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Myths and Misconceptions About Chronic Constipation

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There are many strongly held beliefs about constipation that are not evidence based. The purpose of this review is to address these beliefs concerning various aspects of constipation. There is no evidence to support the theory that diseases may arise via "autointoxication," whereby poisonous substances from stools within the colon are absorbed. Dolichocolon, defined as an elongated colon, should not be seen as a cause of constipation. The role of sex hormones altering gut function during the menstrual cycle appears to be minimal. During pregnancy they may play a role in slowing gut transit. Hypothyroidism can cause constipation, but among patients presenting with constipation, hypothyroidism is rare. A diet poor in fiber should not be assumed to be the cause of chronic constipation. Some patients may be helped by a fiber-rich diet but many patients with more severe constipation get worse symptoms when increasing dietary fiber intake. There is no evidence that constipation can successfully be treated by increasing fluid intake unless there is evidence of dehydration. In the elderly constipation may correlate with decreased physical activity, but many cofactors are likely to play a role. Intervention programs to increase physical activity as part of a broad rehabilitation program may help. It is unlikely that stimulant laxatives at recommended doses are harmful to the colon. A proportion of patients with chronic constipation is dependent of laxatives to achieve satisfactory bowel function, but this is not the result of prior laxative intake. Tolerance to stimulant laxatives is uncommon. There is no indication for the occurrence of "rebound constipation" after stopping laxative intake. While laxatives may be misused, there is no potential for addiction.

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> No organ in the body is so misunderstood, so slandered and maltreated as the colon.
>
> *Sir Arthur Hurst, 1935*

INTRODUCTION

Constipation, both objectively defined and perceived, afflicts many people in the Western world. It is a disorder that is amenable to self-treatment in addition to medical supervision. As with any widespread disorder that has been incompletely understood, there are many strongly held beliefs, which are often not evidence based and have arisen by observations and studies that were not rigorously performed. These beliefs, which are passed down from one generation to the next in oracular fashion, illustrate that certitude is not always the same as correctness.

The colon serves at least three purposes: to conserve water; to allow bacteria to split dietary fiber into absorbable nutrients; and to retain and expel the residue at convenient times and places. A complex interplay between absorption, colonic motility, and intrinsic and extrinsic sphincter function ascertains proper functioning in most instances. Stools may be perceived by the subject as too frequent or too infrequent, as too soft or too hard, and so on, which does not imply that these "deviations from normal" have a negative impact on physical health. However, for centuries people have tried to modify colonic function in order to attain optimal well-being.

The purpose of this review is to address widely held incorrect beliefs concerning various aspects of constipation in order to illustrate the quality of evidence that has been used to support these misconceptions. These beliefs encompass concepts of pathophysiology and treatment of constipation and are widely held in both the medical and lay communities.

WILL A LONG RESIDENCE TIME OF STOOLS IN THE COLON LEAD TO AUTOINTOXICATION?

The belief that diseases may arise via "autointoxication," whereby poisonous substances produced from undigested food in the intestine are absorbed, is an ancient one that was inscribed even in an Egyptian pharmaceutical papyrus dating from the 16th century, B.C. (1). This theory reached its apogee in the early 20th century when "autointoxication" was

advocated as "the most widespread illness in the developed world." The acknowledged "greatest modern interpreter of autointoxication" was an acclaimed surgeon at Guy's Hospital in London, Sir William Arbuthnot Lane, who stated that "autointoxication is the cause of all the chronic diseases of civilization, I have no doubt" (2). Lane's theory was based upon two related concepts (i) the structural origin of colonic stasis and (ii) the resulting autointoxication. The first is discussed in greater detail in Section 2 (dolichocolon).

The concept of autointoxication was related to the local stasis of colonic contents and their purported systemic effects. With stasis, bacterial flora were altered to favor bacteria capable of toxin production (either anaerobes or coliforms) (3). In the earliest stages of autointoxication, only intermittent lassitude might be described, but in more advanced cases a wide variety of gastrointestinal and extraintestinal complaints were enumerated (4). It is of interest that many of these symptoms also coexist in patients with irritable bowel syndrome, either with diarrhea, constipation, or both (5). Eventually, autointoxication was blamed for an unlimited number of disorders including hypertension, arthritis, cholecystitis, atherosclerotic plaque formation, various cancers, and skin disorders (6).

Toxins absorbed from the bowel have never been demonstrated, certainly not by the original advocates of the autointoxication theory. It has been pointed out that the theory of autointoxication was impossible to attack directly by experimentation (6). Because no toxin was considered to be universally present, the absence of any demonstrable toxin did not exclude autointoxication. Nor is it ever possible to disprove the presence of some as yet unidentified toxin in affected patients. However, the nonspecific symptoms attributed to "autointoxication" in constipated persons could be promptly relieved with bowel evacuation, suggesting a mechanical rather than a systemic effect (7). The autointoxication theory contributed to the public's preoccupation with daily and often unnecessary evacuation of stools in the early 20th century. There is no evidence to support this ill-conceived theory that has been long abandoned by the scientific community. Nonetheless, regular colonic cleansing with laxatives and enemas remains not uncommon, although the most aberrant and tragic extension of such thinking, the advocacy of subtotal colectomy for chronic constipation, has largely subsided except for a highly selected subgroup of patients with intractable constipation (8).

