Studies of the effects of therapeutic mediastinal, abdominal and pelvic irradiation on gastrointestinal function

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CHAPTER 2 ASSESSMENT OF THE EFFECTS OF RADIATION ON GASTROINTESTINAL FUNCTION

Summary

There is little information on the effects of therapeutic irradiation on gastrointestinal function in humans. The aims of the six studies reported in this thesis were to determine (i) the acute and subacute effects of therapeutic irradiation on oesophageal, gastric and intestinal function, (ii) the chronic effects of irradiation on gastric, intestinal and anorectal function, and (iii) the effects of loperamide-N-oxide in patients with diarrhoea due to chronic radiation enteritis.

The acute and subacute effects of mediastinal irradiation on oesophageal function were studied in eight patients (Chapter 3). While most patients experienced odynophagia and dysphagia during mediastinal irradiation, only three had endoscopic abnormalities. Irradiation had no significant effect on oesophageal motility or transit and "oesophageal" symptoms during irradiation may therefore potentially reflect increased mucosal sensitvity.

The effects of abdominal and pelvic irradiation on gastric and intestinal function were evaluated in four studies. In each of these the following aspects of gastric and intestinal function were evaluated : (a) gastrointestinal symptoms, (b) absorption of bile acid, vitamin B12, lactose and fat, (c) gastrointestinal transit: gastric emptying, small intestinal and whole gut transit and (d) intestinal permeability and results were compared to a control group of 18 normal volunteers. In 30 patients who had received pelvic irradiation for carcinoma of the cervix between 1 and 6 years previously (Chapter 4), increased stool frequency was associated with decreased bile acid, vitamin B12 and lactose absorption and more rapid gastric emptying and small intestinal transit. Abnormal gastrointestinal function was demonstrable in 29 of the 30 patients, suggesting that it is essentially an inevitable long term sequela of pelvic irradiation.

The acute, subacute and chronic effects of abdominal and pelvic irradiation on gastric and intestinal function were evaluated prospectively in 27 patients (Chapter 5). Gastrointestinal function was evaluated before the commencement of, during, and 6 to 8 weeks, 12 to 16 weeks, and 1 to 2 years following completion of radiation therapy. During radiation treatment, there was increased stool frequency, decreased bile acid and vitamin B12 absorption, increased faecal fat excretion, an increased prevalence of lactose malabsorption and more rapid small intestinal and whole gut transit. Although there was improvement in these changes with time, at 1 to 2 years after completion of irradiation, the frequency of bowel actions was greater, bile acid absorption was less, and small intestinal transit was more rapid when compared with measurements at baseline and the control subjects. This study confirmed that abdominal and pelvic irradiation was usually associated with widespread and persistent effects on gastrointestinal function.

The chronic effects of abdominal irradiation were evaluated in 15 patients who had been treated for seminoma of the testis between 2 and 10 years previously (Chapter 6). There was a higher prevalence of gastrointestinal symptoms and faster gastric emptying in the patients. While other measurements of gastrointestinal function did not differ statistically between the two groups, at least one parameter of gastrointestinal function was abnormal in 11 of the 15 patients. Abnormalities in gastric and to a lesser extent intestinal function therefore occur frequently when abdominal irradiation is used to treat seminoma of the testis.

The effects of loperamide-N-oxide, the precursor of the peripheral opioid agonist, loperamide, on gastric and intestinal function was evaluated in 18 patients with diarrhoea due to chronic radiation enteritis (Chapter 7). Each patient was given, in double-blind randomised order, loperamide-N-oxide and placebo for 14 days, separated by a washout period of 14 days. On placebo, there was an increased frequency of bowel actions, reduced bile acid absorption, a higher prevalence of

lactose malabsorption, and faster small intestinal and whole gut transit in the patients when compared to normal subjects. Treatment with loperamide-N-oxide was associated with a reduction in the frequency of bowel actions, slower small intestinal and total gut transit, more rapid gastric emptying, improved absorption of bile acid and increased permeability to Cr-EDTA. These results indicate that: (i) diarrhoea caused by chronic radiation enteritis is associated with more rapid intestinal transit and a high prevalence of bile acid and lactose absorption, as suggested in both retrospective (Chapter 4) and prospective (Chapter 5) studies, and (ii) loperamide-N-oxide is effective in the treatment of diarrhoea associated with chronic radiation enteritis.

The increased frequency of bowel actions observed as a long term effect of abdominal and pelvic irradiation (Chapters 4, 5 and 7) was not always accompanied by an increase in stool weight suggesting radiation-induced anorectal injury. The chronic effects of pelvic irradiation on anorectal function were evaluated in 15 patients with uterine carcinoma who had received pelvic irradiation between 5 and 10 years previously. Results were compared with those obtained in 9 normal female volunteers (Chapter 8). At least one parameter of anorectal function was outside the control range in 14 of the 15 patients and abnormalities included weakness of the external anal sphincter, stiffness of the rectal wall and an increase in rectal sensitivity. Abnormal anorectal function therefore occurs frequently in patients following pelvic irradiation for gynaecological malignant disease.

The experiments reported in this thesis have yielded important insights into the aetiology and natural history of common sequelae of mediastinal, abdominal and pelvic irradiation such as dysphagia, nausea, diarrhoea and faecal incontinence which have important implications for both diagnosis and therapy.

Declaration ...

The experimental work presented in this thesis is entirely original and was performed by the author between 1987 and 1994. The thesis contains no material which has been accepted for the award of any other degree or diploma in another University. The results have not been previously published by the author other than as scientific papers directly resulting from this work. Figures and tables used in the literature and methodology review were included with kind permission of the relevant authors and publishers, as indicated in the text. Material contained in this thesis may be photocopied, and the thesis may be made available for loan at the discretion of the University.

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Dedication...

To my wife, Ivy and my children, Angela, Daniel and Neil without whose encouragement and forbearance, this work would not have been completed.

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CHAPTER 1

Effects of therapeutic mediastinal, abdominal and pelvic irradiation on gastrointestinal function and approaches to prevention and treatment of sequelae

Introduction

Whilst it is well recognised that damage to the gastrointestinal tract is a major cause of morbidity when radiation is used with curative intent to treat intra-thoracic and intra-abdominal malignant diseases (Kwitko et al 1982; Beer et al 1985; Chowhan 1990), there is relatively little information on the effects of therapeutic mediastinal and abdominal irradiation on gastrointestinal function. Furthermore, the outcome of treatment of the sequelae of radiation is often unsatisfactory. In this chapter, current understanding of the pathogenesis of radiation damage to the gastrointestinal tract and the rationale for approaches to the treatment of common sequelae such as dysphagia, nausea and diarrhoea is reviewed. Concepts relevant to all areas of gastrointestinal radiation damage, including the prevention of radiation injury are discussed initially, before focussing specifically on the diagnosis and treatment of radiation injuries to the oesophagus, stomach, intestine and anorectum. Although radiation damage to other viscera such as liver, pancreas and bladder contributes to the morbidity of abdominal irradiation, these complications will not be considered, partly because of their rarity, but principally because the author's studies were not designed to provide novel information related to these areas.

The mechanisms of radiation damage to the gastrointestinal tract are complex and poorly understood. Energy dissipated from ionising radiation generates a series of biochemical events inside the cell which may lead directly to cell damage and death (Fox & Lajtha 1973). Free radicals, produced by a complex series of chemical reactions between ionising radiation and intercellular water, also interact with

deoxyribonucleic acid to prevent replication, transcription and protein synthesis (Sher et al 1990). Rapidly proliferating cells, such as the mucosal lining of the gastrointestinal tract, are most sensitive to ionising radiation and therefore manifest injury earliest, while effects on the less sensitive vascular and connective tissues evolve more slowly.

In clinical practice, the effects of therapeutic irradiation on normal tissues are usually divided into acute and chronic effects, based on the time interval since completion of irradiation. The acute effects of therapeutic irradiation may be defined as those which appear either during or within three months of the completion of the course of irradiation. Chronic effects are those which are evident more than three months after completion of irradiation (Duncan & Nias 1977). This convention, albeit arbitrary, will be followed throughout this thesis.

Animal experiments have provided some insights into the pathophysiology of radiation injury to the gastrointestinal tract. Almost all of these studies have involved the use of single extremely large doses of radiation, either directed at the entire animal (Chelmar 1969; Summers et al 1970) or abdomen (Bouckaert 1968), often with lethal effects. Whilst such studies have provided objective histological data and dose-response information, the relevance of such observations to the clinical situation (where small incremental doses are given to limited areas of the body) is uncertain. The results of animal studies are not infrequently conflicting, such as those relating to the acute effects of irradiation on gastrointestinal transit (Conrad 1951; Summers et al 1970), which probably reflects both methodological differences and interspecies variations in the response to radiation (Conrad 1956; Dorval et al 1985).

Studies of the effects of radiation on the gastrointestinal tract in humans have hitherto been dominated by retrospective surgical series, which have focussed on florid structural sequelae of chronic radiation enteritis, such as strictures and fistulae

(Phillips & Margolis 1972; Wellwood & Jackson 1973; Palmer & Bush 1976). Because of the paucity of precise, non-invasive techniques that could be used to evaluate the effects of irradiation on the gastrointestinal tract comprehensively, most studies have evaluated specific aspects of gastrointestinal function (Stryker et al; 1977, Stryker et al; 1978, LaManna et al; 1985). It is implicit that the results of such studies are likely to give only limited insights into the pathophysiology of radiation injury to the gastrointestinal tract. In view of the substantial deficiencies in knowledge, it is not surprising that the majority of treatment approaches are based on anecdotal evidence (Rauch & Wieland 1972; Goldstein et al 1976; Chowhan 1990).

During the course of mediastinal and pelvic irradiation virtually all patients experience symptoms such as dysphagia and diarrhoea, usually during the third and fourth week of treatment (Seaman & Ackerman 1957; Stryker et al 1977). When the abdomen is irradiated, nausea is also common (Rubin & Casarret 1968a). These symptoms usually improve considerably within six weeks of completion of radiation therapy, but in approximately 20% of patients their severity leads to an interruption in the planned course of treatment (Seaman & Ackerman 1957; Joslin et al 1972; Salminen 1990). The resulting modification in the planned course of treatment has been implicated as a factor that may compromise the chance of cure (Amdur et al 1990; Barton et al 1992; Fowler & Lindstrom 1992; Fyles et al, 1992).

The prevalence of chronic radiation enteritis is uncertain, partly because of the absence of a definition of "significant" damage. Estimates of major complications ranging from 0-15% have been derived from retrospective surgical series which usually comprise a relatively small number of patients and do not include those patients who died or were lost to follow-up in the interval between completion of radiation treatment and the development of the complication (DeCosse et al 1969; Phillips & Marjolis 1972; Palmer & Bush 1976; Morgenstern et al 1977; Perez et al 1984; Yeoh & Horowitz 1987). One retrospective study of women who had pelvic

radiotherapy for gynaecological malignant disease suggested that up to 70% of patients have a chronic increase in bowel frequency (Newman et al 1973). It is therefore likely that data based on surgical series represent a considerable underestimate of the prevalence of gastrointestinal sequelae.

