Upsala J Med Sci 106: 81–97, 2001

Age-related Changes in Neuroendocrine System of the Gut

Apossible role in the pathogenesis of gastrointestinal disorders in the elderly

Minireview based on a doctoral thesis

Olof Sandström and Magdy El-Salhy

Institution of Public Health and Clinical Medicine, Department of Medicine, Section of Gastroenterology and Hepatology, University Hospital, Umeå, Sweden

INTRODUCTION

The medicine of today and tomorrow is the medicine of old age. Elderly patients predominate in hospitals in Sweden and in the other countries of the Western World. Over the past century, life expectancy in the developed countries has extended by 20–25 years. The expected life span in Sweden for a newborn girl is now 81 years and for a boy, 76 years (80). Generally, 65 years is considered old because this is the age for retirement in Sweden. Today 18% of Sweden's population are 65 years or older, and 25 years from now this proportion is expected to have risen to 23% and keep rising. This is the oldest national population in the world (81).

Although this may be considered an agreeable development, one must be prepared for the accompanying problems, such as increasing costs for health care. This problem has been noticed only in the recent years in the developed countries. However, the ageing of the population in developing countries is even more alarming, as their fertility and mortality figures are decreasing. Between the years 1990 and 2025, the elderly population (older than 65 years) will be more than double, a process that has taken more than 100 years in our part of the world (51). It is therefore an obvious challenge to solve these problems and to learn how to treat age-related diseases.

As ageing is a gradual process that occurs in all multicellular organisms, it is impossible to name one point in time when an individual suddenly becomes old. Sometimes the word senescence is used instead of ageing. Ageing can mean every process that is time dependent, e.g. development, but with senescence we mean the gradual loss of bodily and mental faculties that ultimately brings life to an end for us all.

After observations made in humans (e.g. DNA-repair, physiological performance, maximum heart rate and the number of muscle fibres in the thigh) it would appear that our decline in capacity begins around the age of 30. This loss of capacity then proceeds with 0.5% per year in the slowest ageing individuals up to the age of 80 when the rate of loss increases to at least 1% (120). This decline in capacity varies between individuals and also differs between organ systems in the same body. Physical activity, diet and smoking habits are important factors that modify the ageing rate. A more rapidly ageing organ system can result in premature disease and death, e.g. cerebrovascular disease (120).

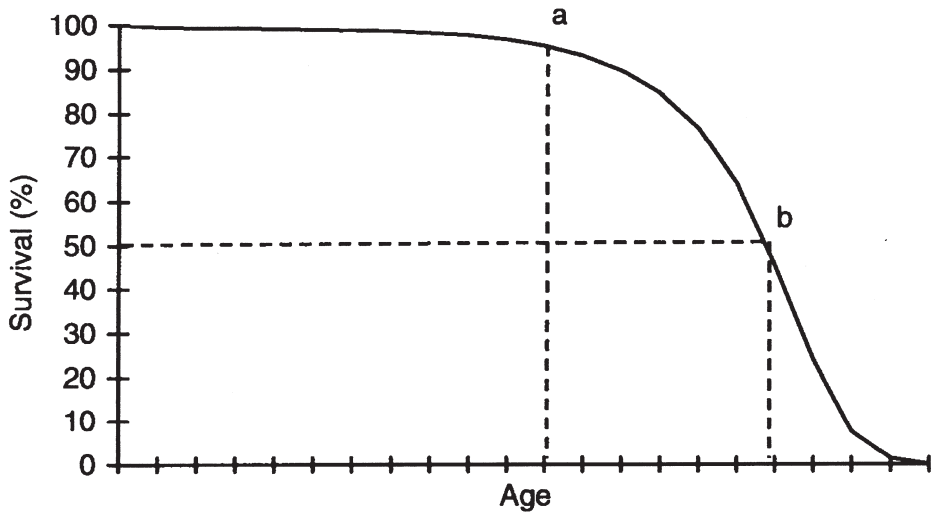

Fig. 1. Individuals older than **a** is regarded as ageing. Individuals older than **b** (the 50% survival point) are regarded as senescent.

When the loss of capacity becomes large enough to affect the survival of the population and influence the survival curve sufficiently to cause a rapid down slope, this is considered to be the point where the individual in the population is ageing and an animal is senescent at the age when half of the population has died (111) (Fig. 1).

Gastrointestinal disorders in the elderly

Esophagus

The term "presby esophagus" indicates age-related disorders of esophageal motility that have been described. There is considerable controversy as to whether such changes are part of the normal ageing or not. Several studies have reported increased dysmotility, e.g. reduced regularity and increased number of disordered contractions (11, 32, 89), while others have not found any age-related changes in esophageal motility (1, 44, 90). The pressure of the lower esophageal sphincter (LES) is greatest below the age of one year, then decreasing up to the age of 15 years (11). However, an increased frequency of reflux, found in the elderly, has been suggested to be the result of changed location and length of the LES (119).

Stomach

Diseases of the stomach are predominantly gastritis, gastric ulcer and gastric cancer. The incidence of both gastric and duodenal ulcers increases with advancing age (9, 61, 82) as does gastritis (37) and gastric cancer (113). Peptic ulcers are generally considered to be the result of an imbalance between aggressive luminal factors and mucosal defence factors. Some of the more important factors are listed in Table 1.

The question of age-related changes in gastric secretion has been discussed frequently. Several studies have found a reduced gastric acid and pepsin secretion in

Table 1. Aggressive and protective factors in the stomach (17)

Aggressive luminal actors	Mucosal defence factors
Virus and bacteria, e.g. *H. pylori*	Immune cells and secretory IgA
Drugs, e.g. NSAID	Mucosal repair and renewal
Alcohol	Tight junctions
Tobacco	Mucosal circulation
Gastric acid	Mucus with bicarbonate
Bile acids	Prostaglandins
Enzymes	Gluthatione
Digestive products	Local endocrine and neural regulation

elderly humans (26, 28, 101) and rats (58, 70). However, several recent studies have shown little or no effect of ageing on gastric secretion. *Helicobacter pylori* has recently been ascribed most of the previously found age-related effects and is present in much higher frequency in elderly persons (7, 68). However, the age-related increase in *H. pylori* infections could represent a secondary colonisation permitted by a decreased acidity of the stomach (7) A decrease in bicarbonate, sodium and mucous secretion has been shown in the elderly (27) In experimental animals, slower repair after mucosal injury (29) and reduced mucosal blood flow have been reported (66). In humans the densityof parietal cells has been found to increase, while the density of mucus-producing cells to decrease (25). In rat, an increase in the gut mucosal thickness due to an increase in connective tissue, has been found (43). Thicker basal lamina around the antral capillaries has been reported in old female mice (63). When all factors are taken together, there are indications that age-related changes in aggressive factors and mucosal defence predispose to mucosal injury, especially when other factors such as *H. pylori* infections and administration of non-steroid anti-inflammatory drugs (NSAIDs, also called COX-inhibitors) also increase with ageing.

The effect of age on gastric emptying has been the subject of several studies, with differing results. Most studies found slower emptying in elderly subjects (13, 22, 47, 79, 116), but others could not detect any differences (62, 34). Studies in the rat are inconclusive–both slower (102) and unchanged emptying has been found (107). It seems likely that the rate of gastric emptying slows down in elderly subjects. A possible mechanism for this disorder is increased pyloric contractions as found in the elderly (14). The possible clinical significance of slower gastric emptying is earlier satiety, which could contribute to the malnutrition seen in the elderly and may also delay the absorption of orally administered drugs.

