Age-Related Changes in the Enteric Nervous System

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Submitted: March 5, 2002
Revised: May 15, 2002
Accepted:

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Abstract

As we enter the 21st century, the segment of the population that is the most rapidly expanding is that comprised of individuals 85 years of age and older. Dysfunctions of the gastrointestinal (GI) system, including dysphagia, constipation, diarrhea, and irritable bowel syndrome are more common complaints of the elderly, yet our knowledge of the aging GI tract is incomplete. Compared to the rapid advances in the neurobiology of aging in the CNS, the understanding of age-related changes in the enteric nervous system (ENS) is poor. In this brief review I recap experiments that reveal neurodegenerative changes, and their functional correlates, in the ENS of mice, rats and guinea pigs. Clinical literature seems indicative of similar structural and functional age-related changes in the human ENS. Current studies that address the mechanisms underlying age-related changes in the ENS are introduced. The future directions for this field include physiological and pharmacological studies, especially at the cellular and molecular level. Research in the aging ENS is poised to make major advances, and this new knowledge will be useful for clinicians seeking to better understand and treat GI dysfunction in the elderly.

Keywords: gastrointestinal tract, autonomic nervous system, degeneration, senescence
**Introduction**

The enteric nervous system (ENS) is the division of the autonomic nervous system that is intrinsic to the GI tract and is a principal regulator of GI function. There is an extensive literature documenting the enteric neurobiology that has lead to our current understanding of the form and function of the ENS as a large and complex nervous system capable of autonomously mediating reflex behaviors underlying GI motility, absorption and secretion (14, 43). The ENS is able to mediate these reflexes independently because the system is comprised of intrinsic sensory neurons, interneurons and motor neurons interconnected in microcircuits. An understanding of what changes occur in the ENS with age, and how its altered state may relate to GI function in the old animal, has increasing relevance to clinical medicine. Individuals over 80 years old comprise the most rapidly growing segment of the U.S. population (33), and generally require more health care (utilizing ~ 1/3rd of annual health care dollars (2)); furthermore, those > 65 years old access medical care for GI-related problems more frequently than do those in other age groups, especially for functional complaints like constipation (8) or irritable bowel syndrome (38). Based on clinical evidence and demographics, physicians – especially gastroenterologists- increasingly will be called upon to understand and discriminate between disease processes with GI complications that are more common in the aged (e.g. diabetes mellitus), the GI side effects of multiple drugs that elderly are often prescribed, and the normally altered bowel function of the elderly. It is therefore necessary to know what “normal” is in the aged gut, and a logical starting point would be to understand the age-related changes in the ENS.
The goal of this short thematic review is to briefly summarize the enteric neurobiology of the aging gut. First, clinical studies that have addressed functional changes possibly related to altered enteric neural control will be discussed. Secondly, the current concepts of aging in the nervous system in general will be outlined as an introduction to a concise review of the structural and functional data on the aging ENS that has been accumulated to date from animal models. Finally, new understanding in this field will be highlighted, together with suggestions for areas where increased research effort may lead to better understanding of the age-related processes involving the ENS that may contribute to altered physiological responses observed in the GI system of the elderly. The imposed limits in the length, and in the number of citations, mean that not every work has been cited, for which I apologize in advance; nevertheless, I have directed the reader to more inclusive literature by referencing appropriate comprehensive reviews throughout.

Before reviewing what is known about the aging ENS, it may be appropriate to think about terminology. Standard medical dictionaries define ‘aging’ as gradually developing changes in structure that are not due to preventable disease and that are associated with decreased functional capacity. In his wonderful book “Longevity, Senescence, and the Genome”, Finch defines ‘aging’ as a “nondescript colloquialism that can mean any change over time”; ‘senescence’ as a “deteriorative change that causes increased mortality”, and ‘age-related’ as “a biological difference that is statistically significant between two age groups and that does not imply dysfunction, specific cause…” (12). In this review the term ‘senescence’ is studiously avoided because it is simply unknown whether changes in the aging ENS lead to increased mortality; rather, I
use the terms ‘aging’ and ‘age-related’ interchangeably because although there are clearly changes in the ENS that occur with time, the specific causes or changes in GI function that may occur because of intrinsic neuronal changes have yet to be determined.

