This chapter covers a collection of microscopic changes that lack diagnostic specificity but occur in different specific diseases, as will become apparent in subsequent chapters. Almost all of these changes are responses to injury, generally involving the squamous epithelium and the lamina propria.

**Fig. 2.1** Papillomatosis, basal cell hyperplasia, and spongiosis. (a) In contrast to normal squamous mucosa in which the papillae of lamina propria are limited to the basal fifth, in this squamous epithelium the papillae extend close to the surface. Each of these papillae is surrounded by several layers of basal cells; in other words, there is an expansion of the proliferative zone, also known as basal cell hyperplasia, which is a common reaction to injury in all squamous surfaces including both skin and mucous membranes. Since the most common injury to the squamous esophagus is gastroesophageal reflux, chances are that reflux is the culprit whenever this is found in a distal esophageal biopsy. Infections and direct toxic injury produce the same response, however, so it lacks specificity. (b) This is a more advanced example with much longer papillae that extend nearly three quarters or more of the way to the surface. The layers of basal cells around the papillae are thicker. In addition, the basal cells and squamous cells are separated so intercellular bridges are easily seen. This is the result of intraepithelial edema or spongiosis. In the esophagus, it is also referred to as dilated intercellular spaces.
Fig. 2.2 Acute papillary hemorrhage. All the fibrovascular papillae that extend into the squamous epithelium from the lamina propria are filled with extravasated blood (i.e., acute hemorrhage). This may be due to trauma from the biopsy procedure but in some cases it may be due to in vivo injuries, reflux being one. In fact, in the past, it was touted as one of the characteristic reflux-associated changes.

Fig. 2.3 Balloon cell change. Within the squamous epithelium, several cells have no nuclei but instead have large smooth proteinaceous inclusions filling the cytoplasm referred to as balloon cell change. This is a response to surface injury in squamous mucosae in different sites, and, in the esophagus, the most common injury inducing this change is reflux. The inclusions are plasma proteins and fluid that presumably have leaked into damaged squamous cells.

Fig. 2.4 Generic acute inflammation with microabscesses. (a) In this field, there is a row of tiny abscesses, also known as microabscesses, in the superficial squamous epithelium. Below this row, the squamous cells appear relatively normal. (b) This is a more intense variant with larger intraepithelial abscesses. This pattern of acute injury usually leads to a search of the slide for an infectious cause, the most common being Candida. However, all too often, no cause is found. In fact, in many cases, a cause may never be identified. We have seen a couple of cases of pill-induced injury with similar acute inflammation. We have virtually no follow-up biopsies to give us a clue as to the natural history of these changes.

Fig. 2.5 Generic ulcer bed. There is no epithelium on the surface. Instead, the mucosa consists entirely of lamina propria, which contains small vessels with hypertrophied endothelial cells, probably capillaries and venules. The lamina propria also contains spindle cells, presumably myofibroblasts, and scattered inflammatory cells including polymorphonuclear leukocytes (PMNs). On the surface are a few strands of fibrin mixed with some of these spindle cells, evidence of organization. This is the bed of an acute superficial ulcer. It lacks chronicity changes, such as plasma cells. The changes have no specificity in terms of defining the injury that caused the ulcer. Most of these are in the distal esophagus where reflux is by far the most common cause.
Fig. 2.6 Hypertrophied myofibroblasts in the bed of an ulcer (ulcerocytes). (a) This is the base of an ulcer with prongs of regenerating squamous cells at the surface. There are numerous large plump spindle cells with large, hyperchromatic, and pleomorphic nuclei in the ulcer bed. (b) At high power, the nuclear changes are striking and the resemblance of these cells to some kind of spindle cell malignancy is obvious. (c) With the keratin stain, the cells are negative whereas the prongs of primitive squamous cells at the ulcer edge are strongly positive. (d) In contrast, in the Vimentin stain, the spindle cells are strongly and diffusely positive. These cells have the ultrastructural features of myofibroblasts and fibroblasts. We refer to them as “ulcerocytes.” For some odd reason, they are more common in the base of esophageal ulcers than anywhere else in the gut. Because the pleomorphism makes them look like a type of spindle cell malignancy, they are a real diagnostic pitfall. We emphasize that these cells should never be called malignant.
Fig. 2.7 Healing ulcer in squamous mucosa. Extending from the thin squamous mucosa with large hyperchromatic nuclei and little cytoplasm on the left, a thinner layer of squamous cells grows beneath some exudate on the right. Because this is typical of changes in squamous mucosa right at the edges of ulcers of all causes, this has no specificity other than to identify the biopsy site as an ulcer edge. The next step in ulcer healing is the extension of the long squamous prongs from this regenerating layer of squamous cells into the stroma. Such prongs are in Fig. 2.8.