DOES DOLICHOCOLON CAUSE CONSTIPATION (AND SHOULD IT BE SHORTENED)?

Dolichocolon, defined as an elongated but not dilated colon, has been implicated as a cause of constipation but with little supportive evidence. It was the outgrowth of an illogical concept developed by Arbuthnot Lane, who conceived a mechanical-anatomical analysis of colonic kinking as a potential cause of chronic constipation (1). This theory embodied the concept that gravitational forces due to upright posture led to "unnatural kinking," initially at the junction of the descending and sigmoid colons, and progressing in ascending fashion to other areas such as the splenic and hepatic flexures. Lane found that limited excision of these fixated sites was rarely effective in alleviating constipation. As a result he eventually advocated total colon resection or bypass that he found to be "remarkably effective." These concepts spread to other countries where many such operations were performed by less skilled surgeons with significant mortality rates. Sir Arthur Hurst was "appalled. . .to see how lightheartedly colectomy has been recommended for comparatively trivial symptoms. . ." (9). By the 1920s, surgical treatment of intestinal stasis had fallen into disfavor, being reserved for only the most severe and refractory cases of constipation, as it is today.

Although refuted in the early 20th century, the concept of an elongated colon as a cause of constipation has persisted (10) and has been found even in recent peer-reviewed publications (11). In addition to the plausible idea that dolichocolon may result in symptomatic "incomplete or complete volvulus," it also has been hypothesized that a long colon could prolong stool residence time (12), thereby increasing water absorption to produce constipation. This has never been demonstrated nor are there studies that have correlated colonic transit with colonic length.

The definition of "dolichocolon" is uncertain as calculated average lengths of colon in normal individuals vary according to methodology (Table 1). In one study, which correlated colon anatomy with other parameters of colonic and anorectal function in constipated women (16), there was no correlation of dolichocolon, defined as >200 cm in length with other tests, nor were there differences between constipated women with or without long colons.

There is no evidence to support the use of shortening procedures in patients with dolichocolons or procedures designed to straighten colonic kinks, or redundant loops of intestine except in the presence of a demonstrable volvulus. The use of colonic function studies such as marker transit and studies of defecation are far more informative and therapeutically useful.

ARE PHYSIOLOGIC AND PATHOLOGIC CHANGES OF HORMONE LEVELS AN IMPORTANT CAUSE OF CONSTIPATION?

Sex Hormones

Constipation in children is more common in boys. However in adults aged 15–50 yr, that is, during the prime reproductive

Table 1. Normal Values for Colonic Length in Humans

Study	Method	Women	Men	Gender Unspecified
13	Autopsy	137 cm	142 cm	
14	Autopsy	157 cm	180 cm	
15	Surgery	115 cm	114 cm	
16	Radiology			167 ± 28 cm
17	*In vivo*			95–125 cm
18	Surgery			Western patients 114 cm Asian patients 111 cm

years, constipation is much more common in women (19). In addition, women often report changes in bowel function during different stages of their menstrual cycle. Lastly women with severe constipation have a high incidence of gynecological surgery. All these features raise the possibility that hormonal or gynecological changes are associated with, or in some way responsible for this condition.

The whole gut transit rate was measured in the follicular and luteal phases of the menstrual cycle in 18 healthy women in whom ovulation was confirmed biochemically (20). Mean transit time in the follicular phase of 45 h was not significantly different from the luteal phase (51 h). Stool weight was also not significantly different in the two phases (132 *vs* 123 g/day). Some subjects did experience more frequent and looser bowel actions on the first day of menstruation; this is thought to relate to the action of prostaglandins secreted locally during the first day of menstruation. This finding is confirmed by another study (21).

The rise in serum progesterone is substantially higher during pregnancy than during the luteal phase. Orocecal transit time was measured in 15 women during the third trimester of their pregnancies and again 4–6 wk following delivery. Transit time was significantly prolonged compared to the postpartum period (22).

While sex hormones therefore do not appear to have a major effect on bowel function under normal physiological conditions, they may contribute to altered gut function, and thereby to gut symptoms during pregnancy.