Small intestine

Manometric studies have shown only minor effects of age on the motility of the small intestine, a lower motility index during fasting (2) and slower phase III of the

migrating motor complex (MMC) (48). The hydrogen breath test has been used to study oro-cecal transit time (OCTT). Several investigations found no change in the OCTT in the elderly (13, 52, 62, 84, 116) and only one detected prolonged OCTT (85). No changes were found when using ordinary passage roentgeography (60) or scintigraphy in humans (3, 4) and rats (107). At least one study using the D-xylose absorption test found test results indicating slower OCTT in the elderly (114). It therefore seems that the effect of age on small intestinal motility is of only minor importance.

Large intestine

Diarrhoea, faecal incontinence, constipation and use of laxative are common in older age and are especially common in the hospitalised population (45, 50, 103, 110). Increased colonic transit time (CTT) has been reported in humans (69, 84, 106) and rats (102), though there is some controversy about this (13, 76).

Pancreas

In large-scale studies on patients undergoing functional tests of pancreatic secretion, reduced total output, secretion of bicarbonate and enzymes (64) and maintained secretion (20) have all been found. Smaller designed studies have shown reduced total output, reduced secretion of bicarbonate and enzymes (108, 109) and maintained secretion (41) in the elderly. As in humans, experimental studies in ageing rats have been controversial, showing reduction in pancreatic output and protein secretion of 50% or more (42, 54) to only small changes in protein output after CCK stimulation (77, 78). Small zymogen granules in rat pancreas (108) and reduced tissue concentrations of amylase with unchanged levels of lipase and trypsinogen in old animals have been found. Slower adaptation to new food has been reported (38). Reduced density of CCK receptors has been found in pancreatic tissue (86) and could, together with atrophy, explain possible changes in secretory capacity.

Gallbladder

In humans the incidence of gallstones increases with age (16) and the volume of the gallbladder increases in the elderly (83). No age-related effect on gallbladder contractility has been found following intraduodenal lipid stimulation (59, 115). However, diminished sensitivity to CCK has been found in humans (54), guinea pigs (49, 87, 88) and rabbits (57). This reduced sensibility seems to be explained by a decreased density of CCK receptors in the gallbladder musculature (67, 88).

The neuroendocrine system (NES) of the gut

A century ago, Pavlov proposed that the central nervous system (CNS) alone controlled the gastrointestinal tract. Since then, another local control mechanism has been discovered, that is even able to control the gut without any involvement of the CNS. This system, called the neuroendocrine system of the gut (NES), consists of

the endocrine/paracrine cells in the mucosa and the enteric nervous system (ENS) both of which secrete bioactive peptides and amines. These substances can be secreted in different ways. Thus, messengers are released from cells into blood vessels to be carried to target organs (endocrine secretion), or released into the interstitial fluid to act on local targets (paracrine secretion). Paracrine cells may have long slender processes and have contact with target cells. Neurones can act either synaptic or in a neurocrine way. Synaptic signalling is the classic way of neural signalling, where a neurone and the target cell come into very close contact and the neurone secrete transmitters that act on receptors on the target cell side. Neurocrine means that the neural signalling is non-synaptic and may mean that messengers act on the local cells but not in a synaptic way, or are carried by blood vessels to target organs. A summary of the main neuroendocrine peptides and amines and their functions is given in Table 1.

Endocrine/paracrine cells

These cells are found between epithelial cells. They are often flask- or basket-shaped, with a broad base, while the apical part reaches the gut lumen. Some of these cells have long slender cytoplasmatic processes projecting to neighbouring cells, making their paracrine action more efficient (e.g. somatostatin and PYY cells). Different endocrine/paracrine cell types are located in specific areas of the gut, but some types are found throughout the gut, namely somatostatin and serotonin-containing cells (100). All cell types in one crypt/villus originate from a pluripotent stemcell of endodermal origin. This means that enterocytes, goblet cells, Paneth cells and endocrine/paracrine cells in one crypt/villus are of monoclonal origin (92).

The enteric nervous system

This system consists of neurones with their cell bodies located in the gut wall. The peptidergic part (including serotonin) is considered to be part of NES. There are two main nerve plexuses, the myenteric plexus (Auerbach´s) located between the longitudinal and the circular muscle layers in the entire gastrointestinal tract and the submucosal plexus (Meissner's) between the submucosa and the circular muscle (71). The myenteric ganglia contains neurones that project predominantly to the muscle layer but also to the mucosa, the submucosal plexus and to other myenteric ganglia and contains most of the neurones involved in motility control and gastric acid control. The submucosal ganglia contains neurones that project predominantly to the mucosa but also to myenteric ganglia, the circular muscle layer and other submucosal ganglia and contains neurones involved in the control of mucosal fluid transport and vasodilator reflexes (71). The ganglia of the two plexuses are connected to a continuous meshwork; the meshwork of the myenteric plexus is more regular (35). The ENS receives some input from CNS, but most input comes from other enteric neurones. More than 20 possible neuropeptides have been identified in addition to classical transmitters such as acetylcholine, noradrenalin and serotonin. True neurotransmitter action has only been established in a few cases. Many of the transmitters are co-localised in the same neurone and one transmitter may have different effects in different parts of the gut (15).

Abnormalities of the NES associated with ageing

In the Esophagus of humans, an age-related decrease has been found in the numbers of neurones in the myenteric plexus (75). The effect of age on plasma gastrin levels is controversial. In humans, both increased (6, 106) and unchanged levels (3, 36, 105) have been found. The number of antral gastrin cells is unaffected by age, as are ECL cells, whereas the number of somatostatin cells has been shown to decrease (36) In the rat, plasma gastrin levels have been shown to decrease and to be accompanied by reduced antral tissue concentrations of gastrin (46, 55, 58) and fewer antral gastrin cells (67). The number of antral ECL cells has been shown to decrease in old rats, but there was no change in A (glucagon) or D cells (somatostatin) (104).

Small intestine

Plasma motilin levels have been shown to increase in the small intestine of elderly (8). Plasma CCK levels have been shown to increase in humans (54) and in guinea pigs, as did tissue concentrations (54, 56). Secretin, on the other hand, has been found to decrease in rats (56). The nerve cell density in the myenteric plexus of the small intestine has been shown to decrease in humans (18), rats (98) and guinea pigs (33). In rats, the density of substance P, VIP and somatostatin neurones has been shown to decrease with ageing (28). Tissue concentrations of substance P decreased with ageing in jejunum but increased in ileum, and VIP was decreased throughout the small intestine (30). In humans, the concentration of substance P in the mucosa of the large intestine has been shown to decrease, but there was no effect on VIP levels (31). In rats, plasma and large intestinal tissue levels of neurotensin increased, but there was no effect on the cell number with ageing (99). The density of nerve cell bodies in the myenteric plexus of the large intestine was shown to decrease in elderly humans (40).A reduced density of CCK receptors has been found in pancreatic tissue (87). Fasting levels of PP increased in the elderly but there was no effect on glucagon and insulin levels (5). In another study, an increased level of PP was found, both in fasting and after glucose stimulation, while the level of glucagon decreased during fasting, but increased after glucose stimulation (72). is unaffected by ageing, with the exception of the submucosal plexus in colon, where there is fewer ganglia per mm. The relative density of nerve fibres in antral muscularis propria is higher in old mice. The density was unchanged in small and large intestine and in the submucosa of all segments of the gut.

