions, and continuation into the mucosa between follicles. These lymphatics emptied into several well-defined collecting ducts in the mesoappendix. These authors thought that the lymphatics afforded direct drainage from the lumen of the moat above the dome (which space they called a "flask-shaped gland") through intercellular canaliculi in the dome epithelium, into subepithelial sinuses in the apex of the nodule. However, since electron microscopic examination has shown tight junctions between cells comprising the dome epithelium, it is unlikely that there is direct drainage from the lumen through lymphatics.

The disposition of the lymphatic sinuses has been demonstrated by scanning electron microscopy (Bockman and Boydsto, 1983). Fluid flow induced by placing ferritin solution in the appendiceal lumen for one hour before sacrifice caused the sinuses to be fixed in an inflated state so that they were demonstrable by scanning cut surfaces of the tissue. It became obvious that the trabeculae between follicles are made up in large part by the walls of sinuses which are not evident in a relaxed or unfilled state.

Fig. 3. Light micrograph of a routine hematoxylin and eosin section of adult rabbit appendix. Stomata (S) where the moats around domes are continuous with the intestinal lumen are seen in two places. Domes (D) and thymus dependent areas (T) are indicated. Germinal centers (G) occupy the central portion of basal nodules. Most of the perifollicular sinuses (arrows) appear as slits since they are collapsed. ×50
The upper limits of the sinuses correspond to the upper part of the basal nodules, the lower lateral part of the domes, and the lower borders of the thymus dependent areas (TDA). At this upper rim, intercellular spaces of the lymphoid tissue are continuous with the lumina of the lymphatic sinuses, providing a route for drainage of fluid and cells from the different regions of the lymphoid follicles.

The three-dimensional arrangement of the lymphatic sinuses has been demonstrated recently (Bockman, 1983) by two methods. In the first method, a silicone rubber compound was injected beneath the serosa of the appendix and allowed to polymerize in place. Portions of the appendix were then dehydrated, cleared by immersion in methyl salicylate, and studied with a dissecting microscope. The silicone rubber filled the sinuses, presenting a honeycomb appearance (Fig. 4). The sinuses were continuous with small lymphatics draining the mucosa between follicles, and with lymphatic vessels accompanying blood vessels on the serosal surface of the appendix (Fig. 4). In the second method, vinyl acetate was injected subserosally and allowed to polymerize in place. The tissue was then removed by immersion in concentrated hydrochloric acid. The vinyl acetate cast was then rinsed well, air dried, mounted on a stub and coated with gold-palladium for observation by scanning electron microscopy. A honeycomb pattern was evident from this method also (Fig. 5). The lymphatic sinuses were

![Figure 4](image-url)
observed to surround each follicle and to branch at the top where they maintain close contact with adjacent follicles. The sinuses are not continuous along the whole wall of each follicle. Rather, there are interruptions in them. The sinuses also are not continuous around the serosal pole of each follicle, although the sinuses frequently curve in toward the center of this pole. Thus it may be seen that an extensive lymphatic sinus is potentially available to each follicle, and that the potential capacity of the lymphatic network of the appendix is great.

The human appendix is organized similarly to the rabbit appendix. The surface of the mucous membrane shows dome-like elevations which are the apical poles of lymphoid follicles, but the very deep recesses of the rabbit appendix are missing. The surface of the mucosa between domes is studded with minute openings of the crypts of Lieberkühn, arranged in rings and in rows radiating from the center of the domes (Kelly and Hurdon, 1905). Lockwood (1900) described a large lymphatic sinus around the base of the follicle in human appendix, referring to it as the “follicular lymph sinus” or “basilar lymph sinus.” He indicated that the sinus was sometimes enlarged and sometimes obliterated by appendicitis. Injection of the lymph vessels reveals an extensive network of lymphatics with large vessels applied to the periphery.

Fig. 5. Scanning electron micrograph of the mold produced by injecting the lymphatic sinuses of adult rabbit appendix with vinyl acetate and removing the tissue by immersion in hydrochloric acid. The honeycomb-like arrangement of the perifollicular sinuses may be appreciated in this micrograph, which was taken from the luminal side. It may be seen that the basal portion of each follicle is surrounded by a sometimes incomplete sleeve of lymphatic sinus. x70
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The lymphatic vessels of the mucosa and submucosa drain through intervals in the muscularis externa and empty into the sub-serosal plexus, which is drained through vessels in the mesoappendix toward regional lymph nodes. The quantity of lymphoid tissue diminishes after 30 years of age (Berry and Lack, 1905).

