Intestinal Malabsorption in the Elderly

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Key Words

Small intestine, structural and functional changes • Intestinal micronutrient absorption • Vitamin B₁₂ malabsorption • Small intestinal bacterial overgrowth syndrome • Pancreatic disease • Investigation of structural changes • Celiac disease

Abstract

Background: Intestinal malabsorption in the elderly is infrequent, and clinical features are muted so that the diagnosis is often missed. Physiologic changes with aging are restricted to altered absorption of calcium and perhaps zinc and magnesium; however, achlorhydria can lead to impaired absorption of vitamin B₁₂, folic acid, and calcium. **Methods and Results:** Small bowel bacterial overgrowth occurs more commonly in elderly than in younger patients, accompanying gastric hypochlorhydria, altered intestinal motor activity, or diseases such as Parkinson's disease. Changes in pancreatic anatomy and secretion occur but are insufficient to produce macronutrient malabsorption. In addition to pancreatic cancer and pancreatic stones, older patients may present with severe pancreatic insufficiency of unknown etiology. Celiac disease is recognized as very common at all ages and may not become evident until late in life. Manifestations of celiac disease in the elderly are occult and the diagnosis often is not considered until serologic tests are performed and confirmed by upper small intestinal biopsy. Associated intestinal lymphoma, esophageal carcinoma, intestinal pseudo-obstruction, and splenic atrophy may be more common

in the elderly. Treatment of older patients with celiac disease with a gluten-free diet may be difficult, and intensive vitamin and micronutrient replacement is mandatory. A pragmatic approach to the evaluation of malabsorption in elderly patients is discussed.

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Introduction

Medical students who are introduced to the subject of malabsorption generally visualize an emaciated child whose major symptoms are diarrhea accompanied by the passage of foul-smelling oily stools. In contrast to this clinical picture, the majority of adult patients with malabsorption describe minimal gastrointestinal symptoms of colonic dysfunction, such as excessive bloating, crampy abdominal pain, and the passage of excess gas. Many others do not have overt gastrointestinal symptoms at all, but present with micronutrient depletion or deficiency. This is particularly pertinent in the elderly, who appear to adjust well to malabsorption-induced colonic dysfunction. The micronutrient depletion most often present includes fat-soluble vitamin deficiency, particularly the consequences of vitamin D deficiency, as well as folate and vitamin B₁₂ depletion, and low serum iron or iron deficiency anemia. Trace metal deficiencies may occur in patients with primary disorders of the small bowel epithelium and frequently are not recognized.

Structural and Functional Changes in the Small Intestine

In order to distinguish diseases that lead to impaired intestinal absorption from changes that may occur with the aging process, it is necessary to be aware of these age-related decrements in digestive and absorptive functions. Based upon older studies, there is the misconception that small intestinal villus height and surface area are reduced compared with that in young controls. However, careful evaluation of jejunal biopsy specimens from healthy elderly volunteers shows that the anatomy of epithelial cells and the surface area does not differ from that found in the young [1]. In the rat, although villus cell numbers in the proximal small intestine are similar in the young and old, crypt cell numbers are greater in Fischer 344 rats over age 24 months [2] accompanied by increased epithelial cell proliferation [3] and altered controls of cell production [4]. Similar changes have been described in the human small bowel epithelium [5]. Thus, abnormalities in upper intestinal villus architecture in an elderly person appear to be the result of disease and not the aging process. There is little evidence for reduction in brush border disaccharides enzymes with aging, with the exception of lactase (lactase-phlorizin hydrolase), the activity of which falls dramatically in the majority of the world's population with age. One careful study of lactose malabsorption and intolerance showed that subjects over age 74 years showed significantly lower lactose absorption based upon breath hydrogen analysis than younger individuals. However, intolerance symptoms amongst patients with malabsorption were less in the elderly [6]. Although there is evidence for a decrease in the small intestinal concentrations of other brush border enzymes in rodents [7], there is little confirmation of this change in humans.

There is abundant discordance in studies of changes in the absorption of macronutrients and some micronutrients with advanced age. One reason for this discrepancy is that mucosal weight and the content of epithelial cell transporters and some enzymes is higher per unit length of intestine in older rodents than in the young. Thus when intestinal absorption is studied as a function of protein concentration, it often is found to be reduced in older animals when compared to the young [8]. However, when calculated as a function of intestinal length, absorption usually is found to be unaltered [9, 10].