A decreased sensitivity to CCK has been found in gallbladder of humans (59), guinea pigs (49, 86, 88) and rabbits (57). Possibly due to a decreased density of CCK receptors in gallbladder musculature (87, 88). Increased levels of CCK have been found in serum (59) and in duodenal tissue from guinea pigs (87), probably as a compensation for reduced receptor density. This type of upregulation has also been noted in dogs (118) and hamsters (91) after cholecystectomy and could be responsible for the preserved sensitivity to intraduodenal fat in humans.

Recently, the age-related changes in the neuroendocrine system of an animal model, namely the mouse has been investigated (23, 93–95). The results of these studies are summarised in Tables 3 and 4. The effect of ageing on intestinal endocrine cells in humans has been studied recently (96, 97). The findings in these investigations are summarised in Table 5.

Table 2. The main neuroendocrine peptides and amines in the gut and their localisations and functions.

Peptide	Mode of action	Cellular origin	Main functions
Somatostatin	Paracrine	Gastric D-cell, myenteric and submucosal neurones.	Inhibitor of neuroendocrine peptides and neurotransmitters and amines release
Secretin	Endocrine	Intestinal S-cell	Regulates gastric emptying, inhibits contractile activity of small and large intestine and lowers resting lower oesophageal sphincter (LES) pressure
Cholecystokinin	Endocrine	Intestinal I-cell, myenteric and submucosal neurones.	Stimulates gallbladder contraction, decreases LES pressure, induces relaxation of the proximal part of the stomach and constriction of the pyloric sphincter, and stimulates motor activity and decreases intestinal transit time
Motilin	Endocrine	Intestinal M-cell	Stimulates contraction of the LES, induces gastroduodenal contraction
Pancreatic polypeptide	Endocrine	Intestinal PP-cell	Relaxes the gallbladder, lowers LES pressure,inhibits the fundic pacemaker
Peptide PYY (PYY)	Endocrine	Intestinal H/L-cell	A potent inhibitor of gastric emptying, decreases intestinal transit time
Neuropeptide Y (NPY)	Transmitter; mediator	Myenteric and submucosal neurones	Regulates LES contractility, inhibits intestinal motility
Neurotensin	Endocrine; Transmitter; mediator	Intestinal N-cell; myenteric and submucosal neurones.	Mediator of the ileal brake, lowers LES pressure, reduces gastric emptying and intestinal transit, inhibits interdigestive migratory complex.
Endothelin	Transmitter; mediator	Myenteric and submucosal neurones.	Stimulates intestinal smooth muscle contraction?
Substance P	Transmitter; mediator	Myenteric and submucosal neurones.	Stimulates gastrointestinal motility.
Gastrin-releasing peptide (GRP)	Transmitter, mediator	Myenteric and submucosal neurones.	Stimulates gut smooth muscle contraction.
Vasoactive intestinal polypeptide (VIP)	Transmitter, mediator	Myenteric and submucosal neurones	Relaxes gastrointestinal smooth muscles and mediates inhibition gastrointestinal motility
Enkephalin	Transmitter; mediator	Myenteric and submucosal neurones	Delays gastric emptying, inhibits intestinal transit.
Calcitonin-gene related peptide (CGRP)	Transmitter; mediator	Nerve fibres in the mucosa, submucosa and muscularis layers of the gastrointestinal tract	Inhibits motor activity of gall bladder, relaxes LES, inhibits spontaneous phasic contractions of the large intestinal smooth muscles
Galanin	Transmitter; mediator	Myenteric and submucosal neurones	Increases LES pressure, inhibits intestinal motility.
Serotonin (5 hydroxitrypt-amine)	Endocrine; mediator	Enterochromaffin (EC) cells and myenteric	Stimulation of smooth muscle contractions through facilitating acetylcholine release
Nitric oxide (NO)	Transmitter	Myenteric and submucosal neurones	Relaxation of smooth muscle

* Data from references 10, 12, 19, 21, 73, 112, 117.

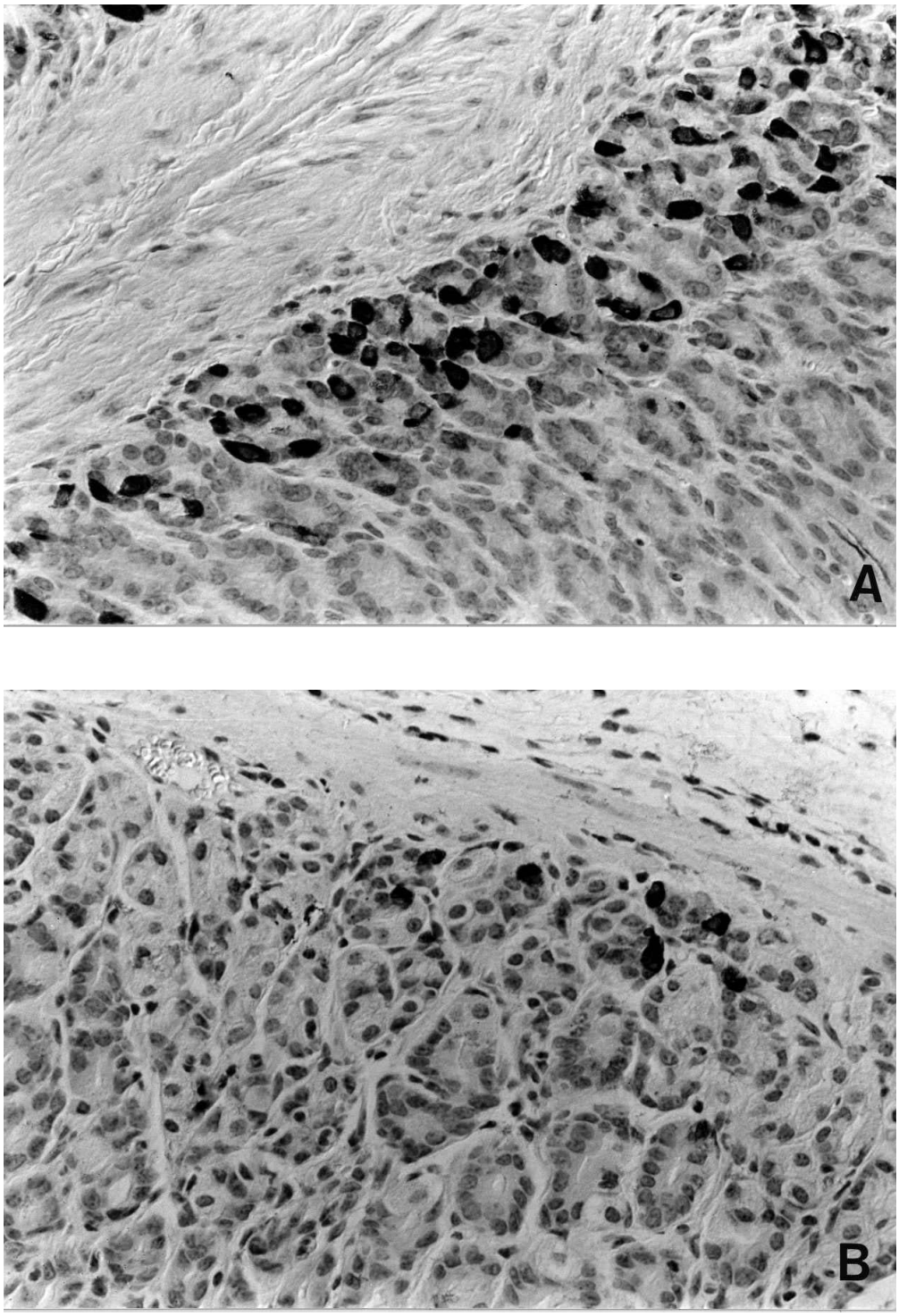

Fig. 2. Antral somatostatin-immunoreactive cells in an old mice (a) and in a young mice (B). Note that the number of these cells increases with ageing. ×250.