DEVELOPMENT OF APPENDIX

The development of the appendix in man (Berry and Lack, 1905; Johnson, 1912; Horowitz, 1933; Bockman and Cooper, 1975) and in the rabbit (Latta, 1921; Crabb and Kelsall, 1940; Stramignoni and Mollo, 1968; Watanabe and Tashiro, 1971; Waksman et al., 1973; Bockman, 1983) is quite similar. The intestines begin as a simple tube of epithelium. Subsequent formation of longitudinal folds and ridges, with segmentation and localized proliferation, leads to the formation of villi not only in the small intestine but also in the large intestine, including the cecum, and the appendix. Figure 6 shows villi in the appendix of a human fetus of 85 mm crown-rump (CR) length. The epithelial cells covering the villi have a characteristic light, open appearance due to

Fig. 6. Light micrograph of a 1 μm thick plastic section of appendix from a human fetus of approximately 13 weeks gestation. Broad villi project into the lumen (L). Most of the epithelial cells are very light because of their glycogen content: some goblet cells (G) are present. ×570
large quantities of intracellular glycogen. Villi reach their maximum height in embryos of 110-140 mm CR length, then gradually diminish, disappearing by birth (JOHNSON, 1912).

The appearance of collections of lymphocytes in the human appendix occurs at approximately 100 mm CR length (Horowitz, 1933). By 170 mm CR length, distinct lymphoid follicles are present in all fetuses (JOHNSON, 1912). Lymphoid stem cells are brought to the mesenchyme of the appendix via blood vessels. Lymphocytes proliferate in the mesenchyme immediately subjacent to the epithelium, and the apical pole impinges upon the surface epithelium in fetuses of 150 mm CR length and older; some lymphoid cells invade the epithelium during this period (BOCKMAN and COOPER, 1975). Hemopoiesis is not limited to lymphocyte formation during this period. Figure 7 shows an island of erythropoiesis in the mesenchyme of appendix from a human fetus of 150 mm CR length. LATTA (1921) described erythropoiesis in rabbit appendix 2-6 weeks postpartum.

Most lymphoid development takes place in the rabbit appendix during the period immediately after birth. At the 28th or 29th day of gestation, accumulations of mesenchymal cells are detectable in the region under the epithelium between the bases of adjacent villi (WATANABE and TASHIRO, 1971). These represent the anlagen of the domes, which become distinctly lymphoid about 3 days after birth and continue to

![Fig. 7. Light micrograph of a 1 μm thick plastic section of appendix from a human fetus of approximately 21 weeks gestation. Islands of erythropoiesis (E) are found in the mesenchyme, clearly outside the developing blood vessels (B). ×790](image-url)
develop thereafter. Alkaline phosphatase activity in the lamina propria of domes precedes the appearance of lymphocytes (HOSTETLER and ACKERMAN, 1966). By day 6, the developing domes are distinct lymphoid structures interposed between previously formed villi (Fig. 8), and the lower, basal nodule part of the follicle has started to expand. Subsequent formation of the definitive structure of the appendix is due to continuing lymphoid proliferation and to disappearance of villi. The latter is really a restructuring of the mucosal surface through fusion of villi. Figure 9 shows fusion of villi as it appears in sections of neonatal appendix. The fusion process is perhaps seen to better advantage by scanning electron microscopy. Figure 10 shows the villi projecting from the mucosal surface 9 days after birth. The developing domes are identifiable between the longer villi. Some fusion of villi is evident. By 15 days after birth (Fig. 11) most of the villi have fused around developing domes. The lateral walls of the villi thus form the cupola which stretches over each dome, and the definitive arrangement of the appendix is established.

CELLULAR CONSTITUENTS

With continuing proliferation of lymphocytes within a maturing mesenchyme, each

Fig. 8. Light micrograph of a section of appendix from a 6-day-old rabbit. Two developing lymphoid follicles (L) are interposed between longer villi. The epithelial cells of the villi are light like those shown in human appendix in Figure 6. The denser dome epithelium is being invaded by lymphoid cells. ×500 (Reprinted with permission from Amer. J. Anat. 136: 455-478, 1973).
lymphoid follicle comes to present a characteristic arrangement of lymphoid cells responding within a connective tissue framework. The framework within the basal nodule and the dome consists of a typical reticular connective tissue. Reticular connective tissue cells with long processes make contact with each other. Reticular fibers are associated with these cells and their processes. The periphery of the follicle is delineated by collagenous connective tissue which forms the walls of the lymphatic sinuses, and which also is continuous into the collagenous connective tissue in the mucosa between lymphoid follicles. Some workers (Stramignoni and Mollo, 1968; Watanabe and Tashiro, 1971) have described extremely branched dendritic cells within the follicles. Dendritic cells are thought to be active in presenting antigen to lymphocytes.