*Clinical Evidence of age-related altered GI function and changes in the human ENS*

Hippocrates observed that in general “…the intestines tend to become sluggish with age”, and contemporary conventional wisdom holds that gut function changes with age; however, the there is less evidence-based support for this idea than one might expect. Much of the clinical literature suggests that as humans age, their GI tracts continue to function adequately despite an age-related loss of enteric neurons. The following is a concise summary that relates gut function, from the upper GI tract to the colon, in the elderly with demonstrated changes in the ENS.

Dysphagia and gastroesophageal reflux disease (GERD) are relatively common complaints in the elderly (25), and morphological studies have shown an age-related loss of enteric neurons in the human esophagus (22). Nevertheless, when objective criteria are assessed, actual age-related changes in esophageal physiology appear to be minimal (35). In fact, quantitative manometry reveals that esophageal contractile wave amplitudes and velocity and duration of LES relaxation in those over age 70 are not different from younger individuals (11). However, there is evidence of reduced amplitude of peristaltic contractions in the lower esophagus of the elderly (23), consistent with the observation that esophageal clearance after GER is impaired in older individuals (11). Continuing down the GI tract, the rates of gastric emptying and small intestinal transit seemingly are unchanged with age in humans (19). The evidence that colonic transit is reduced in the elderly is conflicted, with data demonstrating an absence of age-
related differences in colonic transit directly contradicting reports of increased colonic transit time in the aged [see (4)]. Some of these discrepancies may be due to difficulties in assessing normal changes in colonic motility in the elderly including the presence of overriding chronic disease, and multiple medical therapies – many of which have GI side effects. Morphological data from human tissues suggest that the population of colonic enteric neurons begins to decline relatively early in life, with marked decreases in both submucosal and myenteric plexuses occurring as early as the first four years (41, 42). In later years, this neurodegeneration of aging in the myenteric plexus continues with a further 37% reduction in the total population of neurons between ages 20-35 and 65 (15). Age-related changes in the human colonic submucosal plexus in advanced age have not been reported, and in general morphological studies of the aging human ENS are incomplete compared to the animal studies described below. Additional studies clearly are necessary to understand the paradoxical observations that GI function remains largely intact while the ENS suffers neuronal loss with age, and that the neurodegeneration of aging in the ENS is apparently not a consistent change from one organ to another along the length of the GI tract.

While primarily descriptive studies of the aging ENS have been underway since the 1980s, significant advances have been made in understanding the aging CNS. There are striking morphological similarities between the big brain and the little brains in the gut; notably, both CNS and ENS are comprised of neurons and glia, densely packed together in a synaptically rich neuropil that is devoid of connective tissue and both systems utilize similar repertoires of neurotransmitter and neuromodulatory substances (14). It would be surprising then, if there were not similarities in the morphological,
cellular and molecular changes that occur with age in the CNS and in the ENS. It is therefore useful to briefly consider some of the key lines of investigation in the aging CNS and in the extraintestinal PNS that may guide our thinking about the aging ENS.

**Age-related Changes in the CNS and Extraintestinal PNS**

Normal aging of the brain does not include a global loss of large numbers of neurons; rather, there are more specific, selective, and subtle changes, such as atrophy of pyramidal neurons, loss of synaptic contacts, decreases in specific neurotransmitter receptors, reactive gliosis, and abnormal cytoskeletal structures (18). Mechanisms thought to be involved in neurodegeneration of aging in the CNS that are relevant to the ENS have been reviewed recently (16); these include: altered Ca\(^{2+}\) signaling, mitochondrial dysfunction, the production of reactive oxygen species, and the Janus face of NO (too much or too little may be deleterious). The vast literature on age-related CNS neurodegeneration is well beyond the scope of this brief article and the changes that take place in the CNS at molecular, cellular and functional levels have been reviewed elsewhere (20). In general, the aging mammalian brain shows transcriptional changes that evidence decreased protein turnover (suppression of the ubiquitin-proteasome pathway), a reduction in trophic factors (e.g. GDNF), and an increase in markers of inflammation and stress responses (e.g. Cox-1, c-fos, and heat shock factors such as Hsp40)(18). Not surprisingly, similarities between the aging CNS and the aging ENS are now coming to light, and a good example of these parallels is seen in the neuron-sparing effects of caloric restriction in both nervous systems which prevents many of the changes outlined above ((18) & see below).
In the PNS, pre- and paravertebral sympathetic ganglia of aged humans and rodents exhibit terminal axonal dystrophy and remodeling of synapses more than neuronal cell loss (30). Because the neurodegenerative changes are seen only in some neurons, it has been suggested that certain adult postganglionic sympathetic neurons adapt phenotypes that are resistant to the neurodegeneration of aging. One of the characteristics of the “aging-resistant” postganglionic sympathetic neurons is that they have an increased capacity to take up neurotrophic factors (e.g. NFG) (6). Recent neuroanatomical tracing studies have failed to show neurodegenerative changes in motor or sensory vagal fibers that project to the gut in rats; rather, there is morphometric data demonstrating that the density and distribution of this innervation to the upper GI tract remains stable between the ages of 3 and 24 months, and similar qualitative assessment of the small bowel suggests that its vagal innervation likewise does not change with age (24).