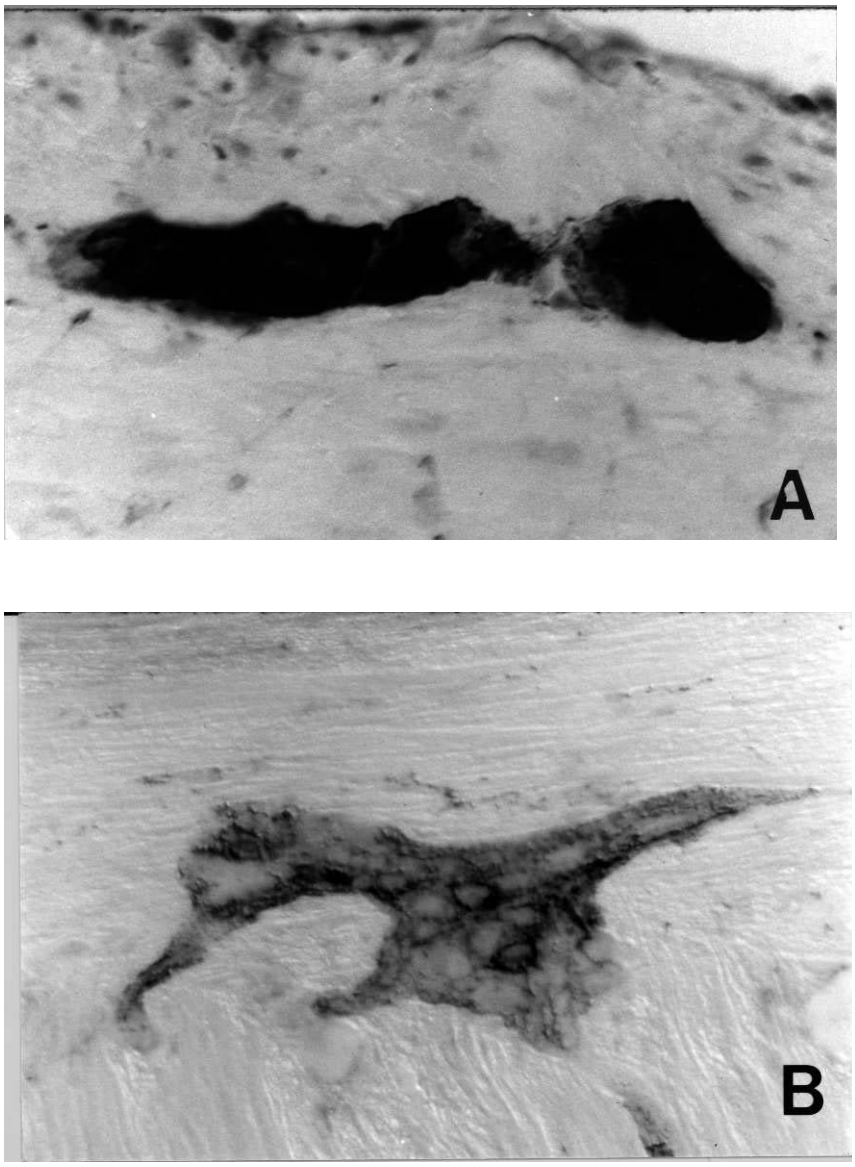

Fig.3. Myenteric ganglion in a young mice (A) and in an old mice (B). The number of nerve cells decreased with ageing. Immunostained by atisera against protein gene product 9.5. ×450

In a recent study, the effect of ageing on the gut enteric nervous of mouse has been studied (23, 24) and it has been reported that there are significantly fewer neurones per ganglion in both myenteric and submucusal plexus in old mice in all gastrointestinal segments. The number of ganglia per mm in old mice.

Table 3. Morphometric measurements and concentrations of neuroendocrine peptides in various segments of the gastrointestinal tract of mice; the age groups are related to the 3 month-olds (young adult mice)

	1 month				12 months				24 months			
Peptide/amine	CN	CSI	NV	TC	CN	CSI	NV	TC	CN	CSI	NV	TC
Antrum												
Gastrin	→	→	u.s.	→	→	→	u.s.	↓	→	→	u.s.	↓
Somatostatin	↑	↑	u.s.	↓	↑	↑	u.s.	↓	↑	↑	u.s.	↓
Neurotensin	u.s.	u.s.	u.s.	↑	u.s.	u.s.	u.s.	↓	u.s.	u.s.	u.s.	↓
Serotonin	↑	↑	u.s.	u.s.	↑	↑	u.s.	u.s.	→	↑	u.s.	u.s.
Duodenum												
Secretin	→	→	↓	↑	→	→	→	↑	↑	↑	→	↑
GIP	→	→	↓	↑	↓	↑	→	↑	→	→	→	↑
Motilin	u.s.	u.s.	u.s.	↓	u.s.	u.s.	u.s.	↓	u.s.	u.s.	u.s.	↓
Gastrin/CCK	→	→	↓	↓	→	→	→	↓	→	→	↑	↓
Somatostatin	→	↑	→	↓	↓	↑	↓	↓	↓	→	→	↓
Neurotensin	u.s.	u.s.	u.s.	↑	u.s.	u.s.	u.s.	↓	u.s.	u.s.	u.s.	→
Serotonin	↓	↓	↓	u.s.	↓	→	→	u.s.	↑	↑	↓	u.s.
Colon												
PYY	↑	→	u.s.	↓	↑	→	u.s.	↓	↑	→	u.s.	↓
Enteroglucagon	↑	↑	u.s.	u.s.	↑	↑	u.s.	u.s.	↑	↑	u.s.	u.s.
Somatostatin	u.s.	u.s.	u.s.	↓	u.s.	u.s.	u.s.	↓	u.s.	u.s.	u.s.	↓
Neurotensin	u.s.	u.s.	u.s.	→	u.s.	u.s.	u.s.	→	u.s.	u.s.	u.s.	→
Serotonin	↑	↑	u.s.	u.s.	↑	↑	u.s.	u.s.	↑	↑	u.s.	u.s.

CN=Cell number. CSI=cell secretory index. NV = nuclear volume. TC = tissue concentration. u.s. = unstudied. ↑ = significantly increased. ↓ = significantly decreased. → = no significant difference.

CONCLUSION

There seem to be impairments in the gastrointestinal functions with senescence, as in other parts of the body (120). The two components of NES, endocrine/paracrine cells and ENS are important in the regulation of the gastrointestinal tract. Both these parts are affected by age. Changes in NES can be either primary or secondary. Secondary changes can be compensatory to preceding changes in receptors or affector

Table 4. Tissue concentrations of neuropeptides inthe gastrointestinal tract of mice; the age groups are compared with the 3-months-old.

