MINIREVIEW

Effect of Aging on the Gastrointestinal Tract and the Pancreas (44120)

ADHIP P. N. MAJUMDAR,*[,1] RICHARD JASZEWSKI,* AND MICHAEL A. DUBICK†[,‡]

Division of Gastroenterology, VA Medical Center and Wayne State University School of Medicine, Detroit, Michigan 48201; U.S. Army Institute of Surgical Research,† Fort Sam Houston, Texas 78234; and Department of Physiology,‡ University of Texas Health Science Center, San Antonio, Texas 78284*

Abstract. **With estimates that about 14% of the U.S. population will be over 65 years old by the end of this century, scientific research has attempted to achieve a better understanding of the aging process and of diseases that are expressed in higher incidence with advancing age. Because of its high rate of cell turnover and continual renewal, the mucosa of the gastrointestinal (GI) tract appears particularly susceptible to age-related disruptions in the normal cell proliferative process. This may translate into altered function that may result in the induction of malnutrition or malabsorption of particular nutrients, or a greater incidence of GI diseases, such as neoplasia. This review will examine the evidence for age-related alterations in the structural and functional properties of different regions of the GI tract and the pancreas, and how they may relate to malnutrition or disease processes.** [P.S.E.B.M. 1997, Vol 215]

Aging has been defined as the progressive accumulation of changes with time which are associated with or are responsible for ever-increasing susceptibility to disease and death, the final event of age. Within the past 50 years or so, the number of people over the age of 65 years, especially in the developed countries, has increased considerably. In the United States alone, 1 out of every 10 citizens are now over the age of 65, and it is projected that by the end of this century about 14% of the U.S. population will be over 65. Thus, the interest in experimental gerontology and on the aging process is becoming paramount.

The nature of the aging process has been the subject of considerable speculation (1). Some of the suggested possibilities include (1): (i) encodement of aging DNA, (ii) progressive deterioration in accuracy in protein synthesis, (iii) cross-linkage of macromolecules, (iv) in higher organisms "attack" of the immune system on self-antigens, and (v) free radical reaction damage. Since the pattern of growth of every tissue is not the same throughout life, further studies on various organs are required for an understanding of the aging process in different organs.

Mammalian tissues normally follow a defined schedule of growth (2). During embryogenesis, the growth of all organs is accomplished by cell division. This, however, ceases dramatically once adolescence is reached; thereafter, much less mitotic activity is required to maintain the steady state. On the basis of mitotic activity, mammalian cells of adult tissues have been classified into three groups (2, 3): (i) continually dividing cells (such as gastrointestinal [GI] and hematopoietic cells): (ii) postmitotic cells, formed early in life and not replaceable after their specialization (such as neurons and striated muscle cells), and reverting postmitotic cells with a potential dividing capacity triggered only after special stimuli (hepatocytes, osteocytes, and renal tubular cells).

[1] To whom requests for reprints should be addressed at Research Service–151, VA Medical Center, Detroit, MI 48201.

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The mucosa of the gastrointestinal tract has one of the most rapid cell turnover rates of any tissue in the body. In the normal mucosa, the continuous cell renewal is assured by a sustained proliferative activity of the so-called progenitor or stem cells (4–7). Resulting cell production not only compensates for cellular shedding from the surface epithelium but also assures the renewal of certain specialized cells in the glandular tubes. An error in any part of this process may accelerate or diminish the growth, resulting in either hyperplasia/hypertrophy or atrophy of the organ. Theoretically, therefore, any substance that affects the growth regulatory process is likely to have an influence on the size and maturation of the GI mucosa, and in turn may affect the functional properties of the organ(s). For example, it is well recognized that the incidence of malnutrition and malabsorption increases with advancing age. However, the extent that these observations relate to aging per se, or to disease states that have a higher incidence of expression with advancing age remains unclear. Knowledge of normal cell proliferation kinetics and regulation of GI mucosal growth at various stages of life is, therefore, essential for the understanding of the pathogenesis of many GI diseases and disorders linked to aging. In this review, age-related changes in structural and functional properties as well as alterations in cell proliferation of various regions of the GI tract and pancreas will be discussed.

Stomach

Like other parts of the GI tract, the gastric mucosa is composed of numerous exocrine and endocrine cells (7), which renew at different rates. In the oxyntic gland area of the stomach, most of the newly produced cells migrate rapidly to the surface while differentiating into mucus cells. The migration time, which represents the time for replacement of the total cell population above the dividing zone, is about 3 days in adult rats (4) and 4–6 days in the adult dog and human (8, 9). Most studies have indicated that parietal cells are unable to divide (9), and some newly formed cells slowly migrate down the gland to differentiate into acid producing cells (9). In the adult mouse, zymogen (chief) cells are replaced by mitosis (10, 11), but after injury they have been found to originate from undifferentiated cells.

