Normal and Pathological Anatomy of the Large Intestine

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I. INTRODUCTION

A clear knowledge of the normal morphology of the large intestine is vital to our understanding of pathological anatomy. Several descriptions have previously been published; however, they either described a segment of the large intestine, that is, the rectum, or discussed the large intestine from patients with colon cancer, neither of which is truly representative of the normal large intestine. The normal large intestine has different features in different segments irrespective of the species (Shamsuddin et al., 1982; Shamsuddin and Trump, 1981a; James et al., 1982). Studies done in our laboratory also demonstrate that the normal appearing mucosa in a patient with large intestinal cancer is far from being normal (Shamsuddin et al., 1981). In view of these observations, I shall try to give a comprehensive account of the characteristics of the normal large intestine. I shall
then familiarize the readers with the various neoplastic processes that commonly affect the large intestine.

II. NORMAL LARGE INTESTINE

Besides the obvious expected variation in the size, the normal large intestine also shows variation in morphology and histochemical reactions between species. The following is a brief description of the human, rat, and mouse large intestine.

A. Human

In the human, the large intestine extends from the end of the ileum to the anus. However, this organ has been loosely called the colon or the colon and the rectum. The colon actually includes only the ascending colon, the transverse colon, the descending colon, and the sigmoid colon; the cecum and the rectum are omitted. In this chapter, I shall, therefore, refer to the large intestine as the large intestine and nothing else.

The large intestine in average adult humans measures approximately 150 cm in length. Its caliber is greatest in the cecum and becomes progressively smaller along the direction of fecal flow, becoming smallest at the rectum. Just before the anal canal, however, there is a dilated portion. The functions of the large intestine are the absorption, secretion, and controlled transit of semisolid waste products from the body. The residue from diet and secreted material constitute the feces. On the average, approximately 10 liters of fluid (ingested through the mouth and combined with secretion from the various digestive glands) enters into the small intestine of an adult. Of that, only 500–600 ml is presented to the large intestine. The colon actually includes only the ascending colon, the transverse colon, the descending colon, and the sigmoid colon; the cecum and the rectum are omitted. In this chapter, I shall, therefore, refer to the large intestine as the large intestine and nothing else.

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The large intestine, like other hollow organs, is made up of layers of tissue. The layers of the large intestine, proceeding from the inside out, are the mucosa, the submucosa, the muscularis (inner circular layer and outer longitudinal layer), and the serosa.
The normal human large intestinal epithelium shows uniform test-tube-shaped glands (crypts). Hematoxylin and eosin, ×304.

Mucous cells are the most abundant of all the cell types in the epithelium of the large intestine, and they show marked variation of differentiation. At the very early stage, mucous cells contain a few profiles of rough endoplasmic reticulum. Golgi and cytoplasm become progressively electron dense, and mucous vacuoles of various sizes are later seen in these cells. The mucus seems to be discharged only after the cells become hyperdistended with mucin. During the process of discharge, individual mucous vacuoles coalesce, their partitioning membranes disappear, and the mucus assumes a fibrillar appearance. Mucous vacuoles showing different densities are also commonly seen in the ascending and transverse colon. Small vacuoles, particularly in the apical cytoplasm, are frequently observed in most of the mucous cells. These vesicles are seen in mucous cells of all segments of the large intestine. They are moderately or markedly electron dense at the ascending colon and mildly dense at the transverse and descending colon. In striking contrast to the ascending colon, the vesicles are electron lucent in the rectum suggesting pinocytotic origin. The size of these vesicles varies from 200 to 650 nm in diameter, and they are occasionally seen to coalesce with the mucous vacuoles. Periodic acid-thiocarbohydrazide-silver proteinate (PAS) stain demonstrates the presence of mucosubstances in these vesicles.