1.1 SEQUELAE OF ACUTE GASTROINTESTINAL RADIATION DAMAGE

Gastrointestinal dysfunction during irradiation has been usually attributed to transient injury to the mucosal lining of the gastrointestinal tract (Kinsella & Bloomer 1980). Depletion of actively proliferating cells in the villous crypts as a consequence of radiation damage results in shortening of villi and a reduction in total epithelial surface (Trier & Browning 1966). It is possible that this mucosal damage, which is associated with infiltration of the lamina propria by plasma cells and polymorphonuclear leucocytes in the segment of gastrointestinal tract irradiated, may be responsible for malabsorption of nutrients such as fat, lactose, bile acid and vitamin B12 (Reeves et al 1959; Dalla Palma 1968; Stryker et al 1978; Yeoh et al 1984) and symptoms such as diarrhoea, nausea and dysphagia. However, histological changes resulting from irradiation of the gastrointestinal tract correlate poorly with symptoms (Trier & Browning 1966; Nicolopoulos et al 1985; Sedgwick et al 1994). Furthermore, malabsorption of xylose and iron have been documented, even though the proximal small intestine is out of the pelvic radiation field (Dalla Palma 1968b). Symptoms and disturbances in absorption may also persist long after histological abnormalities in the mucosa have apparently recovered (Stryker et al 1977; Yeoh et al 1984; Layer et al 1986).

Alterations in gastrointestinal transit have been reported in patients undergoing mediastinal, abdominal and pelvic irradiation (Pelu et al 1964; Reeves et al 1965; Frankendal & Junghagen 1974; Goldstein et al 1975). For example, during mediastinal irradiation, it has been reported that there is a delay in propagation of barium through the oesophagus, with interruption of the primary peristaltic wave at a

level corresponding to the proximal border of the radiation field (Goldstein et al 1975). In contrast, small bowel transit, as assessed by a barium meal has been reported to be faster during pelvic irradiation (Frankendahl & Junghagen 1974). It is therefore possible that abnormalities in gastrointestinal motility and transit contribute to symptoms and functional changes during and immediately after mediastinal and abdominal irradiation.

Radiation could theoretically cause gastrointestinal symptoms by modifying sensory feedback from the gastrointestinal tract. For example, in patients with chronic, unexplained upper abdominal symptoms (not induced by irradiation), there is an increased sensitivity to gastric balloon distension (Coffin et al 1994). It is therefore possible that symptoms such as abdominal cramps and nausea, resulting from irradiation could reflect disordered sensory feedback from the stomach and/or intestine. This has not yet been evaluated.

1.2 SEQUELAE OF CHRONIC GASTROINTESTINAL RADIATION DAMAGE

The florid structural lesions of chronic gastrointestinal injury have been attributed to damage to the vasculo-connective tissue (Rubin & Casarret 1968b), and are characterised histologically by an obliterative endarteritis of the small vessels in the intestinal wall, submucosal fibrosis and lymphatic dilatation (Wellwood & Jackson 1973). It has been postulated that injury sustained by endothelial and connective tissue is subclinical for an interval varying from a few months to many years, and leads to progressive ischaemia of the intestinal wall (Rubin & Casarett 1968b). Mucosal ulceration, necrosis of the intestinal wall and, consequent to this, bleeding, perforation, stricture and fistula formation may follow (Schofield et al 1986). Small intestinal strictures and fistulae are not infrequently associated with small intestinal bacterial overgrowth which may contribute to malabsorption and more rapid intestinal transit (Ludgate & Merrick 1985; Zentler-Munro & Bessell 1987). Abnormalities in gastrointestinal motility and transit in the absence of strictures, have also been

demonstrated following mediastinal and pelvic irradiation (Miholic et al 1989; Seeman et al 1992), and are likely to contribute to chronic radiation sequelae. In support of this concept, histological evidence of damage to the muscle cells in the oesophagus (Seaman & Ackerman 1957), changes in neural structure and increases in the numbers of neuro-endocrine cells have been demonstrated in the bowel wall of patients with chronic radiation enteritis (Pietroletti et al 1989; Hirschowitz & Rode 1991).

1.3 TREATMENT OF GASTROINTESTINAL SEQUELAE OF RADIATION

The medical and surgical treatment of radiation injury to the intestinal tract is unsatisfactory.

Rational medical treatment is not possible in most cases because the pathophysiology is poorly understood and most treatment approaches have accordingly been empirical or inadequately evaluated. An exception is acetylsalicylate, which in a double-blind placebo controlled trial, was demonstrated to reduce gastrointestinal symptoms during pelvic irradiation (Mennie et al 1975). It was speculated that acetylsalicylate reduces the synthesis of prostaglandins, which may be important in mediating the inflammatory response in the bowel mucosa. However, the results of subsequent studies in which other prostaglandin synthetase inhibitors such as ibuprofen were not effective in reducing either gastrointestinal symptoms (Stryker et al 1979) or mucosal damage (Nicolopoulos et al 1985) argue against this hypothesis.

Although diarrhoea in chronic radiation enteritis has been reported to respond to anti-spasmodics, anti-cholinergics, broad spectrum antibiotics, cholestyramine, and drugs used in the management of inflammatory bowel disease, such as corticotrophin gel and sulphasalazine with or without oral predisone, (MacDonald & Hoyt 1956; Goldstein et al 1976; Heusinkveld et al 1978), experience with these measures have been anecdotal.

The diagnosis of chronic structural radiation damage to the gastrointestinal tract can be difficult. Patients may present many years after radiation therapy and the detection of gastrointestinal damage is often delayed because of poor sensitivity and specificity of available methods of investigation. For example, small bowel contrast radiological studies are not only frequently normal, but also often underestimate the extent of the disease process (Mason et al 1970; Ludgate & Merrick 1985). Clinical features may be attributed to recurrent malignant disease (Schofield et al 1983). As a result patients often present with a serious complication such as intestinal obstruction, perforation or bleeding.

Surgical treatment of chronic gastrointestinal radiation injury is fraught with difficulties since the patient is often malnourished, the radiation damage usually widespread, and breakdown of intestinal anastomoses and wound healing are both problematical (Lindahl1970; Dencker et al 1971; Schrock et al 1973; Wellwood & Jackson 1973; van Nagell et al 1974; Morgenstern et al 1977; Kwitko et al 1982; Galland & Spencer 1985). Galland & Spencer (1985), in a study of 70 patients with chronic entero-colitis reported that 11 of the 61 patients who underwent operations on the affected intestine died of causes related to the operations, such as perforation of bypassed bowel, fistula formation and anastomotic stenoses. In addition, 50% of the patients who survived more than three months had persistent symptoms, the majority of which were related to radiation treatment. After operation for chronic radiation gastrointestinal radiation injury, wound healing is frequently delayed and prolonged parenteral feeding may be necessary. As a result of these difficulties, the patient's general condition should be optimised prior to any planned surgical procedure - if possible, to overcome the adverse effects of chronic malnutrition, sepsis and electrolyte imbalance on post-operative recovery including wound healing. Any operation should only be undertaken after careful consideration of the clinical condition of the patient and the extent of radiation damage.

1.4 PREVENTION OF GASTROINTESTINAL RADIATION SEQUELAE

In the last decade, there has been increased interest in the prevention of radiation enteritis. Based on fluoroscopic assessment of the amount of barium filled small intestine fixed in the pelvis and retrospective analyses of patients who have had abdominal irradiation, patient characteristics associated with an increased risk of radiation injury to the gastrointestinal tract have been identified (DeCosse et al 1969; Maruyama et al 1974; LoIudice et al 1977; Kwitko et al 1982; Green et al 1983). Hypertension and diabetes mellitus have been implicated in the development of severe chronic radiation enteropathy (DeCosse et al 1969; Maruyama et al 1974) but this is controversial (LoIudice et al 1977; Kwitko et al 1982). Previous abdominal surgery (LoIudice et al 1977) and pelvic inflammatory disease (van Nagell et al 1977) have also been reported to be predisposing factors for severe chronic radiation injury. This increased risk may be due to adhesions, resulting in fixation of loops of small intestine within the pelvis. In support this concept, Green et al (1983) showed that fixation of the small intestine was evident in 30 of 46 (65%) patients with prior pelvic surgery compared with only 7 of 39 (18%) patients without prior pelvic surgery. A similiar study has not been performed for pelvic inflammatory disease but van Nagell et al (1977) has proposed that localized reactive changes in serosal vessels associated with pelvic inflammation may be an important aetiological factor in radiation enteropathy. However, Carr et al (1984) demonstrated by microradiological studies of radiation bowel disease that intramural, rather than serosal microvascular compromise was an important factor in its natural history. It is likely, therefore, that patients with pelvic inflammatory disease are predisposed to severe chronic radiation enteropathy as a result of fixation of intestinal loops in the pelvis by serosal adhesions rather than through ischaemic changes in the bowel wall.

Two retrospective studies which have related the prevalence of chronic radiation bowel injury with the severity of acute radiation enteritis, suffer from a number of methodological inadequacies including inadequate follow-up and the inaccuracies

inherent in characterising acute radiation sequelae retrospectively, rather than according to a previously agreed protocol. For example, in the larger study involving 1390 patients treated for carcinoma of the cervix, only 784 were evaluable for late bowel complications (defined as intestinal strictures, fistulae, adhesions, perforation and colitis), since the remainder were not able to be followed up for logistical reasons (Bourne et al 1983). Only those patients who had severe acute radiation enteritis, defined as intestinal obstruction, ileus, or symptoms severe enough to necessitate intravenous fluid replacement, were analysed. Although the risk of developing a late bowel complication was increased by a factor of 2.7 in those patients characterised as likely to have severe acute radiation enteritis (8.2% bowel complication) compared with those patients in whom severe acute radiation enteritis was absent (3.0% bowel complication), this is likely to be an underestimate. In support of this in the smaller study of 410 patients who had received high dose radiotherapy for carcinoma of the cervix, radiation bowel complications (defined as intestinal obstruction, fistulae and chronic diarrhoea) developed in 26 (42.6%) of the 61 patients who suffered moderate to severe acute radiation enteritis, compared with 38 (11.2%) of the 340 patients whose acute radiation enteritis was considered to have been mild or absent (Kline et al 1972). Although not reported, a chi-squared comparison between the complication rates in the two groups show that the differences are significant ($p < 0.01$).

The prevalence of chronic radiation enteritis has also been related to the extent of the radiation field and, presumably the amount of the intestine which has been irradiated (Piver et al 1977; Wharton et al 1977; Withers et al, 1977). For example, Wharton et al (1977) related bowel complications such as small and large bowel obstruction, intestinal perforation and fistulae in patients irradiated for carcinoma of the cervix to the extent of the radiation field. The latter was determined by biopsy evidence of involvement of the pelvic and para-aortic nodes. 56 patients with negative biopsies received pelvic irradiation only, whilst 40 patients with involved pelvic nodes had

their radiation field extended to include the fourth lumbar vertebrae and the 24 patients with common iliac and /or aortic nodal metastases had their pelvic radiation field extended to include the twelve thoracic vertebrae. The corresponding radiation bowel complication rate was 11%, 15% and 33% (Although not reported, $p < 0.05$ for a 3 x 2 chi - squared comparison). Withers et al (1977), who treated 45 patients with carcinoma of the rectum post-operatively found only one bowel complication (necrosis of the posterior rectal wall) in 33 patients who had pelvic irradiation but four of the 12 patients who had abdominal and pelvic irradiation developed intestinal obstruction. A chi - squared comparison of the complication rates in the two groups, although not reported, indicate that the differences were statistically significant ($p < 0.01$). Major limitations of both studies are that both were non-randomised and involve relatively small patient numbers. In addition, since the extent of bowel exposure was not quantified in either study, the increased complication rate cannot be attributed with certainty to an increased amount of small bowel within the radiation field. Moreover, since multi-variate analysis of the results was not carried out, other factors such as the extent of surgery, could have contributed to the increased complication rate. Strockbine et al (1970) performed radiation dosimetry on all their patients, and demonstrated that the bowel complication rate(defined as fistulae, sigmoiditis and rectal ulcer) increased with total radiation dose beyond 30.00 Gy. Daily incremental dose, however was found not to be a risk factor for bowel complications (Bourne et al 1983), but this result may be attributable to the narrow range of incremental doses (2.00-2.30 Gy) used and the relatively small number of complications.