Aging is associated with marked changes in the structural and functional properties of the gastric mucosa. In rats, aging is found to be associated with gastric atrophy, as evidenced by a significant reduction in mucosal glandular height, gland density (number of gland/cm^2) and total mucosal DNA content (12, 13). Electron microscopy studies in rats have further demonstrated ultrastructural degenerative changes in both parietal and chief cells (14, 15). Therefore, decreased basal and gastrin-induced acid secretion (13), which we have observed in rats, could partly be attributed to a reduced number of acid secretory cells (12, 14). In contrast, recent studies on healthy humans revealed no significant change in either basal or stimulated gastric acid output with aging (15–17). Earlier studies, which reported a decline in both basal and maximal gastric acid output in aging human populations (18), could be the result of inclusion of subjects with atrophic gastritis, a condition that is recognized to be rather common among the elderly, affecting 25% of those over 60 years of age (19, 20). For example, Bird *et al.* (19), who analyzed 201 gastric biopsy specimens from individuals aged 65–90 years, have observed signs of gastric atrophy in most of the specimens. Another factor that may affect gastric acid secretion in humans is *Helicobacter pylori* infection (15, 21), the incidence of which is also increased with aging (22, 23). *H. pylori* has been recognized as a causative factor in the development of chronic antral gastritis (24).

In rats, basal pepsin secretion as well as mucosal pepsinogen concentration were also found to be lower in aged than in young rats (13, 25). The regulatory mechanism(s) for the age-related decline in mucosal pepsinogen content in rats is not known. However, we have recently reported a decline in steady-state mRNA levels of several gastric proteases, including pepsinogen C, with aging (26). Whether this could result in decreased synthesis of the enzyme remains to be determined. In humans, aging has also been shown to decrease both basal and stimulated gastric pepsin output, and was found to be independent of atrophic gastritis, *H. pylori* infection or smoking (17). On the other hand, serum pepsinogen I levels in normal females, but not in males, were shown to increase with age (27). A similar observation was also made in duodenal ulcer patients aged 50 or over (28).

At times, atrophic gastritis is also associated with intestinal metaplasia, and both conditions are age-related and are considered to be precancerous lesions (29). Thus, aged individuals with gastritis are statistically at risk of developing gastric cancer, but precise measurement of this risk has not been determined. Furthermore, endoscopic examination in asymptomatic individuals who have undergone partial gastrectomy for duodenal ulcer 15 years or earlier has revealed unsuspected mucosal abnormalities, including atrophic gastritis, intestinal metaplasia, or carcinoma of the gastric stump (30). We have recently analyzed time-dependent changes in ornithine decarboxylase activity (ODC), an indicator of proliferative process, in the gastric mucosa of subjects who underwent Billroth I or II gastrectomy (31). We reported that ODC was significantly higher in Billroth II patients in whom gastrectomy had been performed >15 years earlier compared with those in whom it had been performed <15 years earlier or normal controls (31). We suggested that patients who underwent gastrectomy >15 years earlier may be at risk of developing cancer (31).

Since the structural and functional integrity of the mucosa of various parts of the GI tract, including that of the stomach are maintained by the constant renewal of cells, a number of laboratories, including our own have studied the age-related changes in GI mucosal cell proliferation and the regulation of this process at different stages of life. Earlier, we reported that gastric mucosal proliferative activity in

rats, as assessed by DNA synthesis, thymidine kinase activity, and protein synthesis, remained elevated during the first 2 weeks of postnatal life then decreased over the next 2–3 weeks (32). Despite this fall in proliferative activity between 4 and 5 weeks of life in rats, mucosal DNA content rose dramatically during this period, indicating an increase in total mucosal cell populations (32). On the other hand, gastric mucosal proliferative activity in 20- to 24-month-old Fischer rats was found to be higher than in their 4- to 5-month-old counterparts (33). This was evidenced by increased mitotic labeling (34, 35), the rate of DNA synthesis (36, 37), thymidine kinase activity (37), and ODC (38). Several others have also reported a similar phenomenon in both small and large intestine (39, 40), where these investigators found a greater number of crypt cell production relative to villus cell populations (39, 40). However, this was not accompanied by increased growth of the organs. Therefore, the reported increased production of crypt cells could not be explained by formation of more crypts, which suggests that in the small and large intestine of aged rats DNA replication was without cytokinesis. A similar explanation could also be offered for our observation in the gastric mucosa, in which increased mucosal proliferative activity was not accompanied by a concomitant rise in mucosal growth, but rather in which aging resulted in atrophy of the tissue, as evidenced by the decreased mucosal height as well as DNA and RNA content in 24-month-old Fischer-344 rats compared with their 4-month-old counterparts (34, 41). Whether this is the result of increased cell loss or a block in the mitotic or other cell cycle regulatory events remains to be determined.