To investigate the possibility of a sex-hormone abnormality in women with severe constipation, a range of sex hormones during the follicular and luteal phases of the menstrual cycle was compared in 23 healthy women and 26 patients with severe idiopathic constipation (23). In the patients there was a reduction in the follicular phase of progesterone (4.5 *vs* 4 nmol/L, $p = 0.006$, median value, controls *vs* patients), 17 hydroxyprogesterone (9.7 *vs* 5.8 nmol/L, $p = 0.01$), cortisol (387 *vs* 245 nmol/L, $p = 0.008$), testosterone (2.3 *vs* 1.8 nmol/L, $p < 0.001$), androstenedione (10.3 *vs* 8.4 nmol/L, $p = 0.02$), and dehydroepiandrosterone sulphate (5.1 *vs* 3.0 nmol/L, $p = 0.03$). In the luteal phase there was a reduction of estradiol (483 *vs* 350 pmol/L, $p = 0.015$), cortisol (322 *vs* 242 nmol/L, $p = 0.047$), and testosterone (2.4 *vs* 1.7 nmol/L, $p = 0.003$). Thus, women with severe idiopathic constipation do have a consistent reduction in steroid hormones. However, these hormone changes are most likely to be secondary to altered gut transit, with alterations in the enterohepatic circulation and gut-wall breakdown of sex hormones.

Pelvic ultrasonography was undertaken in 26 patients with severe idiopathic constipation and 21 age-matched control women to detect any gynecological abnormality (24). No difference was found in ovarian, uterine, or pelvic vein morphology or size. The increased incidence of gynecological surgery in these patients appears to be due to a poor recognition that such pain can be associated with bowel dysfunction.

Gastrointestinal Hormones

Nonsex gastrointestinal hormones such as motilin, pancreatic polypeptide (PP), and gastrin blood concentrations in response to drinking water was assessed in patients with severe constipation and compared with two groups of healthy control subjects (25). Patients showed impaired motilin, PP, and gastrin release.

In another study 12 female patients (median age 34 yr) with severe idiopathic constipation and 12 healthy controls (8 female, median age 32 yr) were studied in relation to the hormone response to a meal (26). Patients showed higher somatostatin levels but a significantly lower somatostatin integrated incremental meal response. Pancreatic glucagon was significantly decreased. Enteroglucagon levels were significantly lower in patients between 30 and 60 min after the meal. The postprandial peak found in normal subjects was absent. No significant differences between the two groups could be found for insulin, gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), gastrin, pancreatic polypeptide, motilin, neurotensin, and peptide tyrosine tyrosine (PYY). Patients with severe idiopathic constipation therefore do have specific abnormalities of circulating gut hormones that may play a role in influencing gastrointestinal motility, and that may be of pathophysiological significance. Which of these changes are primary and which are secondary to the condition is unknown.

Systemic Nonsex, Nongastrointestinal Hormones

Constipation is a recognized symptom in patients with untreated hypothyroidism. Figure 1 demonstrates the range of bowel frequency in patients with hyperthyroidism, hypothyroidism, and in patients without thyroid disease (27).

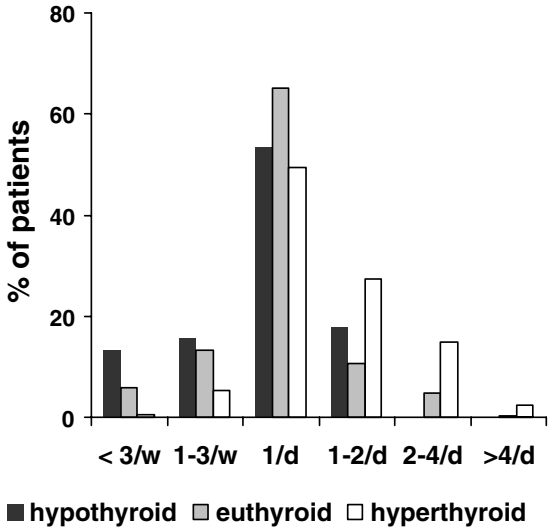

Figure 1. Stool frequency in patients attending an endocrinologic outpatients department. Though there is a shift of hypothyroid patients to lower frequencies and of hyperthyroid patients to higher frequencies, more than 70% of patients from all groups defecate every day or every other day. Data from Reference 27.

Although it is often recommended that thyroid function be checked to exclude hypothyroidism, in patients presenting with the primary symptom of constipation, there are few data to support this. To our knowledge the prevalence of hypothyroidism in patients presenting with idiopathic constipation has not been determined. In clinical practice, in young and middle-aged women presenting with idiopathic constipation, the prevalence of hypothyroidism appears to be very low. We would therefore not recommend routine thyroid testing in this patient population, unless there are other clinical features to suggest the presence of thyroid dysfunction.

In conclusion, the role of sex hormones altering gut function in normal healthy women during the menstrual cycle appears to be minimal. During pregnancy, when sex hormone changes are greater, they may play a role in slowing gut transit and increasing constipation. Among patients presenting with constipation, hypothyroidism is rare.

IS CONSTIPATION DUE TO A DIET POOR IN FIBER, AND IS IT BEST TREATED BY DIETARY FIBER?

Fiber binds water, but this property is lost when it is split and absorbed. Hence only fiber that is poorly split by bacteria such as bran retains its ability to bind water (28). This complicates the interpretation of studies on dietary fiber intake.

