**Introduction:**
Man has been plagued by chronic constipation and other digestion-related problems for more than 7,000 years or at least ever since we stopped feeding solely on berries, roots and grains, but turned to a wide variety of meat products (3). Constipation is still an important problem today, plaguing modern society more than ever, because approximately one-fifth of all adults suffer from chronic constipation (24). In general terms, constipation has been defined as the delayed evacuation of dry, hard stools (20). Constipation per se is diagnosed if no bowel movement occurs for three or more days and if this irregularity persists for more than six months (14, 19).

In addition to the adverse effect on a person's well-being, the following symptoms may also occur: intestinal sluggishness, sensation of bloating, putrefaction, headache, fatigue, skin rashes and halitosis (6).

**Causes of Constipation**
Constipation has several causes (1, 5, 16), the most common ones being associated with nutritional factors such as the consumption of food with a poor dietary fibre content resulting in the insufficient filling of the intestine or the intake of readily absorbed food with a reduced water-binding capacity. Other causes of constipation include factors related to organ dysfunction or organ damage including gastrointestinal disorders, changes in the intestinal wall (due to a tumour or chronic inflammation), metabolic and endocrine disorders (diabetes mellitus, hypothyroidism) as well as functional and organic disturbances of the nervous system such as spinal-column injury, Parkinson's disease, trauma and stress, etc. Constipation can also be caused by the side-effects of drugs, especially analgesics, anticholinergics, antidepressants, antipsychotics, antispasmodics, sedatives and cation-containing agents such as iron-preparations, aluminium (antacids) and neutrally active agents i.e. opiates, antihypertensives etc. (see Table 1, Causes of Constipation.)

*Clinical experience acquired with EUCARBON® (TRENKA, Vienna)
Effects of Constipation

Colonic transit time is often prolonged during constipation. This depends mainly on abnormal motility of the whole or parts of the colon or on poor response to the defaecation reflex. Due to prolonged retention within the bowel, fluid absorption is excessive; the stool becomes hard (faecal soiling) and the stool volume decreases (19, 28).

Putrific bacteria take on greater significance due to the prolonged retention of food pulp in the intestine. Whereas, under normal conditions, these bacteria are excreted, they now remain in the intestine and stay in contact with the intestinal wall. This phenomenon can lead to disorders such as headache, malaise, skin diseases, self-intoxication and finally, liver damage (6,18).

Constipation may be partly responsible for very severe disorders due to the retention of food pulp in the niches and corners of the intestine. This leads to the formation of faecal stones in the rectum, to straining and consequently burdens the body with foreign-bodies. Other sequelae of constipation include haemorrhoids, diverticulitis, proctitis, fissures and tumours as well as pathogenic protuberances of the peritoneum and projection of the viscera (hernia, rupture). Due to the build-up of pressure, constipation can compromise wound healing or open wounds in the case of recent lesions or in patients who have recently undergone surgery (14).

Constipation is unpleasant. The constant feeling of abdominal bloating combined with flatulence and pain reminiscent of colic generally lead to the administration of laxatives.

Medical diagnosis is absolutely essential in the patients with:
- Blood and phlegm in the stools
- Sickness/nausea
- Abdominal pains of unknown aetiology
- and
- in patients suspected of laxative abuse.

Medical diagnosis is also required in small children presenting with the symptoms of constipation.

**Constipation treatment considerations**

Treatment should be adapted to suit the individual, taking the following considerations into account:
- the age of the patient
- the duration and severity of the constipation
- the potential contributing factors
- the patient's concerns
- and expectations.

**Approaches**

Non-surgical treatment can be divided into several categories such as:
- dietary approaches (e.g. fibre supplementation)
regeneration of healthy intestinal flora
behavioural approaches (e.g. habit training)
contingency management
physiotherapy
change of lifestyle
biofeedback
pharmacological approaches.

**Laxatives**
The use of laxatives is deeply rooted in medical and social traditions. Laxatives are useful in order to prevent undue straining at the stool which may result in hernia, rectal prolapse, fainting or even cerebrovascular incidents.

Laxatives are given to remove toxic substances from the alimentary canal, to prepare patients for sigmoidoscopy or radiological examination of the colon, to remove parasites from the gut after treatment with anthelmintic drugs, to empty the bowel before surgery and to counteract the constipating effects of drugs.

Laxatives are used in conjunction with other therapeutic measures such as a change in dietary habits or lifestyle, physiotherapy and regeneration of healthy flora in the management of chronic constipation. Unfortunately, laxatives are often used all too frequently and without justification by lay-persons as a result of massive advertising campaigns (11, 15).