Although the importance of all the above risk factors have not been verified by prospective studies, in most centres patients considered at increased risk of small intestinal injury have had their radiation treatment modified. When the risk of small intestinal radiation injury is unacceptably high, avoidance of irradiation is sometimes advised, especially if there is a viable alternative treatment modality, such as in

operable carcinoma of the cervix. Attempts have been made to displace mobile loops of bowel out of the pelvic radiation field, either by exploiting the effect of bladder distension (Green et al 1983; Gunderson et al 1985; Gallagher et al 1986), (Fig 1.1), or using an omental or absorbable mesh sling in the pelvis to hold small intestine out of the radiation field (Deluca & Ragins 1985; Rodier et al 1991). In relatively fixed parts of the gastrointestinal tract, such as the oesophagus and rectum, where the latter approach is not possible, the use of computerised assisted radiation planning, with multiple cross-firing radiation fields has made radiation treatment more precise and enabled the radiation dose to parts of the gastrointestinal tract to be minimised. Although some studies utilising these approaches have reported a decrease in gastrointestinal symptoms during abdominal irradiation (Green, 1983; Gallagher et al 1986), in all cases the study design was suboptimal and, in particular, none was randomised. Furthermore, it is well documented that the absence of gastrointestinal symptoms during abdominal irradiation does not preclude later "serious" gastrointestinal complications (Kline et al 1972; Bourne et al 1983).

1.5 EFFECTS OF THERAPEUTIC IRRADIATION ON OESOPHAGEAL FUNCTION

1.5.1 Acute effects

Prevalence

Mediastinal irradiation is commonly employed in the treatment of intra-thoracic malignant diseases, such as bronchogenic carcinoma and Hodgkin's lymphoma. During the course of mediastinal irradiation, symptoms such as substernal burning and dysphagia are almost inevitable (Roswit et al 1972).

Animal studies

In animals, the histological changes in the oesophagus resulting from therapeutic irradiation have been evaluated using single large doses of radiation (Jennings & Arden 1960; Northway et al, 1980). Jennings & Arden (1960) evaluated the effects of a single massive dose of 30.00Gy (3000rads) to the oesophagus of the rat. At 4 days

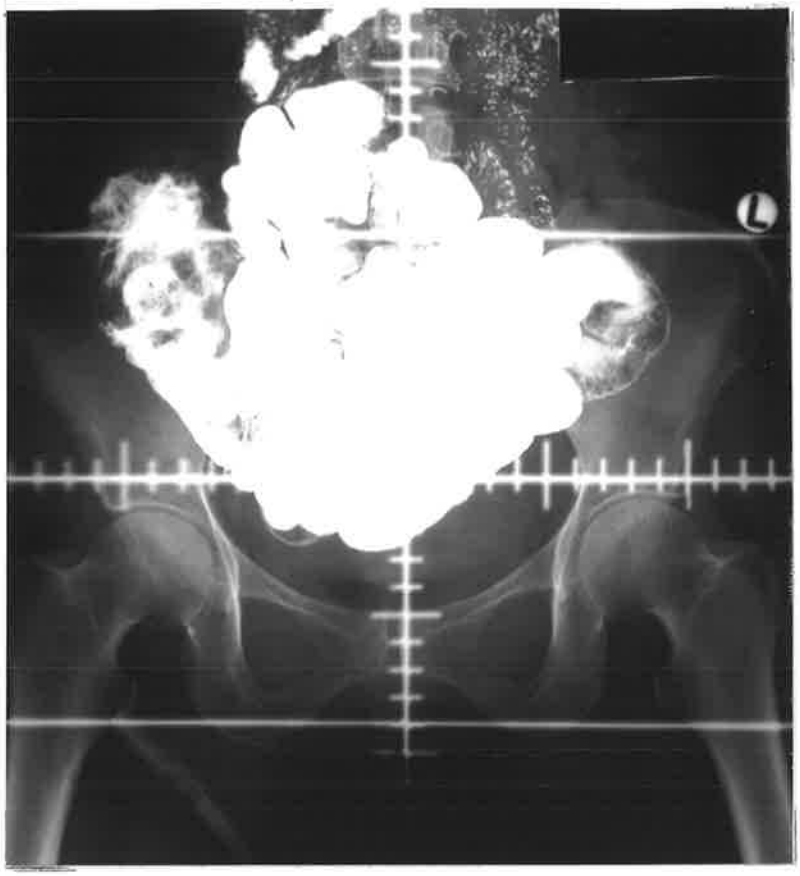
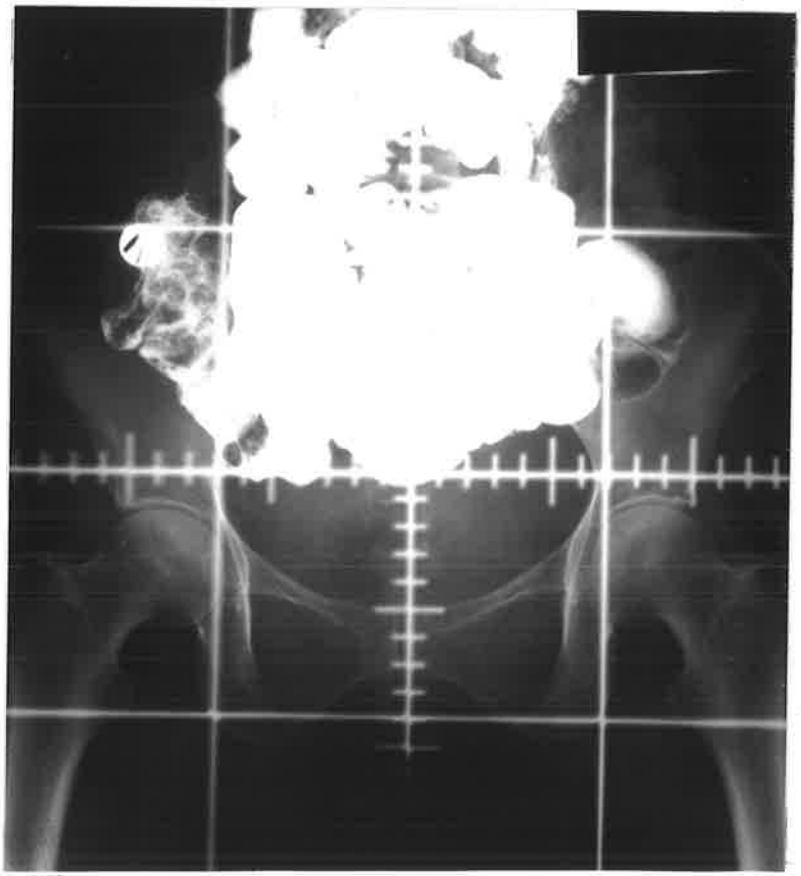


Figure 1.1 Barium small bowel meal showing the amount of small intestine in the pelvis without (above) and with (below) bladder distension. Less small intestine is exposed to the effects of therapeutic pelvic irradiation with bladder distension during treatment. *(Yeoh).*



there was submucosal oedema associated with a leucocyte infiltrate. At 6 days mucosal necrosis with loss of the superficial epithelium was evident, which progressed to sloughing of the necrotic epithelium that was maximal at 10 days. Regeneration of the epithelium began at 14 days and complete reepithelialization had occurred by the 25th day. At this time, moderate submucosal fibrosis was apparent which persisted. At 6-12 weeks, small oesophageal diverticulae, which were considered to result from defects in the muscle wall secondary to muscle necrosis, were prominent.

The severity of radiation induced oesophagitis (in laboratory animals) can be reduced by prophylactic adminstration of cyclooxygenase inhibitors such as indomethacin and sodium meclofenamate (Northway et al 1980; Ambrus et al 1984; Tochner et al 1990), possibly by reducing the inflammatory response mediated by prostaglandins on the oesophageal mucosa. This notion is supported by Northway et al (1980), who found that oesophagitis as assessed by endoscopy, histology and barium oesophagram was most severe in opossums which received irradiation and prostaglandin E-2 (PGE-2) by subcutaneous injection, compared with control animals, whilst indomethacin-treated (also adminstered by subcutaneous injection) opossums showed either no or only mild signs of oesophagitis.

Northway et al (1979) also studied the effects of a range of single large doses of irradiation (15 - 22.5 Gy) to the oesophagus in 4 opossums with 2 animals serving as controls. Preirradiation, fibreoptic endoscopy, mucosal biopsy, double contrast barium oesophagraphy, and manometry were performed. Postirradiation, fibreoptic endoscopy was evaluated once only, a week following completion of irradiation, but barium oesophagraphy and intraluminal manometry were repeated biweekly and monthly respectively until the animals were sacrificed at 8 months following completion of irradiation. All 4 opossums had endoscopic signs of oesophagitis, characterised by erythema, exudate, and areas of mucosal ulceration, associated with

histological evidence of inflammation in mucosal biopsies, a week following completion of irradiation. Double contrast barium oesophagrams also showed evidence of mucosal ulceration. The severity of macroscopic mucosal damage was related to the dose of radiation. Motility changes on barium oesophagram were also apparently related to the radiation dose, being evident only in the animal receiving the highest radiation dose, and were demonstrable 4 weeks following irradiation. These changes consisted of incomplete peristalsis associated with impaired propulsion of the column of barium through the oesophagus and non-peristaltic tertiary contractions distal to disruption of the primary wave. Manometric abnormalities were also documented only in this animal. Although the lower oesophageal sphincter (LOS) appeared to show progressive failure of relaxation in response to induced swallowing, beginning 1 month post-irradiation, the apparatus used for recording LOS pressures did not incorporate a sleeve sensor (Dent 1976) tolerant of longitudinal axial movement during swallowing. It is possible therefore, that descent of the recording assembly into the stomach with swallowing may have led to falsely high LOS pressures. This finding may have been misinterpreted as failure of the LOS to relax. On the other hand, the abnormal motor activity of the oesophageal body in response to balloon distension of the upper oesophagus evident at eight weeks post-irradiation, is likely to have been a true effect of mediastinal irradiation. These results suggest that the oesophageal mucosa in opossums is more sensitive to the effects of single doses of mediastinal irradiation than the muscular and or neural tissues but the effects on the latter are more persistent (v.i.).