There are only a few studies that looked for dietary fiber intake by people with chronic constipation (Table 2). No differences were found in comparison to controls. The agreement between the studies regarding fiber eaten is remarkable. However, there are no data available on the consumption and effect of fiber in constipated patients from primary care.

There is no doubt that dietary fiber increases stool bulk and frequency, and decreases consistency in healthy people. There is also a reduction of the mean transit time and an increase of mean stool weight during treatment with wheat bran (32). It is interesting to note, however, that the transit times of the patients are always longer, and the stool weights are always lower in patients than in controls, irrespective of whether they are given bran or not (Fig. 2). It may also be seen that the gain in stool weight is smaller in patients than in controls, whereas the decrease in transit time is larger in patients. The patient, however perceives the stool volume, not the transit time, and therefore considers the effect of bran as smaller as the reader of Figure 3 will possibly do.

In a trial with a proprietary fiber product, less than half of the patients with self-defined constipation responded (33). The patients were also evaluated for transit time and disordered defecation. Only 20% of slow transit patients and some more with disordered defecation profited from fiber, whereas more than 80% of patients without identifiable cause of their complaints had a partial or complete improvement of their symptoms. These patients may be considered to suffer from a "relative fiber deficiency." It should be noted that gas production from fiber metabolism may limit acceptance. This is particularly true for bran (34) and other insoluble fibers. On the contrary, soluble fibers (psyllium, ispaghula, calcium polycarbophil, and glucomannan) appear to be better tolerated and accepted (35).

In conclusion, a diet poor in fiber should not be assumed to be the cause of chronic constipation in general but may be a contributory factor in a subgroup. Some patients may be helped by a fiber-rich diet but many patients with more severe constipation get worse symptoms when increasing dietary fiber intake.

IS CONSTIPATION DUE TO LOW FLUID INTAKE, AND CAN IT BE IMPROVED BY DRINKING AN ADEQUATE AMOUNT?

Comparatively small changes of the water content of stools lead to considerable changes in consistency (36). Hence it is obvious to the lay that the body may lose water via the colon. This might explain why people got the idea that hard small stools could be softened and enlarged by adding water, and that this could be accomplished by drinking more.

When fluid intake in healthy volunteers was varied from more than 2500 ml to less than 500 ml daily for 1 wk, each in random order, stool frequency diminished from 6.9 ± 0.9 to 4.9 ± 0.3 (mean $\pm$ SEM) defecations per week ($p = 0.041$), and stool weight from 1.29 ± 0.20 to 0.94 ± 0.17 kg per week ($p = 0.048$) during fluid restriction (37). Mean oroanal transit times were similar in the 2 wk. A lack of any effect on stool weight was observed in a similar experiment in controls

Table 2. Fiber and Fluid Intake in Samples of Patients with Chronic Constipation and Controls

Subjects	Number	Females	Fiber Intake (g/day)	SE	Fluid Intake (L/day)	SE	References
Slow transit constipation	64	64	14.7	0.7	1.2	0.1	19
Controls	64	64	15.0	0.6	1.2	0.1	
Self-defined constipated women in third trimester of pregnancy	9	9	18.2	1.8	1.7	0.1	29
Controls in third trimester of pregnancy	9	9	18.3	2.5	2.0	0.2	
Self-defined constipation	62	51	18.1	0.9	2.1	0.1	30
Controls	100	72	18.8	0.8	2.0	0.1	
Slow-transit constipation	19	15	17.4	1.5	2.0	0.1	30
Normal-transit constipation	21	20	19.8	1.8	2.2	0.2	
Controls	18	8	14.7		1.2		31
Self-defined constipation	18	10	17.3		1.1		

Diet was recorded by 7-day diaries and fiber intake was estimated from standard tables of food composition.

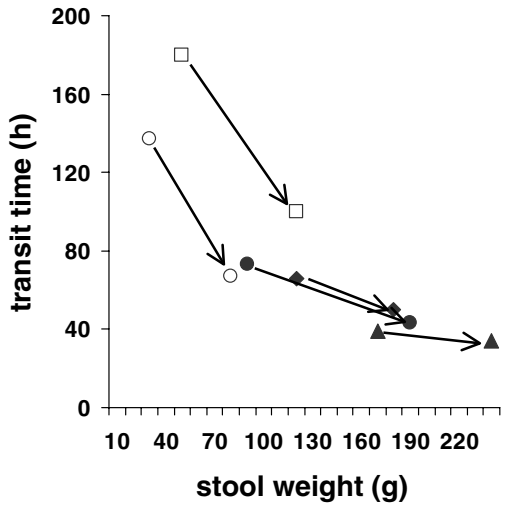

Figure 2. Effect of wheat bran on transit time and stool weight in patients with chronic constipation (open symbols) and healthy controls (closed symbols). Each point gives the mean of the group during experimental periods without (origin of arrow) and with addition of 25 g/day of wheat bran (peak of arrow). Data from Reference 32.

where fluid intake was increased by 1 and 2 L, respectively, for 1 wk each, irrespective whether pure water or an isotonic solution were given (38).