**Mode of action**
Laxatives accelerate the bowel evaluation process. Most of the laxative and purgative drugs act by increasing intraluminal volume. They subsequently induce peristaltic waves and stimulate local peristaltic activity. This effect is caused by swelling and water absorption (i.e. swelling agents, bulk agents etc). Laxatives then go on to expand the bulk in the contents of the colon via an osmotic action i.e. by retaining water in the intestine (saline or osmotic laxatives), inhibiting Na⁺ and water absorption in the intestinal lumen and/or enhancing and stimulating intestinal fluid and electrolyte secretion by increasing mucosal cyclic AMP (emollient laxatives) [5, 10, 20].

Hyperosmolar agents such as polyethylene glycol and non-absorbable sugars including lactose are degraded by colonic bacteria to low-molecular-weight acids that increase stool acidity and osmolarity.

Stimulant laxatives increase fluid and electrolyte accumulation in the distal ileum and colon. Lubricant laxatives, such as liquid paraffin, have been used to soften and lubricate the passage of the stool and to ease defecation. Surfactants with lubricant laxative properties soften the faecal mass by lowering the surface tension thereby facilitating the penetration of water (18) [see Table 2].

Prokinetic agents are a new class of drugs that stimulate gastrointestinal motility in order to promote the transit of intraluminal contents.

<table>
<thead>
<tr>
<th>Type of laxative</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk-forming laxatives and swelling agents: fibres, bulk substances</td>
<td>Swelling with water absorption and proliferation of intestinal flora</td>
</tr>
<tr>
<td>e.g. wheatgerm, linseed, carboxymethyl cellulose</td>
<td>Direct osmotic water retention; degradation in the colon to short-chain fatty acids (local stimulant effect), increase in faecal mass due to proliferation of microflora in the colon</td>
</tr>
<tr>
<td>saline and osmotic-acting laxatives: Glauber’s salt, magnesium sulphate, lactulose, sorbitol</td>
<td>Inhibition of Na⁺ and thus also of water absorption from the intestinal lumen and/or increase in water secretion in the intestinal lumen</td>
</tr>
<tr>
<td>stimulating or anti-absorptive and secretion-stimulating laxatives: e.g. castor oil, diphenyl methane derivatives, bisacodyl, phenolphthalein, anthraquinone derivatives</td>
<td>To facilitate defaecation via ‘lubricant effect’</td>
</tr>
<tr>
<td>Lubricants: E.g. Na-diocylsulphosuccinate, Paraﬁn oil, glycerine</td>
<td>Inhibition of water absorption, active secretion of electrolytes and water in the intestinal lumen</td>
</tr>
<tr>
<td>Plant laxatives / anthranoids comprising Folia sennae, Radix rhei</td>
<td></td>
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</tbody>
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**Table 2: Laxatives and their physiological effect (10)**
Plant laxatives
Anthraquinone-containing laxatives

Anthraquinone laxatives are the main group of plant-based drugs used in the treatment of constipation. The conventional drugs such as aloe (Aloe barbadensis, Aloe capensis), Frangulae cortex, Rhamni purshianae cortex, Rhei radix, Senna (Senna folium, Senna fructus acutifoliae, Senna fructus angustifoliae) are found in the most widely varied medicinal products as well as in tea preparations (11, 15).

Senna is the most widely used anthranoid drug (29). Most of the pharmacological experiments and clinical trials were not carried out with the actual plants but rather with dianthrone (1,8-dihydroxyanthraquinone). This substance has a more complex, pharmacological profile than that of the biologically formed anthraquinone derivatives which frequently act as pro-drugs such as sennosides A, B, and C (see Table 3). The main purgative constituents of senna are the glycosides principally sennoside A, B, and C. Sennosides are high-molecular-weight glycosides of rhein dianthrone (30). They are prodrugs and have a complex pharmacokinetic profile. The U-linked glucosides (sennosides) are not absorbed in the upper gut but are hydrolysed by the bacterial “reductase” enzymes in the colon into the active metabolite rhein-9-anthrone. Rhein anthrone is not further metabolised through bacterial flora but is partially absorbed through intestinal epithelial cells and is thus subjected to enterohepatic-circulation (17). In contact with oxygen, rhein anthrone is oxidised into rhein and sennidins which can be found in the blood chiefly in the form of glucuronides and sulphates. After oral administration of sennosides, 3 - 6 % of the metabolites are excreted in urine and others in bile. Most of the sennosides are excreted in faeces as polymers (polyquinones) together with unchanged sennosides, sennidins, rhein anthrone and rhein (10, 12, 13).

It is interesting to note that small quantities of rhein anthrone pass into breast milk (0.01 % of the total amount ingested by the mother). In nursing mothers, the active principles may appear in the milk but in insufficient quantities to induce diarrhoea in the breast-fed infants.