Small lymphocytes predominate in the peripheral part of the basal nodule, i.e., immediately outside the germinal center. Medium and large lymphocytes are more common in the germinal center and dome. Thymus-dependent (T) lymphocytes predominate in the TDA (Waksman et al., 1973), whereas thymus-independent (B) lymphocytes predominate in the germinal center area. The population is mixed in the dome.

Macrophages appear shortly after lymphocytes during early development. They become numerous in the germinal center and the dome. Many macrophages engulf and break down other lymphoid cells. These are referred to as tingible-body macro-

Fig. 9. Light micrograph of 1μm thick plastic section of appendix from a newborn rabbit. The fusion of villi is evident. ×490
phages because of the characteristic darkly stained remains of cells evident in their cytoplasm. Many macrophages have numerous bacteria in their cytoplasm, the result of a process of phagocytosis of bacteria from the lumen of the appendix. This process will be described in more detail below.

The epithelium of the appendix is modified over each dome. The epithelium of the luminal surface and of the crypts in the mucosa between follicles consists of columnar absorptive cells and a large number of goblet cells, as is characteristic of the large intestine. A very high concentration of goblet cells occupies the cupola above the dome. Goblet cells are rare in the dome epithelium. In addition, the dome epithelium contains specialized cells, which have been named follicle associated epithelial (FAE) cells (Fig. 12). The characteristics of FAE cells include short, irregular microvilli on the surface, vesicles and vacuoles in the apical regions, and a capacity to transport material efficiently from the lumen to underlying lymphoid tissue (Bockman and Cooper, 1971, 1973) as well as in the opposite direction (Bockman and Stevens, 1977).

The dome epithelium is referred to as a lymphoepithelium because of the intimate association of lymphoid cells with epithelial cells. Large numbers of lymphocytes invade the dome epithelium and come to lie, in a very orderly fashion, in clusters mainly between epithelial cells (Shimizu and Andrew, 1967; Schmedtje, 1980). Macrophages, in smaller numbers, are found in the dome epithelium (Crabb and Kelsall, 1940; Watanabe and Tashiro, 1971; Bockman and Boydston, 1983), as are plasma cells.

Fig. 10. Scanning electron micrograph of the mucosal surface of appendix from a 9-day-old rabbit. Individual villi are evident, and the domes (D) of developing lymphoid follicles may be identified. Some fusion of villi is also seen (arrows). ×100
(Bockman and Boydston, 1983). The large volume of lymphoid cellular traffic between epithelium and underlying connective tissue space leads to disruption of the basal lamina beneath dome epithelium (Shimizu and Andrew, 1967). Therefore, the macrophages and plasma cells which lie immediately beneath the epithelial layer are functionally intraepithelial, due to the absence of the potential selective filtration of the basal lamina (Bockman et al., 1983). The presence of lymphocytes may be important in inducing differentiation of epithelial cells into FAE cells (Bockman and Cooper, 1973; Schmedtje, 1980).

Figure 13 presents in diagrammatic fashion the cellular association and locations in the dome region.

**TRANSPORT**

It has been known for many years that bacteria may be seen in the lymphoid structures of rabbit's appendix (Enticknap, 1953; Friedenstein and Goncharenko, 1965; Shimizu and Andrew, 1967). Bacteria occur normally in very large numbers in the lumen of the appendix. They become easily detectable at about the second week after birth, a