Peptide	Antrum			Duodenum			Colon		
Age (month)	1	12	24	1	12	24	1	12	24
Substance P	↓	↓	↓	↓	↓	→	↓	↓	↑
VIP	↓	↓	↓	↓	↓	↓	↓	↓	↓
NPY	↑	↓	↓	↓	↓	↓	→	↓	→
Galanin	→	↓	↓	↓	↓	↓	↓	↓	→

↓ = significantly increased. ↓ = significantly decreased. → = no significantly difference.

organs. An example of this is the postulated upregulation of CCK in duodenum secondary to reduced density of CCK receptors in the gallbladder (86, 88). Another example is the increase in the number of serotonin IR cells observed in mouse antrum, duodenum and colon (93–95). Serotonin has been suggested to initiate the peristaltic wave [79], and an increase in the number of cells could be compensatory to the degeneration of the ENS. Even though changes are secondary, they could lead to gastrointestinal disorders. Since most neuroendocrine messengers have more than one target organ, upregulation as a compensation for loss of capacity in one organ could lead to over-stimulation/-inhibition in another.

There are a species difference regarding the age-related changes in the neuroendocrine system, and experimental animals show far more age-related changes than did those of humans (Table 6). Thus, great caution must be taken when extrapolating results from experimental animals to humans. However, several age-related changes in the neuroendocrine system of humans, have been reported, that may have an impact on development of gastrointestinal symptoms in elderly. The number of somatostatin antral cells is decreased with ageing. As somatostatin inhibits gastrin secretion, it is not surprising that the plasma level of gastrin is high in elderly. Somatostatin inhibits also gastric acid secretion. The low somatostatin and high gastrin would result in high gastric acid secretion. The number of CCK cells as well as plasma level increased with ageing which could cause slow gastric emptying. Furthermore, high CCK and PP could lower the LES pressure. High gastric acid secretion, slow gastric emptying and low LES pressure can lead to reflux oesophagitis in elderly, which is indeed the case. It is important to keep this in mind clinically, as chest pain in elderly could be caused by reflux oesophagitis rather than angina pectoris, which is also common in this age.

Table 5. Morphometric results of the endocrine cells obtained in human small and large intestine; the age groups are related to the 20–29-year-olds.

	1–2 years			40–49 years			60–69 years		
Peptide/amine	CN	CSI	NV	CN	CSI	NV	CN	CSI	NV
Duodenum									
Chromogranin A	↓	↑	u.s.	→	→	u.s.	→	→	u.s.
GIP	→	↑	u.s.	→	→	u.s.	→	→	u.s.
Gastrin/CCK	↑	↑	u.s.	→	→	u.s.	↑	→	u.s.
Secretin	→	→	u.s.	→	→	u.s.	→	→	u.s.
Somatostatin	→	↑	u.s.	↑	→	u.s.	→	↑	u.s.
Serotonin	↓	→	u.s.	→	→	u.s.	→	→	u.s.
Rectum									
Enteroglucagon	u.s.	u.s.	u.s.	→	→	→	→	→	→
PP	u.s.	u.s.	u.s.	→	→	↑	→	→	→
PYY	u.s.	u.s.	u.s.	→	→	→	→	→	→
Somatostatin	u.s.	u.s.	u.s.	→	→	→	→	→	→
Serotonin	u.s.	u.s.	u.s.	→	→	→	→	→	→

CN = cell number. CSI = cell secretory index. NV = nuclear volume. u.s. = unstudied. ↑ = significantly increased. ↓ = significantly decreased. → = no significant difference.

Table 6. Summary of age-related changes in the gut neuroendocrine peptides and other signal substances

Peptide	Changes with increasing age
Secretin	Decreased duodenal tissue level in rat and increased in mice.
Gastrin	Increased or decreased plasma level in humans. Decreased blood level and in gastric tissue extracts and decreased number of antral gastrin cells in rats. In mouse, decreased number of antral gastrin cells.
CCK	Increased number of duodenal cells and high blood concentrations in humans. Increased level in blood and duodenal tissue extracts in guinea-pig. Low concentration in murine duodenum.
GIP	High levels in tissue extracts of murine duodenum.
Motilin	Increased blood level in humans. Decreased concentration in murine duodenum.
Somatostatin	Decreased number in the antrum of humans. Increased number of antral cells, but decreased level in tissue extract in mice. Decreased cell number and concentration in the murine duodenum. Decreased number of nerve fibres in the rat small intestine.
PP	High blood level in humans.
PYY	Increased number of cells in murine colon.
Enteroglucagon	Increased number of cells in murine colon.
Serotonin	Increased number of cells in murine small and large intestine.
Histamine	Decreased number of cells in rat.
Substance P	Low concentration in the human large intestine. Decreased number of nerve fibres and concentration in rat small intestine. Decreased level in the stomach, but increased level in the small and large intestine of mice.
VIP	Decreased number of nerve fibres and concentration in rat small intestine of rat. Low level in the murine stomach and intestine.
NPY	Low concentration in stomach and small intestine of mice.
Neuroteinsin	High concentration in human large intestine. Low concentration in murine stomach.
Galanin	Low level in the murine stomach and small intestine.

Substance P has been found to be low and motilin to be high in elderly. Whereas low substance P can cause low gastrointestinal motility, high motilin can lead to increase gastrointestinal contractibility . one can speculate that the balance between these neuroendocrine peptide that can lead to either diarrhoea or constipation in elderly.

The pathogenesis of gastrointestinal disorders in the elderly is probably multifactorial. The changes in the NES with ageing suggest that disorders in the NES of the gut might be one of these factors. If this hypothesis were to prove true, new therapeutic strategies might be used in these disorders, as agonists and antagonists of almost all neuroendocrine peptides are available.

REFERENCES

Adamek, J., Wegener, M., Wienbeck, M. & Gielen, B.: Long-term esophageal manometry in healthy subjects. Dig Dis Sci 39: 2069–2077, 1999.

Anuras, S. & Sutherland, J.: Small intestinal manometry in healthy elderly subjects. J Am Geriatr Soc 32: 581–583, 1984.

Archimandratis, A., Alegakis, G., Theodoropoulos, G., Kalas, A., Drivas, G. & Melissinos, K.: Serum gastrin concentrations in healthy males and females of various ages. Acta Hepatogastroenterol (Stuttg) 26: 58–63, 1979.