Over the past three decades numerous reports have appeared which indicate that several GI hormones/growth factors, including gastrin, bombesin, EGF, and TGFα, stimulate GI mucosal cell proliferation in young adult animals (42, 43). However, at least in the gastric mucosa, the age-related rise in mucosal proliferative activity cannot be attributed to gastrin (36). In fact, we have observed that aging is associated with a loss of responsiveness to the growth-promoting action of gastrin (44). A similar phenomenon was also observed for bombesin (an amphibian peptide which is structurally and functionally analogous to gastrin releasing peptide [GRP]) (44), which has also been shown to stimulate gastric mucosal cell proliferation in young mature animals (42). Although the underlying mechanisms for the age-related loss of growth stimulatory effect of either gastrin or bombesin remain to be fully elucidated, at least for gastrin it could be attributed in part to the loss of functional receptors since Singh *et al.* (45) found an age-related decrease in the number of gastrin binding sites in the gastric mucosa. In contrast to what has been observed for gastrin and bombesin, EGF and its structural and functional analog TGFα have been shown to inhibit gastric mucosal proliferative activity in aged rats (37, 46). Our recent data suggest that this inhibition could be due in part to increased sensitivity of aged gastric mucosa to these peptides such that low doses of these peptides are stimulatory, whereas high doses inhibit proliferative processes (46). In support of this postulation we have observed that the concentration of TGFα needed to induce maximal stimulation in EGF-receptor tyrosine kinase activity in gastric mucosal membrane preparations from aged rats is at least 1/1000th of that required for the same induction in young rats (46). Responsiveness of the intestinal mucosa to the growth stimulatory effects of gastrin, bombesin, EGF, or TGFα during advancing age has not yet been investigated. However, neurotensin, a GI peptide which has been shown to stimulate mucosal growth in different parts of the GI tract in mature young rats, also stimulates small and large intestinal mucosal cell proliferation in aged rats (47, 48).

In addition to hormones, nutritional factors are also known to regulate GI mucosal cell proliferation. In the stomach, food deprivation decreases mucosal cell proliferation and refeeding reverses the situation (49). A similar phenomenon has also been observed in the small and large intestine. Holt and Yeh (50, 51) have compared the effect of fasting and refeeding on small and large intestinal mucosal proliferative activity in young and aged rats. They reported that, whereas in young rats fasting for 3 days decreased intestinal mucosal proliferative activity by 40%–60%, in aged rats this resulted in only a 10%–20% reduction when compared with the corresponding *ad libitum*–fed controls (50, 51). Furthermore, the food-induced stimulation in proliferative activity in the small intestine in aged, but not in young, rats was associated with broadening of the proliferative zone (50, 51). In fasted aged rats, proliferative responsiveness of the large intestine to food was found to be blunted (51). Although these observations indicate that nutritional regulation of mucosal cell proliferation is affected by aging, little information is available about the role of different nutrients in GI mucosal cell proliferation during advancing age. However, calorie restriction has been shown to prevent the age-related rise in intestinal crypt hyperplasia in rats (52).

In evaluating the intracellular events regulating the age-related rise in gastric mucosal cell proliferation, we have assessed the role of tyrosine kinases (Tyr-k), which are known to play a critical role in cell proliferation and differentiation (53, 54). Tyr-k's are associated with receptors of many growth factors receptors and products of a number of proto-oncogenes (53, 54). That Tyr-k's may play a role in regulating GI mucosal cell proliferation during aging came from the observation that the age-related rise in gastric mucosal proliferative processes was also accompanied by a parallel increase in overall Tyr-k activity and tyrosine phosphorylation of several membrane proteins (33). The latter included a phosphotyrosine membrane protein with apparent molecular mass of 53–55 kDa. Additionally, we have observed that stimulation of gastric mucosal proliferative activity, whether the result of aging, injury, or administration of gastrin, bombesin, or EGF to young adult rats, is associated with a marked rise in tyrosine phosphorylation of