Lipid absorption overall appears to be little altered by the aging process [11]. Lymphatic fat and apolipo-

protein A4 transport was shown to be similar in mesenteric lymph-cannulated 8- to 10- and 24- to 26-month-old Wistar rats [12] and fecal fat excretion was maintained in volunteers provided 100 g [13] or >300 g [14] of fat. However, Thomson's group [15] recently described some reduction in rat ileal uptake of fatty acids in vitro, accompanied by up to 50% reduction in intestinal fatty acid-binding protein. It is possible that the reserve capacity of the small intestine in humans is large enough so that little malabsorption is observed until functional defects are severe.

Intestinal Micronutrient Absorption

Although there is little evidence for major malabsorption of macronutrients as a physiologic function of age, selected impaired absorption of several micronutrients does occur. Very early studies suggested that atrophy of the colonic mucosa occurs with advancing age [16], associated with alterations in water and electrolyte transport. Renal responses to sodium restriction are impaired in the elderly [17]; however in a recent study, mineralocorticoid-sensitive electrogenic sodium absorption was not lower in biopsies from the colon of human volunteers over the age of seventy [18]. The absorption of metal ions as a function of age has not received much attention; however, a recent report of careful studies in the rat suggests that zinc absorption may be considerably decreased, magnesium absorption decreased only moderately, and copper absorption is unaffected [19]. To the author's knowledge, detailed examination of small intestinal metal transporters as a function of age in humans or rodents has not been performed.

It is well known that calcium absorption falls with advancing age, which contributes to age-associated osteopenia [20]. Reduced calcium absorption appears to result from alteration of vitamin D metabolism or their effects at the intestinal level [21]. Plasma 1,25-dihydroxy vitamin D₃ (1,25(OH)₂D₃) levels are lower in the elderly than in the young [21], and this has been ascribed to impaired formation of this hormone at the level of the kidney [22]. It is now recognized that intestinal epithelial cells can synthesize the active form of vitamin D 1,25(OH)₂D₃ from circulating 25-hydroxy vitamin D₃ [23]. Such local production of 1,25(OH)₂D₃ may determine vitamin D activity in the intestine. Whether this function is altered in the elderly is unknown.

Vitamin B₁₂ Malabsorption

Vitamin B₁₂ depletion is very common in the elderly. In an evaluation of the Farmingham study population, up to 15% of people over the age of 65 were described as showing evidence of vitamin B₁₂ deficiency and many of these had serum vitamin B₁₂ levels within the conventionally defined normal range [24]. Vitamin B₁₂ absorption requires hydrolysis of food-bound vitamin B₁₂ in the stomach, binding of the released B₁₂ to a gastric protein – the R binder with the subsequent release of vitamin B₁₂ from R binding by acid and pancreatic enzymes. B₁₂ binding to intrinsic factor and absorption of the B₁₂ intrinsic factor complex is accomplished by specific receptors in the ileum. Pernicious anemia, due to atrophic gastritis, with failure to secrete intrinsic factor into the stomach as well as surgical resection or diseases of the ileum preventing intestinal absorption, represent the cause of vitamin B₁₂ deficiency in only a minority of elderly patients. The most common cause of such deficiency is food-bound vitamin B₁₂ malabsorption, associated with reduced gastric acid secretion and atrophic gastritis. In such patients, although intrinsic factor secretion is maintained, the absence of gastric acid results in failure of vitamin B₁₂ to be released from food [25]. Food-bound B₁₂ malabsorption may be associated with significant neurologic, psychologic, and hematologic abnormalities [26]. Malabsorption of food-bound B₁₂ responds not only to parental vitamin B₁₂ therapy, but the disorder may be treated with oral crystalline vitamin B₁₂ in doses of 250–1,000 µg/day. This regimen eliminates B₁₂ depletion and maintains normal serum vitamin B₁₂ levels, together with reversal of clinical abnormalities in most patients.

Folic acid is absorbed mainly in the upper small intestine so that diseases of this area of the bowel frequently lead to reduced circulating folic acid and evidence of megaloblastic anemia. In addition, it should be recognized that folic acid in foods is present as the heptapeptide requiring hydrolysis by pancreatic enzymes with the release of monoglutamate folic acid. Optimal absorption of folate monoglutamate requires a pH <7 [27], thus achlorhydria can result in reduced folic acid absorption and folate depletion [28]. One factor that may modify folate depletion in the presence of achlorhydria is jejunal bacterial overgrowth, since the abundance of bacteria in the upper small intestine may produce folic acid, overcoming folate malabsorption due to the high pH. It should also be remembered that, whereas vitamin B₁₂ stores often are sufficient in the presence of B₁₂ malabsorption to prevent vitamin B₁₂ deficiency for many years, folate

stores are quite limited and folic acid deficiency in the absence of absorption of food folate may occur within weeks or months.