Four studies found drinking volume in constipated subjects and controls to be similar (Table 2). Interviews in 883 elderly people (>70 yr) did not reveal an association between their estimated amount of fluid intake and constipation (39). Nursing home residents (n = 21,012) who were at least 65 yr of age had assessments at baseline and at 3 months. By the 3-month assessment, 7% (n = 1,291) had developed constipation, which was defined as two or less bowel movements per week and/or straining upon defecation on >25% of occasions. Some factors were weakly associated with the development of constipation, namely (in order of magnitude and odds ratio in parenthesis) race (1.50), decreased fluid intake (1.49), pneumonia (1.45), and Parkinson's disease (1.44) (40).

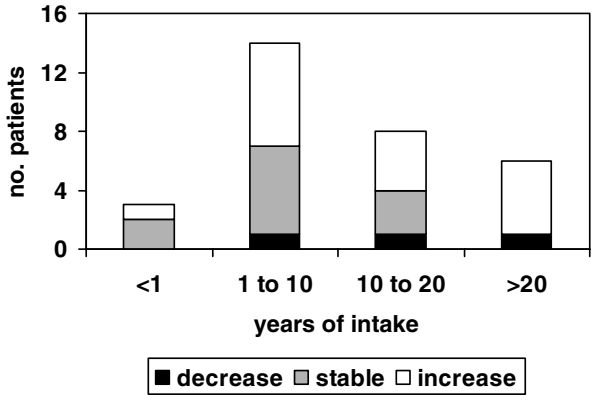

Figure 3. Number of patients with a decrease of dose, stable dose, or increase of dose over the period of intake of sodium picosulfate. Data were taken from the figure in Reference 94. Stable dose was defined as a change of less than five drops.

There are two studies examining whether constipation can be improved by drinking more fluid. One hundred and eight constipated children between the ages of 2 and 12 yr were randomized to a control group and two interventional groups. After a 3-day food record, one interventional group was instructed to increase daily water intake by 50%, while the other was asked to ingest additional hyperosmolar liquids such as juices. There were no changes regarding stool frequency, consistency (assessed by its appearance), or ease of defecation by either intervention (41). The other study was conducted in 117 adults with constipation defined as less than three bowel movements per week (42). Patients were randomized to either fluid intake at libitum or 2 L of mineral water daily, preferably between meals for 2 months. Stool frequency increased by 1.3/wk in the control group and by 2.4/wk in the interventional group. Laxative intake decreased by 0.8 and 2.2 doses/wk, respectively. In this trial the baseline data were assessed by patient recall. Hence the quoted numbers are not reliable. Further, the mineral water contained magnesium and other ions that may have acted as a light laxative.

Finally, there is a study challenging the recommendation to ingest dietary fiber supplements with extra water (43). Healthy volunteers were treated with 15 g/day of wheat bran for two experimental weeks. In a crossover design, the bran was ingested with or without 300 ml of additional water during 1 wk each. No effect of extra water was found. In view of the large amount of fluid that the human intestine handles each day (7–10 L) this result may not seem astonishing. However, the experimental proof is a valuable argument against the defendants of additional fluid intake.

In conclusion, available data do not suggest that stools can be manipulated to a clinically relevant extent by modifying fluid ingestion. There is no evidence that constipation can successfully be treated by increasing fluid intake unless there is evidence of dehydration.

DOES A SEDENTARY LIFE STYLE CONTRIBUTE TO CONSTIPATION? IS PHYSICAL ACTIVITY BENEFICIAL?

Physical activity does affect colonic motor function, with changes in function probably proportional to the extent of activity. There does appear to be a relationship between wakefulness and colonic activity. In health, during sleep, the bowel is relatively quiescent; there is an increase in bowel activity after waking. Both high- and low-amplitude propagated contractions, the manometric equivalent of mass movements, are a constant physiological propulsive pattern, related to sleep-wake cycles (44). Eighty percent of low-amplitude propagated contractions occur during the day, with a significant increase after meals and after morning awakening. In 25% of the subjects, these waves were accompanied by emission of flatus.

In patients with constipation and healthy subjects, motility in the descending and sigmoid colon was almost absent during sleep and significantly increased after waking, with

no difference in values between both groups (45). Population data do support the notion that those who undertake more physical activity do have a lesser incidence of constipation. However, it is not clear that this is a causative relationship. It may be that factors that lead to constipation may also lead to diminished physical activity.

In a cross-sectional study, the Australian Longitudinal Study on Women's Health, 14,502 young women (18–23 yr), 13,609 middle-aged women (45–50 yr), and 11,421 older women (70–75 yr), answered questions about vigorous and less vigorous exercise (used to determine a physical activity score), well-being (SF-36), symptoms, and medical conditions (46). There were significant associations between the physical activity score and SF-36 in each cohort. The odds ratio of 0.76 (CI, 0.65–0.89) for constipation was lower for women who reported low to moderate activity than for sedentary women, in the younger age group. Questionnaires were completed by 93 randomly selected runners and 95 age, sex-matched sedentary controls. The runners had more frequent bowel movements that were more often loose or urgent (47).