a membrane protein with an apparent molecular mass of 55 kDa (34, 37, 44, 55). Moreover, the dose of EGF that inhibits gastric mucosal proliferative activity in aged rats also causes a reduction in tyrosine phosphorylation of 55-kDa membrane protein; an opposite phenomenon occurs in young rats (37). In an effort to characterize the 55-kDa phosphotyrosine membrane protein and to determine its role in gastric mucosal cell proliferation, we have raised polyclonal antibodies against this protein. Subsequent purification and immunoprecipitation studies showed that not only is the 55-kDa gastric mucosal membrane protein a Tyr-k but the enzyme activity is substantially higher in aged than in young rats (56, 57; and unpublished observation). In addition, we have also observed that stimulation of gastric mucosal proliferative activity at 24 hr after injury (58) is accompanied by a marked rise in relative abundance of immunoreactive 55-kDa protein in the mucous neck area of the gastric mucosa (unpublished observation). The role of this protein in regulating gastric mucosal cell proliferation during or in response to various GI hormones/growth factors remains to be determined.

The significance of increased mucosal proliferative activity with aging, accompanied by a rise in Tyr-k activity, is not fully understood. However, increased Tyr-k activity is generally associated with both preneoplastic and neoplastic lesions. In the GI tract, a positive relationship between the hyperproliferative state and Tyr-k activity has been demonstrated in various premalignant and malignant lesions (59–62). We have also observed an age-associated rise in Tyr-k activity of $pp60^{c\text{-}src}$ and EGF-R in the gastric mucosa of Fischer-344 rats. This, together with the finding of an increased mucosal proliferative activity, suggests that they may be contributing factors in the development of neoplasia at later stages of life.

Small Intestine

Maintenance of the structural-functional integrity of the small intestine with advancing age remains incompletely understood. Although structural changes suggesting involution of the small intestine resembling the small intestine in newborn and weanling animals have been reported (63), it appears that the small intestine has a large reserve capacity whereby generally impaired absorption of nutrients in the elderly is not a widespread observation. For example, lactose/mannitol absorption test in older individuals (>60 years old) revealed no significant disruption in small intestinal mucosal integrity (64). In weanling as well as in 5- and 15-month-old rats, no significant reduction in uptake of polystyrene latex microspheres was observed in either the proximal or distal small intestine as a function of age (65). Nevertheless, evidence suggests that the uptake of certain nutrients is affected by aging. It has been reported that the uptake of vitamin D, folic acid, vitamin B_{12}, calcium, copper, zinc, fatty acids, and cholesterol is decreased in the aged, whereas vitamin A and glucose absorption are increased in these animals (63, 66, 67). However, others have reported an opposite or absence of effect of nutrient absorption in the aged that reflect species variations. Although some of the altered nutrient uptake with age may be related to the well-observed decrease in splanchnic blood flow and changes in gastrointestinal motility (the latter will not be discussed here), the possibility of age-related alterations in the continual replication of small intestinal cells makes this a high-priority area for research into the effects of aging on small intestinal function. In a recent study, Yoshinaga *et al.* (68) compared the duodenal responses in 4- and 25-month-old rats to 70% distal bowel resection. Both groups of rats showed similar hyperplastic responses on the 20th postoperative day. Although duodenal disaccharidase activities were increased in young rats, no such increase was observed in the aged animals. These data suggest that the aged rats retain sufficient proliferative potential, but the return of intestinal function may be impaired in these animals.

Since intestinal surface area is an important determinant of absorption, Meshkinpour *et al.* (69) evaluated the surface area across the entire small intestine in rats ranging in age from 2.5 to 92 weeks. They observed that the intestinal length and surface area did not change significantly after 6 weeks of age, despite continuing increases in the animal's body weight.

A number of studies in rats and mice have examined the changes in the morphology of the small intestine with advancing age. Hohn *et al.* (70) observed that, in 30-month-old rats, the mucosa of the duodenum and jejunum appeared atrophic compared with the same area of the small intestine in 4-month-old rats. Villi height was approximately 20%–25% lower in the older rats compared with their younger counterparts. However, no age-related changes were observed in the ileum (70). In addition, they observed lower acid and alkaline phosphatase in aged than young rats, which they attributed to a reduction in enterocytes associated with atrophy in the older rats (70). In contrast, Moog (71) observed taller villi in the small intestine from 2-year-old than 6-month-old mice, but found similar alkaline phosphatase-, maltase-, and sucrase-specific activities in both age groups. However, since the total intestinal weight in the older mice was greater than in young animals, total enzyme activity was calculated to be higher in the older mice.