![Fig. 11. Scanning electron micrograph of the mucosal surface of appendix from a 15-day-old rabbit. Fusion of the villi has proceeded to clearly delineate the formation of the continuous walls which surround domes (D). Thus it may be seen how the sides of villi come to form the cupolas which arch over the definitive domes. ×150](image-url)
Fig. 12. Transmission electron micrograph of the appendix from a 6-day-old rabbit, in the dome epithelium. A follicle associated epithelial (FAE) cell with short, irregular microvilli and apical vesicles occupies most of the field. A lymphocyte (L) is located within the epithelium. The ease with which material could be transmitted from lumen to lymphocyte by the FAE cells is evident. ×17,000 (Reprinted with permission from Amer. J. Anat. 136: 455–478, 1973).
Fig. 13. Legend on the opposite page.
time which corresponds with the formation of nests of lymphocytes in the dome epithelium. They form a pasty mass in the appendiceal lumen. There is considerable heterogeneity in size and shape of the bacteria in the lumen. The bacteria come to lie upon the surface of FAE cells of the dome (Fig. 14), are transported through the FAE cells, and may be phagocytized by macrophages within the epithelium (Fig. 15) or beneath it. Not all bacteria are phagocytized immediately, for single bacteria commonly are seen in the intercellular space. Therefore, some of them may pass through the lymphatics into regional lymph nodes before they are phagocytized. The macrophages migrate; many enter the germinal center. Some macrophages may migrate to regional lymph nodes after bacteria have been engulfed. ENTICKNAP (1953) suggested that the transport of bacteria is selective, since only rod forms were evident in macrophages. The degree of selectivity has not been tested using modern techniques.

Fig. 13. Diagram showing the dome area of a lymphoid follicle. Specialized follicle associated epithelial (FAE) cells comprise part of the dome epithelium. Lymphocytes (blue) are most numerous and invade the epithelium. Plasma cells (red) are located within and immediately beneath the epithelium. Macrophages (yellow), which are intraepithelial and also distributed throughout the follicle, engulf material transmitted by FAE cells from the lumen, and also engulf lymphocytes and plasma cells. A capillary plexus is located immediately beneath the follicle. (Reprinted with permission from J. B. Solomon, editor: Aspects of developmental and comparative immunology I, Pergamon Press, Oxford, 1980, p. 273-277).

Fig. 14. Scanning electron micrograph of the mucosal surface of rabbit appendix. Bacteria are shown adhering to the surface of an FAE cell, which is surrounded by columnar absorptive cells of the dome epithelium. ×3,700 (Reprinted with permission from Scanning Electron Microscopy/1982).
bacteria are degraded by the macrophages. The presence of these bacteria does not elicit an inflammatory response, and plasma cells are not present in the germinal center. **Friedenstein and Goncharenko (1965)** suggested that this situation may represent a natural tolerance to a bacterial antigen. The rabbit's tolerance or immunity to these bacteria have not been tested formally by immunological techniques.

Transport from the appendiceal lumen is not limited to bacteria. After introduction of experimental tracers (ferritin and/or India ink) into the lumen of rabbit appendix, the tracers are taken up into vesicles and vacuoles of FAE cells (Fig. 16), and transmitted to the underlying lymphoid tissue (**Bockman and Cooper, 1971, 1973**). The FAE cells in rabbit appendix thus seem to be efficient in transporting many materials, some with antigenic potential, from the lumen. **Hanaoka et al. (1971)** studied the localization of India ink 10–60 min after intraluminal administration. They described carbon particles in and beneath the endothelial cells of small vessels and later in perivascular macrophages of the lamina propria and isthmus region, and to a lesser extent in the dome. It seems unlikely that this distribution would occur without disruption of the epithelium, since it is the FAE cells of the dome which are most efficient at transmitting material from the lumen.

Transport through appendiceal epithelium is not limited to one direction. **Bockman and Stevens (1977)** administered horseradish peroxidase (HRP) as a tracer to rabbits.
by intracardiac injection. Within 15 min, HRP was localized within dome epithelial cells in greater concentration than in the epithelial cells of the cupola. Peroxidase activity could be detected in saline washings of the appendiceal lumen. Thus the dome epithelium seems capable of transporting macromolecules into the lumen, as well as from the lumen. It should be pointed out that Lupetti and Dolfi (1980) have questioned this conclusion, suggesting that the HRP may have been excreted in bile and made its way along the gastrointestinal tract to the appendiceal lumen. Although it seems unlikely that this would occur within 15 min, the possibility has not been eliminated.