Human studies

There is surprisingly little information relating to the effects of fractionated mediastinal irradiation on oesophageal structure and function. In 20 patients undergoing mediastinal irradiation for carcinoma of the lung, Seaman & Ackerman (1957) reported that while oesophageal symptoms occurred in all patients who had received fractionated doses of irradiation (of the order of 20.00Gy-25.00Gy (2000-

2500rads) in 2 weeks to 40.00Gy-45.00Gy (4000-4500rads) in 4 weeks), barium swallows, were normal except for the occasional demonstration of fine serrations of the margin of the barium column. The absence of radiological abnormalities in this study may be attributable to the relative insensitivity of single barium contrast studies in demonstrating mucosal abnormalities (Laufer, 1979). However, in a more recent study of 14 patients irradiated for carcinoma of the lung, the majority showed either no histological evidence of oesophageal damage or focal mucosal changes three weeks after commencing mediastinal irradiation (Nicolopoulos et al 1985). The less severe mucosal damage observed in human when compared with animal studies is likely to be attributable to recovery which has been shown to occur between doses of radiation when it is fractionated (Belli et al 1967).

In contrast to the low prevalence of mucosal abnormalities, prolonged oesophageal transit of a radioisotopically labelled water bolus has been reported in the majority of patients undergoing mediastinal irradiation (LaManna et al 1985). Although the degree of dysphagia during mediastinal irradiation did not correlate with radionuclide transit, the findings of this study suggest that disordered motility occurs frequently during mediastinal irradiation. It is not known whether the delayed transit represents a disturbance of primary or secondary oesophageal peristalsis (Kendall et al 1987).

Treatment

The treatment of symptoms, such as dysphagia, during mediastinal irradiation has not been adequately evaluated. Dietary modification is often necessary to maintain nutrition, as patients may only be able to tolerate a soft diet. Avoidance of alcohol and tobacco is still advocated, along with the prescription of metoclopramide (Chowhan 1990). The rationale of these measures is based on the assumption that the underlying major mechanism of radiation oesophagitis is the same as that previously attributed to reflux oesophagitis, viz., defective basal lower oesophageal sphincter (LOS) tone (Fisher et al 1977). However, as it is now known that the predominant mechanism of

symptomatic gastrooesophageal reflux is transient LOS relaxation (Dent et al 1988), this assumption is no longer tenable. Topically acting anaesthetics, such as viscous lignocaine or oxethazine, are commonly prescribed, and apparently effective in relieving odynophagia (Vanagunas et al 1990). Although the mechanism of action of topically acting anaesthetics on radiation induced oesophagitis has not been elucidated, it is possible that they increase the sensory threshold to luminal stimuli. More severe pain induced by swallowing has been attributed to oesophageal spasm and an uncontrolled study has suggested that the calcium channel blocker, nifedipine may be beneficial (Finkelstein 1986). For persistent severe symptoms, shielding the oesophagus at the level of the cricopharyngeus muscle from the effects of irradiation whilst continuing mediastinal irradiation has been advocated (Rubin & Casarett 1968a), but this approach is of unproven benefit and may potentially compromise cure by shielding tumour. A double-blind placebo controlled trial of indomethacin administered to patients undergoing mediastinal irradiation for bronchogenic carcinoma failed to document histological improvement to the damaged oesophagus although clinically significant improvement occurred in the indomethacin treated group of patients who had milder gross endoscopic findings and symptoms (Nicolopoulos et al 1985). The most likely explanation for the discrepant findings in the human and animal subjects is that the radiation dose given in the animal studies (Northway et al 1980; Ambrus et al 1984; Tochner et al 1990) was several orders of biological magnitude greater than that absorbed by human subjects and that the mucosal damage in the latter may not have been severe enough for any improvement resulting from indomethacin to be apparent. The dose of indomethacin used in the human experiments was relatively less, and this may also have contributed to the lack of effect.

Conclusions

The pathogenesis of symptoms such as dysphagia during mediastinal irradiation is poorly understood. Data from animal studies which show early florid mucosal lesions

and motility changes after recovery of the mucosal damage, contrast with limited data from human studies demonstrating minor mucosal changes associated with apparent prolongation of oesophageal transit. Mucosal damage and delayed oesophageal transit do not however, correlate with symptoms in human studies. Since there have been no manometric studies performed to evaluate the effects of mediastinal irradiation, the underlying motor correlates of possible changes in oesophageal transit have not been documented. As a result, current approaches to the treatment of oesophageal symptoms during mediastinal irradiation is largely based on anecdotal observations.

1.5.2 Chronic effects

Prevalence

The prevalence of chronic radiation damage to the oesophagus is uncertain. Retrospective studies, based on small numbers of patients, suggest that the risk of strictures due to chronic radiation damage to the oesophagus is dose dependent, with a prevalence of between 5 and 50% (Phillips & Margolis 1972). These figures represent crude approximations because of the small patient numbers and the exclusion of patients who died since completing mediastinal irradiation (e.g. the majority of patients with bronchogenic carcinoma die within 2 years of completing radiation therapy). In a study of 30 patients with persistent dysphagia 3 - 18 months following mediastinal irradiation, only 5 patients had oesophageal strictures on barium oesophagram, but all had disordered oesophageal motility (Goldstein et al 1975, discussed in Section 1.1). It is likely therefore that disordered oesophageal motility occurs frequently as a long term complication of radiation therapy. However, there have been no longitudinal studies of oesophageal function following mediastinal irradiation to establish the prevalence of radiation sequelae in unselected patients.

Animal studies

Northway et al (1979) reported changes in oesophageal motility evaluated by barium oesophagraphy and manometry, up to eight months following a range of single large

radiation doses to the oesophagus of 4 opossums (experimental protocol as detailed in Section 1.5.1 Acute effects, Animal studies). At eight months morphological changes, consisting of luminal narrowing and thickening of the wall of the oesophagus associated histologically with focal necrosis of the muscularis mucosa and deep muscles of the oesophagus, were evident only in the animal receiving the highest radiation dose. In contrast, barium oesophagraphic evidence of impaired motility was noted in all animals except the one receiving the lowest radiation dose. Although these abnormalities improved in two of the 3 opossums between three and four months after irradiation, the motility changes persisted in all 3 animals up to eight months and was most marked in the animal receiving the highest radiation dose. Reported manometric abnormalities of peristalsis in response to balloon distention of the upper oesophagus and decreased LOS relaxation were related to radiation dose. Abnormal motor responses to balloon distension occurred only in the two animals receiving the higher radiation doses. The time of appearance and disappearance of these changes varied with the radiation dose in these two animals, appearing earlier (eight weeks versus fourteen weeks post-irradiation) and persisting longer (fourteen weeks versus eight months) in the opossum receiving the highest radiation dose. The animal receiving the highest radiation exposure to the oesophagus was also observed to show progressive decrease in relaxation of the LOS during induced swallowing from 1-5 months after irradiation beyond which time LOS pressure values could not be determined. However, as discussed in Section 1.5.1 (Acute effects, Animal studies), this observation is likely to have been an artefact inherent in the methodology.

Human studies

Seaman & Ackerman (1957) were the first to document the marked histological changes in the muscle and submucosa of the oesophagus occurring in patients irradiated for bronchogenic carcinoma, consisting of submucosal thickening and degenerative changes in the muscle, with minimal changes in the blood vessels.

Although the most frequent radiological abnormality in patients with persistent oesophageal symptoms following mediastinal irradiation was abnormal motility (Goldstein et al 1975), the manometric correlates of these motility changes have only recently been reported (Seeman et al 1992). In the recent study, three patients with dysphagia 3-30+ years after mediastinal irradiation and with no radiological evidence of oesophageal strictures underwent oesophageal manometry (Seeman et al 1992). The manometric assembly consisted of pneumohydraulically infused catheters attached to pressure transducers and a recording system. The catheters had three distal radially orientated sideholes for measurement of LOS pressure and leads with sideholes 5 and 10 cm proximally for assessment of motility in the oesophageal body. Low amplitude contractions in the oesophageal body in response to swallowing were found in two out three patients, and there was absence of peristalsis in one of these. Based on histological changes in muscle reported previously (Seaman & Ackerman 1957), it was postulated that the motor abnormalities resulted, at least in part, from direct radiation injury to muscle. The possibility that mediastinal irradiation could damage neural mechanisms, such as the local neural reflex mediating secondary peristalsis, has not been evaluated.

Treatment

Rational treatment of chronic dysphagia in the absence of oesophageal strictures following mediastinal irradiation is not possible since its pathogenesis is uncertain.

Strictures of the oesophagus resulting from mediastinal irradiation require frequent dilatations. In one series, an average of 2.5 dilatations were required in 5 months to provide relief of dysphagia (O'Rourke et al 1988). In the radiation damaged oesophagus, there is a high risk of perforation and careful endoscopic placement of guide-wires with radiological assistance is mandatory. Treatment of bleeding, perforation and fistula formation is usually conservative with blood transfusions, broad spectrum antibiotics and hyperalimentation. Resections of the damaged

oesophagus using colon transplants have been done, but are rarely advocated because surgery of the irradiated mediastinum is extremely hazardous.

Conclusions

Animal and human studies suggest that disordered oesophageal motility occurs frequently as a chronic sequela of mediastinal irradiation and may be responsible for symptoms such as dysphagia occurring in the absence of strictures. Although damage to the muscle in the wall of the oesophagus has been implicated, the possibility that neural damage may also contribute to motility changes has not been investigated. The possibility that oesophageal symptoms could result from abnormal sensory feedback has also not been examined. It is therefore not surprising that treatment of chronic oesophageal symptoms following mediastinal irradiation is at present unsatisfactory.

1.6 EFFECTS OF THERAPEUTIC IRRADIATION ON GASTRIC FUNCTION.

1.6.1 Acute effects

Prevalence

Abdominal with or without pelvic irradiation is often used either solely or as an adjunct to surgery in the curative treatment of lymphomas, testicular cancer (mainly seminoma), ovarian carcinoma and, occasionally, endometrial carcinoma. During the course of fractionated radiation therapy to the abdomen, nausea and vomiting occur in approximately 50% of patients (Priestman et al 1987; Yeoh et al 1993).

Animal studies

Engelstadt (1938) reported the histopathological changes in the stomach of rabbits in response to both single and up to four fractionated doses of radiation. The radiation dose effects were observed over a range of between 1.212 and 43.60 Gy* for single doses in contrast to the narrower range of 29.10 to 43.60 Gy* spread over intervals varying between 3 days and 1 month for the fractionated doses. Whilst mucosal hyperaemia was observed with single doses as low as 1.212 and 2.425 Gy*, gastric

ulcers localised to the lesser curvature could only be predictably induced by 14.55 Gy* and above. The macroscopic and microscopic features of these radiation-induced gastric ulcers were similiar to peptic ulcers and became evident between two and four weeks of irradiation in the majority of the animals. However, free perforation into the peritoneal cavity and haemorrhage from these ulcers occurred frequently, accounting for a 50% mortality rate in the animals receiving 14.55 Gy* and greater than 90% fatality rate among the animals in which absorbed dose of radiation was 29.10 Gy*. Although gastric ulcers were as reliably caused by fractionated irradiation as single doses of radiation of 14.55 Gy* and above, the associated histological changes were less marked and mortality rates were also lower, particularly in the animals in which the intervals between doses of radiation were prolonged. Although the results of this study give some information about the morphological response of the stomach to fractionated doses of radiation, the data from this study is of limited value since the individual dose fractions are several orders of magnitude larger, and the time intervals between them quite different from those which are used clinically.

In contrast, much of the current understanding of the aetiology of radiation-induced vomiting in clinical practice is largely derived from animal experiments. It is evident from recent experiments that peripheral "gastric" mechanisms are important in the aetiology of vomiting due to radiation, even though vomiting is controlled centrally.