Endocrine cells contain electron-dense granules surrounded by limiting membranes with a variable clear space or halo between the central dense core and the limiting membrane. Endocrine cells are seen in the basement membrane of the crypts as well as on the surface epithelium. Only rarely are they seen to reach the crypt lumen, although many or all may do so. The rectum contains an unusual number of endocrine cells; not only are they more than in the other segments, but they are also more frequently seen adjacent to each other, often appearing in clusters. This correlates with the relatively high incidence of carcinoid tumors in the rectum. There are many different types of granules, which vary in size, shape, and electron density, measuring from 100 to 670 nm in diameter. Although a few cells contain different types of granules, different types of granules usually seem to be compartmentalized in different cells. The cytoplasm of endocrine cells is usually electron lucent, but some are moderately electron dense. There is a variable amount of microfilaments, a few mitochondria, and occasional short strands of rough endoplasmic reticulum. Some cells contain a few polysomes. Usually, the nuclei are rounded with occasional indentations. The dense core granules are usually located in the infranuclear part of the cytoplasm and are close to the basal plasma membranes. Rarely, however, they may be in the supranuclear cytoplasm as well.

The surface epithelium lying between the crypts and directly lining the lumen of the large intestine is characterized by mucous cells and columnar cells. There are usually five to ten cells between the crypt openings. The surface epithelium is
usually the site for exfoliation of the cells. The tall columnar epithelial cells lining the luminal surface between the crypts are the columnar cells. Columnar cells have slender elongated cytoplasm with basal rounded nuclei and abundant supranuclear Golgi, mitochondria, some profiles of RER, and free polysomes. The apical part of the cytoplasm contains numerous vesicles (200 to 300 nm) with usually clear content, microfilaments (6 to 8 nm), a well-developed terminal web, and microvillar core rootlets.

The lamina propria, which is situated between the basement membrane of the epithelial crypts and the muscularis mucosae, shows fibroblastic cells, capillaries, macrophages, eosinophils, neutrophils, lymphocytes, and plasma cells, and peripheral nerves. Lymphocytes or eosinophils are occasionally seen between the epithelial cells. These are clearly separated from the adjacent epithelial cells by the plasma membranes.

B. Rat

The large intestine of the rat measures approximately 10–15 cm in length, varying with the size of the rat. Unlike the human colon, the rat colon has no definite ascending, transverse, and descending segments. However, the segment immediately following the ileocecal valve is distended into a bag-like structure reminiscent of the cecum, and measures 3–4 cm. The wall of the intestine is thin in this region and measures 0.1 cm in maximum thickness. There are some mucosal folds. The remainder of the colon beyond the cecum is shaped like an inverted V, the ascending ramus of which has been called the ascending colon, and the descending ramus the descending colon. These two segments are grossly, histologically, and histochemically different. Grossly, the ascending colon is characterized by mucosal folds that display a herringbone pattern, while the descending segment is relatively smooth with two to four longitudinal folds.

The wall of the colon of the Fisher 344 rat is composed of three layers. The outer layer is the adventitia, followed by the outer longitudinal and inner circular smooth muscle layers. The submucosa is immediately adjacent to the muscle coat and is composed of loose connective tissue, which is rich in blood vessels and lymphatics. It is separated from the mucous membrane by the muscularis mucosae, a thin layer of smooth muscle cells. The mucosa is the innermost layer, lying between the lumen and the submucosa. The mucosa of the rat colon is characterized by crypts and surface epithelium. Throughout the entire organ the crypts are straight, elongated, and test-tube-shaped, except in the cecum where the basal third of the crypt is branched.

The ascending segment of the colon is characterized by straight, tubular crypts, with abundant mucus-secreting cells in the lower one-third of the crypt, and less in the upper one-third, which is populated predominantly by tall columnar cells with eosinophilic cytoplasm and a few mucus cells. The middle

Fig. 2. Normal mouse colon epithelial cell showing the presence of large crystalline organelles. Transmission electron microscopy, ×9375.
third contains an admixture of columnar and mucous cells. The lower third of the crypt has a predominance of acidic mucopolysaccharide which shows a combination of sialo- and sulfomucin, with a predominance of the former. The cells in the upper one-third of the crypt contain neutral or both neutral and acidic mucopolysaccharides.

In marked contrast to the ascending colon, the crypts of the descending colon show a smaller population of mucous cells at the bottom of the crypt, and the cells are less distended than those of the ascending part. This differs from the human descending colon, in which a few cells with neutral mucopolysaccharide can be seen in the base of the crypts. In the rat descending colon, the acidic mucosubstance is predominantly or exclusively sulfomucin. As in humans, the mucus-secreting cells of the rat large intestinal epithelium show a wide range of morphological variation.