In their study, Raul *et al.* (72) observed that small intestinal mass and protein content were higher in 29-month-old rats than in their 3- and 12-month-old counterparts. In addition, villus height in the duodenum, jejunum, and proximal ileum were significantly lower in 12- and 29-month-old rats than in 3-month-old animals, whereas in the distal ileum they were found to increase with advancing age. In addition, specific activities of intestinal disaccharidases and aminopeptidase were also found to be higher in aged than in young rats (72), which could partly be due to altered cellular maturation along the villi in the proximal small intestine.

Holt *et al.* (73) observed a decrease in small intestinal hydrolases in 27-month-old rats compared with 4- to 5-month-old rats, and have attributed this to an increase in

the proportion of relatively undifferentiated villus epithelial cells in the older animals, which translated into delayed enzyme expression. Such delayed enzyme expression could lead to impaired nutrient absorption with aging, independent of any age-related structural changes. In addition, it was observed that the age-related decreases in jejunal or ileal maltase-, sucrase-, and alkaline phosphatase-specific activities did not occur gradually with advancing age, but rather occurred abruptly (52). Further, studies by Holt and Yeh (50) found that crypt cell proliferation rates in all segments of the small intestine were greater in 26- to 28-month-old rats compared with their 4- to 5-month-old counterparts, and suggested that this increase in cell production resulted from a greater number of crypt cells undergoing cell division. In summary, the results from these studies indicate that, whereas the villi height in the duodenum and jejunum is reduced, crypt cell proliferation rates as well as the proliferative zone are increased in the aged. However, there is a delayed expression of brush border enzymes in the proximal intestine with aging, which suggests altered function that may impair absorption of nutrients. Although the crypt height was not decreased, activity of the brush border enzymes in the ileum was either increased or unchanged in aged compared with young adult rats. This may cause some ileal hypertrophy in the aged animals as a consequence of increased substrates present in the ileal lumen, possibly as a result of some degree of impaired absorption of nutrients in the proximal intestine.

It is recognized that intake of many micronutrients and overall food intake are reduced in elderly populations and that the elderly may require higher nutrient intakes compared with younger adults to improve indices of nutrient status (66, 74). Because of an apparent age-related decline in digestive and absorptive capacity in humans, and despite the small intestine retaining somewhat of a reserve capacity with advancing age, it is important to understand how the aging small intestine responds and adapts to changes in dietary composition. A number of studies have examined the structural-functional changes in the small intestine as a consequence of food deprivation. These earlier studies have been reviewed (75) and it was observed that short-term starvation led to a reduction in villus height and epithelial cell production and migration. This appeared to be limited to the proximal small intestine and was not observed in the ileum. Few studies, however, have investigated these changes in response to advancing age.

Holt *et al.* (76) have reported that acute starvation in adult rats reduced the rate of crypt cell production and the number of villous cells in the proximal small intestine. This resulted in fewer proliferating crypt cells, a prolonged cell cycle, and a slower rate of cell migration. These effects were reversed by refeeding. They also demonstrated that the response to starvation, with regard to crypt cell production rates, in 27-month-old rats was similar to that of their younger counterparts, but in the duodenum of older animals the decreased rate was much less than in younger rats (50). Refeeding increased crypt cell number in both young and old rats, but the increase was minimal in the aged animals (50). However, in the duodenum of aged rats, refeeding resulted in a small increase in [^{3}H]thymidine labeling and an expansion of the zone of proliferating crypt cells. Thus, the effect of 3-day starvation and refeeding on cell production and proliferation in aged small intestine is of a lesser magnitude than the changes seen in young rats. Interestingly, Heller *et al.* (52) reported that the age-related decreases in certain intestinal disaccharidases and alkaline phosphatase could be delayed or reduced by dietary food restriction. It would be interesting to evaluate whether the age-related changes in crypt cell proliferation and migration rates would also be modified by lifetime dietary restriction, which has been reported to reduce the changes associated with aging in other organs. Nevertheless, it is clear that the response of the aged small intestine to changes in dietary composition is poorly understood and has primarily been investigated in response to short-term starvation and refeeding. Continued research with alterations in specific nutrients would add much to our understanding of the adaptive capacity of the aged small intestine.

Colon

The normal aging process has numerous and diverse effects on the large intestine as reflected by alterations in mucosal cell growth, differentiation, metabolism, and immunity. It is critical to differentiate these alterations with specific regard to their evolution in the context of the physiologic process of aging or sequelae of age-related pathogenic processes. Perhaps it would be most relevant to discuss specific changes in the structural and functional integrity of the colonic mucosa with advancing age as they relate to pathologic entities more commonly encountered in the elderly population, specifically cancer, diverticulosis, and dysfunctional bowel habits.