Small Intestinal Bacterial Overgrowth Syndrome

Small intestinal bacterial overgrowth may induce occult malabsorption in the elderly, although the frequency of this disorder has been disputed [29, 30]. Structural causes such as post-gastrectomy states and intestinal strictures may result in bacterial overgrowth as also occurs in younger subjects; upper intestinal diverticulosis is common in advanced age, but rarely induces complications such as malabsorption [31]. Bacterial overgrowth in the absence of structural abnormalities appears to occur in older individuals based on breath H₂ analysis after a 50-gram glucose challenge [32] and may lead to nutritional deficiencies [33]. Such small bowel bacterial overgrowth may be associated with gastric achlorhydria [34, 35], but in some subjects appears to result from altered intestinal motor function rather than changes in gastric pH or changes in luminal IgA secretion [36]. Thorough studies of motor activity in the elderly demonstrate some delay in gastric emptying, but little effect in overall small and large bowel transit [37, 38]. The classic observations of Vantrappen's group [38] showed that changes in interdigestive motor complexes occur in patients with bacterial overgrowth and it has been suggested that this is the mechanism for malabsorption in the absence of structural alterations. However, one study in a small number of elderly subjects showed no evidence of abnormalities in the interdigestive (housekeeping) motor complex [39]. More important, probably, are diseases such as depression, hypothyroidism, and Parkinson's disease and the use of certain drugs such as antidepressants, analgesics, and calcium channel antagonists that slow gastrointestinal transit [40]. Enteric nervous system neuron dysfunction clearly can occur as a function of age [41], although consistent clinical effects are not universal.

Pancreatic Disease

Cross-sectional studies comparing younger with older individuals suggest that minor decrements in pancreatic enzyme output occur with advancing age. However, functional as well as structural changes do not occur in everyone, nor do they begin at a specific age or progress continuously. It has been suggested that arteriosclerosis may

reduce pancreatic blood flow and that intralobular fibrosis, accompanied by ductal epithelial hyperplasia and pancreatic atrophy, occurs to a modest extent [42]. Irregularity and dilatation of the main pancreatic duct and its secondary duct branches may be seen in abdominal ultrasound examinations [43] and by endoscopic retrograde cholangiopancreatography (ERCP) in elderly patients [44]. Overall, however, such structural changes are not necessarily associated with decrements in pancreatic function. Some studies have suggested a reduction of up to 40% in secretin-pancreozymin-stimulated lipase, trypsinogen and bicarbonate secretions [45]. However, it should be remembered that malabsorption does not occur until 80–90% of pancreatic enzyme secretion is lost. Some studies have suggested that serum levels of pancreatic enzymes may be elevated in elderly patients without evidence of pancreatic disease [46].

Pancreatic insufficiency with enough reduction in function and enzyme secretion to produce malabsorption may become apparent in the elderly without a previous history of pancreatic disorders. The classical description of pancreatic insufficiency of unknown etiology by Amman and Sulser [47] showed that 75% of pancreatic insufficiency of unknown etiology throughout the life span was present in the older age range. Amman's group suggested that 'vascular insufficiency' was responsible for pancreatic insufficiency in the elderly. Patients with pancreatic exocrine insufficiency and pancreatic calcification without the usual associated etiologic factors have been described from France [48] and Japan [49]. It is possible that the diagnosis in some of these patients was the more recently reported disease of immune-mediated lymphocytic chronic pancreatitis [50, 51]. Indeed, the patients described by Laugier and Sarles [48] in France may have had this disorder since they were originally described as having hyperglobulinemia and elevations of IgG4 have now become recognized as occurring frequently in autoimmune idiopathic pancreatitis. Some authors have suggested that pancreatic insufficiency should be sought in older patients who suffer from weight loss of unknown etiology [52] or 'geriatric cachexia', but this is probably rarely the cause. Pancreatic insufficiency also, of course, may occur as a result of chronic alcohol consumption, and individuals with chronic pancreatitis secondary to excessive alcohol intake may survive into the geriatric age group. Gallstone pancreatitis, although more frequent in the elderly than in the young, uncommonly results in chronic atrophic pancreatitis. Diabetes mellitus has been associated with pancreatic insufficiency in several studies [53].