### C. Mouse

The large intestine of the mouse measures approximately 10 cm in length and is distinctly different from both rats and humans in terms of mucin histochemical properties and cell types (James et al., 1982). The distal colon and rectum in mice show a mixture of sialomucin and sulfomucin. Both the mucous cells and the undifferentiated cells divide. This led to some confusion in the literature of the past (Shamsuddin and Trump, 1982). The murine colon also shows some unique features, such as the presence of 1–2-µm-diameter organelles (Fig. 2) with crystalline inner structure and intracellular bacteria (Shamsuddin and Elsayed, 1986).

### III. PRECURSORS OF CARCINOMAS

Almost all of the cancers of the large intestine are epithelial in origin, with sarcomas being extremely rare. The epithelial neoplasms have been divided into two categories: benign polyps and malignant carcinomas.

Epithelial polyps are protuberant outgrowths that arise from the mucosa and compromise the luminal space to a variable degree. Several different types of epithelial polyps have been identified in the large intestine. Some of these polyps are considered to have a higher potential for progressing to carcinomas than others, and not all polyps are considered neoplastic (Fenoglio and Lane, 1974). Hyperplastic polyps are the most common (90%) of polyloid outgrowths from the large intestinal epithelium and are generally considered nonneoplastic. As their name indicates, these lesions are characterized by crypts with a hyperplastic epithelium and a serrated outline of the crypt lining. These polyps are small, measuring 1–5 mm in diameter, and are mostly located in the rectosigmoid area.

Autoradiographic studies have demonstrated that there is a slight expansion in the zone of cell division (Lane et al., 1971). It had been considered certain that hyperplastic polyps are incapable of progressing to carcinomas, and therefore, these lesions have not been considered preneoplastic. However, there are reports of carcinomatous changes within hyperplastic polyps (Cooper et al., 1979), and many of these express markers of cancer (Boland et al., 1982a,b). Thus, hyperplastic polyps may become carcinomas.

Juvenile polyps are so named because of their predilection for young people. These polyps are characterized by abundant fibrovascular connective tissue stroma and large distended crypts; they have been given the name retention polyp for that reason. Like hyperplastic polyps, these have been considered non-neoplastic polyps that do not progress to carcinomas. Once again, however, there are reports describing the progression of juvenile polyps to adenocarcinomas (Liu, 1979).

Adenomatous and villous polyps are considered neoplastic and are commonly believed to be the precursors of the large intestinal carcinomas. Many authors also describe these as adenomas. This term has also been loosely used to describe variable neoplastic changes in the crypts. Thus, the use of the term adenoma with respect to the large intestine is extremely confusing, since, as in any other epithelium, the relationship between adenoma and carcinoma and the transition point from adenoma to carcinoma remains to be pinpointed. It may be worthwhile to mention here that, in different organs, many lesions considered by light microscopy to be benign adenomas have subsequently been demonstrated by electron microscopy and patient follow-up to be invasive carcinomas. Thus, I shall refrain from using the term adenoma in the subsequent section.

Adenomatous polyps have probably been misrepresented and misdiagnosed, particularly in animal models, more than any other single pathological condition. Any lesion that even vaguely resembled a human adenomatous polyp was so named in animal models. Thus, it is important to be familiar with adenomatous polyps in humans before determining whether such a lesion even exists in animals!

Adenomatous polyps are typically drumstick-shaped structures that almost stand out from the mucosa (Fig. 3). The polyp has a neoplastic and a non-neoplastic component. The long stalk of the polyp is the nonneoplastic component and is composed of an internal connective tissue core lined externally by nonneoplastic mucosa that is not unlike that in the rest of the large intestine. Although these are typically pedunculated, a rare sessile one may also be seen. It must be emphasized that the only neoplastic component of these polyps is the head of the drumstick, which is composed of neoplastic crypts, many of which are dilated, distorted, and branched and show varying degrees of general features of malignancy, such as increased cytoplasmic basophilia, an increased nuclear cytoplasmic ratio, and a loss of polarity of cells and nuclei (Fig. 4). Numerically, the adenomatous polyps are the more common of the two so-called neoplastic
ADENOMATOUS POLYP

Fig. 3. Schematic diagram of an adenomatous polyp. The polyp is pedunculated and contains a neoplastic head. The stalk is composed of mucosa and submucosa and is considered to be non-neoplastic. Various degrees of malignant changes can be seen in the head, but these are not alarming unless there is an invasion of the muscularis mucosae and the cancer cells are in the submucosa.