A consistent pathologic observation in senescent animals as well as humans is the increased incidence of colorectal neoplasia, a leading cause of morbidity and mortality with more than 150,000 newly diagnosed cases annually in the United States alone (77). Several explanations have been offered to explain the age-dependent increase in colon cancer incidence, including altered carcinogen metabolism and the cumulative effects of long-term exposure to certain cancer-causing agents (78–80). However, there is a growing body of evidence suggesting that aging itself is associated with alterations in cellular proliferation and enhanced susceptibility to transformation upon exposure to carcinogens. Although colorectal neoplasia is a multistage process, hyperproliferation is thought to be central to the initiation of carcinogenesis (81). As stated earlier, studies by Holt and Yeh (51) have demonstrated that crypt cell production rate is considerably higher in aged Fischer-344 rats than in their younger counterparts. They further noted widening of the proliferative zone in the colon of aged animals (51). Since these changes are considered central to the development of

carcinogenesis in the GI tract (82), it is suggested that aging may predispose the colon to malignant transformation.

In assessing the age-related susceptibility of the colonic mucosa to carcinogens, we have recently examined the changes in ODC and Tyr-k activity in the colonic mucosa *in vitro* in response to methylazoxymethanol (MAOM), the active metabolite of the colonic carcinogen azoxymethane (AOM). We have reported that MAOM causes a greater stimulation in ODC and tyrosine kinase activities in aged than in young colonic mucosa over the respective controls, indicating an increased susceptibility of the colonic mucosa of aged rats to this carcinogen (82). A similar phenomenon was also noted with TGFα (83), a potent mitogen for various tissues of the GI tract, including the colon (84, 85). A growing body of evidence also suggests that TGFα may play a critical role in the development of colorectal neoplasia through an autocrine/paracrine mechanism. This comes from the observation that cell lines derived from adenocarcinomas of various tissues, including the colon, express TGFα and its receptor, EGF-R (86–90). Since TGFα exerts its mitogenic action by activating the intrinsic Tyr-k of EGF-R (91), we have compared the changes in TGFα-mediated activation of EGF-R associated Tyr-k activity between young and aged rats (83). We have observed that in isolated colonic mucosal membrane preparations, TGFα produces a significantly greater stimulation of EGF-R Tyr-k activity and tyrosine phosphorylation of several proteins in aged than in young rats, when compared with the corresponding basal levels (83). Since this occurred despite a higher basal EGF-R Tyr-k activity in aged rats, we suggested that aging is associated with increased responsiveness of the colonic mucosa to TGFα (83). We have also reported an age-related increase in overall Tyr-k activity and tyrosine phosphorylation proteins as well as ODC activity in the colonic mucosa from patients with adenomatous polyps (62). Since these changes are considered central to the development of carcinogenesis in the GI tract (81), it is tempting to speculate that aging may predispose the colon to malignant transformation.

Diverticular disease of the colon is particularly common in Western societies, and its prevalence is clearly correlated with advancing age (92). This age-related increase in diverticular disease may be related in part to a progressive reduction in the mechanical integrity of the colon (93, 94). Indeed, the ability of the colon wall to resist increases in intraluminal pressure may be compromised with aging (95). The specific structural defenses of the colon to resist increases in intraluminal pressure are the collagens, which form a submucosal network of fibrils (96), which become smaller and more densely aggregated with aging. Christensen *et al.* (94) examined the biochemical properties and intestinal wall composition in young and old rats. They noted that aging was characterized by an increase in collagenous protein accumulation in the colon wall and that this was accompanied by a significant decrease in tensile strength. On the other hand, in examining the changes in the healing of left colonic anastomoses in rats, others have found no significant difference in collagen content and tensile strength between young and old animals (97). Clearly, further studies are warranted to assess fully the underlying mechanisms for the age-related rise in diverticular disease of the colon.

Another GI dysfunction associated with advancing age is constipation. The control of colonic motility is complex and influenced by myenteric plexus neuron density, neurotransmitter(s) release, smooth muscle responsiveness, and nutritional and hormonal factors. There is still considerable debate regarding age-associated alterations in colonic transit time. Some studies using clinical markers detected no significant difference in colonic transit between young and elderly subjects (98–100), while others have found a significant increase in colonic transit time with aging (101, 102). Aging is also associated with a reduction in the number of neurons in the colonic myenteric plexus (103, 104). One study has noted an age-dependent reduction in acetylcholine release in the rat colon myenteric plexus which was associated with diminished influx in membrane channels (105). Clearly, little is known about the regulatory mechanisms for the age-related changes (if any) in colonic transit.