*Neurodegeneration in the ENS is a characteristic of aging in rodents.*

The general architectural form of the ENS consists of two ganglionated plexuses, the myenteric plexus situated between layers of the muscularis externa, and the submucosal plexus in the connective tissue between the inner circular layer of smooth muscle and the muscularis mucosae (14). This plan is relatively constant throughout the length of the gut, and similar across mammalian species, although there are regional differences in the population densities of enteric neurons, and in the phenotypes of these neurons, as well as interspecies differences in the ENS. It is therefore important to assess what age-related changes take place along the entire the GI tract, and to learn if these changes occur in several species. This section summarizes the evidence for an enteric
neurodegeneration of aging that has been accumulated from three commonly studied species: guinea pig, rat and mouse. [N.B. The question that may arise is: how old is “old” in a laboratory raised rodent? Although the answer to this fundamental question is beyond the scope of this review, laboratory raised mice may live as long as 4-5 yr, rats as long as 5-6 yr (12), and guinea pigs as long as 7-8 yr (Gershon, personal communication).

**Guinea pig.** This species has been widely used in enteric neurobiology, and was one of the first animals in which an age-related decrease in the total population of neurons was noted; nevertheless, there is a paucity of evidence concerning regional changes in the ENS that occur over time. Gabella (13) studied whole mount preparations of small intestine consisting of longitudinal muscle and myenteric plexus (LMMP), stained with Nitro Blue Tetrazolium (NBT) for β-nicotinamide adenine dinucleotide (NADH) reductase, and determined that the population of neurons decreased by approximately half between the ages of 3 and 30 months. Recently, we have been using immunocytochemistry for RNA binding proteins (Hu C/D) ubiquitously expressed in all vertebrate neurons to estimate enteric neuronal populations, and our preliminary evidence is that a significant neuronal loss (~18%) occurs in the submucosal plexus in guinea pig distal colon between 5 and 20 months, and before neurodegeneration of the myenteric plexus can be detected (by 27 months neuronal loss in the myenteric plexus was ~40% (40)). Evidently no other comparable studies have been completed in regions of the guinea pig gut outside the small intestine and distal colon.

**Rat.** The ENS of the rat has been extensively studied and rats have also been used in a number of studies of the age-related changes in the ENS. One of the first studies was
based on the NBT NADH staining (described above) of jejunal, ileal, colonic and rectal LMMPs, and revealed a loss of approximately 40% of myenteric neurons between the ages of 6 and 24 months small bowel, and up to 60% neuronal loss in the colon (29). Powley’s group recently used cuprolinic blue-stained LMMP whole mounts to estimate changes in myenteric neuron populations throughout the rat GI tract at five time points between 3 and 27 months (24). This elegant, comprehensive study revealed no age-related loss of myenteric neurons in the gastric corpus or antrum, but showed decreases of 20 – 30% in the duodenum, 15 – 20% in the jejunoileum, and 30-40% in the colon and rectum. Many investigations on age-related changes in the ENS typically have been based on only two ages; however Philips and Powley, by virtue of employing multiple time points, were able to calculate a rate of neuron loss for each organ of the rat GI tract, and showed that there is neuronal loss as early as 12 months of age, and that the neurodegeneration continues in an approximately linear fashion throughout the remainder of the animal’s life.

*Mouse.* Comparable studies based on whole mount preparations of mouse gut apparently have not been carried out; however, point-counting stereological analyses of histological sections of mouse gut, immunostained for the neuronally expressed protein gene product 9.5, has been reported (9). The number of submucosal and myenteric ganglia remains constant in the gastric antrum, duodenum and distal colon of mice between 1 – 24 months; however, the number of neurons per ganglion declines by ~30% in the antrum and by 50-60% in the duodenum and distal colon between 3 and 12 months of age. Notably, the population of both submucosal and myenteric neurons is apparently stable between 12 and 24 months of age in mice. It is surprising, given the relative ease of
manipulating the mouse genome, that more studies have not been done establishing a mouse model for the aging ENS.