Another form of chronic pancreatitis that is important in older patients is obstructive pancreatitis, caused either by an ampullary tumor or by carcinoma at the head of the pancreas. This usually is not associated with pancreatic calcification and protein plugs since it is of relatively acute onset. In this situation the main pancreatic duct often is dilated, which is uncommonly found in patients with alcoholic or idiopathic pancreatitis. Occasionally, stones may obstruct the pancreatic ducts, leading to chronic pancreatitis and malabsorption. Pancreatic duct stones increase in prevalence with advancing age and is seen in as many as 15% of patients older than 90 years [49].

Most patients with severe pancreatic insufficiency present with voluminous oily stools, near-normal serum albumin levels, and a normal xylose tolerance test. Tests of pancreatic insufficiency as the cause of malabsorption may be invasive and specific, noninvasive and indirect, or anatomical. Specific testing for a reduction in pancreatic enzyme output, following stimulation with a meal or cholecystokinin-pancreozymin requires the passage of a duodenal tube and is rarely performed in elderly patients, except in research facilities. Anatomical tests of pancreatic abnormalities include the presence of extensive pancreatic calcification, ultrasound examination, CT scanning, and/or ERCP to demonstrate widening of major and minor ducts. These changes imply but do not prove the presence of atrophy of parenchymal acinar tissue. Indirect functional tests include pancreatic lauryl testing, the *p*-aminobenzoic acid test and measurement of fecal elastase. All of these tests will be diagnostic if pancreatic insufficiency is severe. Fecal elastase determination has been utilized to evaluate subclinical covert reductions in exocrine pancreatic function in elderly individuals. One study of 914 subjects 50–75 years of age showed some reduction in fecal elastase (<200 per µg feces) in 11.5% and severe insufficiency (<100 per µg feces) in over 5% [54]. Since other studies have also shown reduction in fecal elastase with advancing age, this test may be optimal to evaluate pancreatic function in older individuals.

Investigation of Structural Changes

Evaluation of structural diseases of the small intestine classically has required barium studies of the small bowel or endoscopy, such as push enteroscopy and colonoscopy with evaluation of the distal ileum. Recently, capsule endoscopy has been introduced and has greatly expanded our ability to evaluate small bowel disorders

using a minimally invasive method that is more suitable for older patients than complex visual endoscopy. How could capsule endoscopy assist in the diagnosis management of disorders resulting from malabsorption? Capsule endoscopy has increasingly been used for the diagnosis of early Crohn's disease of the distal bowel [55]. Furthermore, it has been used to evaluate patients with suspected celiac diseases or malabsorption of unknown etiology [56, 57]. In celiac disease that is unresponsive to a gluten-free diet, capsule endoscopy can be used to determine whether patients may have ulcerative jejunitis and the presence of small bowel lymphoma. Capsule endoscopy is a painless and relatively noninvasive diagnostic tool but has the rare risk of entrapment of the capsule in strictures or diverticula. Thus, some authors recommend that small bowel X-rays should be performed to exclude these disorders prior to the administration of the capsule [58].

Celiac Disease

Celiac disease now is recognized as a very common genetic disorder that occurs in 1 in 100–150 of the population in many parts of the world [59, 60]. Most patients display no or minimal symptoms so that the diagnosis is often delayed [61] and must be suspected in individuals who are at increased risk, including patients with dermatitis herpetiformis, family members of patients with celiac disease, patients with certain autoimmune disorders, including autoimmune thyroiditis [62] and those with juvenile diabetes. In addition, physicians should suspect the disease in patients with pronounced or early osteoporosis, unexplained low serum iron determinations or iron deficiency anemia, or low serum folic acid measurements [63, 64]. In the absence of symptoms, the diagnosis often is made by tests for the antibody to tissue transglutaminase. Even if symptoms of malabsorption are present, elderly individuals display less severe complaints than younger adult patients with celiac disease, thus, the disease is very covert and often is not diagnosed until serologic tests or small bowel biopsy [65] are performed. Serologic testing for tissue transglutaminase has not been standardized at the present time, so that small bowel biopsy confirmation is important to confirm the diagnosis. In any case, celiac disease is much more common in the elderly than generally is recognized. About one quarter of the newly diagnosed patients with celiac disease are over the age of 60 [66], and many celiacs diagnosed young are reaching 'old age'. The usual colonic symptoms that are seen in patients with celiac disease that result from

the passage of unabsorbed macronutrients and bile acids into the large intestine are muted in the elderly, who may complain only of vague dyspepsia [67] or have manifestations only of micronutrient deficiencies. Celiac disease also may behave different in the elderly than in the young, because lymphoma of the small intestine may be more common [68] and small intestinal and squamous cell esophageal carcinomas occur in excess of expected estimates from age-adjusted cancer registries [69]. Some patients with celiac disease also have weight loss and chronic gastrointestinal blood loss associated with diffuse intestinal ulceration [70]. Splenic atrophy, associated with cavitation of mesenteric lymph nodes [71] or intestinal pseudo-obstruction, also occurs [72].