The control of vomiting involves two regions of the hind brain, the chemoreceptor trigger zone (CTZ) in the area postrema in the floor of the fourth ventricle and the vomiting centre located in the brainstem (Westbrook et al 1987). Whilst the concept of a vomiting "centre" is useful for the purposes of discussion, it is clear that the anatomical substrate involves a number of functional areas within the brainstem, including the reticular formation, the nucleus tractus solitarius, the dorsal motor vagal nucleus and somatic nuclei, rather than a discrete entity (Andrews et al 1988). These anatomical areas within the brainstem coordinate the complex sequence of somatic

and autonomic events involved in emesis, such as licking, opening the mouth, contraction of the intercostal muscles and diaphragm, salivation, tachycardia, pallor, relaxation of the proximal stomach and retropropulsion of the gastric contents. The vomiting centre is the final common pathway for emetic stimuli. Stimuli from higher centres, emotion, smell and taste, raised intracranial pressure and the vestibular apparatus act directly through the vomiting centre, whilst emetic drugs, including chemotherapeutic agents and metabolic disturbances, such as irradiation, probably cause vomiting by stimulating dopaminergic, alpha-adrenergic, histamine H1 and H2, peptide and opiate receptors (Atweh & Kuhar 1977) within the area postrema of the fourth ventricle i.e., the CTZ. This concept is supported by observations that vomiting after whole body irradiation is abolished by surgical resection of the CTZ in dogs and by thermal coagulation of the CTZ in monkeys (Chinn & Wang 1954; Brizzee 1956). Shielding of the CTZ from the effects of whole body irradiation does not, however, prevent vomiting (Chinn & Wang 1954). It has also been demonstrated in dogs and monkeys that vomiting induced by whole body irradiation is accompanied by suppression of gastric emptying(Dubois et al 1984; Dorval et al 1985). In rats, (a species which does vomit), irradiation of the upper half of the abdomen suppresses gastric emptying (Hulse 1966). Dubois et al (1984) have proposed that whole body and abdominal irradiation cause vomiting by stimulating the CTZ indirectly through peripheral afferent nerve activation, or the release of emetogenic substances such as metenkephalin (Cooper & Mattsson 1979), histamine (Barc & Alexander 1961) and dopamine(Westbrook et al 1987) from the upper small bowel. The suppression of gastric emptying accompanying abdominal and whole body irradiation in animals, is thought to be mediated through vagal nuclei, as a result of stimulation by impulses originating in the CTZ (Dubois et al 1984). The anti-dopaminergic drug, domperidone has been found to suppress vomiting, but not the retardation of gastric emptying due to irradiation in dogs (Dubois et al 1984), suggesting that the two effects of radiation are independent of each other, or that the dopamine receptors involved in the two effects have different sensitivity thresholds. The observation that whole body

irradiation induces vomiting after complete excision of the stomach, small intestine and colon in dogs (Conrad 1956) favours the former possibility. In contrast to dogs Dorval et al (1985) found that domperidone had no effect on either vomiting or gastric emptying in monkeys, which may be attributable to species differences in the emetic response.

Evidence that peripheral afferent nerve stimulation is important in the pathogenesis of radiation-induced emesis comes from experiments in ferrets in which the emetic response to a variety of oral and systemic agents, including whole body irradiation, was evaluated before and after dorsal and ventral truncal vagotomy (Andrews et al 1988). Vomiting, and to a lesser extent retching, were inhibited by vagotomy implicating the abdominal vagus in the triggering of vomiting. Experiments involving selective electrical stimulation of abdominal vagal afferent fibres from the gastrointestinal tract have established that afferents from the upper gastrointestinal tract are most sensitive to emetic stimuli (Andrews et al 1990). This probably accounts for the clinical observation that upper half body irradiation is associated with a greater frequency and severity of nausea and vomiting than lower half body irradiation (Fitzpatrick & Rider 1976; Danjoux et al 1979). It has been postulated that mucosal receptors respond to emetic stimuli by releasing 5 hydroxytrpytamine (5 HT) which causes discharge from afferent fibres (Newson et al 1982). This is a plausible explanation for the observation that in the ferret, vomiting induced by whole body irradiation can be reduced or abolished by both abdominal vagotomy and 5 HT-3 receptor antagonists (Andrews & Hawthorn 1987; Andrews et al 1988; Andrews & Davidson 1990).

There have been few animal studies employing radiation dose regimes similiar to those used clinically. Following the demonstration that gastric emptying was slowed in animals exposed to single dose irradiation (Conrad 1956; Bouckaert 1968; Chelmar et al 1969; Summers et al 1970), it was assumed that abdominal irradiation when used

in humans clinically produced the same effect. Scintigraphic measurements of gastric emptying of a isotopically labelled liquid meal in mice exposed to two different fractionated doses of abdominal irradiation (2.50 and 5.00 Gy up to total doses of 40.00 Gy each), showed that gastric emptying did not slow in response to the lower fractionated dose regime, even up to a total radiation dose of 40.00 Gy (Frankendal 1973). As the lower radiation dose regime is comparable to that used in clinical abdominal irradiation, the results of this study caution against extrapolating data from animal experiments utilising single radiation doses to the clinical situation.

Human studies

Low total doses of fractionated abdominal radiation therapy of the order of 14.55-15.52 Gy* delivered over 10-21 days have been reported to reduce gastric acid and pepsin secretion (Doig et al 1951; Goldgraber et al 1954). Serial biopsies of the gastric mucosa after irradiation of the stomach showed a poor correlation between morphological changes and suppression of hydrochloric acid and pepsin secretions. For example, a fall in gastric secretion, particularly of hydrochloric acid, preceded any histological evidence of mucosal damage. Although the continued suppression in acid secretion was associated with a reduction in the number of parietal cells and increasing degenerative change in them, the reduction in secretions persisted even after the mucosal changes had recovered.

In contrast, the effects of higher doses of fractionated irradiation in the order of 40 - 45 Gy over 4-5 weeks, such as that used clinically for the treatment of abdominal malignant disease, is poorly documented. Clinical studies have focussed on factors which may influence the prevalence and severity of radiation induced emesis (Fitzpatrick & Rider 1976; Westbrook et al 1987; Roberts & Priestman 1993) and it has been established that the size of the radiation field, the radiation dose per fraction, site of irradiation, age and possibly anxiety are all important. For example, total body irradiation (used in conditioning patients with malignant disease for bone marrow

transplantation) presents the greatest emetic challenge (Westbrook et al 1987; Roberts & Priestman 1993), and patients receiving single doses of 6 Gy or beyond are more likely to vomit than those receiving doses of 2 Gy or less per fraction (Danjoux et al 1979; Priestman et al 1987; Roberts & Priestman 1993). Children less than 10 years of age tolerate whole body irradiation better than older children and adults, which may reflect lower levels of anxiety (Westbrook et al 1987).

The effects of abdominal irradiation on gastric motor function have not been adequately documented. In particular, gastric motor function has usually been evaluated with barium contrast fluoroscopy which is both inaccurate and non-physiological (Embring & Mattson 1966). For example, reports of accelerated gastric emptying (Korneeva 1963) and antral dysmotility (Rubin & Casarett 1968a), have both involved barium contrast radiology of the stomach. As yet there have been no studies of gastric motility using more optimal techniques, such as scintigraphy.

The possibilty that nausea and vomiting associated with abdominal irradiation arises from abnormal sensory feedback from the stomach or small intestine has also not been evaluated. This would require the use of more invasive techniques (Coffin et al 1994).

Treatment

Since nausea and vomiting frequently occur within two hours of abdominal irradiation, patients are often advised to fast several hours before treatment (Salazar et al 1978; Westbrook et al 1987) but the efficacy of this approach has not been evaluated. The medical treatment of nausea and vomiting during abdominal irradiation has previously relied on conventional anti-emetic drugs, such as metoclopramide and prochloperazine, but control of symptoms can be expected in only about 50% of patients receiving fractionated radiation therapy (Priestman et al 1987). Recent randomised studies suggest that the 5 HT-3 antagonist, ondansetron is

more effective than metoclopramide in controlling vomiting following single high radiation dose exposure to the upper abdomen in patients (Priestman et al 1990) and more effective than prochloperazine in control of emesis induced by fractionated radiotherapy (Priestman et al 1993). One of the criticisms of these studies was that the doses of the conventional anti-emetic drugs, metoclopramide and prochlorperazine, prescribed were sub-optimal compared with the doses used in chemotherapy-induced emesis (Marty et al 1990) and that control of symptoms with higher doses of metoclopramide may be more comparable. However, at high doses metoclopramide also acts as a 5 HT-3 receptor antagonist (Fozard & Mobarok Ali 1978) and its use in high dosage is limited by an increased prevalence of extra-pyramidal side-effects such as dystonia.

Conclusions

Evidence largely from animal experiments supports the concept that indirect stimulation of the CTZ through peripheral afferent vagal nerve stimulation occurring as a result of release of 5-HT from the gastric mucosa is important in the aetiology of nausea and vomiting during abdominal irradiation. Although disordered gastric motility has been reported as a result of abdominal irradiation in humans, its prevalence is uncertain and the relationship between gastric dysmotility and symptoms has not been evaluated.

1.6.2 Chronic effects

Prevalence

Retrospective studies have reported a 6-9 % prevalence of peptic ulceration and a lesser, but unspecified, prevalence of a variety of gastrointestinal complications including "dyspepsia" as long term effects of therapeutic abdominal irradiation (Goldstein et al 1975; Hamilton et al 1986; Coia & Hanks 1988; Fossa et al 1989). Friedman (1952), reported a higher prevalence of radiation injury to the stomach in a total of 200 patients with testicular cancer who had received para-aortic and pelvic

nodal irradiation at least 5 years previously. The analysis was based on data obtained at autopsy (65 patients) and detailed clinical examination including barium contrast fluoroscopy of the stomach and gastroscopy (135 patients). Radiation dyspepsia, defined as epigastric symptoms with no demonstrable gastric morphological abnormalities, occurred in 18% of patients whilst the 74% of patients characterised as having radiation gastritis had symptoms associated with radiological and/or gastroscopic abnormalities such as permanent strictures of the antrum, loss of gastric rugal folds and in some cases mucosal atrophy. Gastric ulcers occurred in 65% of patients and in 29% of cases these were associated with perforation or obstruction. The much higher prevalence of radiation-induced gastric lesions, particularly ulcers, in this study is probably a function of the higher radiation doses delivered which ranged from 24.25 to 62.08 Gy* compared with 25.00 - 45.00 Gy in a more recent study (Coia & Hanks 1988). In support of this, the prevalence of all radiation gastric lesions including ulcers in Friedman's study (1952) was directly related to radiation dose. For example, whilst the prevalence of all radiation gastric lesions increased from 20% in patients who received 24.25-32.98 Gy to 63% of those in whom the absorbed dose of radiation was 53.35 Gy or more, the corresponding prevalence of gastric ulcers increased from 7% to 34%.

Animal studies

In contrast to the innumerable experiments on the acute effects of radiation on the stomach, there have been no animal models of chronic radiation injury.