Argenyi, E., Soffer, E.E., Madsen, M.T., Berbaum, K.S. & Alker, W.O.: Scintigraphic evaluation of small bowel transit in healthy subjects: inter and intrasubject variability. Am J Gastroenterol 90: 938–941, 1995.
Berger, D., Crowther, R.C., Floyd, J.C., Pek, S. & Fajans, S.S.: Effect of age on fasting plasma levels of pancreatic hormones in man. J Clin Endocrinol Metab 47: 1183–1189, 1978.
Blair, E.L., Greenwell, J.R., Grund, E.R., Reed, J.D. & Sanders, D.J.: Gastric response to meals of different compostions in normal subjects. Gut 16:766–773, 1975.
Blaser, M.J.: Gastric Champylobacter-like organisms, gastritis and peptic ulcer disease. Gastroenterology 93: 371–383, 1987.
Bonara, G., Vezzadini, P., Fradà, G., Toni, R., Sangiorgi, G.B. & Labò G.: Interdigestive plasma motilin concentrations in aged adults. J Gastroenterol 41: 723–726, 1986.
Bonnevie, O.: The incidence of gastric ulcer in Copenhagen County. Scand J Gastroenterol 10: 249–259, 1975.
Burks, T.F.: Neurotransmission and neurotransmitters. In: Physiology of the Gastrointestinal Tract(ed. L.R. Johnson), pp. 211–242. 3rd edn, Raven Press, New York, 1994.
Csedes, A., Guiraldes, E., Bancalari, A., Braghetto, I. & Ayala, M.: Relation of gastroesophageal sphincter pressure and esophageal contractile waves and age in man. Scand J Gastroenterol 13: 443–447, 1978.
Chang, E.B. & Rao, M.C.: Intestinal water and elecrolyte transports. . In: Physiology of the Gastrointestinal Tract(ed. L.R. Johnson), pp.. 2028–2069. 3rd edn, Raven Press, New York, 1994.
Clarkston, W.K., Pantano, M.M., Morley, J.E., Horowitz, M., Littlefield, J.M. & Burton, F.R.: Evidence for anorexia of aging: gastrointestinal transit and hunger in healthy elderly vs young adults. Am J Physiol 272: R243–248, 1997.
Cock, C.G., Andrews, J.M., Jones, K.L., Wittert, G.A,, Chapman, I.M. & Morley, J.E.: Effects of small intestinal nutrient infusion on appetite and pyloric motility are modified by age. Am J Physiol 273: R755–761, 1997.
Costa, M. & Brookes, S.J.H.: The enteric nervous system. Am J Gastroenterol 89: 129–137, 1994.
Crump, C.: The incidence of gall stones and gall-bladder disease. Surg Gynecol Obstet 41: 447–455. 1931.
Danielsson, Å.: Sjukdomar i ventrikel och duodenum. . In: Internmedicin. (ed. H. Hallberg, G. Holm, N. Lindholm & L. Werkö), pp. 746–760., Stockholm, 1996.
de Souza, R.R., Moratelli, H.B., Borges, N. & Liberti, .EA.: Age-induced nerve cell loss in the myenteric plexus of the small intestine in man. Gerontology 39: 183–188, 1993.
Dockray, G.J.: Physiology of enteric neuropeptides. . In: Physiology of the Gastrointestinal Tract(ed. L.R. Johnson), pp. 169–209. 3rd edn, Raven Press, New York, 1994.
Dreiling, D.A., Treibling, A.T. & Koller, M.: Human exocrine secretion changes associated with age. Mater Med Pol 1: 17–19, 1991.
Dy, D.Y., Whitehead, R.H. & Morris D.L.: SMS 201.995 inhibits in vitro and in vivo growth of human colon cancer. Cancer Res 52: 917–923, 1992.
Evans, M.A., Triggs, E.J., Cheung, M. & Broe GA.: Gastric emptying in the elderly, implications for drug therapy. J Am Geriatr Soc 29: 201–205, 1981.
El-Salhy, M. & Sandström, O.: How age changes the content of neuroendocrine peptides in the murine gastrointestinal tract. Gerontology 45: 17–22, 1999.
El-Salhy, M., Sandström, O. & Holmlund, F.: Age-induced changes in the enteric nervous system in mouse. Mech Ageing Dev 107: 93–103, 1999.
Farinati, F,, Formentini, S., DellaLibera. G., Vallante, F., Fanton, F. & DiMario, F.:. Changes in parietal and mucous cell mass in the gastric mucosa of normal subjects with age: a morphometeric study. Gerontology 39:146–145, 1993.
Fehér, E. & Pénes, L.: Dentsity of substance P, vasoactive intestinal peptide and somatostatin containing nerve fibers in the ageing small intestine of the rat. Gerontology 33: 341–348, 1987.
Feldman, M. & Cryer, B.: Effects of age on gastric alkaline and nonparietal fluid secretion in humans. Gerontology 44: 222–227, 1998
Feldman, M., Cryer, B., McArthur, K.E., Huet, B.A. & Lee, E.: Effects of aging and gastritis on gastric acid and pepsin secretion in humans: a prospective study. Gastroenterology 110: 1043–1052, 1996.
Fliegel, S.E.G., Relan, N.K., Dutta, S., Tureaud, J., Hatfield, J.S. & Majumdar, A.P.N.: Ageing diminishes gastric mucosal regeneration: relationship to thyrosine kinases. Lab Invest 70: 764–774, 1994.
Ferrente, F., Gepetti, P. & Amenta, F.: Age-related changes in substance P and vasoactive intestinal polypeptide in the rat stomach and small intestine. Arch Gerontol Geriatr 13: 81–87, 1991.

Ferri, G.L., Soimero, L., Morreale, R.A. & Rebecchi, L.: A new approach to gut neuro-endocrinology in aging towards the integrated assessment of neuro-endocrine structure and intramural distribution of regulatory peptides. In: Neuroendocrine System and (ed. P. Vezzadini, A. Facchini & G. EURAGE, 1986

Ferrolli, E., Dantas, R.O., Olivera, R.B. & Braga F.J.N.H.: The influence of ageing on esophageal motility after ingestion of liquids with different viscosities. Eur Gastroenterol Hepatol 8: 793–798, 1996.

Gabella, G. : Fall in the number of myenteric neurons in aging guinea-pigs. Gastroenterology 96: 1487–1493, 1989.

Gainsborough, N., Maskrey, V.L., Nelson, M.L & Deating, J.: The association of age with gastric emptying. Age Ageing 22: 37–40, 1993.

Gershon, M.D., Kirchgessner, A.L. & Wade, P.R.: Functional anatomy of the enteric nervous system. In: Physiology of the Gastrointestinal Tract(ed. L.R. Johnson), pp. 381–422. 3rd edn, Raven Press, New York, 1994.

Green, D.M., Bishop, A.E., Rindi, G., Lee, F.I., Daly, M.J. & Domin, J.: Enterochromaffin-like cell populations in human fundic mucosa: quantitative studies of their variations with age, sex and plasma gastrin levels. J Pathol 157: 235–2341, 1989.

Green, L.K. & Graham, D.Y.: Gastritis in the elderly. Gastroenterol Clin North Am 19: 273–292, 1990.

Greenberg, R,. &, Holt, P,R.: Influence of aging upon pancreatic digestive enzymes. Dig Dis Sci 29: 970–977, 1986.

Geoghegan, J. & Pappas, T.N.: Clinical uses of gut peptides. Ann Surg 225 :145–154, 1997.

Gomes, O.A., de Souza, R.R. & Liberti, E.A.: A preliminary investigation of the effects of aging on the nerve cell number in the myenteric ganglia of the human colon. Gerontology 43: 210–217, 1997.

Gullo, L, Priori, P., Danielle, C., Ventrucci, M., Gasbarnni, G. & Labò, G. : Exocrine pancreatic function in the elderly. Gerontology 29: 407–411, 1983.

Hollander, D. & Dadufalza, V,D.: Ageing-associated pancreatic exocrine insufficiency in the unanesthetized rat. Gerontology 30:218–227, 1984.

Hollander, D., Tarnawski, A., Stacchura, J. & Gergely H.: Morphological changes in gastric mucosa of ageing rats. Dig Dis Sci 34: 1692–700, 1989.

Hollis, J.B. & Castell D.O.: Oesophageal function in elderly man. A new look at “Presby sophagus”. Ann Intern Med 80: 371–374, 1974.

Holt, P.R.: Diarrhea and malobsorption in the elderly. Gastroenterol Clin North Am 19: 345–359, 1990.

Holt, P.R. & Yeh, K.: Aging and gastrin production: changes in serum and antral gastrin concentrations in the rat. J Gerontol 44: M62–65, 1988.

Horowitz, M., Maddeun, G.J., Chatterton, B.E., Collins, P.J., Harding, P.E. & Shaerman, D.J.C.: Changes in gastric emptying rates with age. Clin Sci 67: 213–218, 1984.

Husebye, E. & Engedal, K.: The patterns of motility are maintained in the human small intestine throughout the process of aging. Scand J Gastroenterol 27: 397–404, 1992.