**Anthranoids: Modes of action**

In 1934, in laboratory animal experiments, STRAUB and TRIENDL (26) found that laxatives not only stimulate intestinal peristalsis, but also initiate fluid retention in the intestinal lumen. Enhanced colonic motility and increased electrolyte and water transportation in the colon with inversion of the physiological pattern (8, 9) are the most crucial modes of action of anthraquinones. Two different mechanisms of action are therefore assumed:

1. an effect on large intestine motility (stimulation of peristaltic contraction and inhibition of local contractions) resulting in accelerated colonic transit, thus reducing fluid absorption;
2. an effect on secretion processes (stimulation of mucus and active chloride secretion) resulting in enhanced fluid absorption.

Little is known about the action of anthraquinones at cellular level (11).

Mechanisms involved in the regulation of transintestinal electrolytes and water movements include the energy- providing Na+/K+/-ATPase, the mediators of membrane permeability and active Cl-secretion such as c-AMP and Calcium.

In addition, the mechanism of action may include mediators such as prostaglandin and serotonin. The extent to which inhibition of sodium- and potassium-ATPase and inhibition of prostaglandins are involved in the laxative effect of anthraquinones has not yet been elucidated (15, 31).

Clinical experiences with different medicinal products, i.e. with indomethacin and morphine show that these drugs are capable of inhibiting the laxative effect of the anthraquinone (27, 31).

Experiences with a combination of senna leaves with rhubarb extract and Carbo ligni as a laxative drug EUCARBON is a medicine that was developed by Dr. Wolfgang Pauli (son of the Nobel Prize winner for Physics) and pharmacist F. Trenka. Since 1909, EUCARBON has been considered one of the best-established and widely used drugs in the world.

EUCARBON is a unique and well-balanced combination of plant components such as senna, rhubarb and Carbo lingo. The ingredients are well-known agents used particularly in the treatment of constipation. The safety and efficacy of the active ingredients have been confirmed over several years.

Each EUCARBON tablet contains 105 mg Folium sennae, 25 mg Extractum rhei and 180 mg Carbo lignii.
ligni (plant charcoal), 50 mg Sulfur depuratum, 0.50 mg Aether oleum foeniculi and 0.5 mg Aether oleum menthae pip.

EUCARBON: Stimulant laxatives - Pharmacodynamics

With its combination of senna, rhubarb and Carbo ligni as well as sulphur, EUCARBON is classed as a stimulant laxative due to pharmaco logical and pharmacodynamic properties. These agents stimulate accumulation of water and electrolytes in the colonic lumen and also enhance intestinal motility. The stimulant effects of EUCARBON on intestinal fluxes of electrolytes and water are readily demonstrated in vitro or in situ under conditions in which the effects on motility are excluded. Concentrations of these agents that reduce the net absorption of electrolytes and water also increase the permeability of the mucosa, possibly by causing watertight junctions to leak.

Stimulant laxatives may inhibit intestinal Na⁺/K⁺-ATPase; this action could account for at least some of their laxative effect. Many of the stimulant laxatives also increase the synthesis of prostaglandins and cyclic AMP, and this action may contribute to increased water and electrolyte secretion. Inhibition of prostaglandin synthesis with indomethacin reduces the effects of many of these agents on net water flux (Goodman & Gilman's, The Pharmacological Basis of Therapeutics).

Carbo ligni in EUCARBON:

Each EUCARBON tablet contains 180 mg of Carbo ligni. A maximum daily dose of 6 EUCARBON tablets is equivalent to a total of 1.080 g Carbo ligni. According to the manufacturer's recommendation and previous observations, EUCARBON presents mild absorbent effects following administration of 1-3 tablets per day, and laxative effects at a daily dose of 4 - 6 tablets daily. The absorption capacity of Carbo ligni as a nonactive charcoal was investigated in in-vitro and in-vivo studies:

In-vitro studies:

Koch et al. (Trenka, Internal paper 1986), University of Vienna conducted an experimental study of the role of Carbo ligni under the following conditions:

- Evaluation of Carbo ligni under standard conditions (200 mg Carbo ligni incubated with 5 mg agents in solution in water) with regard to absorption of the following substances: phenazone, pilocarpin, HCl, (-) epicatechin, methylene blue, quinine and caffeine in that order between 7.5 and 22 %.
- Test performed on 180 mg Carbo ligni after incubation with pure Sennosid A (5 mg) from the hydrosolution with no adsorbance (adsorption: 0.144%).

Further experimental studies were undertaken in 1994 at the University of Padua PALUMBO et al. (Trenka, Internal paper 1994). These studies showed that phenol, methylene blue, iodine and phenazone were adsorbed from Carbo ligni. The adsorption of these substances was 8 - 15 times less than that of activated charcoal.