Human studies

Gastroparesis, characterised by gastric stasis, atony, and dilatation with postprandial nausea and vomiting in the absence of mechanical obstruction of the pylorus or duodenum has been reported following abdominal irradiation for testicular seminoma (Layer et al 1986). In this case report, gastroduodenoscopy showed a dilated stomach with abnormal retention of gastric contents, but normal gastric mucosa and no

evidence of gastric outlet obstruction. Barium meal fluoroscopy confirmed marked gastric dilatation associated with absent peristalsis in the antrum and prepyloric region even though vigorous peristaltic contractions were observed in the fundus and corpus. Gastric manometry showed absence of antral pressure activity for 8 hr in the fasted state with no response to intravenous metoclopramide. In contrast, intramuscular adminstration of the cholinomimetic drug, carbachol stimulated antral motility and gastric emptying. The suggestion that antral hypomotility was caused by abdominal irradiation is plausible since the gastric antrum, but not the fundus or corpus, is within the radiation field for testicular seminoma (Friedman 1952). The prevalence of disordered gastric motility after abdominal irradiation is however, unknown.

Treatment

Treatment of chronic sequelae of abdominal irradiation, such as dyspepsia in the absence of peptic ulceration, is based on anecdotal experience. For example, although the reported success of the cholinomimetic drug, carbachol in improving gastric emptying in gastroparesis due to abdominal irradiation has been attributed to a local transient deficiency of acetylcholine release in the antral neuromuscular synapses (Layer et al 1986), no neuropharmacological studies have been performed to support this concept.

Conservative treatment of radiation-induced gastric ulcers with dietary modification, antacids and anti-cholinergic drugs such as propantheline has been advocated in the past (Hamilton 1947; Rubin & Casarett 1968a). However, the rationale for the use of these measures is questionable, since there is no evidence that they contribute to healing of gastric ulcers generally and drugs with anticholinergic properties could exacerbate any associated gastroparesis. The lack of evidence that drugs which suppress gastric acid secretion, such as ranitidine and omeprazole, are useful in the treatment of radiation-induced gastric ulcers is not surprising since achlorhydria is a well documented effect of gastric irradiation (Doig et al 1951; Goldgraber et al 1954).

Although the majority of radiation-induced gastric ulcers have been reported to heal with conservative treatment (Hamilton 1947), marked antral stenosis due to submucosal fibrosis persists (Friedman 1952; Goldstein et al 1975). For this reason partial gastrectomy is usually performed with re-anastomosis of the stomach remnant with small intestine beyond the duodenum, since the duodenum is likely to show the effects of irradiation and faulty healing of the anastomosis is likely to ensue if the stomach remnant is re-anastomosed to the duodenum (Rubin & Casarett 1968a). Complications of radiation gastric ulcers, such as bleeding and perforation, require emergency surgery after blood transfusion and/or intravenous fluids.

Conclusions

The pathogenesis of chronic sequelae of abdominal irradiation is poorly understood. Mucosal changes are often minimal or absent. Although gastroparesis and symptoms such as dyspepsia have been reported following abdominal irradiation, the prevalence of disorders of gastric motility and their relationship to symptoms such as dyspepsia have not been evaluated.

*Absorbed dose in tissue expressed in Gy is derived by multiplying exposed dose in air expressed in Roentgen in the original experiments by a factor of 0.0097.

1.7 EFFECTS OF THERAPEUTIC IRRADIATION ON INTESTINAL FUNCTION.

1.7.1 Acute effects

Prevalence

Acute radiation enteritis characterized by diarrhoea with or without abdominal cramps is almost inevitable during the course of curative pelvic irradiation for common gynaecological and urological malignant diseases, such as carcinoma of the cervix, endometrium and urinary bladder (Yeoh & Horowitz, 1987).

Human studies

The rectum, sigmoid colon and a varying amount of small intestine are included in a standard pelvic radiation field for curative treatment of malignant disease (Kinsella & Bloomer 1980). Diarrhoea during abdominal and pelvic irradiation has been attributed to a transient protocolitis (Carr et al 1984), but damage to the distal small intestine, particularly the terminal ileum, also contributes to the pathogenesis of diarrhoea (Kinsella & Bloomer, 1980). As the small intestine is more sensitive to irradiation than the rectum, the major component of diarrhoea during pelvic irradiation is likely to be of small intestinal origin.

Small intestinal dysfunction may lead to diarrhoea by a number of mechanisms. There may be the loss of absorptive surface due to mucosal villus atrophy. Fat malabsorption is associated with the passage of abnormally large amounts of long chain fatty acids and bile acids into the colon where bacteria convert them into highly laxative compounds, which increase colonic secretion and propulsion. Small intestinal mucosal injury may also result in active secretion of ions into the intestinal lumen. This leads to a net movement of fluid into the small bowel lumen even during fasting, resulting in watery diarrhoea. Malabsorption of protein and carbohydrates, such as lactose, causes diarrhoea by the osmotic effects of these nutrients within the small bowel lumen resulting in the retention of water . When the volume and rate of ileal effluent reaching the colon exceeds its capacity to salvage nutrients through bacterial fermentation into fatty acids and gas, diarrhoea results. Faster intestinal transit (both small intestinal and colonic) by reducing the time available for absorption of nutrients and electrolytes may also contribute to diarrhoea (Dalla Palma 1968; Yeoh et al 1984).

Studies which have attempted to characterise the effects of irradiation on small intestinal function have generally involved techniques which are inaccurate and/or non-physiological. For example, bile acid absorption has been evaluated by the C-14

cholylglycine breath test (Stryker et al 1977) and by radioimmunoassay of the glycine conjugates cholic and chenodeoxycholic acid (Stryker & Demers 1979). The C-14 cholylglycine breath test has been used without concomitant measurement of faecal C-14 activity (Newman et al 1973). The latter is required because an abnormal breath test may reflect either small intestinal bacterial overgrowth or accelerated small intestinal transit (Heaton 1977). Radioimmunoassay of glycine conjugated bile acid also does not accurately reflect ileal absorption, since passive diffusion may occur in the jejunum and colon (Hislop et al 1967). A more recent study (Yeoh et al 1984) employed the synthetic bile acid, Se-75 labelled homotaurocholic acid (SeHcat), which has been shown to behave like the naturally occurring bile acid, cholic acid and, as a taurine conjugate, is not absorbed by passive diffusion. SeHcat is therefore closer to an ideal marker of ileal function (Ferraris et al 1986).

Evaluation of gastrointestinal transit by quantification of the movement of barium sulphate suspension through the gut is non-physiological and inaccurate (Embring & Mattison 1966). More recent techniques to measure gastrointestinal transit using radio-isotopically labelled test meals are more physiological. More rapid gastro-caecal transit of a technetium-99m labelled liquid lactulose-containing meal has been reported in patients during the fourth week of conventional pelvic irradiation (LaManna et al 1985), but only the arrival of the meal at the caecum was assessed. Without concomitant breath hydrogen measurements, it is not possible to verify meal arrival at the caecum by scintigraphic techniques since overlap of terminal ileum and the caecum may occur (Read et al 1986). By incorporating radio-opaque markers, it is now possible to measure whole gut and small intestinal transit as well as gastric emptying accurately (Read et al 1980). Using scintigraphic techniques, mean rates of small intestinal transit can be derived (Read et al 1986). Although scintigraphic and breath hydrogen analysis of a radio-isotopically labelled non-absorbable carbohydrate meal can now be combined (Read et al 1986), no studies have evaluated

gastrointestinal transit during abdominal and pelvic irradiation using these newly developed techniques.

The possible contribution of secretory changes to diarrhoea during and after radiation therapy has not been assessed. This is not surprising because there is no satisfactory test to evaluate intestinal secretion at present (Morris & Turnberg 1979). In particular, 24-hour stool collections are cumbersome and inaccurate in the presence of diarrhoea, whilst prolonged fasting only provides a qualitative assessment of secretory diarrhoea.

Animal studies

There have been few animal studies employing radiation dose regimes similiar to those used clinically. Furthermore, the results of studies which have evaluated small intestinal motility after single large doses of radiation to the whole abdomen or whole body are conflicting (Summers et al 1970). In a more recent experiment in 5 dogs (Summers et al 1992), the whole abdomen was irradiated with doses of 9.38Gy on four separate occasions two weeks apart to determine the effect of repeated doses of radiation on jejunal myoelectric activity and morphology and also to ascertain if any changes persist. Recordings of jejunal myoelectrical activity by means of bipolar electrodes sutured to the serosa of the jejunum at laparotomy were made before, three to four days and ten to eleven days after, each radiation exposure. Histological changes in the mucosa, submucosa, muscularis propria and myenteric plexus were evaluated at post-mortem performed 4 weeks after the last radiation exposure. At ten to eleven days after the first radiation exposure, the animals had recovered completely from the acute radiation syndrome characterised by anorexia, occasional vomiting and diarrhoea, and the myoelectrical abnormalities recorded three to four days after the first radiation exposure had disappeared. These transient alterations in myoelectrical activity consisted of slow waves of highly variable configuration and irregular rhythm, with frequent uncoupling and reduction in spike burst activity, duration, and length of migration, in association with disruption of the migrating myoelectric

complex. After subsequent radiation exposures, persistent diarrhoea and profound weight loss occurred, and the abnormalities in jejunal myoelectric activity recorded after the first exposure persisted, even though histological abnomalities were mild. It was suggested that disordered myoelectrical activity was likely to be associated with disordered propulsion and contribute to impaired nutrition. However, neither intestinal transit nor absorption were evaluated. Furthermore, although the radiation doses were fractionated the individual dose increments used were approximately five times larger than those employed clinically .

The effects of two (2.50 and 5.00 Gy) different fractionated doses of abdominal irradiation (to total doses of up to 40.00 Gy) on small intestinal propulsion of a radioisotopically labelled liquid meal in mice has been reported (Frankendahl 1973). The lower of these two fractionated dose regimes is more comparable to normal clinical radiotherapeutic practice and was associated with faster small intestinal transit in those animals who had absorbed a total radiation dose of 30-40 Gy. The underlying motor abnormalities responsible for more rapid small intestinal transit due to irradiation has only recently been evaluated (Otterson et al 1988; Otterson et al 1992). In dogs fractionated abdominal irradiation led to a dramatically increased incidence of giant migrating and retrograde giant contractions in the fasted state (Otterson et al 1988), (Figs1.2a). In contrast, postprandial small intestinal contractile activity decreased being most marked in the ileum (Otterson 1992), (Fig1.2b). Although it was proposed that radiation accelerates the overall transit of intestinal contents because giant migrating contractions are probably highly propulsive (Otterson 1992), this remains uncertain since the flow of intestinal contents was not evaluated.

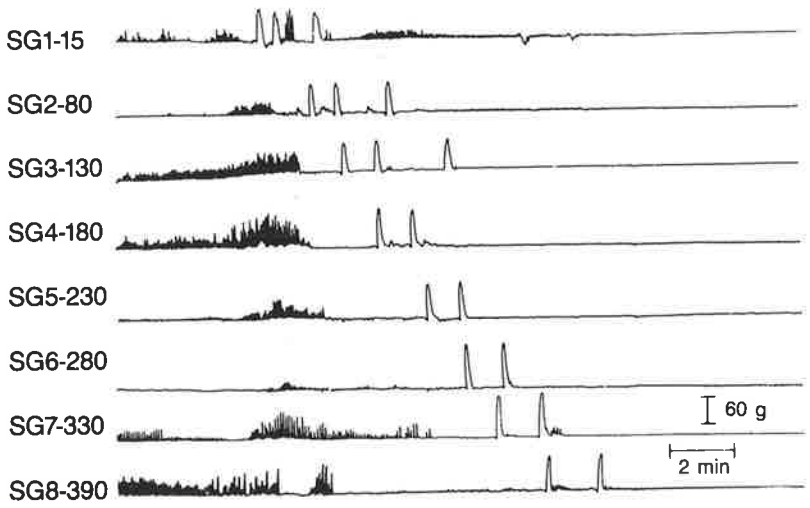


Figure 1.2a Three giant migrating contractions (GMCS) originating in the duodenum on the day of the seventh fractionated dose of radiation. The numbers on the left-hand side indicate the distance (in centimetres) of strain gauge transducers (SG, used for recording circular muscle contractions) from the pylorus. The first two GMCS migrated to the ileocolonic junction but the third stopped at 130 cm from the pylorus.
(Reproduced with permission from Otterson et al 1988).