Studies of younger celiac patients who have been treated with a gluten-free diet for a long period of time have shown that the intestinal architecture is usually distorted and that modest malabsorption may be present [73]. This decrement in intestinal absorptive function may be added to the minor changes that occur as a function of age, and thus be exaggerated in such celiac disease individuals. The recorded prevalence of several malignancies amongst patients with celiac disease ranges from 11 to 14% and appears to increase with the duration of clinical follow-up.

When the diagnosis of celiac disease is made, the management of older patients with a gluten-free diet does not differ from that of younger individuals. However, older patients may have difficulty in changing lifestyles, and careful introduction of the diet is crucial. The patient may tend to neglect maintaining such a gluten-free diet, so that intense involvement of trained dietitians usually is needed to effect a satisfactory dietary regimen. Furthermore, secondary vitamin and micronutrient deficiencies must be treated more intensively than in the young, since the effect of the disease is added to changes in vitamin homeostasis that occur in the elderly. Particular care should be taken in the management of calcium and vitamin D homeostasis in older patients with celiac disease who already may have underlying osteopenia before the development of overt disease. In order to lower the frequency of crippling and disabling fractures, repeated measurements of bone densitometry is important to insure adequate treatment of calcium or vitamin D deficiency, often in conjunction with bisphosphonates. A strict gluten-free diet also will increase bone density.

Small bowel resection involving significant length of the ileum leads to malabsorption of bile salts with or without steatorrhea and carbohydrate and protein as well as micronutrient malabsorption if the resection involves

primarily the jejunum. Older patients recover small bowel function following intestinal resection at a slower rate than the young.

A pragmatic workup of suspected malabsorption in an elderly patient usually avoids complex and invasive testing. Prolonged fecal collections are poorly tolerated, but a simple qualitative test for fat malabsorption will diagnose steatorrhea of >15 g/day. The 25-gram xylose test with 1- and 2-hour xylose determinations has been validated in the elderly. The 1-gram ¹⁴C-xylose breath test has high specificity and sensitivity for diagnosing bacterial

overgrowth, but is not available in many centers – often the response to therapeutic testing with antibiotics is the way that such bacterial overgrowth is diagnosed. Upper gastrointestinal endoscopy with biopsy is the only specific test for celiac disease and collection of luminal contents for quantitative bacterial counting can be performed simultaneously. Pancreatic insufficiency can be diagnosed using fecal elastase testing, and imaging of the pancreas can suggest the presence of chronic pancreatitis.