Pancreas

Since the structural and functional properties differ significantly between the exocrine and endocrine pancreas, age-related changes of these organs will be discussed separately.

Exocrine Pancreas. A number of structural changes have been described in the aging pancreas. Results from earlier literature report that the organ decreases in weight after the seventh decade of life in humans, and it becomes harder and atrophic (106–108). In addition, histological changes such as ductal epithelial hyperplasia, intralobular fibrosis, and acinar cell degranulation have been described. These morphologic changes in the aging pancreas have been ascribed to pancreatic involution leading to decreased secretory capacity of the exocrine pancreas (107, 109).

Despite these morphological changes, an evaluation of previous studies has revealed little to no significant deficit in exocrine pancreatic function in elderly humans. For example, Gullo *et al.* (110) found that following continuous iv infusion of secretin and caerulin, bicarbonate, enzyme, and volume output from the pancreas was within normal control levels in groups of individuals over 60 and over 70 years of age. When a noninvasive fluorescein dilaurate test was employed, normal pancreatic function was also observed in elderly subjects over 80 years of age (111). In addition, Carrere *et al.* (112) found no significant difference in serum levels of immunoreactive trypsin-1 and lipase, or lipase activity in elderly subjects with a mean age of 72 compared with younger populations (mean age of 30).

In contrast, Vellas *et al.* (109) reported a parallel 45% decrease in bicarbonate and enzyme output and 15%–23% decreases in bicarbonate and enzyme concentrations in pan-

creatic aspirates collected from 28 elderly subjects (mean age of 72 years) compared with those with an average age of 36 years, following continuous iv infusion of secretin and caerulin. Statistically lower secretory volume and bicarbonate and enzyme output after an iv bolus infusion of secretin were observed in elderly individuals over 65 years old compared with younger subjects (113). Also, significantly lower fecal chymotrypsin activity was observed in elderly subjects (mean age of 77.6) compared with young controls (114). A longitudinal study that measured pancreatic juice output following a single iv injection of secretin and CCK in individuals ranging in age from 16 to 83 years revealed that the volume and the maximum concentrations and outputs of bicarbonate, lipase, phospholipase, and chymotrypsin began to decrease slightly after the third or fourth decade of life (107). In a similar study, where secretin tests were given to men and women of various ages, when the data were stratified to evaluate those over 45 years old compared with those under 45, older men showed higher amylase and lipase secretions (115). In contrast, women over 45 years of age showed lower bicarbonate concentrations and output compared with younger women (115).

Taken together, none of these studies in humans demonstrate a clinically significant decline in exocrine pancreatic function in aged populations. However, some of them support the hypothesis of pancreatic involution with advancing age (109, 116), which might explain the onset of pancreatic insufficiency in certain individuals. Therefore, to better understand the mechanisms for pancreatic insufficiency when observed in the elderly, a number of studies utilizing Fischer-344 and Sprague-Dawley rats have investigated pancreatic function and trophic responses to hormones with advancing age.

Wang *et al.* (117) investigated pancreatic lipolytic activity among 3-, 12-, and 27-month-old rats, and found that the specific activity of lipase II declined with age while the activities of lipase I and cholesterol esterase remained unchanged. Utilizing rats of ages varying from 1 to 27 months, Hollander and Dadufalza (118) observed that pancreatic output dropped nearly 50% after 3 months of age, and decreased slowly thereafter such that output in 27 months old rats was about half the level of young adults. Similarly protein and amylase output dropped dramatically in 7-month-old rats compared with their younger counterparts, and in 27 months old rats they were about 20%–25% of the levels of young adults.

A number of studies have also examined the age-related changes in exocrine pancreatic secretion in response to different secretagogs, including secretin and CCK. Basal secretion of fluid, bicarbonate, and protein were not significantly affected by aging in either male or female rats (119, 120). However, the response to graded doses of CCK was attenuated in old rats compared with their younger counterparts (119, 120). Khalil *et al.* (121) also observed that the secretory responses to graded doses of secretin and CCK were reduced in 26-month-old rats compared with 6-month-old controls, but they also observed lower basal secretion of volume, bicarbonate, and protein in the old rats. Although the mechanisms for the lower responsiveness of the aged pancreas to various secretagogues is not well understood, Poston *et al.* (122) demonstrated that the number of pancreatic CCK receptors in 3-year-old guinea pigs is about one-third that of weanling animals and slightly lower than in 12-month-old animals. Although the data did not achieve statistical significance, there also was a similar decrease in CCK receptor binding affinity between the 3-year-old and weanling guinea pigs. Whether a similar phenomenon occurs in humans remains to be determined.