Fig. 2.8 Ulcer edge changes in squamous mucosa. (a) This mucosa has a thin layer of superficial squamous cells from the base of which project prongs of dark squamous cells which project into the hyper-vascular lamina propria almost to the inner fibers of the muscularis mucosae. We refer to this locally as “long-prong disease.” (b) In the higher-power image, the cells in these prongs have a high N:C ratio and frequent mitoses. There is little cytoplasmic differentiation, but there is some spongiosis toward the top. This pattern of regeneration is typical of what happens at the edges and eventually at the bases of ulcers in squamous mucosae. With time, these prongs become thicker and more differentiated and the superficial layer also becomes thicker, thus recon-stituting the normal squamous epithelium.
Fig. 2.9 Florid ulcer edge changes, mimicking squamous cell carcinoma. (a), In this example, the prongs of regenerating squamous epithelium are very long and thin, and they have extensive interconnections. (b), At higher magnification, the poor differentiation of the cells in these prongs is evident. There is considerable nuclear pleomorphism and many nuclei have prominent nuclei. Mitoses are also present. Because of the complex architecture and the primitive appearance to the cells, it may be tempting to diagnose this as squamous cell carcinoma. It is basically a form of pseudoepitheliomatous hyperplasia.

Fig. 2.10 Maturing ulcer edge changes. In comparison with Figs. 2.8 and 2.9, the superficial layers of squamous cells and basal prongs are thicker and the squamous cells are more mature. This squamous epithelium is much closer to normal.
Fig. 2.13 Atypical regenerative changes in squamous epithelium with multinucleation and nuclear pleomorphism. This is hyperplastic squamous epithelium at the edge of an ulcer. Many of the nuclei in the deeper cells are enlarged and hyperchromatic. Toward the right, there is a collection of such cells with more pleomorphic nuclei, and some of these cells are even multinucleated. This is a well-recognized pattern of squamous repair or regeneration that can be seen in a number of situations including following radiation or after the use of several drugs that are toxic for esophageal squamous epithelium. The key in separating this pattern from squamous dysplasia is that this epithelium matures normally. Further, the cells with the atypical nuclei have abundant cytoplasm, so although it looks frighteningly bizarre there is little change in the N:C ratio.

Fig. 2.11 Long prong and ulcerocytes in a single biopsy, a great temptation for a malignant diagnosis. (a). From the thinned surface, the typical long prongs of regenerating primitive squamous epithelium extend into the lamina propria, which contains many atypical stromal cells with atypical nuclei characteristic of the weird myofibroblasts in ulcer beds described in Fig. 2.5. (b) This can be seen in better detail in higher magnification. Based on these changes, one must resist the temptation to call this spindle cell squamous carcinoma when it is nothing more than the edge of an ulcer in the squamous esophagus.

Fig. 2.12 Keratinizing surface epithelial metaplasia, also referred to as hyperkeratosis. The normal esophagus has no granular layer or surface keratin; because both are present in these images, the epithelium resembles hyperkeratotic epidermis. The cause is not well defined but presumably is a response to surface injury. Surprisingly, there is very little published information about this change, either in the literature or in the textbooks. Yet, in a busy biopsy service, this appears periodically. Sometimes the endoscopist will recognize it as a white area or plaque.
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