The adsorption capacity of Carbo ligni was recently studied by JORDIS et al. (Trenka, Internal paper 1999). JORDIS et al. developed a method for evaluating the adsorption capacity of Carbo ligni used as a raw material in EUCARBON. The study by JORDIS demonstrated that:

Carbo ligni has an adsorption capacity of 2 - 6 mg phenol/g Carbo ligni under specific
conditions. These values were estimated and calculated in 17 manufacturing batches between 1995-1998.

A comparison of Carbo ligni and activated charcoal revealed that the absorption capacity of activated charcoal was 10 - 20 times greater than that of Carbo ligni.

**In-vivo examinations:**

The pharmacological action of EUCARBON regarding intestinal motility was studied in Florence at the University Institute of Pharmacology and Toxicology (PEPEU et al. Trenka, Internal paper 1981). The aim of the study was to confirm:

- the doses of senna and rhubarb contained in EUCARBON to stimulate intestinal motility;
- that charcoal (Carbo Ligni) and other components present in EUCARBON do not hinder the action of senna;
- the adsorbent action of charcoal at the doses contained in EUCARBON.

The experiments of PEPEU et al. showed that recommended doses of EUCARBON decrease intestinal transit time. The charcoal contained in EUCARBON clearly curbs the effect of senna on intestinal motility only in mice, but not in rats. On the other hand, the dose of charcoal present in EUCARBON was able to adsorb, albeit to limited extent, the toxic substances present in the intestinal lumen, as demonstrated by the reduction in strychnine toxicity (PEPEU).

Therefore, EUCARBON contains a rational association of its two main components. In fact, senna is present in active doses, and charcoal, while not hindering the action of senna itself, exerts adsorbent properties which can be useful in case of intestinal flatulence.

As regards the other components of EUCARBON, sulphur and rhubarb can enhance the laxative action of senna despite their low doses. At these therapeutic doses, the product is not toxic at all. Senna has been administered to man at dose levels about 10-20 times greater than those contained in EUCARBON (PEPEU). The administration of Carbo ligni at the dose level of 4-6 tablets/day, equivalent to 1.080 g/day, was confirmed by DAVIS et al. (Ped. Res. 1983). According to this study, 3-4 g/kg/day over a period of 8 weeks did not lead to disturbances or weight gain. This approved composition is used in more than 40 countries, i.e. Austria, Switzerland, Turkey and Italy. The composition was changed only slightly in Italy where EUCARBON contains 5 mg less of Extractum rhei. No differences between the Italian and Austrian formulations have come to light in clinical trials as regards efficacy and safety.

The advantage of EUCARBON is that the combination comprises only natural components and there is only a very low risk of side effects even with long-term therapy. This is particularly important in the case of intestinal disorders as a minimum treatment period of 4-5 weeks is necessary in order to continue regulating intestinal activity. EUCARBON belongs to a group of medicines possessing mild laxative and purgative properties and having a wide spectrum of pharmacological effects. It is not only a mild laxative but also a digestive regulator, the effect of which has been documented for many years. This drug has been used successfully in clinical practice for approximately 100 years in the treatment of constipation, flatulence, meteorism, digestive problems, haemorrhoids and anal fissures as well as in cardiology, e.g. for patients with heart disorders (strong flatulence places considerable pressure on the diaphragm).

EUCARBON is mainly indicated in the treatment of patients suffering from constipation and indigestion and in bedridden patients. It is also used in radiology - especially where preparation is required prior to kidney and gallbladder examinations or for irritable bowel syndrome. In cardiology, EUCARBON may also be used to stop/reduce flatulence and hence diminish the pressure on the diaphragm (thus causing heart rate to revert to normal). EUCARBON is also used in surgery, in intensive care medicine as well as in gynaecology, paediatrics and in ophthalmology (to reduce the internal ocular pressure due to straining-related pressure).

Clinical studies with EUCARBON, for example in urology (7,23,25), practical medicine (4), internal medicine (2), radiology (21) and gastroenterology (22), etc. confirm the general consensus and long-term experience that a combination of plant laxatives such as EUCARBON constitutes appropriate therapy in clinical practice for the treatment of chronic constipation not only in terms of principal efficacy and safety,
but also as regards administration and duration of treatment. To summarise, the afore-mentioned in-vivo and in-vitro studies confirm the results and long-term observations documented over many years with EUCARBON and confirm that a combination of Carbo ligni and senna and rhubarb is not only beneficial, but pharmacologically proven and effective in the management of gastrointestinal disorders. The laxative effect of EUCARBON continues to be one of its major modes of action.

References:

22. NAHLER, G., PETTO, H.: Multicenter Study with EUCARBON. Treatment of patients with irritable bowel syndrome with EUCARBON, Efficacy and tolerance of two different formulations. Double blind, controlled, randomised prospective clinical trial in patients with irritable bowel syndrome, receiving EUCARBON, either as formulation with or without sulfur. Multicentre Trial, 22 Centres. Ongoing clinical study/ unpublished