Gut, 1974, **15**, 758-766

Progress report

Laxative abuse

Amongst the patients of every gastroenterologist there is probably one, a woman, with a long history of abdominal discomfort and diarrhoea, perhaps with vomiting, weight loss, weakness, thirst, and a psychiatric illness. There may be a past history of an ill defined metabolic disorder or renal disease. Numerous investigations will have proved fruitless although a low serum potassium, a rather distensible, featureless colon on radiographs and non-specific inflammatory changes on rectal biopsy may not have been fully explained. The latest medication is of only temporary benefit and the notes become progressively thicker. This is the picture of a patient who is taking laxatives to excess and probably concealing the fact from her doctor.

Abuse of laxatives to this extent is one end of a spectrum of laxative taking which is well entrenched in our culture. The association of a regular bowel habit with physical and spiritual well being has its origins in early history (*katharsis* from the Greek cleansing; purgo from the Latin to purify, to make clean) and continues today with immense annual sales[1,2,3]. Well over 200 preparations are available over the counter in chemists' shops[4] with between 15 and 30% of people aged over 60 taking more than one dose weekly[5]. In general these preparations are safe with few reports of their danger[6,7] when taken in recommended doses. Oxyphenisatin has proved to be an exception as it has been closely linked with the development of hepatitis and cirrhosis[2,8,9,10], particularly when given with dioctylsodium sulphosuccinate[11,12]. Death due to laxatives is rare[13,14,15] but the syndrome of chronic ill health, sometimes called, but not identical with, the cathartic colon[16,17,18,19], and due to long-continued and often surreptitious overindulgence in laxatives has been widely reported[15–51].

Clinical Features

Over 90% of patients suffering from this condition are women. They present most commonly with diarrhoea, weakness, abdominal pain, nausea, vomiting, and an associated psychiatric disorder. However, these presenting features may become blurred with the passing of time so that in addition there may be weight loss, abdominal distension, amenorrhoea, thirst, or oedema. A history of childhood constipation is often a significant feature[33,45] and the patients are not infrequently nurses or associated with medicine in some way[30,35,36,51]. Although diarrhoea is the single most common complaint, they may report constipation and even go to great lengths to conceal both the diarrhoea and laxative taking from the physician[37,50,51]. Indeed constipation is often the starting point for their consumption of laxatives. However, patients who develop what the pathologist or radiologist calls a 'cathartic colon' from prolonged laxative ingestion for constipation but without these other clinical features should not be included in the syndrome of laxative abuse. The commonly associated psychiatric disorders include depression,

anorexia nervosa, or a personality problem. In anorexia nervosa particularly there may be self-medication with many drugs, the favourite of which seems to be diuretics[31,34,49,51,52]. Less frequently reported clinical features include bone pain and tetany[16,20,21,23,31], fever[30,53], clubbing[35], and skin pigmentation[32,37,45,48].

Patients who conceal their laxative taking frequently undergo prolonged and uncomfortable investigations often culminating in a fruitless laparotomy. Hypokalaemia is by far the commonest abnormal investigation (over 50% of patients) with characteristic radiological and pathological features occurring less frequently (less than 30%). A wide variety of other findings have been reported and may add confusion to the picture. These include steatorrhoea[16,25,35,45,48], low urinary xylose excretion[23,35,48], hypocalcaemia[16,23,31], gastrointestinal protein loss[48], abnormal renal function, raised renin and aldosterone secretion[36,37,47,49,50,51], achlorhydria, abnormal pancreatic function tests[35], parathormone, secretin and enteroglucagon assays[31,35], and a diabetic glucose tolerance test[35,48,50].

The discovery of steatorrhoea may be quite misleading in these circumstances but the levels reported are all, with one exception[16], below 10 g of fat per day. Steatorrhoea has been reported in a normal person[48] and in ileostomists[54] after taking magnesium salts but the way in which fat absorption is reduced by cathartics is unknown.