Several studies have suggested that increased physical activity is associated with decreased rates of constipation. Donald *et al.* (48) undertook a cross-sectional survey of bowel habit in 201 elderly patients living at home. Although symptoms of constipation were common, reported bowel frequency was similar to younger people. Constipation was most clearly associated with poor mobility and depression.

Kinnunen *et al.* (49) undertook a study of constipation and related factors in 439 geriatric hospital patients, 183 people living in two old people's homes, and 78 patients visiting a geriatric day hospital. The results suggested an increased risk of constipation for those walking less than 0.5 km daily (relative risk (RR) = 1.7), walking with help (RR = 3.4), chairbound (RR = 6.9), and bedbound (RR = 15.9).

Prolonged physical inactivity in those who are normally physically active, especially in the elderly, can reduce colonic transit. Physical inactivity was achieved by a restriction of all kinds of physical exercise and by staying at home in nine elderly subjects. The mean total colonic transit time of 10.9 h was significantly prolonged to 19.5 h during physical inactivity ($p < 0.01$) (50).

In healthy subjects moderate increased activity does not change bowel function but vigorous physical activity such as marathon running will increase gut (including colonic) activity. This can lead to a dramatic increase in large bowel function (51).

Modest physical activity may help individuals with mild constipation but there is no evidence that more severe constipation is helped. Eight patients with chronic idiopathic constipation were studied for 6 wk, including 2 wk of rest and 4 wk of regular exercise. In addition to their routine daily activities, they exercised 1 h a day, 5 days a week. Patients covered a mean of 1.8 and 3.2 miles per day in the rest period and during the exercise period, respectively. This level of exercise did not improve their constipation indices (52).

A bowel management was instituted in a nursing home, which involved increasing the amount of fiber, fluids, and exercise. The program demonstrated a decrease in the consumption of laxatives as well as an increase in the number of spontaneous bowel movements (53). Similar findings were observed in uncontrolled studies instituting a major bowel program consisting of many aspects, all of which might have had an effect on bowel function (54).

In conclusion, bowel function may correlate to some extent with physical activity, but other cofactors such as diet and personality may be important. In the elderly constipation may correlate with decreased physical activity, but many cofactors are likely to play a role, such as cognitive function, medications, and diet. Intervention programs to increase physical activity probably do not improve bowel function in the young severely constipated patient. In the elderly they may help, but probably as part of a broad rehabilitation program containing many aspects of care.

IS THE CHRONIC USE OF LAXATIVES UNHEALTHY?

Laxatives are among the most widely used medications. Many factors, including aging of the population, misconceptions about the normal (and desirable) frequency of bowel movements, fear of the consequences of constipation, and the availability of laxatives over the counter have resulted in their widespread use. At the same time, concern about potential side effects may result in underuse by patients who profit from laxatives for regulation of bowel habits.

Stimulant laxatives are traditionally advocated for short-term use only, as their long-term use is claimed by many to impair normal colonic function, produce laxative dependency, cause damage to the enteric nervous system and/or intestinal smooth muscle, and increases the risk of colorectal and perhaps other cancers.

DOES CHRONIC LAXATIVE INTAKE CAUSE ENTERIC NEURONAL DAMAGE?

The greatest concern that stimulant laxatives can induce permanent enteric nerve or muscle damage has been expressed about anthraquinones. In part, this may be due to the development of *melanosis coli*, an easily visible brown discoloration of the colon. It may occur within months of regular use and can last for months after discontinuing laxative use (55, 56). This pigmentation is related to cell debris formed during apoptosis of colonic epithelia, is stained by anthraquinones, and then taken up by submucosal macrophages (57). Melanosis does apparently not have any functional significance.

The belief that chronic use of stimulant laxatives damages the colonic myenteric system is largely derived from uncontrolled observations in humans and from conflicting data obtained in prospective studies of animals (for review see Ref. (58)).

The original study in humans (59) included 12 "purgative addicts" who underwent examination of their colons that had been removed in an attempt to obtain relief of severe constipation. Although damage to enteric nerves as well as smooth muscle atrophy was reported, it is hard to ascertain if it was due to a primary motility disorder, to laxatives no longer currently in use, or to chronic ingestion of currently used laxatives.

Electron microscopic studies have shown that constipated patients with long-term laxative use exhibited distension or ballooning of axons, reduction of nerve-specific cell structures and increase in lysosomes, and sometimes a total degeneration of whole nerve fibers (60, 61). Most of the patients studied had used laxatives for more than 10 yr in daily doses that exceed the recommended daily dose by a factor of 18. It is worth mentioning however that the above findings may not be specific to laxatives and have been reported in patients with diabetic autonomic neuropathy and chronic inflammatory bowel disease (61).