References

- Corazza GR, Frazzoni M, Gatto MR, Gasbarrini G: Ageing and small-bowel mucosa: a morphometric study. *Gerontology* 1986; 32:60–65.
- Holt PR, Pascal RR, Kotler DP: Effect of aging upon small intestinal structure in the Fischer rat. *J Gerontol* 1984;39:642–647.
- Holt PR, Yeh KY: Small intestinal crypt cell proliferation rates are increased in senescent rats. *J Gerontol* 1989;44:B9–B14.
- Holt PR, Yeh KY, Kotler DP: Altered controls of proliferation in proximal small intestine of the senescent rat. *Proc Natl Acad Sci USA* 1988;85:2771–2775.
- Corazza GR, Ginaldi L, Quaglione G, Ponzielli F, Vecchio L, Biagi F, Quagliano D: Proliferating cell nuclear antigen expression is increased in small bowel epithelium in the elderly. *Mech Ageing Dev* 1998;104:1–9.
- Di Stefano M, Veneto G, Malservisi S, Strocchi A, Corazza GR: Lactose malabsorption and intolerance in the elderly. *Scand J Gastroenterol* 2001;36:1274–1278.
- Jang I, Jung K, Cho J: Influence of age on duodenal brush border membrane and specific activities of brush border membrane enzymes in Wistar rats. *Exp Anim* 2000;49: 281–287.
- Chen TS, Currier GJ, Wabner CL: Intestinal transport during the life span of the mouse. *J Gerontol* 1990;45:B129–B133.
- Ferraris RP, Hsiao J, Hernandez R, Hirayama B: Site density of mouse intestinal glucose transporters declines with age. *Am J Physiol* 1993;264:G285–G293.
- Hollander D, Dadufalza VD: Increased intestinal absorption of oleic acid with aging in the rat. *Exp Gerontol* 1983;18:287–292.
- Holt PR, Balint JA: Effects of aging on intestinal lipid absorption. *Am J Physiol* 1993; 264:G1–G6.
- Hayashi H, Sato Y, Kanai S, Masuda M, Ohta M, Funakoshi A, Nagao K, Imaizumi K, Miyasaka K: Lymphatic lipid transport is not impaired in ageing rat intestine. *Mech Ageing Dev* 2000;113:219–225.
- Arora S, Kassarian Z, Krasinski SD, Croffey B, Kaplan MM, Russell RM: Effect of age on tests of intestinal and hepatic function in healthy humans. *Gastroenterology* 1989;96: 1560–1565.
- Simko V, Michael S: Absorptive capacity for dietary fat in elderly patients with debilitating disorders. *Arch Intern Med* 1989;149: 557–560.
- Woudstra TD, Drozdowski LA, Wild GE, Clandinin MT, Agellon LB, Thomson AB: The age-related decline in intestinal lipid uptake is associated with a reduced abundance of fatty acid-binding protein. *Lipids* 2004;39: 603–610.
- Yamagata A: Histopathological studies of the colon in relation to age. *Jpn J Gastroenterol* 1965;62:229–235.
- Crane MG: Effects of aging on renin activity and aldosterone activity. *J Lab Clin Med* 1976;87:947–959.
- Greig ER, Mathialahan T, Boot-Handford RP, Sandle GI: Molecular and functional studies of electrogenic Na⁺ transport in the distal colon and rectum of young and elderly subjects. *Gut* 2003;52:1607–1615.
- Coudray C, Feillet-Coudray C, Rambeau M, Tressol JC, Gueux E, Mazur A, Rayssiguier Y: The effect of aging on intestinal absorption and status of calcium, magnesium, zinc, and copper in rats: a stable isotope study. *J Trace Elem Med Biol* 2006;20:73–81.
- Bullamore JR, Wilkinson R, Gallagher JC, Nordin BE, Marshall DH: Effect of age on calcium absorption. *Lancet* 1970;ii:535–537.
- Gallagher JC, Riggs BL, Eisman J, Hamstra A, Arnaud SB, DeLuca HF: Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients: effect of age and dietary calcium. *J Clin Invest* 1979;64:729–736.
- Tsai KS, Heath H 3rd, Kumar R, Riggs BL: Impaired vitamin D metabolism with aging in women. Possible role in pathogenesis of senile osteoporosis. *J Clin Invest* 1984;73: 1668–1672.
- Tangpricha V, Flanagan JN, Whitlatch LW, Tseng CC, Chen TC, Holt PR, Lipkin MS, Holick MF: 25-Hydroxyvitamin-D_{1α}-hydroxylase in normal and malignant colon tissue. *Lancet* 2001;357:1673–1674.
- Lindenbaum J, Rosenberg IH, Wilson PW, Stabler SP, Allen RH: Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;60:2–11.
- Carmel R, Sinow RM, Siegel ME, Samloff IM: Food cobalamin malabsorption occurs frequently in patients with unexplained low serum cobalamin levels. *Arch Intern Med* 1988;148:1715–1719.
- Andres E, Affenberger S, Vinzio S, Kurtz JE, Noel E, Kaltenbach G, Maloisel F, Schlienger JL, Bickel JF: Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. *Am J Med* 2005;118: 1154–1159.
- MacKenzie JF, Russell RI: The effect of pH on folic acid absorption in man. *Clin Sci Mol Med* 1976;51:363–368.
- Russell RM, Krasinski SD, Samloff IM, Jacob RA, Hartz SC, Brovender SR: Folic acid malabsorption in atrophic gastritis. Possible compensation by bacterial folate synthesis. *Gastroenterology* 1986;91:1476–1482.
- Holt PR: Diarrhea and malabsorption in the elderly. *Gastroenterol Clin North Am* 2001; 30:427–444.
- Saltzman JR, Kowdley KV, Pedrosa MC, Sepe T, Golner B, Perrone G, Russell RM: Bacterial overgrowth without clinical malabsorption in elderly hypochlorhydric subjects. *Gastroenterology* 1994;106:615–623.
- Akhress R, Yaffe MB, Fischer C, Ponsky J, Shuck JM: Small-bowel diverticulosis: perceptions and reality. *J Am Coll Surg* 1997; 184:383–388.
- Parlesak A, Klein B, Schecher K, Bode JC, Bode C: Prevalence of small bowel bacterial overgrowth and its association with nutrition intake in nonhospitalized older adults. *J Am Geriatr Soc* 2003;51:768–773.