Radiology[17,38-43]

Characteristic radiological changes occur in the terminal ileum and colon in cathartic abuse, but are found in only about 30% of reported cases and the true incidence may be as low as 10%[35,43,55]. The terminal ileum loses its normal mucosal pattern and takes on the appearance of a smooth, tube-like structure[38,39,42], whilst the ileo-caecal sphincter becomes wide and gaping. The colonic changes are usually first seen in the caecal region and affect predominantly the right side of the colon. Rectal changes have not been reported. The colon becomes dilated, distensible, and featureless, losing its normal haustral and mucosal pattern. Transient areas of narrowing or pseudo-strictures appear and there may be shortening of the ascending colon. These features have sometimes been confused with chronic ulcerative colitis but may be differentiated from it by the distensibility, absence of mucosal ulceration, presence of colonic dilatation without systemic illness, and predilection for the right side with rectal sparing[16,39,43]. On stopping the laxatives a return of the *x*-ray appearances towards normal has been reported[38,40,48].

Pathology

The textbook descriptions of this syndrome[56] include the finding of melanosis coli on sigmoidoscopy or rectal biopsy. Whilst these investigations are important only about one in three patients will have a sigmoidoscopic abnormality although biopsy may show melanosis not visible to the naked eye[57]. The presence of melanosis is virtually diagnostic of recent and prolonged cathartic intake. In four reported series totalling almost 1000 patients with melanosis coli over 95% had a definite history of habitual laxative intake[58,59,60]. In patients who stopped the laxatives the melanosis disappeared

over a period of four to 12 months. Polyps occurring in an area of melanosis coli are not pigmented and the pigment usually stops abruptly at the ileocaecal valve. The chemical nature of the pigment is in dispute[1,57] but it has long been associated with taking laxatives[61] and almost exclusively with the anthraquinone group (senna, cascara, aloes)[35]. Melanosis has been produced experimentally in monkeys by giving them cascara[62].

Melanosis is not the only pathological feature of laxative abuse. Both Morson[63] and Smith[1,64] have described a group of distinctive features seen in these patients which include (in addition to melanosis), mucosal inflammation, hypertrophy of the muscularis mucosae, and thinning or atrophy of the outer muscle layers. Using special stains, Smith[65] has also shown damage to and loss of the myenteric plexus neurones in the cathartic colon and produced similar lesions in mice treated with senna. This progressive toxic damage to the intrinsic nerve plexuses of the colon may account for the need of some constipated patients to increase gradually their dose of senna in order to produce the desired effect[1]. There is little evidence at present to suggest that laxatives other than the anthraquinones lead to these pathological, or radiological, features.

Electrolyte Disturbances

The metabolic disorder which arises in 25-50% of patients taking too many laxatives has been extensively studied. The features of this are hypokalaemia, sodium and potassium depletion, raised renin and aldosterone secretion, impaired renal function, thirst, muscular weakness, and oedema. It is possible to relate all these findings in a single pathophysiological process. Chronic diarrhoea causes excessive faecal sodium loss, faecal sodium output having been shown to increase almost linearly with increasing faecal output[66,67]. Sodium and water depletion in turn stimulate renin and thus aldosterone which leads to sodium conservation and potassium loss by the kidney. Potassium is also lost in the faeces but the extra faecal potassium loss in diarrhoea[66] compared with normals[68] is much less than the extra faecal sodium loss in these circumstances[66,68]. The renal potassium-losing effect of aldosterone in these patients has been demonstrated by Fleischer *et al* (1969)[50] who were able to reduce urinary potassium levels by giving spironolactone.

Potassium loss may be increased further through renal damage and into the gut. Aldosterone increases potassium secretion into the gut[69,70] but it is not clear whether the laxatives themselves also have a significant effect on renal and gut electrolyte transport. Although the patient described by Sladen (1972)[67] showed a pronounced effect of aldosterone on faecal composition, other hypokalemic patients have not shown this[35] and there are few studies of faecal electrolyte losses in diarrhoea available for comparison. Hypokalaemia itself causes renal damage[44,47,71,72,73], the commonest form being vacuolization of the tubules with consequent impairment of concentrating ability. Juxtaglomerular hyperplasia[50] and more severe forms of renal damage have also been reported[46,74] but their genesis is in dispute. Further potassium loss may therefore occur as a consequence of the renal damage[44,75]. The primary metabolic deficit is thus one of sodium and water depletion but various secondary events lead to a final picture dominated by severe potassium depletion with its attendant thirst, muscular weakness,

and polyuria[49,75]. Normal homeostatic mechanisms such as the inhibitory effect potassium depletion has on aldosterone secretion[76] may be overwhelmed either by the concurrent sodium deficit or by the patient's poor appetite, vomiting, and simultaneous self-medication with other drugs such as diuretics. The problem is complex and accurate metabolic studies in these patients are fraught with difficulties[49,50,51].