Ishizuka, J., Murakami, M., Nichols, A., Cooper, C.W., Greeley, G.H.J. & Thompson, J.C.: Age-related changes in gallbladder contractility and cytoplasmic Ca2+ concentration in the guinea pig. Am J Physiol 264: G624–629, 1993.

Johanson, J.F., Sonnenberg, A. & Koch, R.T. : Clinical epidemiology of chronic constipation. J Clin Gastroenterol 11: 525–536, 1989.

Kalache, A:. Ageing worldwide. In: Epidemiology in Old Age (ed. S. Ebrahim & A. Kalache). pp. 22–31. BMJ publishing group, London, 1996.

Kagaya, M., Iwata, N., Toda, Y., Nakae, Y. & Kondo, T.: Small bowel transit and colonic fermentation in young and elderly women. J Gastroenterol 32: 453–456, 1997.

Kawaguchi, H., Haruma, K., Komoto, K., Yoshihara, M., Sumis, K. & Kajiyama G.: Helicobacter pylori infection is the major risk factor for atrophic gastritis. Am J Gastroenterol 91: 959–962, 1996.

Khalil, T., Fujimura, M., Greeley, G.H.J. & Thompson, J.C.: Effect of aging on small intestinal tissue concentrations of cholecystokinin and secretin in rats. Gastroenterology 88: 1446. 1985.

Khalil, T., Fujimura, M., Greeley, G.H.J., Townsend, C.M.J. & Thompson .JC.: Effect of aging on serum gastrin content in Sprague-Dowley rats (abstr). Gastroenterology 88: 1445, 1985.

Khalil, T., Fujimura, M., Townsend, C.M.J., Greeley, G.H. & Thompson, J,C. :Effect of aging on pancreatic secretion in rats. Am J Surg 149: 120–125, 1985.

Khalil, T., Mate, L., Greeley, G.H.J. & Thompson, J.C.: Decreased gallbladder responsiveness to CCK-8 in aged rabbits (abstr). Gastroenterology 86: 1134, 1984.

Khalil, T., Singh, P., Fujimura, M., Townsend, C.M.J., Greeley, G.H.J. & Thompson, J.C.: Effect of

aging on gastric acid secretion, serum gastrin and antral gastrin content in rats. Dig Dis Sci 33: 1544–1548. 1988.
Khalil, T., Walker, P., Wiener, I., Fagan, J.F., Townsend, C.M.J. & Greeley, G.H.J.: Effect of aging on gallbladder contractility and release of cholecystokinin-33 in humans. Surgery 98: 423–429, 1985.
Kim, S.K.: Small intestine transit in the normal small intestine study. Am J Roentgenol Radium Ther Nucl Med 104: 522–524, 1968.
Kurata, J.H.: Ulcer epidemiology: an overview and proposed research framework. Gastroenterology 96: 569–580, 1989.
Kupfer, R.M., Heppell, M., Haggith, J.W. & Bateman, D.N.: Gastric emptying and small-bowel transit in the elderly. J Am Geriatr Soc 33: 340–343, 1985.
Kurumadu, K. & Yamakawa, T.: Study on changes in basal lamina width of mucosal and capillary in the lamina propria of murine stomach in advance of age. Gerontology 35: 283–288, 1989.
Laugier, R., Bernard, J.P., Berhezene, P. & Dupuy P.: Changes in pancreatic exocrine secretion with age: pancreatic exocrine secretion does decrease in the elderly. Digestion 50: 202–211. 1991.
Lee, M.: Age-related changes in gastric blood flow in rats. Gerontology;42: 290–293, 1996.
Lee, M., Hardman, W.E. & Cameron, I.: Age-related changes in gastric mucosal repair and proliferative activities in rats exposed acutely to aspirin. Gerontology 44: 198–203, 1998.
Lehy, T., Gres, L., & Ferreira de Castro, E.: Quantification of gastrin and somatostatin cell population in the antral mucosa of rat. Cell Tissue Res 198: 325–333, 1979.
Lindkvist, P., Asrat, D., Nilsson, I., Tsega, E., Olsson. G,L. & Wretlind, B.: Age at aquisition of Helicobacter pylori infection:comparison of high and a low prevalence country. Scand J Infect Dis 28: 181–184, 1996.
Madsen, J.L.: Effect of gender, age and body mass index on gastrointestinal transit times. Dig Dis Sci 37: 1548–1553, 1992.
Maitra, R.S-, Edgerton. E.A. & Majumdar, A.P.N.: Gastric secretion during aging in pyloric-ligated rats and effects of pentagastrin. Exp Gerontol 23: 463–472, 1988.
McConalogue, K. & Furness, J.B.: Gastrointestinal neurotransmitters. Baillieres Clin Endocrinol Metab 8: 51–76, 1994.
McConnell, J.G., Alam, M.J., O´Hare, M.M.T., Buchanan, K.D,. & Stout, R.W. : The effect of age and sex on the response of enteropancreatic polypeptides to oral glucose. Age Ageing 12: 54–62, 1983.
McDonald, T.J.: Gastroenteropancreatic regulatory peptide structures: an overview. In: . Neuropeptide Function in the Gastrointestinal Tract (ed. E.E. Daniel), pp. 19–86. CRC Press, Boca Raton, 1990.
McDougal, J.N., Miller, M.S., Burks, T.F. & Kreulen, D.L.: Age-related changes in colonic functions in rats. Am J Physiol 247: G542–546, 1984.
Mechiano, J.F-, Carvalho. V.C. & de Souza, R.R.: Nerve cell loss in the myenteric plexus of human esophagus in relation to age: a preliminary investigation. Gerontology 41: 18–21, 1995.
Metcalf, A.M-, Philips, S.F-, Zinsmeister, A.R., MacCarty, R.,L, Beart, R.W. & Wolff B.G.: Simplified assessment of segmental colonic transit. Gastroenterology 92: 40–47, 1987.
Miyasaka, K. & Kitani, K.: Aging and pancreatic exocrine function: studies in conscious male rats. Pancreas 2: 523–530, 1987.
Miyasaka, K. & Kitani, K.: Aging and pancreatic exocrine function: studies in female conscious rats. Dig Dis Sci 34: 841–848, 1989.
Moore, J.G., Tweedy, C., Christian, P.E. & Datz, F.L.: Effect of age on gastric emptying of liquid-solid meals in man. Dig Dis Sci 28: 340–344, 1983.
Official Statistics of Sweden. Örebro: Statistics Sweden, 1997.
Official Statistics of Sweden. Örebro: Statistics Sweden, 1995.
Ostensen, H., Gudmundsen, T.E., Boliz, K.D., Burhol, P.G. & Bonnevie, O.: The incidence of gastric ulcer and duodenal ulcer in north Norway. A prospective epidemiological study. Scand J Gastroenterol 20: 189–192, 1985.
Palasciano, G., Serio, G., Portincasa, P., Palmieri, V., Farelli, M. & Velardi, A,: Gallbladder volume in adults, and relationship to age, sex, body mass index and gallstone: a sonographic population study. Am J Gastroenterol 87: 493–497, 1992.
Piccone, P.R., Holt, P.R., Culpepper-Morgan, J.A., Paris, P., O'Bryan, L. & Ferdinands, L. : Intestinal dysmotility in the elderly: measurements of orocaecal transit time. Am J Gastroenterol 85: 161–164, 1990.
Pilotto, A., Franceshi, M., Del Favero, G., Fabrello, R., Di Mario, F. & Valerio G.: The effect of aging on oro-cecal transit time in normal subjects and patient with gallstone disease. Aging 7: 234–237, 1995.