**FUNCTIONAL CONSIDERATIONS**

It is quite clear that the appendix responds dynamically to material which is brought into the lumen in the normal course of events. Isolation of the appendix from normally occurring intestinal contents during the neonatal period prevents development of the lymphoid tissue. Perey and Good (1968) isolated the appendix of neonatal rabbits by placing a ligature around the cecum, taking care not to interfere with the blood supply. The lymphoid follicles were markedly smaller throughout the 8 month study period than sham-operated or non-treated controls. When the appendix was reexposed
to the contents of the cecum by reestablishing the continuity surgically, rapid lymphoid
development occurred, provided it occurred within 5 months of birth. STRAMIGNONI
et al. (1969) ligated the appendix of neonatal rabbits midway in its length. They cut
through the appendix just distal to the ligature, leaving the appendiceal lumen exposed
to the peritoneal cavity. Some of the distal halves were left in place to preserve their
blood supply. Others were severed from their blood supply and either left free in the
peritoneal cavity or transplanted into the eye. The distal portions without normal
luminal contents failed to develop the large lymphoid follicles, but contained some
lymphoid cells. The distal portions without normal luminal contents and without
the normal blood supply were alymphoid upon subsequent histological examination.
Obvious differences in lymphoid development between proximal (control) and distal
segments developed in the second week of life; the segments were similar during the
first week. These experiments indicate that stimuli from the intestinal lumen play a
major role in the development of the lymphoid tissue of the appendix.

The lymphoid tissue of the appendix responds to antigenic stimulation by produc-
ing a large number of cells which mainly migrate to other locations, such as mucosal
surfaces, where they differentiate into plasma cells which secrete immunoglobulin. An
intermediate period in lymph nodes and/or spleen may be interposed (HANAOKA and
WAKSMAN, 1970). Stimulation of B cells to proliferate, differentiate, and migrate, is
preceded by the activities of other cells in the appendix. Antigen from the lumen is
transmitted by FAE cells. Some of the antigen may be degraded by FAE cells. It is
also possible that FAE cells are capable of presenting antigen to responding lympho-
cytes in a manner similar to that carried out by macrophages (BOCKMAN et al., 1983).
Antigen which has been transmitted through the epithelium may be engulfed by
macrophages either in the epithelial layer or below it. Macrophages, T cells, and B
cells may then cooperate to stimulate B cell reaction. The stimulated B cells incor-
porate thymidine in the basal part of the germinal center area, and divide in great
numbers along the lateral part of this area (WAKSMAN et al., 1973). Most of the cells
then leave the appendix by entering the upper portion of the perifollicular lymphatic
sinuses. Some may leave by entering postcapillary venules in the TDA. Some remain
within the follicle, differentiating into plasma cells either immediately beneath or with-
in the dome epithelium. Some may migrate through connective tissue to differentiate
into plasma cells in the lamina propria of the interdomal mucosa. LATTA (1921) has
indicated that lymphocytes may divide with the epithelium, in addition to migrating
there after dividing in another location. Lymphocytes probably differentiate into
plasma cells within the epithelium as well, since intraepithelial plasma cells seem to be
in earlier stages of differentiation than those in the lamina propria of the interdomal
mucosa.

Lymphoid reactivity results in a considerable amount of cell death. Many lym-
phocytes, and some plasma cells, are engulfed by macrophages, to form the tingible-
body macrophages. Macrophages containing bacteria, presumably other engulfed
antigenic material, and/or tingible bodies tend to migrate to and accumulate in the
germinal center.

Many of the cells which migrate from the appendix differentiate into plasma cells
which secrete IgA, which is then transported onto mucosal surfaces as secretory IgA,
through the addition of secretory component by the epithelial cells through which it
traverses. This may modulate further antigen entry by mechanisms such as the in-
hibition of adherence of bacteria to epithelial surfaces. Local modification of antigen
uptake is possible as well. GROSSI et al. (1977) have demonstrated the presence of
extracellular immunoglobulins in the rabbit appendix. Immunoglobulins may be released from lymphocytes in the follicle, and from plasma cells within and beneath the dome epithelium. Immunoglobulins may also be conducted from other locations and be released from the capillary plexus beneath dome epithelium. Immunoglobulins may be conducted into the appendiceal lumen by FAE cells. Antigen and antibody may combine either in the lumen or in FAE cells to modulate uptake and reactivity by lymphoid cells.

A migration of lymphoid cells, of considerable magnitude, into the appendiceal lumen has been suggested as a normal event which would provide for immune reactivity within the lumen. Heatley and Bienenstock (1982) were able to obtain a mean of 8.5 million cells by irrigating the appendiceal lumen. Approximately 73% of these were lymphocytes and 22% were macrophages. It has been pointed out earlier that the marked lymphocyte traffic between lamina propria and epithelium in the dome disrupts the basal lamina. The result of this disruption is that the epithelial connection is very tenuous. The epithelium frequently is disrupted over the dome, and not over the interdomal mucosa, for instance, during routine histological preparation. Appendiceal irrigation probably disrupts dome epithelium, allowing dome lymphoid cells to escape into the lumen. It is possible, however, that the fragility of the dome epithelium would lead to its disruption during mild trauma, and that this could have a protective effect in the gut lumen. It is also possible that very small numbers of lymphoid cells might normally migrate through dome epithelium into the appendiceal lumen. There is little evidence for mass migration through intact epithelium.

