Myths and Misconceptions About Chronic Constipation

Stefan A. Müller-Lissner, M.D., Michael A. Kamm, M.D., F.R.C.P.,
Carmelo Scarpignato, M.D., D.Sc., F.A.C.G., and Arnold Wald, M.D., F.A.C.G.
Park-Klinik Weissee, Berlin, Germany; St. Marks Hospital, London, UK; Laboratory of Clinical
Pharmacology, Department of Human Anatomy, Pharmacology and Forensic Sciences, University of Parma,
Parma, Italy; and University of Pittsburgh Medical Center, Pittsburgh, USA

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.

(Am J Gastroenterol 2005;100:232–242)

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 wa-
ter; 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,
colic motility, and intrinsic and extrinsic sphincter func-
tion ascertains proper functioning in most instances. Stools
may be perceived by the subject as too frequent or too in-
frequent, as too soft or too hard, and so on, which does not
imply that these “deviations from normal” have a negative im-
 pact 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 in-
correct beliefs concerning various aspects of constipation
in order to illustrate the quality of evidence that has been
used to support these misconceptions. These beliefs encom-
pass concepts of pathophysiology and treatment of consti-
pation 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 dat-
ing 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 “auto-
tointoxication is the cause of all the chronic diseases of civi-
ization, 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 sta-
sis of colonic contents and their purported systemic effects. With stasis, bacterial flora were altered to favor bacteria capa-
cable 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 com-
plaints were enumerated (4). It is of interest that many of these symptoms also coexist in patients with irritable bowel syn-
drome, either with diarrhea, constipation, or both (5). Eventu-
ally, 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 demon-
strated, certainly not by the original advocates of the autoin-
toxication theory. It has been pointed out that the theory of autointoxication was impossible to attack directly by experi-
mentation (6). Because no toxin was considered to be univer-
sally 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 pa-
ients. However, the nonspecific symptoms attributed to “au-
tointoxication” in constipated persons could be promptly re-
lieved with bowel evacuation, suggesting a mechanical rather
than a systemic effect (7). The autointoxication theory con-
tributed to the public’s preoccupation with daily and often un-
necessary 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. Nonethe-
less, regular colonic cleansing with laxatives and enemas re-
mains not uncommon, although the most aberrant and tragic extension of such thinking, the advocacy of subtotal cole-
tomy 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 lit-
tle supportive evidence. It was the outgrowth of an illogi-
cal concept developed by Arbuthnot Lane, who conceived a mechanical-anatomical analysis of colonic kinking as a po-
tential cause of chronic constipation (1). This theory embod-
exted the concept that gravitational forces due to upright pos-
ture led to “unnatural kinking,” initially at the junction of the
descending and sigmoid colons, and progressing in ascend-
ing 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 re-

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 mortal-
ity rates. Sir Arthur Hurst was “appalled . . . to see how light-
heartedly colectomy has been recommended for compara-
trively trivial symptoms . . . ” (9). By the 1920s, surgical treat-
ment of intestinal stasis had fallen into disfavor, being re-
served for only the most severe and refractory cases of con-
stitution, 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 pub-
lications (11). In addition to the plausible idea that dolicho-
colon may result in symptomatic “incomplete or complete volvulus,” it also has been hypothesized that a long colon could prolong stool residence time (12), thereby increas-
ing 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 proce-
dures 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 reproduc-
tive