Fig. 4. Human adenomatous polyp showing the presence of many abnormal (dilated, branched, hypercellular) crypts in the neoplastic head. Hematoxylin and eosin, ×120.

It appears that the size of the polyps is correlated with the frequency of malignant foci. Common adenomatous polyps are usually 1 cm or less in diameter (their size range is usually 0.3–3 cm in diameter). Muto et al. (1975) reported that adenomatous polyps that are less than 1 cm in diameter (the most common size) have a very low prevalence of malignant foci (1%), while the prevalence rate of malignant foci increases with the size of the polyp. Adenomatous polyps in U.S. populations are most often seen in the left colon. In about 30–40% of the cases, there are 2 or more polyps per individual. It has been estimated that once a polyp has been removed from a patient, there is a 20% chance of finding additional polyp(s) in the next 5 years.

Villous polyps (often called villous adenoma) are less common than adenomatous polyps and have distinctly different morphological and biological features. They are most often sessile lesions with a broad base. Unlike adenomatous polyps, the entire polyp is neoplastic. The polyp looks as if it has been plastered onto the mucosa. The surface of the villous polyp is characterized by finger-shaped structures reminiscent of the villi in the small intestine, from which the polyp derives its name. In classical pathology, one must see more than 50% villous architecture in a polyp to call it a villous adenoma. Generally, the morphological features of malignancy are more predominant throughout the entire polyp than in adenomatous polyps. Villous polyps are generally larger than adenomatous ones, and the potential to progress to carcinomas is likewise much higher than in the other polyps described previously (Muto et al., 1975). Villous polyps commonly cause rectal bleeding. Sometimes they secrete copious amounts of protein, water, and electrolytes, giving rise to hypokalemia.

Although epidemiological data indicate that the incidence of large intestinal carcinoma is associated mainly with environmental factors, there are some hereditary disorders of the large intestine that increase the risk of cancer in the patient. The most important of these is the hereditary predisposition to develop polyps of the large intestine. In the commonest form of this disorder, familial polyposis coli is transmitted as an autosomal dominant trait. The large intestine harbors the polyps, which are adenomatous in type, and their number may vary from a few scattered polyps to hundreds and thousands. In some cases, the intestine may be so densely populated with polyps that the normal mucosa is no longer visible. Patients with polyposis develop carcinoma of the large intestine at a much earlier age than nonpolyposis individuals. There is also a very high incidence of malignant transformation of the polyps. Thus, this condition serves as a model for studying some of the aspects of colon carcinogenesis. However, like any other model system, one has to be aware of its limitations. Since the bulk of large intestinal carcinomas are seen in nonpolyposis individuals, one has to be cautious in extrapolating data obtained from such models.
IV. CARCINOMA OF THE LARGE INTESTINE

The malignant neoplasms of epithelial origin are adenocarcinomas, carcinoids, and squamous cell carcinomas, in that order of frequency. Carcinomas constitute over 98% of all malignancies of the large intestine. Ninety-five percent of the carcinomas are adenocarcinomas.

Adenocarcinomas are neoplasms that show features of glandular differentiation. The commonest variety, called glandular adenocarcinomas, show gland formation with variable degrees of mucus production.

The great majority of the carcinomas of the large intestine are found in the left colon (descending and sigmoid colon), followed by the rectum, cecum, transverse colon, and ascending colon, in that order. Recent data suggest that there has been a trend of a decreasing percentage of distal rectal and an increasing percentage of proximal cecal large intestinal carcinomas during the last 30–40 years (Rhodes et al., 1977; Snyder et al., 1977). Analyzing a total of 40,771 cases of large intestinal carcinomas during a 34-year period, Snyder et al. (1977) found that the incidence of carcinomas in the right colon increased from 13.4% in 1940–1944 to 21.8% in 1970–1973. During the same period, the proportion of carcinomas in the rectum and anal areas has decreased from 45.5% to 34.5%.