Poston, G.J., Singh, P., Draviam, E.J., Upp, J.R.J. & Thomson J.C.: Development and age-related changes in pancreatic cholecystokinin receptors and duodenal cholecystokinin in guinea-pigs. Mech Ageing Dev 46: 59–66, 1988.
Poston, G.J., Singh, P., MacLellan, D.G., Yao, C.Z., Uchida, T. & Townsend C.M.J.: Age-related changes in gallbladder contractility and gallbladder cholecystokinin receptor population in the guinea-pig. Mech Ageing Dev 46: 225–236, 1988.
Poston, G.J-, Draviam, E.J., Yao, C,Z., Townsend, C.M.J. &Thompson, J.C.: Effect of age and sensitivity to cholecystokinin on gallstone formation in the guinea pig. Gastroenterology 98: 993–999, 1990.
Ribeiro, A.C-, Klinger, P.J-, Hinder, R.A. & DeVaul,t K.: Esophageal manometry: a comparison of findings in younger and older patients. Am J Gastroenterol 93: 706–710, 1998.
Richter, J.E., Wu, W.C., Johns, D.N-, Blackwell, J.N., Nelson, J.L. & Castell J.A. : Esophageal manometry in 95 healthy adult volunteers. Dig Dis Sci 1987;32:583–92.
Rosenberg, L., Duguid, W.P. & Fried, G.M.: Association of cholecystectomy with pancreatic growth and increased plasma levels of cholecystokinin in syrian golden hamster. J Surg Res 44: 235–241, 1988.
Roth, K., Kim, S. & Gordin, J.L.: Immunocytochemical studies suggest two pathways for enteroendocrine cell differentation in the colon. Am J Physiol 263: G174–180, 1992.
Sandström, O., Madhavi, J. & El-Salhy, M.: Age-related changes in antral endocrine cells in mice. Histol Histopathol 14: 31–36, 1999.
Sandström, O. & El-Salhy, M.: Duodenal endocrine cells in mice with special regard to age-related changes. Histol Histopathol 15: 347–353, 2000.
Sandström, O., Madhavi, J. & El-Salhy, M.: Effect of ageing on colonic endocrine cell population in mouse: Geronolgy 44: 324–330, 1998.
Sandström, O. & El-Salhy, M.: Ageing and endocrine cells of the human duodenum. Mech Ageing Dev 108: 39–48, 1999.
Sandström, O. & El-Salhy, M.: Human rectal endocrine cells and ageing. Mech Ageing Dev, 108: 219–226, 1999.
Santer, R.M. & Baker, D.M.: Enteric neuron number and sizes of Auerbach's plexus in the small and large intestine of adult and aged rats. J Auton Nerv Syst 25: 59–67, 1988.
Shimoda, I., Evers, B.M., Sato, K., Ishizuka, J., Rajaraman, S. & Chung, D.H.: Age-dependent increase of neurotensin expression in the ileum. Am J Physiol 266: G706–712, 1994.
Sjölund, K., Sandén, G., Håkansson, R. & Sundler, F.: Endocrine cells in human intestine. Gastroenterology 85: 1120–130, 1983.
Steinheber, F.U: Ageing and the stomach. Clin Gastroenterol 14: 657–688, 1985.
Smith, G.J.M. & Lefebvre, R.A.: Influence of aging on gastric emptying of liquids, small intestine transit, and fecal output in rats. Exp Gerontol 31: 589–651, 1996.
Sonnenberg, A. & Koch, T.R.: Physician visits in the united states for constipation: 1958–1986. Dig Dis Sci 34: 606–611, 1989.
Stachura, J., Tarnawski, A., Hollander, D., Ulich, T.R. & Gergely, H.: Aging associated hyperplasia of enterochromaffin-like cells in the gastric oxyntic mucosa of rats. A potential factor predisponating to carcinoids (abstr). Gastroenterology 92: 1513. 1987.
Track, N.S-, Walters, L.M. & Gauldie, J.: Motilin, human panceratic polypeptide (HPP) and gastrin plasma concentrations in fasting subjects. Clin Biochem 12: 109–117, 1979.
Trudeau, W.T. & McGuigan, J.E.: Serum gastrin levels in patients with peptic ulcer disease. Gastroenterology 59: 6–12. 1970.
Varga, F.: Transit time changes with age in the gastrointestinal tract of the rat. Digestion 14: 319–324, 1976.
Vellas, B., Balas, D., Moreau, J., Bouisson, M., Senegas-Balas, F. & Guidet, A.: Exocrine pancreatic secretion in the elderly. Int J Pancreatol 3: 497–502, 1988.
Vellas, B., Moureau, J., Bouisson, M., Guidet, D., Balas, D. & Senegas-Balas, F.: Age and pancreas: evidence for functional involution of exocrine pancreas in rat and man (abstr). Digestion 35: 59–60, 1986.
Wald, A.: Constipation and fecal incontinence in the elderly. Gastroenterol Clin North Am 19 :405–418, 1990.
Walford, R.L.: When is a mouse old? J Immunol 117: 352–354, 1976.
Walsh, J.H.: Gastrointestinal hormones. In: Physiology of the Gastrointestinal Tract (ed. L.R. Johnson), pp. 1–128. 3rd edn, Raven Press, New York, 1994.

Wallach, C.B. & Kurtz, R.C.: Gastrointestinal cancer in the elderly. Gastroenterol Clin North Am 19: 419–432, 1990.
Webster, S.G.P. & Loening, J.T.: Assessment of small bowel function in the elderly using modified xylose tolerance test. Gut 16: 109–113, 1975.
Wedmann, B., Schmidt, G., Wegener, M., Coenen, C., Ricken, D & Althoff, J.: Effects of age and gender on fat induced gallbladder contraction and gastric emptying of a caloric liquid meal: a sonographic study. Am J Gastroenterol 86: 1765–1770, 1991.
Wegener, M., Borsch, G., Schaffstein, J., Luth, I., Rickels, R. & Ricken, D.: Effect of ageing on the gastro-intestinal transit of lactulose-supplemented mixed solid-liquid meals in humans. Digestion 39: 40–46, 1988.
Whittle, B.: Nitric oxide in gastrointestinal physiology and pathology. In: Physiology of the Gastrointestinal Tract(ed. L.R. Johnson), pp. 267–294. 3rd edn, Raven Press, New York, 1994.
Wiener, I., Walker, J.P., Townsend, C.M.J. & Thomson, J.C.: Increased release of cholecystokinin with intraduodenal fat after cholecystectomy in dogs. Surg Forum 35: 196–198, 1984.
Xie, P., Ren, J., Bardan, E., Mittal, R.K., Sui,.Z. & Shaker, R.: Frequency of gastro-oesophageal reflux events induced by pharyngeal water stimulation in young and elderly subjects. Am J Physiol 272: G233–237, 1997.
Yates, F.E.: Theories of aging: biological. In. Encyclopedia of Gerontology (ed. J.E. Girren), pp. 545–555. vol. 2. Academic Press, San Diego, 1996.

Correspondence to: Magdy El-Salhy, MD, PhD,
Section for Gastroenterology and Hepatology
Department of Medicine
University Hospital
S-901 85 Umeå
Sweden
Tel: +46-90-7853867
Fax: +46-90-143986
E-mail: magdy.el-salhy@ medicin.umu.se