An understanding of the functional characteristics of the appendix must include a consideration of the other lymphoid follicles of the gastrointestinal tract, whether they occur singly or as aggregates in Peyer’s patches. It is reasonable to assume that the lymphoid follicles in the appendix, as examples of GALT, respond to alimentary antigens similarly to lymphoid follicles elsewhere.

The number of lymphoid follicles in the gastrointestinal tract is great. The mean number of Peyer’s patches (each consisting of more than five follicles) in human small intestine at puberty is 239 (Cornes, 1965). Over 100 of these contain more than 25 follicles. In addition to Peyer’s patches there are numerous individual, or solitary, follicles. Joel et al. (1978) observed 150 to 200 solitary follicles per intestine in mice. The solitary follicles had an epithelium similar to that over Peyer’s patch follicles, and took up carbon from the lumen in a similar fashion.

The morphology of follicles in Peyer’s patches is quite comparable to that of the appendix (Kimura, 1977; Abe and Ito, 1978; Lause and Bockman, 1981). This correlates quite well with evidence for a similar handling for luminal antigens. Involvement of lymphoid follicles of the ileum and cecum in infection of mice with intragastrically administered Salmonella enteritidis (Carter and Collins, 1974), and selective uptake and transmission of reovirus by FAE cells in Peyer’s patches (Wolf et al., 1981) are examples of special associations of pathological organisms with GALT. Phillips et al. (1978) demonstrated, by scanning electron microscopy, preferential adherence of bacteria to FAE cells over lymphoid follicles in the duodenum of a child with protracted diarrhea. The appearance was quite similar to the bacteria adhering to the FAE of the appendix in Figure 14. Kimura (1977) administered killed Salmonella typhi orally to rabbits, and observed bacteria in FAE cells and macrophages in Peyer’s patches of animals which had been immunized by previous intravenous injections. No similar localization occurred either without previous immunization or without oral administration. There can be little doubt that many other antigenic materials normally are taken
up and reacted to by GALT. Occasionally, pathological changes occur. Usually, re-
action maintains the healthy state.

The response by GALT to enteric antigens may be characterized as one which
emphasizes IgA as a secretory antibody which provides local protection, and which
dean emphasisizes the response by other classes of immunoglobulins, which could be de-
structive. The follicles in GALT contain competent lymphoid cells which may respond
by cooperating with each other. This includes competent macrophages (Richman et
al., 1981a). Response to luminally administered bacteria has been shown directly by
using isolated ileal loops in rabbits (Keren et al., 1978). Greater secretion of IgA into
the lumen was correlated with a large number of follicles. Similar loops were shown
to secrete IgA antibodies to bacterial antigens when bacteria were given orally after
the loops were formed, thus isolating them from antigen presentation (Keren et al.,
1982). The use of live bacteria for immunization also allowed these workers to demon-
strate a striking IgA memory response 60 days later. Richman et al. (1981b) have
demonstrated the mechanism by which oral antigens may stimulate secretory IgA and
suppress systemic reactions. They fed ovalbumin as a dietary protein antigen, and
observed the formation within Peyer’s patches of class specific regulatory cells.
Separate populations of T cells which help the IgA response and which suppress the
IgG response were demonstrated.

It is sobering to consider that, despite our increasing knowledge of the immuno-
logical capabilities of GALT in general and the appendix in particular, we still lack
some fundamental understandings. We did not understand the pathophysiology of
appendicitis at the first of this century (Kelly and Hurdon, 1905) and we still do not.
Although there are definite correlations with obstruction and the occurrence of fe-
caliths, there are numerous examples of appendicitis without evidence of these (Butler,
1981). The intriguing association of appendicitis with cystic fibrosis has been noted
but not explained (Schwachman and HolscLaw, 1972; Ostreich and Adelste1n, 1982).
A clear understanding of the protocols necessary for effective enteric immunization
or avoidance of destructive immunologically-based reactions remains to be gained. It
is hoped that this brief review will stimulate work which will provide some of these
answers.

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