A. Morphology

Two morphological types of large intestinal carcinomas have been recognized: the fungating exophytic type and the flat infiltrative "napkin-ring" type. The fungating exophytic type is usually a large cauliflower-like mass that protrudes in the lumen of the large intestine. This variety of neoplasm is almost restricted to the proximal part of the large intestine. In the cecum, which has a large capacity, these neoplasms may attain a very large size without causing any sign or symptom of obstruction. The fluidity of cecal contents also contributes to the silent nature of these neoplasms. The flat infiltrative type does not protrude into the intestinal lumen; it infiltrates through the entire circumference of the intestinal wall in an annular fashion. This causes considerable narrowing of the lumen of the intestine. Coupled with the fact that the feces are more formed in the distal intestine, this type of neoplasm gives rise to early symptoms of obstruction. Grossly, these neoplasms appear to cause napkin-ring constriction of the intestine. On cut section, the intestinal wall shows infiltration by gray-white carcinoma. The luminal part of the neoplasm frequently shows ulceration. Thus, the macroscopic morphology of the carcinomas is different in the left and right side of the large intestine, although on rare occasions, one may see an inverse pattern.

The adenocarcinomas show a variable degree of differentiation. The predominant pattern is of well-differentiated adenocarcinomas characterized by well-formed glands containing a varying amount of mucus (Fig. 5). Such a neoplasm...
usually demonstrates the standard features of malignancy in glandular epithelia: the stratification of cells and nuclei, an increased nuclear-cytoplasmic ratio, bizarre nuclei and enlarged nucleoli, and a loss of polarity of cells and nuclei. However, one can sometimes see extremely well differentiated carcinoma, particularly at the edge of adjacent tissue invasion. In some instances, it even appears as normal epithelium (Fig. 6). Thus, the morphological features of malignancy are not absolute. This is not at all unique for the large intestine. Indeed, most carcinomas of the endocrine gland demonstrate a deceivingly benign appearance, yet metastasize to distant organs. This is also relevant to carcinomas of the large intestine in animal models, which often do not show the classical cytologic criteria of malignancy.

The less differentiated adenocarcinomas demonstrate a reduced tendency to reproduce glandular structure and display marked anaplasia (Fig. 7). An interesting feature of the large intestinal carcinomas is the presence of acute and chronic inflammatory cells in the glands as well as in the stroma. The cells of chronic inflammation, such as lymphocytes, are probably related to the host-tumor immune interaction. The presence of polymorphonuclear leukocytes had been considered to be related to necrosis of tumor and/or infection. However, studies of the morphogenesis of large intestinal carcinoma in animal models demonstrate that the polymorphonuclear cells appear at a very early stage of carcinogenesis (Shamsuddin and Trump, 1981b; Shamsuddin, 1982).

A variant adenocarcinoma, which is commonly seen in the elderly, is the mucinous or colloid carcinoma. It is characterized by an excessive production of mucus, causing the hyperdistension and "signet-ring" appearance of cancer cells that are in "lakes" of mucus (Fig. 8). Its natural incidence in the elderly human is 5–15% (Falterman et al., 1974; Symonds and Vickery, 1976). Similarly, its incidence in experimental animals following chemical carcinogenesis is also low. However, the incidence of mucinous or colloid carcinoma is very high in patients with ulcerative colitis (Symonds and Vickery, 1976), in adolescents (Pratt et al., 1977; Mills and Allen, 1979), and following radiation (Castro et al., 1973). Experimental animals exposed to X-rays also demonstrate a high incidence of this variety of carcinoma (Denman et al., 1978). It thus appears that the differentiation of carcinomas may be related to the type of carcinogenic stimuli, the age of the host, and other as yet unidentified factors.

Most of the carcinomas induced in animal models are also adenocarcinomas. Squamous papillomas and squamous metaplasia in adenocarcinomas are very rarely observed. This discussion will therefore be restricted to adenocarcinomas.
few adenocarcinomas are of a mucinous colloid type and are characterized by abundant intracellular and extracellular mucin. Like their human counterpart, these are also seen to invade and metastasize rapidly (Shamsuddin, 1984a).