The metabolic disturbances and renal damage are reversible if the laxatives can be stopped[27,44], although some patients may have an increased susceptibility to pyelonephritis[47,73]. An improvement in glucose tolerance has also been noted[50]. The oedema, however, which is more a feature of the recovery phase, may require dietary sodium restriction for some months[48].

Pharmacology of Laxative Diarrhoea

Although laxatives are confidently grouped according to their alleged mode of action[77,78,79,80] little is in fact known about how and where in the gut they act. Saline purges such as magnesium sulphate (Epsom salts), magnesium hydroxide (Milk of Magnesia), sodium sulphate (Glaubers salts), and sodium potassium tartrate (Rochelle salt; Seidlitz powder) are salts of poorly absorbed ions which are thought to retain fluid in the bowel lumen by virtue of their osmotic properties and so increase stool bulk. Ileostomy output is increased by magnesium sulphate[54] but the exact mode of action has never been demonstrated. Harvey and Read (1973)[81] have suggested that these purgatives act by stimulating the release of cholecystokinin (CCK) from the duodenum which in turn promotes small intestinal and pancreatic secretion. These effects are compounded by the stimulation of small bowel and colonic motor activity by CCK. Another 'osmotic' laxative, the non-absorbable disaccharide lactulose, acts mainly in the colon[82] where it is metabolized by bacteria to short-chain fatty acids which are themselves relatively non-absorbable, and so increase stool volume. However, lactulose could also effect fluid transport in the small intestine in a way analogous to that of lactose in lactase deficiency or as after the ingestion of mannitol[83,84].

A second group which act primarily in the small intestine are the plant resins colocynth, jalap, and podophyllum[85,86,87,88]. Early work in animals showed that they stimulated motor activity[87], increased transit rate[86], and more recently inhibition of sodium transport has been demonstrated[88]. These resins of course contain many different compounds the precise function of which has yet to be determined. Castor oil, another potent laxative, may also affect the small gut. Its active principle, ricinoleic acid, has been shown in rats to be less well activated by mucosal thiokinase than other fatty acids and so could accumulate in the jejunum[89,90] where it may inhibit water and electrolyte absorption[91].

Bisacodyl (Dulcolax) is thought to stimulate peristalsis in the colon but only after deacetylation, absorption from the small intestine, and excretion in the bile[92]. Bile duct ligation will prevent its cathartic effect. This may not be the whole story because Hart and McColl (1967-8) have shown that both bisacodyl and the chemically similar oxyphenisatin inhibit glucose absorption in the small intestine of rats and man[93,94] and others have demonstrated its potential to induce secretion of water and electrolytes in the colon[95,96]. However, its main action in man is probably colonic, as Hardcastle and Mann (1968)[97] have shown that colonic peristalsis may be stimulated by

local administration alone: when given to ileostomists it does not increase ileostomy output (T. D. Kellock, personal communication). Phenolphthalein, which has some chemical similarity to bisacodyl, was once thought to act solely on colonic smooth muscle[98,99] but is in fact absorbed, conjugated with glucuronide and excreted in the bile before it causes laxation[100]. Like bisacodyl it loses its cathartic effect in obstructive jaundice or after ligation of the bile duct[101]. On reaching the systemic circulation it is partly (1-20%) excreted in the urine[102] and also like the other diphenylmethanes (bisacodyl, oxyphenisatin) may inhibit small intestinal sodium[88] and glucose transport[103, 104].

The most widely prescribed and probably most extensively investigated laxatives are the anthraquinones. Although once thought to require absorption before being effective[105], this now seems unlikely. Fairbairn[106,107] has pointed out that they occur as glycoside conjugates and can only be absorbed from the intestine after hydrolysis yielding the free anthraquinones and glucose. Hydrolysis cannot occur in the small gut but the colonic bacteria liberate the free anthraquinones which then promote colonic peristalsis via a local effect on the myenteric plexus. This cycle of events has been confirmed by Hardcastle and Wilkins (1970)[108], whilst the role of the anthraquinones in altering small intestinal secretory function remains unclear[88,93].

The bulk laxatives such as methyl cellulose, psyllium seeds (metamucil), isphagula (Isogel), sterculia (Normacol), and agar are assumed to work by virtue of their hygroscopic properties[109,110]. However, these plant polysaccharides are chemically similar to bran. Bran may affect laxation not only by its water-retaining action but also through its metabolites such as the short-chain fatty acids, and by its capacity to influence bile salt metabolism[111, 112]. It is hoped that eventually terms such as stimulant, lubricant, irritant, and bulk will give way to more meaningful words as the precise pharmacological properties of these compounds become known.