Oral (sodium phosphate and anthraquinones) and rectal (sodium phosphate and bisacodyl) administration of laxatives have been reported to cause short-lived superficial damage to the mucosa (62–64).

It is difficult to understand whether the abnormalities observed in humans are a consequence of the excessive laxative intake or whether they represent preexisting changes of unknown etiology that lead to a functional impairment (disordered absorption or motility). The recent demonstration that patients with severe colonic inertia have decreased volume or numbers of interstitial cells of Cajal and enteric neurons (65, 66) suggests that previous abnormalities may have been misattributed to the chronic use of stimulant laxatives (67). Indeed, there is only one study comparing the morphology of the autonomous nervous system of constipated patients taking anthraquinones (aloe) to that of an appropriate control group of constipated patients without laxative intake (68). It does not support the hypothesis that anthraquinone containing laxatives are able to provoke relevant degenerative changes in the colonic nerve tissue of superficial layers accessible by endoscopic biopsies.

In conclusion, the arguments in favor of laxative-induced damage to the autonomous nervous system of the colon have been advocated on the basis of poorly documented experiments. In contrast, investigations that do not support such damage are well done and performed by using a variety of techniques. It is therefore unlikely that stimulant laxatives at recommended doses are harmful to the colon.

DOES CHRONIC USE OF LAXATIVES INCREASE THE RISK OF COLORECTAL OR OTHER CANCERS?

Results from *in vitro* and animal studies have suggested that anthraquinone laxatives have a tumorigenic potential and may therefore be associated with an increased risk of colorectal cancer (CRC) (69). However, care should be taken when extrapolating the findings of animal studies to humans since the above results have been obtained using very high doses of anthranoids for a relatively long period compared to the lifespan of animals. Furthermore, the available epidemiological studies are reassuring.

The study that first suggested an increased risk of colorectal cancer in patients taking anthraquinone laxatives consisted of both retrospective and prospective analyses (70). In the retrospective cohort, the incidence of *melanosis coli* was increased among patients with colorectal adenomas but not among those with carcinomas, whereas in the prospective study, it was increased among patients with carcinoma but not among those with adenomas. A subsequent investigation (71) found no association between CRC and *melanosis coli* or laxative use and proposed that the association of adenomas with *melanosis coli* can be explained by the ease of detection of even tiny polyps as bright spots within a dark-colored colonic mucosa.

A metaanalysis of 14 previously published case–control studies (72) revealed statistically significant risks for CRC associated with both constipation and use of cathartics, the pooled odds ratios being 1.48 (1.32–166) and 1.46 (1.33–1.61), respectively. Since constipation and cathartics are associated with much lower odds ratios than various dietary components (whose risk factors range between 2 and 4), such as fat, meat, alcohol, and low-vegetable or low-residue diets, it appears that their risk reflects the confounding influence of underlying dietary habits. All subsequent studies (71–78) failed to find an association between anthranoid laxative intake and CRC. In a case–control study (74), performed on middle-aged adults, both constipation and laxative use were associated with increased risk of CRC. However, when these variables were adjusted for each other, the association with commercial laxative use disappeared, whereas that with constipation remained strong, a finding confirmed in a recent population-based, case–control investigation (78).

Among diphenylmethane derivatives, phenolphthalein was found to increase the incidence of ovarian, adrenal, renal, and hematopoietic neoplasms among treated animals (79). Phenolphthalein was therefore banned by the U.S. Food and Drug Administration (FDA) and almost all the phenolphthalein-containing preparations were voluntarily withdrawn from the market not only in the United States but also in several European countries. However, a subsequent large case–control study (80) "exonerated" phenolphthalein. The authors emphasized that the rodents had been given much higher doses of the agent than are commonly used by patients, that is, from 10 to 1,000 times the human dose. And indeed an additional case–control study (81) provides reassurance that phenolphtalein-containing laxatives do not increase the risk of ovarian cancer in humans.

A thorough carcinogenetic study was performed with bisacodyl (another diphenylmethane laxative) in heterozygous transgenic mice, and the results were submitted to the FDA (FDA docket #7BN-036L) which concluded that, used at the recommended doses, this compound does not display any tumorigenic risk for humans. As a consequence, bisacodyl was classified as a Category I (safe and effective)

OTC laxative ingredient. As picosulphate is structurally similar to bisacodyl and both prodrugs share the same active metabolite (*i.e.*, bis-(p-hydroxyphenyl)-pyridyl-2-methane) (82), the extensive toxicological investigation on bisacodyl is also relevant to the safety assessment of picosulphate, enabling extrapolation of the available data of the former compound to the latter.

In conclusion, although chronic constipation appears to be associated with an increased risk of CRC, there are no data to support that stimulant laxatives are an independent risk factor for CRC.

CAN LAXATIVE INTAKE CAUSE ELECTROLYTE DISTURBANCES AND ABDOMINAL COMPLAINTS?