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Women</th>
<th>Men</th>
<th>Gender Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Autopsy</td>
<td>137 cm</td>
<td>142 cm</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Autopsy</td>
<td>157 cm</td>
<td>180 cm</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Surgery</td>
<td>115 cm</td>
<td>114 cm</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Radiology</td>
<td>167 ± 28 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>In vivo</td>
<td></td>
<td>95–125 cm</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Surgery</td>
<td>Western patients 114 cm</td>
<td>Asian patients 111 cm</td>
<td></td>
</tr>
</tbody>
</table>
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. Oroccecal 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.](image-url)
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 ± SEM) defections 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**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Number</th>
<th>Females</th>
<th>Fiber Intake (g/day)</th>
<th>SE</th>
<th>Fluid Intake (L/day)</th>
<th>SE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow transit constipation</td>
<td>64</td>
<td>64</td>
<td>14.7</td>
<td>0.7</td>
<td>1.2</td>
<td>0.1</td>
<td>19</td>
</tr>
<tr>
<td>Controls</td>
<td>64</td>
<td>64</td>
<td>15.0</td>
<td>0.6</td>
<td>1.2</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Self-defined constipated women in third trimester of pregnancy</td>
<td>9</td>
<td>9</td>
<td>18.2</td>
<td>1.8</td>
<td>1.7</td>
<td>0.1</td>
<td>29</td>
</tr>
<tr>
<td>Controls in third trimester of pregnancy</td>
<td>9</td>
<td>9</td>
<td>18.3</td>
<td>2.5</td>
<td>2.0</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>Self-defined constipation</td>
<td>62</td>
<td>51</td>
<td>18.1</td>
<td>0.9</td>
<td>2.1</td>
<td>0.1</td>
<td>30</td>
</tr>
<tr>
<td>Controls</td>
<td>100</td>
<td>72</td>
<td>18.8</td>
<td>0.8</td>
<td>2.0</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Slow-transit constipation</td>
<td>19</td>
<td>15</td>
<td>17.4</td>
<td>1.5</td>
<td>2.0</td>
<td>0.1</td>
<td>30</td>
</tr>
<tr>
<td>Normal-transit constipation</td>
<td>21</td>
<td>20</td>
<td>19.8</td>
<td>1.8</td>
<td>2.2</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>Controls</td>
<td>18</td>
<td>8</td>
<td>14.7</td>
<td>1.2</td>
<td>1.1</td>
<td></td>
<td>31</td>
</tr>
</tbody>
</table>

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

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 daily activities, they exercised < 5 days a week. Pa-

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 “purga-
tive 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 struc-
tures and increase in lysosomes, and sometimes a total de-
generation of whole nerve fibers (60, 61). Most of the patients
studied had used laxatives for more than 10 yr in daily doses
that exceeded 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 inflamma-
tory bowel disease (61).

Oral (sodium phosphate and anthraquinone) 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 ob-
served in humans are a consequence of the excessive laxative
intake or whether they represent preexisting changes of un-
known etiology that lead to a functional impairment (disor-
dered 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 con-
taining laxatives are able to provoke relevant degenerative
changes in the colonic nerve tissue of superficial layers ac-
cessible 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 experi-
ments. 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 ex-
trapolating 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 epidemiolog-
ical studies are reassuring.

The study that first suggested an increased risk of colorec-
tal cancer in patients taking anthraquinone laxatives consisted
of both retrospective and prospective analyses (70). In the
retrospective cohort, the incidence of *melanosis coli* was in-
creased 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 detec-
tion of even tiny polyps as bright spots within a dark-colored
colon 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 as-
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 in-
take 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 con-
stipation 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). Phe-
olphthalein 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 Eu-
pean countries. However, a subsequent large case–control
study (80) “exonerated” phenolphthalein. The authors em-
phasized 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 ad-
ditional case–control study (81) provides reassurance that
phenolphthalein-containing laxatives do not increase the risk
of ovarian cancer in humans.

A thorough carcinogenic study was performed with
bisacodyl (another diphenylmethane laxative) in heterozy-
gous 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)
O谭 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 adaptation 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 (Münchausen’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.

Reprint requests and correspondence: Stefan Mueller-Lissner, M.D., Abteilung Immere Medizin, Park-Klinik Weissensee, Schonstrasse 80, 13086 Berlin, Germany.

Received July 1, 2004; accepted July 26, 2004.

REFERENCES


42. Anti M, Pignataro G, Armuzzi A, et al. Water supplementation enhances the effect of high-fiber diet on stool frequency and laxative consumption in adult patients with functional constipation. Hepatogastroenterology 1998;45:727–32.