Morphogenetic studies done in our laboratory demonstrate that, following carcinogen administration, epithelial crypts undergo a series of changes (Fig. 9). In the very early stage (called crypt dilatation), there is increased mucus secretion, and the mucous cells have an exhausted appearance. This is followed by progressive dilatation of the crypt lumen, which is infiltrated by polymorphonuclear cells. During this time, the crypt lumen appears hyperdistended with mucus, mostly sialomucin. A variable number of polymorphonuclear leukocytes are seen within the mucus. Polymorphonuclear cells have been observed to emigrate from the pericryptal space into the crypt lumen (Shamsuddin, 1982). Once outside the crypt lumen, some of the polymorphonuclear cells rest on the basement membrane, which is otherwise almost bare except for an occasional undifferentiated

Fig. 8. Mucinous carcinoma of the colon (human). Only a few cancer cells are seen in virtual "lakes" of mucin (empty-looking spaces). Hematoxylin and eosin, x300.

induced neoplasms differs in different species and within the same species. For instance, the neoplasms induced in C57BL/6 mice are an infiltrating type with early tendency to invade the underlying tissue, whereas those in ICR/Ha mice are usually exophytic in type (James et al., 1983). As described previously, adenomatous polyps are characterized by a neoplastic component (head) and a fibrovascular connective tissue stalk that does not show features of neoplasia (Fig. 3). Careful examination of the induced exophytic lesions in animals as well as published photomicrographs of adenomatous polyps reveals that most of these lesions do not fit the criteria for adenomatous polyps. Lev and Herp (1978) reported similar observations with the N-methyl-N-nitrosourea model. Many infiltrating and metastasizing carcinomas do not fit into the classical textbook description of malignancy; they do not show an increased nucleocytoplasmic ratio, bizarre nuclei, and anaplasia, yet they may metastasize. When intraepithelial, some of these neoplasms may be so benign looking that one may hesitate to call them carcinomas. However, electron microscopy studies of some of these intraepithelial lesions demonstrate that they may show evidence of invasion of the basement membrane of the gland (Shamsuddin and Trump, 1981b). Thus, although the intraepithelial foci of neoplasms in animals may look deceptively benign, they may invade through the basement membrane and are therefore malignant. Induced adenocarcinomas in experimental animals may be extremely well differentiated, not showing anaplasia as much as human adenocarcinomas do. A

Fig. 9. Schematic representation of the steps in the morphogenesis of large intestinal carcinoma
In the next stage (called crypt repopulation), the hyperdistended crypts, which are much bigger than their normal counterpart, are repopulated, probably from the surviving undifferentiated cells. An increased amount of mitosis is seen in this stage. It is presumed that the progression of this stage leads to in situ carcinoma and subsequently to invasive carcinomas. There is evidence that such progressive changes take place in other species, including humans (Shamsuddin et al., 1986).

B. Natural History

Cancers of the large intestine spread by: (1) direct extension to adjacent tissues and (2) metastasis via the lymphatic and venous channels to regional lymph nodes and the liver, lung, and other distant organs.

The prognosis of patients with large intestinal cancer depends mostly on the stage of the disease. Histologic differentiation is often related to prognosis; better differentiated neoplasms offer a better prognosis.

The most widely accepted method for monitoring patients with large intestinal carcinoma is Dukes classification. Although several modifications of Dukes classification exist (and many more will probably be designed), this system of histopathological evaluation of the disease offers an excellent guide to the prognosis. The original Dukes classification was based on carcinoma of the rectum and is as follows (Dukes, 1932):

A. The cancer has spread by direct continuity into the submucosa or muscle (but not beyond). There is no lymph node involvement.
B. The cancer has spread beyond the muscle layers into the serosa and pericolic or perirectal tissues but no lymph node involvement.
C. The cancer has spread to the lymph nodes.

Five-year survival, a standard way of expressing the prognosis of a cancer patient, is also used for large intestinal cancer. The approximate 5-year survival rates for various stages are as follows: Dukes A, 100%; Dukes B, 50–65%; and Dukes C, 20–40%. The presence of metastatic carcinomas in distal sites carries a bad prognosis, with the liver being the most common site for metastasis of large intestinal carcinomas except for the regional lymph nodes (Fig. 10).

The use of azoxymethane in Fischer 344 rats induces carcinomas in the large intestine that metastasize to the lymph nodes and liver (Shamsuddin and Trump, 1981b; Shamsuddin, 1984b; Shamsuddin and Hogan, 1984). Interestingly, an otherwise well-differentiated adenocarcinoma (by light microscopy) shows the
presence not only of mucous cells but also of undifferentiated and endocrine cells (Fig. 11).