Diagnosis of Laxative Abuse

Once the diagnosis of laxative abuse is suspected a sigmoidoscopy and rectal biopsy should be done, together with a serum potassium and barium enema. An attempt should then be made to identify the laxative. Unfortunately the diversity of available laxative preparations makes comprehensive chemical testing impossible. The easiest to detect are those which contain phenolphthalein, which is perhaps why this is the most commonly reported compound taken by patients. Phenolphthalein may be demonstrated in either urine or faeces by alkalinization when a pinkish-red colour develops. Aloes and aloin also turn alkaline urine red[4] as may beetroot, but the test for phenolphthalein may be made more specific by one of a variety of extraction procedures[25,27,42]. A chromatographic method has been described for bisacodyl[48] and doubtless could be applied to other chemically pure organic purgative compounds. The anthraquinones may be detected by any of the current pharmacological assays for senna[113,114,115]. These assays are of necessity quantitative and therefore too tedious for routine clinical use. However, a simple modification of the method should be possible and if shown to be free from cross reactivity with other drugs would provide a useful aid to diagnosis.

The saline purges (magnesium and sodium salts) are much more difficult to detect because these ions are normal body constituents. The normal urinary magnesium (up to 16 m-equiv/day)[116,117] and sulphate (up to 56 m-equiv/day)[116,117] excretion may be exceeded although there are no firm data available on this. Excess faecal sulphate can be shown by adding barium chloride solution to an acid extract of faeces, or it can be measured quantitatively by standard techniques[68]. Both in normal subjects and in diarrhoea faecal sulphate concentrations are less than 4·5 m-equiv/l[35,68,118] but increase when sodium sulphate is taken[119]. Faecal magnesium excretion is less useful as there is a wide range of normal values[68]. All these tests should be repeated as the patients may take the laxatives only intermittently, or may change from one brand to another. No methods exist for the detection of bulk laxatives, or of preparations such as liquid paraffin, and the plant resins.

Because there is no certain way of making the diagnosis by accepted procedures it becomes necessary to search the patient's possessions for laxatives[23,35,36,46,48,120], although even this may prove negative[25]. Advice from the Medical Defence Union states that 'it is legally quite unjustifiable to search a patient's possessions without his knowledge and consent although it is difficult to see how a patient could sue for this and what offence is committed which is triable in a magistrate's court'. The search is best conducted by isolating the patient in a side ward and then allowing him to go to the X-ray Department, for example. It is wisest to conduct it in the presence of the ward sister or similar responsible person as one might be accused of theft should anything of value be missing later. It may be worth replacing any tablets found and recounting them at a later date to see how many have been taken[35].

Management and Prognosis

No long-term follow up of these patients has been reported and few guide lines have been laid down for their management. Some authors describe patients who were able to give up the laxatives[20,22,27,30,32,48] but the majority of patients do not and live a life of chronic ill health. The prognosis is particularly poor in those who also have anorexia nervosa[34,121]. Because the laxative habit is so often concealed the physician must first decide whether, and how, to tell the patient that the cause of the illness is known. Although telling them would seem to offer the only hope of breaking the habit some patients continue to deny taking laxatives and may discharge themselves from hospital[35]. Before this point is reached psychiatric help should be sought as many have an associated illness, such as depression, which is amenable to treatment.

Many of these patients have a fear of constipation so an attempt should be made to wean them off laxatives such as the anthraquinones which may damage the bowel[1,65] and substitute a high-fibre diet and bulk preparations or a saline laxative. Patients who have developed the radiological and pathological features of the cathartic colon have been submitted to colectomy with ileo-rectal anastomosis, often with great benefit[53,55]. Such a step, however, cannot be lightly undertaken in the more disturbed patients. Finally, if no headway can be made, the patient should be followed up as an outpatient where support can be given and the metabolic problems com-

bated with potassium supplements and spironolactone. Such attention at least prevents them from taking their illness to another physician to be investigated anew.

The author wishes to thank Dr T. D. Kellock, Dr J. J. Misiewicz, Dr H. S. Wiggins, and Dr E. N. Rowlands for helpful criticism during the preparation of this progress report.

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