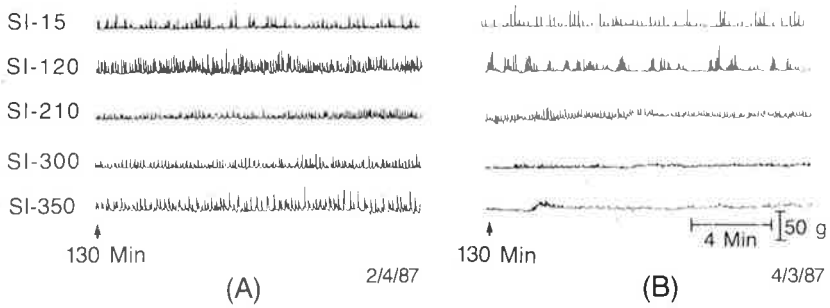


Figure 1.2b Postprandial contractile activity 130 min after a 650-kcal solid meal: (A) prior to receiving irradiation; (B) following 22.50 Gy radiation administered in 9 fractions over three weeks. The numbers on the left-hand side indicate the distance (in centimetres) of the strain gauge transducers from the pylorus on the small intestine (SI). SI-15 is on the duodenum, SI-120 and -210 are placed on the jejunum and SI-300 and -350 are on the ileum. Note the marked decrease in frequency, amplitude, and area of contractions, particularly in the ileum.
(Reproduced with permission from Otterson et al 1992).

Treatment

Acute radiation enteritis is often treated with anticholinergic drugs, opiates, or both. Although reported to be effective (Chapaux et al 1974; Geginat et al 1978), there have been no randomised placebo-controlled studies to evaluate efficacy. Patients with symptoms refractory to anti-diarrhoeal medication may respond to the bile salt sequestrating agent, cholestyramine, although such reports are also anecdoctal (Condon et al 1978). However, in a recent double blind placebo controlled trial oral sucralfate reduced the frequency of defaecation and improved stool consistency in patients undergoing pelvic irradiation for urological malignant disease (Henriksson et al 1992). The efficacy of the sucralfate was attributed to its ability to bind to either intestinal mucosa and/or bile acids thereby protecting the gut from the irritant effects of luminal enzymes and bile acids. However, there is no evidence that irradiation of the small intestine in the clinical setting results in ulceration of the mucosa. It is unlikely that sucralfate will bind to the same extent to intestinal mucosa as gastric ulcers (Nagashima, 1981). Furthermore, although sucralfate has been shown to bind bile acids in vitro, in vivo binding is pH dependent and occurs predominantly in an acidic environment (Tanghoj et al 1985). It is therefore also improbable that sufficient binding of bile acid occurs in the alkaline intestinal contents to account for the efficacy of sucralfate in the treatment of diarrhoea induced by radiation.

Although randomised prospective studies have evaluated the efficacy of elemental diets in reducing the prevalence and severity of radiation-induced diarrhoea (Bounous et al 1975; Douglass et al 1978; Brown et al 1980), they suffer from the criticism that the magnitude of the placebo effect cannot be determined since in all cases their design was not double blind. In the first study (Bounous et al 1975), 18 patients who underwent radiotherapy for malignant disease of the abdomen and pelvis were randomised to receive either a semi-hydrolysed elemental diet, or an isocaloric normal diet. Only one of the 9 patients in the elemental group developed diarrhoea, in contrast to six of the 9 patients in the group receiving a normal diet. The diarrhoea

which occurred in the one patient in the elemental diet group was mild and readily controlled by medication, whilst the course of radiation treatment was interrupted in three patients in the normal diet group due to severe diarrhoea. Interestingly, when these three patients began the elemental diet, ten days after discontinuation of radiation treatment, two were able to tolerate further treatment. In addition, improvement in radiation-induced diarrhoea in the elemental diet group was associated with abolition of a decrease in body weight and serum protein levels. In contrast, other studies (Douglas et al 1978; Brown et al 1980) have found no effect of elemental diets on the tolerance to radiation therapy. These discrepant results may partly reflect the different composition and palatability of the diets used. For example, over half the patients randomised to the elemental diet in one of the studies which failed to show a beneficial effect, did not take the diet for the whole course (Brown et al 1980). Although it is not possible to exclude a placebo effect in the first study, it is unlikely that this factor alone could have contributed to such a marked difference in effect favouring the elemental diet. The effect of total parenteral nutrition (TPN) in improving tolerance to radiation therapy of the abdomen, pelvis or both, has been assessed in three studies (Solassol et al 1979; Kinsella et al 1981; Donaldson et al 1982). In both the studies on adult patients (Solassol et al 1979; Kinsella et al 1981), interruptions to the planned course of radiation treatment because of gastrointestinal side effects occurred in less (sometimes none) patients randomised to receive TPN, when compared to patients who received a normal diet. For example, Solassol et al (1979) found that only 8 out of 42 (19%) patients in the TPN arm had their radiation treatment schedule interrupted compared with 20 out of 39 (51%) patients in the "controls". In the third study in children, 7 of 11 (64%) patients receiving TPN maintained or improved their nutritional status, compared with only 2 of 11 (18%) patients receiving a normal diet. This difference was statistically significant ($p < 0.05$). In contrast, there was no difference in tolerance of radiation therapy, whether evaluated by actual radiation dose received or of unplanned alterations in the scheduling of radiation therapy, between the two groups (Donaldson et al 1982). The

most likely explanation for the differences in findings in this experiment, compared with the results of the studies in adults, is the lower radiation doses employed in the paediatric study. In support of this, radiation therapy was not interrupted because of gastrointestinal side effects in either group in the latter study.

Conclusions

Whilst diarrhoea during therapeutic abdominal and pelvic irradiation is mainly associated with small intestinal dysfunction, the relative importance of various pathogenetic mechanisms such as malabsorption of nutrients and bile acids, faster intestinal transit and secretory changes has not been established.

1.7.2 Chronic effects

Prevalence

As discussed in Chapter 1, Introduction, the prevalence of chronic radiation injury after pelvic irradiation is uncertain.

Human studies

There are many potential mechanisms for diarrhoea in chronic radiation enteritis including malabsorption of bile acids and fat (due to damage to the terminal ileum, surgery, or small bowel bacterial colonisation), malabsorption of lactose, alterations in small intestinal and colonic transit and proctocolitis. Clearly, these factors are not mutually exclusive. Clinical studies have provided limited insights, either because the investigations have either not been comprehensive enough to evaluate the various pathogenetic mechanisms, or the tests used have been suboptimal. Newman et al (1973) reported that 16 of 17 unselected patients who had pelvic radiotherapy 1-26 years previously had malabsorption of bile salts, including all 12 patients with diarrhoea. However, as absorption of bile acid was assessed by the C-14 cholylglycine breath test without faecal measurements of C-14, it is possible that rapid small intestinal transit or small bowel colonisation contributed to these results. In this study,

8 out of 11 small bowel x-rays were abnormal, with thickened ileal mucosal folds (5 patients), dilated small intestinal loops (2 patients), and failure of the ileum to retain barium (1 patient). Evaluation of small intestinal morphology was not performed in a study of vitamin B12 and bile acid absorption in 26 patients presenting with persistent diarrhoea following pelvic irradiation (Ludgate & Merrick 1985). Vitamin B12 and bile acid absorption were measured simultaneously by evaluating whole body retention of orally administered doses of Co-58 labelled vitamin B12 and Se-75 labelled homotaurocholic acid (SeHcat). Thirteen patients had bile acid malabsorption but normal B12 absorption, two patients had vitamin B12 malabsorption but normal bile acid absorption, whilst three patients had malabsorption of both and eight patients had normal absorption of both bile acid and vitamin B12 (Fig 1.3). Breath hydrogen measurements after an oral glucose dose were performed in the two patients with isolated vitamin B12 malabsorption, and these were elevated, indicative of small intestinal bacterial overgrowth. As breath hydrogen testing was not done in all subjects, the overall prevalence of small intestinal bacterial overgrowth could not be determined. Small intestinal bacterial overgrowth may arise as a result of stagnation of luminal contents, such as in small intestinal strictures, or because of bacterial contamination of the lumen of the small intestine by colonic bacteria as in entero-colic fistulae. Although SeHcat has been shown to be more resistant to bacterial deconjugation in humans when compared to the naturally occurring taurocholic acid (Ferraris et al 1986) faster small intestinal transit, by reducing the time available for absorption, may have contributed to reduced retention of SeHcat (Schiller et al 1987; Sciarretta et al 1987). Small intestinal transit was, however, not measured in this study of Ludgate & Merrick (1985).

More rapid small intestinal and colonic transit has been implicated as a factor contributing to diarrhoea and bile acid malabsorption in a study of small bowel function after surgery for chronic radiation enteritis (Miholic et al 1989). Bile acid, vitamins B12 and D absorption, orocaecal transit and small intestinal bacterial