In other studies, Greenberg *et al.* (123) examined the trophic responses of the pancreas to chronic administration of caerulin and secretin. Although both hormones produced increased pancreatic weight, as well as protein, DNA, enzyme, and polyamine concentrations, in both young (3-month) and old (27-month) rats, the magnitude of stimulation was significantly higher for most of the variables in young rats compared with their old counterparts. Similar changes were also observed after chronic administration of CCK, bombesin, or pentagastrin to 3- and 24-month-old rats (124). In addition, it was also observed that amylase and trypsinogen steady-state mRNA levels were 2- to 2.5-fold higher in 16-month-old than in 3-month-old rats (125). Interestingly, whereas chronic administration of gastrin increased the amylase and trypsinogen steady-state mRNA levels in 3-month-old rats, compared with controls, the same treatment decreased the enzyme mRNA levels in 16-month-old rats when compared with their age-matched controls (125). In another study, chronic administration of bombesin increased trypsin activity and steady-state trypsinogen mRNA levels compared with controls in 4-month-old rats, but in 20-month-old rats bombesin treatment resulted in 15% lower steady-state trypsinogen mRNA levels compared with controls (126). These data support the hypothesis that the responsiveness of the pancreas to hormones is diminished with advancing age.

Studies in experimental animals have also examined the adaptability of the aged pancreas to changes in dietary composition and nutrient intake. Greenberg and Holt (127) examined the pancreatic response to feeding a high fat (72% of calories) or high sucrose (75% of calories) diet to 3- or 27-month-old rats. They found that young rats were able to increase their pancreatic lipase or amylase content in response to either diet, while this was not the case in the old rats. Similarly, old (26-month-old) rats fed a protein-free diet, and then refed a normal diet, were not able to raise the diminished pancreatic chymotrypsin and protein content as well as young (8-month-old) rats (128). Little adaptive capability in altering pancreatic enzyme concentrations to different levels of fat or carbohydrate in the diet was observed in aged rats (129). Results from these studies suggest that, despite evidence for diminished pancreatic function and response to trophic hormones with advancing age, the exocrine pancreas possesses sufficient reserve to maintain a

normal digestive capacity throughout a lifetime. However, under conditions of dietary stress, the aged pancreas may not adapt quickly or sufficiently to prevent some clinical expression of malnutrition. Further studies to evaluate the adaptive capacity of the aged pancreas under different dietary and physiologic stresses are warranted.

Endocrine Pancreas. A well-known observation of aging is the development of impaired glucose tolerance, which begins in the third or fourth decade of life and progresses thereafter (130). However, elderly individuals typically have normal or slightly elevated serum insulin levels (131).

An interesting observation is that in rats there is an increase in the size of pancreatic islets with advancing age. On the other hand, in aged rats the population of small islets loses its ability to respond rapidly to glucose *in vitro,* whereas this ability is retained in the large islets (132), indicating that overall insulin secretion by the aged pancreas in response to glucose remains normal. This contention has been supported by Hara *et al.* (133), who, utilizing isolated perfused pancreas or isolated islets of Langerhans from rats, observed no age-related changes in insulin secretion in response to glucose. In studies with isolated perfused pancreas from 2- to 30-month-old rats, Starnes *et al.* (134) reported that insulin, glucagon, and somatostatin release is well maintained throughout their lifespan. But, total pancreatic insulin content declined about 25% with advancing age from the peak observed at 18 months (134). Elahi *et al.* (135), however, observed that isolated perfused pancreas from 23-month-old rats show a reduced insulin release in response to low, but not high, concentrations of glucose, an observation not seen in their younger counterparts. It should also be mentioned that in isolated perfused pancreas from 24- to 27-month-old rats, somatostatin induced a greater inhibition of glucose-stimulated insulin release than seen in young (3-month-old) animals (136). In addition, Perfetti *et al.* (137) reported an age-dependent decrease in insulin, but not glucagon or somatostatin mRNA levels, when pancreas from 3-, 9-, and 30-month-old mice were examined. The current data suggest some selective dysfunction of the β cell in aged and senescent pancreas that may lead to an impairment of the insulin response to glucose, but that other factors contribute more to the impaired glucose tolerance observed in the elderly (138).

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