Serum potassium was found to be slightly lower among laxative users compared to nonusers (3.94 *vs* 4.04 mmol/L) (83). In patients abusing laxatives in high doses, wasting of potassium and water are common (84). However, in prospective studies no changes in serum electrolyte levels where found with recommended doses of sennosides taken for more than 1 yr (85, 86).

Abdominal complaints may occur with all types of laxatives. Since constipation by itself is often associated with abdominal complaints, the causative role of laxatives is not always apparent. Compounds that can be digested by the colonic bacteria (*e.g.*, fibers or lactulose) produce mainly bloating and flatulence. Stimulant laxatives may induce abdominal discomfort and even cramping abdominal pain with a frequency three times higher than placebo (87).

In conclusion, laxatives can cause electrolyte disturbances or abdominal complaints but this can be minimized with appropriate drug and dose selection for a given patient.

DO LAXATIVES INDUCE HABITUATION AND TOLERANCE?

Long-term use of laxatives is often said to result in habituation (*i.e.*, the reduction or even disappearance of laxative response) and/or tolerance (*i.e.*, the need to increase the laxative dose in order to maintain the desired response). Both could theoretically be induced by damage to the colon or by an adaptive mechanism counteracting the laxative effect on motility or secretion. While chronic sennoside treatment does not affect colonic motility in rats (88) there are conflicting animal studies on serum aldosterone levels. Bisacodyl increased serum aldosterone levels and was less effective on water and sodium secretion after chronic pretreatment (89). Similarly, the efficacy of rhein, bisacodyl, and phenolphthalein decreased during a 10-day treatment in guinea pigs (90). In contrast, studies in rats suggest that long-term sennoside treatment in diarrheagenic doses does not induce habituation and does not lead to secondary hyperaldosteronism (91).

Tolerance to laxatives has not been systematically studied in humans. Clinical studies do not show a loss of effect of laxatives but some patients with slow-transit constipation report the need to increase the laxative dose in order to maintain the desired effect (19). In a trial, where bisacodyl was used for periods ranging from 2 to 34 yr by patients with spinal cord injuries, no loss of effect has been reported (92). Similarly, no tolerance was observed in patients taking picosulphate during their hospital stay (93). When current users of sodium picosulphate were asked about the length of intake and time course of laxative dose, two-thirds claimed to have increased the dose over time (Fig. 3) (94). Dose escalation could, of course, reflect worsening of constipation over time rather than true tolerance. The fact that a proportion of patients with chronic laxative intake could be switched to dietary fiber (95–97), rectal laxatives (98), or prokinetics (99), or could be "weaned" by behavioral treatment (100) is a strong argument against the development of tolerance.

In conclusion, the development of tolerance to stimulant laxatives occurs in the most severe patient group with slow colonic transit in whom other types of laxatives are ineffective. Tolerance seems to be uncommon in the majority of users.

DO LAXATIVES INDUCE PHYSICAL DEPENDENCE ("REBOUND" CONSTIPATION) AND ADDICTION?

Physical dependence is a state of adaption that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (101). After an overdose of a laxative leading to diarrhea (*e.g.*, for diagnostic bowel preparation) the colon may be near empty, and it may take some time until spontaneous defecation is resumed. This is not related to chronic laxative use in recommended doses. In the latter, there are three possible scenarios when a patient stops taking laxatives after chronic use. (i) The patient may be "cured": transit studies have demonstrated that some patients have just normal bowel function after stopping laxatives. This is supported by the reduction of laxative intake observed in the placebo arm of trials with cisapride (102) and tegaserod (103). (ii) Other patients remain constipated following laxative withdrawal (100). (iii) Constipation could be worse than prior to the use of laxatives ("rebound") but there are no data to support this last scenario.

Addiction to a drug is characterized by an impaired control over intake, compulsive use, continued use despite apparent harm, and craving for the substance. The classic "abuse drugs" enter the CNS and locally affect the dopamine system in the primitive brain (101). Since most laxatives are not absorbed and none does cross the blood brain barrier there is no pharmacologic basis for addiction. However, there are people abusing laxatives and taking diarrheagenic doses for extended time periods. These are mostly psychiatric patients (Münchhausen's syndrome) (84). Sometimes, diarrheagenic doses of laxatives are taken in the belief that it contributes to weight loss (104). Of course, laxative-induced diarrhea

may induce an acute weight loss, and stopping the laxative may conversely be followed by an acute weight restoration. A small effect of chronic laxative intake on dry body weight has been reported (105) and may be explained by the loss of energy from split products of dietary fiber that would otherwise be absorbed from the colon.

In conclusion, a proportion of patients with chronic constipation is dependent on laxatives to achieve bowel movements without complaints such as severe straining, but this is not the result of prior laxative intake. There is no indication for the occurrence of "rebound constipation" after stopping laxative intake. There is no potential for addiction to laxatives, but laxatives may be misused by psychiatric patients.

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