Thus, by a variety of approaches, the phenomenon of age-related neurodegeneration of the ENS has been established in three rodent species commonly used in enteric neurobiology. Beyond the general observation that significant numbers of neurons in the ENS are lost as these animals age, comparatively little else is known. In order to understand the changes in GI function that are observed in advanced age, it will be necessary to learn the fate of specific neuronal phenotypes within the aging ENS.

Evidence of age-related changes in specific phenotypes of enteric neurons

The earliest descriptions of the ENS in rodents of advanced age showed marked loss of neurons (see above), but the investigators also wanted to know the characteristics of neurons that were lost. Based solely on morphological properties of surviving neurons, Gabella determined that especially large neurons in the guinea pig small bowel myenteric plexus were lost in advanced age (13). Through combinations of electrophysiology, nerve tracing, and immunocytchemistry, distinct classes of neurons are now recognizable in the guinea pig (3), and utilizing this large database, it should be quite possible to learn about age-related changes of specific component neurons in the ENS of this species, however few such studies have been reported. Calbindin is a calcium binding protein that has been used as a marker of intrinsic sensory neurons in the guinea pig ENS (3), and our preliminary evidence is that the age-related loss of calbindin-IR neurons in the submucosal plexus of the guinea pig distal colon is greater than that of the total population of submucosal neurons (40). Furthermore, the amount of lipofuscin seems to accumulate with age in the surviving calbindin-IR neurons to a
greater extent than in other submucosal neurons (40). Lipofuscin, also known as “age pigment”, is a fluorescent substance (excitation maximum ~440nm, emission maximum ~600nm) that accumulates in lysosomes, and is thought to be an indicator of oxidative stress as well as of aging (17). It is interesting to note that although lipofuscin is also present in many neurons of the aged rat ENS, it has recently been demonstrated to be absent in the neurocalcin-IR neurons of aged rats (5). Additional new data suggest that the relative size of the subpopulation of serotonin-IR myenteric neurons in guinea pig distal colon is the same in young as in old animals (40). Brookes distinguishes 18 classes of enteric neuron in the guinea pig small intestine (3), and there are likely comparable classes in other regions of this animal’s GI tract. Many more studies will need to be completed before there is a clear understanding of the effects of aging on the various classes of neuron present throughout the guinea pig ENS.

When Santer and Baker initially studied the age-related changes in the rat ENS they observed that the neurons lost over time were of all sizes and shapes (29), suggesting that the neurodegeneration of aging was not limited to a particular class of neuron. When immunocytochemistry began to be employed in similar studies, other investigations suggest that different phenotypes of enteric neuron in the rat may not be equally susceptible to, or protected from, the neurodegeneration of aging. In fact one of the earliest immunocytochemical studies illustrated a decline in the density of substance P (SP), vasoactive intestinal polypeptide (VIP) and somatostatin (SOM) immunoreactive (IR) fibers with age in the rat small bowel ENS, primarily in very old age (24-36 mo) (10). Since only neuronal processes were specifically counted, and not cell bodies, one is
left to infer from this study that sensory neurons (SP-IR), inhibitory motor neurons (VIP-IR) and interneurons (SOM) are affected by the aging process in rats.

In addition to VIP, nitric oxide (NO) is an important inhibitory neurotransmitter synthesized and released by a subset of neurons in the ENS [Gershon, et al., 1994]. In these enteric neurons, NO is generated as a byproduct of the L-arginine conversion to L-citrulline that is catalyzed by the enzyme NO synthase (NOS). There are three main isoforms of NOS and enteric nitrergic neurons constitutively express, a Ca$^{2+}$-dependent isoform (neuronal, or nNOS). Nitrergic neurons can be immunostained with antibodies to nNOS, or they can be histochemically stained by the NADPH-diaphorase reaction (1). NADPH-diaphorase histochemical studies revealed a 15% decrease in the population of nitrergic myenteric neurons between the ages of 4 and 24 months in the small bowel of rats (compared to a 40% decrease in all myenteric neurons (29))(28), suggesting that nitrergic neurons are spared during the aging process. Even more striking is the finding that nearly 100% of myenteric neurons in the rat proximal colon were positively stained for NADPH-diaphorase at 26 months of age (1). Recently, Takahashi and coworkers obtained conflicting data by immunostaining LMMPs of rat colon with antibodies raised against nNOS; they determined that the number of nNOS-IR neurons per ganglion decreased >50% between 4 and 28 months (36).