- 33 Roberts SH, James O, Jarvis EH: Bacterial overgrowth syndrome without 'blind loop': a cause for malnutrition in the elderly. *Lancet* 1977;ii:1193-1195.
- 34 Pereira SP, Gainsborough N, Dowling RH: Drug-induced hypochlorhydria causes high duodenal bacterial counts in the elderly. *Aliment Pharmacol Ther* 1998;12:99-104.
- 35 Husebye E, Skar V, Hoverstad T, Melby K: Fasting hypochlorhydria with Gram-positive gastric flora is highly prevalent in healthy old people. *Gut* 1992;33:1331-1337.
- 36 Riordan SM, McIver CJ, Wakefield D, Bolin TD, Duncombe VM, Thomas MC: Small intestinal bacterial overgrowth in the symptomatic elderly. *Am J Gastroenterol* 1997;92:47-51.
- 37 Brogna A, Ferrara R, Bucceri AM, Lanteri E, Catalano F: Influence of aging on gastrointestinal transit time. An ultrasonographic and radiologic study. *Invest Radiol* 1999;34:357-359.
- 38 Vantrappen G, Janssens J, Hellemans J, Ghooys Y: The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. *J Clin Invest* 1977;59:1158-1166.
- 39 Husebye E, Engedal K: The patterns of motility are maintained in the human small intestine throughout the process of aging. *Scand J Gastroenterol* 1992;27:397-404.
- 40 O'Mahony D, O'Leary P, Quigley EM: Aging and intestinal motility: a review of factors that affect intestinal motility in the aged. *Drugs Aging* 2002;19:515-527.
- 41 Wade PR: Aging and neural control of the gastrointestinal tract. I. Age-related changes in the enteric nervous system. *Am J Physiol* 2002;283:G489-G495.
- 42 Kreel L, Sandin B: Changes in pancreatic morphology associated with aging. *Gut* 1973;14:962-970.
- 43 Glaser J, Hogemann B, Krummenerl T, Schneider M, Hultsch E, van Husen N, Gerlach U: Sonographic imaging of the pancreatic duct. New diagnostic possibilities using secretin stimulation. *Dig Dis Sci* 1987;32:1075-1081.
- 44 Anand BS, Vij JC, Mac HS, Chowdhury V, Kumar A: Effect of aging on the pancreatic ducts: a study based on endoscopic retrograde pancreatography. *Gastrointest Endosc* 1989;35:210-213.
- 45 Vellas BJ, Balas D, Lafont C, Senegas-Balas F, Albaredo JL, Ribet A: Adaptive response of pancreatic and intestinal function to nutritional intake in the aged. *J Am Geriatr Soc* 1990;38:254-258.
- 46 Mohiuddin J, Katrak A, Junglee D, Green MF, Dandona P: Serum pancreatic enzymes in the elderly. *Ann Clin Biochem* 1984;21:102-104.
- 47 Amman RW, Sulser H: Die senile chronische Pankreatitis: eine neue nosologische Einheit? *Schweiz Med Wschr* 1976;106:429-437.
- 48 Laugier R, Sarles H: The pancreas; in James OFW (ed): *Clinics in Gastroenterology*. Philadelphia, Saunders, 1985, p 749.
- 49 Nagai H, Ohtsubo K: Pancreatic lithiasis in the aged. Its clinicopathology and pathogenesis. *Gastroenterology* 1984;86:331-338.
- 50 Nahon Uzan K, Levy P, O'Toole D, Belmont N, Vullierme MP, Couvelard A, Ponsot P, Palazzo L, Abbas A, Hammel P, Ruszniewski P: Is idiopathic chronic pancreatitis an autoimmune disease? *Clin Gastroenterol Hepatol* 2005;3:903-909.
- 51 Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, Clain JE, Pearson RK, Petersen BT, Vege SS, Farnell MB: Diagnosis of autoimmune pancreatitis: the Mayo clinic experience. *Clin Gastroenterol Hepatol* 2006;4:1010-1016.
- 52 Baschetti R: Pancreatic insufficiency and weight loss in older patients. *Q J Med* 2004;97:377-380.
- 53 Hardt PD, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, Bretzel RG, Hollenhorst M, Kloer HU: High prevalence of exocrine pancreatic insufficiency in diabetes mellitus. A multicenter study screening fecal elastase-1 concentrations in 1,021 diabetic patients. *Pancreatology* 2003;3:395-402.