This finding leads us to the issues of tumor-cell heterogeneity and the concept of target cell(s) in malignant transformation. Heterogeneity of tumor cells was seen not only in the metastatic sites, but also in transplanted tumors and their parent primaries (Shamsuddin, 1984b). This phenomenon may indicate that (1) all three basic types in the large intestinal epithelium (the undifferentiated cells, the mucous cells, and the endocrine cells) are responding to the carcinogenic stimuli at a variable rate, or (2) the undifferentiated stem cells undergo a neoplastic transformation that shows a variable degree of differentiation to the other two cell types. It is plausible to explain the presence of various histological types of carcinomas of the large intestine on the basis of the second hypothesis (Fig. 12).

In the liver, another interesting finding was the presence of intercellular junctional complexes between the host hepatocyte and the metastatic carcinoma cells (Fig. 13). This finding is not totally surprising since it seems that cancer cells ("seeds") find certain organs ("soil") more appropriate for growth (Paget, 1889); the host tissue must be supportive of the nutrition and growth of the recently arrived metastatic cells. The presence of intercellular junctions between the metastatic cancer cell and host hepatocytes was also observed in human cancers (Iseri and Shamsuddin, 1980). It is quite likely that the establishment of cell to cell communication by way of intercellular junctions may be important in metastasis.

Fig. 11. Adenocarcinoma of the colon. Ultrastructural features of the carcinomatous glands exemplifying tumor-cell heterogeneity. The obvious mucous cells near the lumen (upper left), endocrine cells (EC), and undifferentiated cells (UC) are seen in this gland. Transmission electron microscopy, ×4568.

Fig. 12. Hypothesis to explain the genesis of histologic variety of tumors from three basic cell types in the large intestine.
2 Normal and Pathological Anatomy

C. Markers

Several markers of malignancy have been studied in order to diagnose intestinal cancer at an early stage. Attempts have been made to look for the expression of some of these markers in precancer stages; others have been studied for their expression in body fluids. There have been extensive studies of carcinoembryonic antigen (CEA), colon-specific antigen (CSA), mucin, its chemical changes, expression of cell surface glycoconjugates as determined by lectin-binding properties, and several enzymes. Although CEA was expected to be a specific marker for large intestinal cancer, it was subsequently demonstrated that it is expressed in noncancerous conditions. Recent studies in our laboratory, however, demonstrate that expression of CEA in tissue sections is determined by the choice of histological fixative (Phelps et al., 1986). Furthermore, we have discovered that a variety of precancerous lesions of the stomach, and large intestine express CEA in tissues (A. M. Shamsuddin and D. M. Purnell, unpublished observation). These findings may explain why, for example, smokers (with squamous metaplasia of the bronchus) have elevated CEA in the blood. Further studies on CEA are thus needed, as the CEA story is far from complete.

It has been demonstrated that the mucus in cancer and precancer tissue is abnormal (Shamsuddin and Trump, 1981b). We have also demonstrated that apparently normal mucosa remote from the cancer site may show phenotypic characteristics of cancer insofar as the mucin property is concerned (Shamsuddin et al., 1981). Boland et al. (1982a) demonstrated that the goblet-cell mucus in cancer binds specifically to peanut agglutinin (PNA), indicating the presence of sialic-acid-free terminal disaccharide B-D-Gal (1→3)-D-GalNAc. Work in our laboratory subsequently confirmed the expression of the sugar moiety in precancerous lesions of humans and experimental animals (Elsayed et al., 1986).

By exploiting the facts that (1) the mucosa that is remote from the cancer in the large intestine shows a variety of changes indicative of malignancy and (2) PNA binds to the B-D-Gal (1→3)-D-GalNAc not only of the goblet-cell mucus but also of the secreted mucin, as well as to neuraminidase-treated red blood cells of ABO type, we have recently developed assays that may have potential application in screening populations for early diagnosis of large intestinal cancer (Shamsuddin and Elsayed, 1987).

In summary, a clearer understanding of the normal characteristics of the colon is crucial to the study of the diseases, including carcinomas. The morphology of the carcinomas show marked variation within the same tumor. Further careful studies are thus needed to better understand the tumor-cell differentiation (or de-differentiation) in order to correlate the biologic behavior.
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