As additional information comes to light, it seems increasingly evident that not all enteric neurons necessarily suffer the onslaught of aging in the same fashion; some classes of neurons may decline sooner, others later, some may increase and these changes may be regionally specific. There is clearly a need for a more complete understanding of the age-related changes within subpopulations of enteric neurons. Additionally, there is a
void in the literature on age-related changes that occur in the upper GI tract of commonly studied mammalian species, and few studies have focused on the specialized sphincteric regions of the gut.

*Evidence from physiological studies in animals suggests age-related changes in ENS-mediated function.*

This article began with a summary of the functional changes in the aging human GI tract that may have a basis in age-related changes in the ENS. Having summarized the morphology of the aging ENS in both human and laboratory animal studies, a logical question is to ask: what evidence is there that GI function changes as these laboratory animals age? This evidence is organized here according to studies aimed at understanding age-related changes in either GI motility or mucosal function.

**Motility.** Despite the fact that the ENS is equipped with a large functional reserve of neurons, it would be surprising if neurodegeneration in the range of 40 – 60% of the entire population did not lead to altered physiological states of the bowel. There is evidence of functional motility changes in both the upper and lower GI tract of aged animals. The rate of gastric emptying in rats remains the same between 3 and 12 months (31); but whether gastric emptying is slower in rats of advanced age is controversial, with one study demonstrating an insignificant decrease between 5 and 28 months (21), and another showing a 50% decreases between the ages of 12 and 24 months (31). These different results could be due to the meals (1.5% methylcellulose vs. polyethylene glycol), methods of detection (phenol red colorimetry vs. $^{51}$Cr gamma counting), or strains of rat (Wistar vs. Fischer 344) employed in the studies. Small bowel transit was also investigated in these two studies, and the rates were not different between young and
old rats in either study. Other functional data on age-related changes in the small bowel suggest an alteration in a specific neurotransmitter: when non-adrenergic, non-cholinergic relaxation in the isolated jejunum was evoked by electrical field stimulation (EFS), the NO-mediated component decreased with age (2 wks to 50 months) and was absent in the oldest rats (37).

As described above, the largest age-related decreases in neuronal populations within the ENS occur in the colon and physiological studies consistently suggest that colonic function is altered with age. Fecal output (number of fecal pellets and fecal mass) decreases by nearly 50% between 3 and 24 months in rats maintained on *ad libitum* food and water (31) and there is a 45% reduction in colonic transit of a $^{51}\text{Cr}$ marker between 5 and 28 months in Fischer 344 rats (21). Because there is evidence of age-related changes in the extrinsic innervation of the bowel (see above), it is important to know what component of altered colonic function is due to intrinsic changes. Insights are provided by *in vitro* measurements of contractile responses of rat colon evoked by EFS, or the application of drugs (21, 27). In these studies, the maximal contractions to EFS decreased between 30 and 80% with age. Again, experimental design may have contributed to the large differences in the magnitude of decreased responsiveness; alternatively, it could be an issue of how one defines “young” and “old”. In these studies the largest decrease was observed between rats aged 4 – 8 months, vs. 22 – 28 months, and the smaller decrease was observed in the study in which “young” included rats up to 12 months old. We have observed that the rate of propulsion of a solid pellet in isolated Fischer 344 rat distal colon is reduced by ~20% with age (4-7 mo. vs. 24-27 mo.)(39).
A reduction in the number of myenteric neurons suggests that there may be a reduction in the releasable pool of neurotransmitter substances as well as fewer neurons to respond to signals. The maximal twitch response of rat colonic preparations to acetylcholine (ACh) decreases by 50% with age (27). Interestingly, the release of ACh in response to EFS is due to a reduction in the activity of neuronal ω-conotoxin-sensitive (N-type) Ca\(^{2+}\) channels, and not a reduced ability of neurons in tissues from aged rats to synthesize ACh. In fact ACh release could be restored to levels seen in tissues from younger animals by the addition of the Ca\(^{2+}\) ionophore, ionomycin (27). Molecular approaches to age-related changes in the ENS should provide answers to many questions concerning the function of enteric neurons that survive into old age. Northern blot analyses have revealed that mRNA encoding nNOS is down regulated by as much as 70% in old (22 – 28 months) rats, and immunoblots reveal an estimated reduction of nNOS protein by as much as 50% (36). In the same study, both the basal and veratridine-stimulated activity of nNOS (as measured by production of L-citrulline) was reduced by approximately 50% with age. Notably, ACh and NO are only two of a dozen or more neuroactive substances released by enteric neurons. Since few studies aimed at understanding age-related changes in myenteric neuronal function have been carried out, and apparently none using mice, there is clearly a need for further research.