- 54 Rothenbacher D, Low M, Hardt PD, Klor HU, Ziegler H, Brenner H: Prevalence and determinants of exocrine pancreatic insufficiency among older adults: results of a population-based study. *Scand J Gastroenterol* 2005;40:697-704.
- 55 Fireman Z, Eliakim R, Adler S, Scapa E: Capsule endoscopy in real life: a four-centre experience of 160 consecutive patients in Israel. *Eur J Gastroenterol Hepatol* 2004;16:927-931.
- 56 Teramoto Matsubara O, Zamarripa Dorsey F, Lopez Acosta ME: Capsule endoscopy: The evolution in the diagnosis of small bowel diseases (in Spanish). *Rev Gastroenterol Mex* 2005;70:138-142.
- 57 Biagi F, Rondonotti E, Campanella J, Villa F, Bianchi PI, Klersy C, De Franchis R, Corazza GR: Video capsule endoscopy and histology for small-bowel mucosa evaluation: a comparison performed by blinded observers. *Clin Gastroenterol Hepatol* 2006;4:998-1003.
- 58 Fireman Z: The light from the beginning to the end of the tunnel. *Gastroenterology* 2004;126:914-916.
- 59 Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Gualdini S, Hill ID, Pietzak M, Ventura A, Thorpe M, Kryszak D, Fornaroli F, Wasserman SS, Murray JA, Horvath K: Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;163:286-292.
- 60 Maki M, Mustalahti K, Kokkonen J, Kulmala P, Haapalahti M, Karttunen T, Ilonen J, Laurila K, Dahlbom I, Hansson T, Hopfl P, Knip M: Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003;348:2517-2524.
- 61 Gasbarrini G, Ciccocioppo R, De Vitis I, Corazza GR: Coeliac disease in the elderly. A multicentre Italian study. *Gerontology* 2001;47:306-310.
- 62 Ravaglia G, Forti P, Maioli F, Volta U, Arnone G, Pantieri G, Talerico T, Muscari A, Zoli M: Increased prevalence of coeliac disease in autoimmune thyroiditis is restricted to aged patients. *Exp Gerontol* 2003;38:589-595.
- 63 McIntyre AS, Long RG: Prospective survey of investigations in outpatients referred with iron deficiency anaemia. *Gut* 1993;34:1102-1107.
- 64 Pare P, Douville P, Caron D, Lagace R: Adult celiac sprue: changes in the pattern of clinical recognition. *J Clin Gastroenterol* 1988;10:395-400.
- 65 Gillberg R, Dotevall G, Kastrup W, Lindstedt G, Mobacken H, Swolin B: Conventional malabsorption tests: do they detect the adult patient with villous atrophy? *Scand J Clin Lab Invest* 1984;44:91-98.
- 66 Logan RF, Rifkin EA, Busuttill A, Gilmour HM, Ferguson A: Prevalence and 'incidence' of celiac disease in Edinburgh and the Lothian region of Scotland. *Gastroenterology* 1986;90:334-342.
- 67 Swinson CM, Levi AJ: Is coeliac disease underdiagnosed? *BMJ* 1980;281:1258-1260.
- 68 Holmes GK, Stokes PL, Sorahan TM, Prior P, Waterhouse JA, Cooke WT: Coeliac disease, gluten-free diet, and malignancy. *Gut* 1976;17:612-619.
- 69 Swinson CM, Slavin G, Coles EC, Booth CC: Coeliac disease and malignancy. *Lancet* 1983;i:1111-1115.
- 70 Robertson DA, Dixon MF, Scott BB, Simpson FG, Losowsky MS: Small intestinal ulceration: diagnostic difficulties in relation to coeliac disease. *Gut* 1983;24:565-574.
- 71 Matuchansky C, Colin R, Hemet J, Touchard G, Babin P, Eugene C, Bergue A, Zeitoun P, Barboteau MA: Cavitation of mesenteric lymph nodes, splenic atrophy, and a flat small intestinal mucosa. Report of six cases. *Gastroenterology* 1984;87:606-614.
- 72 Dawson DJ, Sciberras CM, Whitwell H: Coeliac disease presenting with intestinal pseudo-obstruction. *Gut* 1984;25:1003-1008.
- 73 Kumar PJ, Walker-Smith J, Milla P, Harris G, Colyer J, Halliday R: The teenage coeliac: follow-up study of 102 patients. *Arch Dis Child* 1988;63:916-920.