Mucosal function. Evidence of age-related neurodegenerative changes in the submucosal plexus exists (9, 40), but few studies have focused on changes in mucosal function that occur with age. Reddix and co-workers (26) have recently observed that the spontaneous, neurally mediated secretory activity recorded in colonic tissues from young (3 – 4 mo.) guinea pigs is absent in the same preparations derived from mature (12-15
mo.) guinea pigs. Furthermore, the colonic tissues from the mature animals mount diminished secretory responses to both EFS, and to nicotinic agonists, when compared with the preparations from young guinea pigs. Since there was no age-related difference in the epithelial secretory response of these preparations to muscarinic stimulation, it seems that it is the submucosal component of the ENS – which regulates absorption and secretion across the mucosa – that is functionally altered in an age-related process.

Back to the Future of the Aging ENS

The state of the science in the neurobiology of the aging ENS is on the cusp of moving beyond recognizing certain phenomena, such as the loss of enteric neurons and altered motility or secretory states, to addressing the mechanisms by which neuronal loss and/or dysfunction in surviving neurons occurs. Organizers of a workshop on the aging GI tract convened in the late 1980s concluded that in order to properly understand how the neuromuscular apparatus of the bowel changed with age, certain key pieces of information needed to be known with respect to the ENS (34): e.g., do certain types of neurons disappear in the ENS as animals age?; are there age-related changes in neuronal membrane Ca\(^{2+}\) channels, or in intracellular Ca\(^{2+}\) metabolism?; does the expression of receptors change with age?; and what happens to the levels of specific neurotransmitters? As outlined above, researchers have now begun to answer many of these questions. There is evidence that specific neuronal phenotypes may be more vulnerable to the aging process than others (28, 36, 39, 40), that neuronal N-type Ca\(^{2+}\) channels may be functionally impaired in the ENS (27), that there may be a decline in the ability of inhibitory motor neurons to synthesize NO (36), and there may be a decrease in the expression or function of submucosal nicotinic receptors (26). There are clearly many
unanswered questions, and these studies exemplify the future directions in which this field can rapidly advance.

Future research into the aging of the ENS will continue to move beyond phenomenology and into the realm of age-related functional changes and alteration in the underlying mechanisms. Information gleaned from work on the aging CNS and new technologies will continue to aide in the advance of understanding the aging ENS. Novel techniques such as the use of oligonucleotide microarrays that have been used to profile gene expression in the aging CNS (18) could be used to identify age-related changes in gene expression in the ENS. Caloric restriction (CR) has been shown to radically alter the profile of gene expression in the CNS of old mice compared to age-matched animals fed ad lib, down regulating the genes associated with inflammation and with stress responses normally seen in the aging CNS, and up-regulating those associated with neurotrophic factors (18). Taking a page from this line of CNS research, CR has been demonstrated to reduce the neurodegeneration of aging in the myenteric plexus of rats (7) and in the submucosal plexus of mice (Reddix, personal communication). The neurotrophins, NT3 (32) and GDNF (Reddix, ibid.) are factors that seem to provide protection from neurodegeneration in the ENS, and not coincidentally have been used to decrease colonic transit time in patients with constipation (4). Electrophysiological studies have not been carried out on the aging ENS, so it is unknown at this time whether there are remarkable differences in the membrane properties or synaptic behavior of enteric neurons in old animals. Contemporary molecular techniques should also aid in the identification of altered neurotransmitter and receptor expression in the aging ENS.
Aging-by definition- clearly occurs in the ENS, but this remarkable nervous system of the gut seems to age rather gracefully; even a 36-month-old rat continues to eat, digest and eliminate waste. This is not to say that the ENS of the very old animal, including human, is not normally altered with age; quite the contrary, evidence suggests that it is morphologically and functionally changed. Nevertheless, additional detailed knowledge of the aging process in the ENS is needed, and should be useful in the development of effective medical therapy for common GI disorders that are encountered more frequently in the elderly.

**Acknowledgments:** Supported by NIH P20RR 15553.

**References**