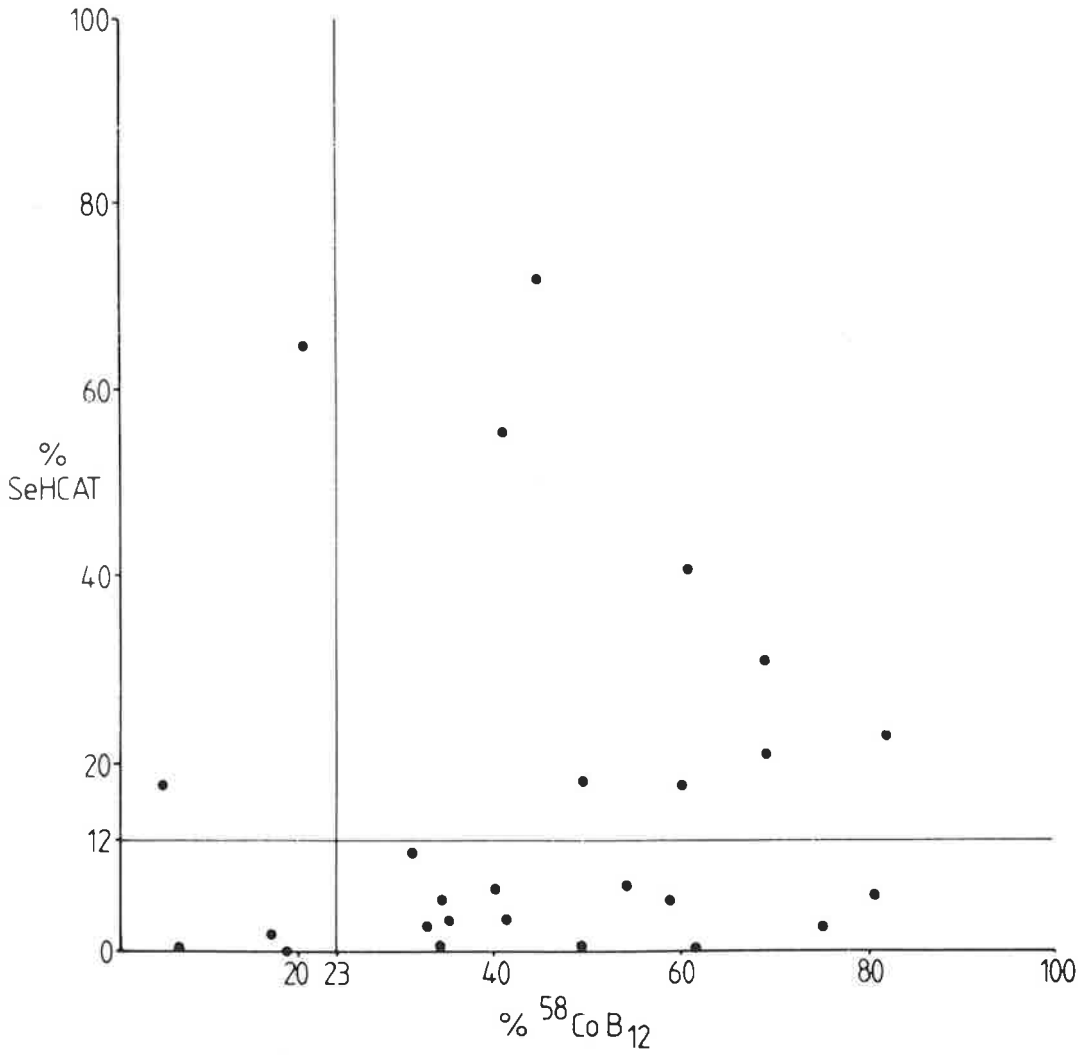


Figure 1.3 Percentage of the administered activity of SeHCAT retained at 7 days plotted against the percentage of Co-58 retained in 26 patients with chronic post-radiotherapy diarrhoea. The horizontal and vertical lines on the graph represent the lower limits of normal for SeHCAT and Co-58 retention at 7 days respectively. *(Reproduced with permission Ludgate & Merrick 1985).*

overgrowth were evaluated in ten patients after ileal resection for radiation injury, six patients suffering chronic post-irradiation diarrhoea and six patients who had undergone ileal resection for other reasons. Although most patients suffered diarrhoea after ileal resection, there was no correlation between the severity of diarrhoea and the extent of ileal resection. In particular, the six patients with the most extensive ileal resections performed for other indications had the least severe diarrhoea whilst diarrhoea was most severe in the ten patients who had ileal resections for radiation injury. Those patients who had undergone ileal resection for radiation injury also had faster orocaecal transit when compared to patients with post radiation diarrhoea and those who had undergone resection for other indications. The lack of correlation between diarrhoea and macroscopic bowel injury in the patients with radiation injury supports the concept that other factors, such as accelerated small bowel transit, contribute to diarrhoea. The inclusion of patients who had surgical resection of radiation injured intestine in this study only confounds assessment of the aetiology of diarrhoea, especially as a small bowel radiological series was not performed following surgery. For example, it is possible that fistulous communication between remaining small intestine and colon could have supervened subsequent to surgery (Morgenstern et al 1977; Galland & Spencer 1985) which could explain both diarrhoea and faster orocaecal transit. Furthermore, ileal resection itself results in faster small bowel transit and reduced nutrient absorption (Neal et al 1984). This may be due to disruption of the potent feedback mechanism in normal subjects whereby the presence of unabsorbed food in the ileum prolongs gastric emptying and small bowel transit of the remainder of the meal, and thereby enhances absorption (Read et al 1984; Kinsman & Read 1984). While the physiological basis of this so called "ileal brake" is uncertain, peptide Y-Y (PYY) may be important (Adrian et al, 1986, Papas et al, 1986). Although functional impairment of the terminal ileum associated with diarrhoea and/or steattorhoea is common after pelvic radiotherapy, the function of the ileal brake has not been studied in chronic radiation enteritis.

Malabsorption of lactose may also contribute to diarrhoea following abdominal irradiation. For example Beer et al (1985) found evidence of lactose intolerance in six out of eight patients with chronic diarrhoea following curative doses of irradiation for pelvic malignancies. This high prevalence probably reflects the severity of radiation damage since seven out of eight patients were malnourished, including the five patients who had required previous surgical resection to the distal ileum. Another possible explanation of the high prevalence of lactose malabsorption may have been the possible racial characteristics of the study group which are not stated. If the composition of patients had been predominanly of Afro-Asian origin, this factor alone could be responsible for the reported high prevalence of lactose malabsorption (Ferguson 1981). Assuming that the study group was predominantly Caucasian, the most likely explanation for the high prevalence of lactose malabsorption is mucosal damage. Even though histological changes in jejunal biopsies in the patients were either normal or only mildly abnormal, levels of mucosal lactase were decreased in all but two patients. It is also possible that faster small intestinal transit could have contributed to lactose malabsorption, but this possibility was not evaluated.

The possible contribution of secretory changes to the genesis of diarrhoea has also not been studied in chronic radiation enteritis.

As previously discussed in Section 1.3, the diagnosis of diarrhoea and other clinical manifestations of chronic radiation enteritis such as intestinal obstruction can be difficult and often delayed, partly because of poor sensitivity and specificity of current methods of investigations. The results of recent studies suggest that measurement of intestinal permeability promises to have widespread application in the investigation of intestinal diseases such as coeliac disease and inflammatory bowel disease (Editorial, Lancet 1985). Intestinal permeability can be assessed by the Cr-51 EDTA absorption test and, the double sugar (lactulose/rhamnose) absorption test (discussed in Chapter 2, Section 2.5). Increased permeabilty to Cr-EDTA has been reported in patients

following abdominal irradiation (Ruppin et al 1985), but a number of factors affect the results of the Cr-EDTA absorption test, including gastrointestinal transit, and hence, the interpretation of the documented abnormalities is uncertain. In the double sugar (lactulose/rhamnose) absorption test, the urinary excretion of the two sugar probes is expressed as a ratio, and the result is thus indepedent of variables such as small intestinal transit (Menzies et al 1979), but there have been no studies of intestinal permeability using this technique during abdominal irradiation.

Animal studies

In contrast to the large number of experiments of the acute effects of radiation on the intestine, there is a paucity of animal studies relating to chronic radiation effects. Histological changes in the wall of the rat small intestine following radiation were evaluated by Hauer Jensen et al (1983). In this study, isolated intestinal loops were irradiated with single doses of radiation ranging from 17 to 23 Gy. Parameters of radiation injury such as vascular sclerosis, fibrosis, lymphatic dilatation and ileitis cystica profunda were scored at post-mortem in groups of rats 2, 4 and 8 weeks, and thereafter every 6 weeks until 50 weeks after single radiation doses of 17, 19 and 21Gy. Animals who received the highest radiation dose were examined only at 8, 26 and 38 weeks after irradiation because of the high mortality in this group. Injury scores increased two weeks after irradiation and stabilized about 8 weeks following irradiation, beyond which there was no further progression. Based on the stabilization of histological abnormalities at this time in the rat model of chronic radiation enteritis, Summers et al (1992) argued that the persistent abnormalities of jejunal myoelectrical activity (discussed in Section 1.7.1, Acute effects, Animal studies) which he demonstrated in dogs exposed to repeated doses of abdominal irradiation up to 70 days post-irradiation were likely to reflect chronic radiation injury. Given the well documented species differences in radiation response (Conrad 1956; Dorval et al 1985), the validity of this assumption is questionable. For example, despite the

accumulation of radiation dose levels comparable, or greater than the single dose experiments in rats, the associated mucosal changes in the dogs were mild.

There have been no animal studies which have evaluated the chronic effects of irradiation on the small intestine using fractionated radiation doses comparable to those used in clinical practice.

Treatment

As discussed in Section 1.3, the treatment of chronic diarrhoea is often unsuccessful (Yeoh & Horowitz 1987; Zentler-Munro & Bessell 1987).

The role of dietary measures in the management of chronic radiation enteritis has not been adequately evaluated. For example, Bosaeus et al (1979) treated nine patients with chronic diarrhoea and bile acid malabsorption (defined as >18% faecal excretion of an intravenous dose of C-14 labelled cholic acid) after pelvic irradiation for gynaecological malignant disease with a low fat diet (40g fat/day). Although improvment in diarrhoea in association with decreased excretion of faecal bile acids was reported, the mechanism of the response is uncertain. It was speculated that the decreased faecal loss of bile salts on the low fat diet implied that the colon was less exposed to their cholerrheic effect. In support their hypothesis, data from another study of thirteen patients with terminal ileal disease or resection (predominantly Crohn's disease, but including one patient with radiation ileal damage), (Andersson et al 1974) was used to account for the efficacy of the low fat diet in alleviating diarrhoea in the first study. Andersson et al (1974) showed that when the dietary fat content was reduced from 100 g to 40 g/day, the improvement in diarrhoea which occurred in ten of the 13 patients was associated with decreased faecal fat excretion, no change in fractional absorption of fat and a marked decrease in faecal water and sodium. Although it is not possible to exclude a placebo effect, since neither study was randomised nor double blind, it is likely that selected patients with diarrhoea

associated with chronic radiation enteritis may benefit from a low fat diet. Such efficacy may be attributable to the reduced amounts of fat entering the colon and/or decreased secretion of bile acids with less colonic bacterial conversion of both fat and bile acids into laxative compounds. Donaldson et al (1975) evaluated the effects of a low residue, low fat, gluten and lactose free diet in five children with small bowel obstruction, presenting about 2 months after the completion of abdominal irradiation. In this study, small bowel roentgenograms and peroral jejunal biopsies for histological assessment were performed before institution of the diet and following clinical improvement. Clinical improvement was associated with resolution of radiological and histological changes, but this cannot be ascribed to the diet with certainty as the study was uncontrolled. Resolution of symptoms of recurrent sub-acute obstruction has also been reported following long term treatment with an elemental diet (Haddad et al 1974).

In a randomised study of 24 patients with severe radiation injury of the small bowel (defined as obstruction, protracted diarrhoea, fistulisation, and malabsorption), four treatments were compared viz, methylprednisolone 80 mg intravenously plus an elemental diet (Vivonex-HN, 2 L/day), methylprednisolone 80 mg intravenously plus total parenteral nutrition, 2.5 L/day, total parenteral nutrition, 2.5 L/day alone, and an elemental diet (Vivonex-HN, 2 L/day) alone (Loiudice & Lang 1983). Patients were aware of the treatment they had been assigned to and the magnitude of any placebo effect cannot therefore be determined. Significant improvement in nutritional status parameters (midarm muscle circumference, triceps skinfold thickness and delayed hypersensitivity skin tests), nitrogen balance, radiological (small bowel radiological series) and clinical (Schilling's test, faecal fat estimation and D-xylose absorption test) measurements were found in patients assigned to the parenteral nutrition groups, but not in the groups randomised to the elemental diet. Total parenteral nutrition has also been used successfully, usually as an adjunct to operation and has been reported to induce weight gain, correct hypoalbuminaemia and to reduce the size and output of

intestinal fistulae due to radiation treatment (Ford et al 1972; Miller et al 1979). Although the design of these studies was neither randomised nor double blind, improvement clinically has ben associated with objective evidence of improvement in nutritional status, thus reducing the likelihood of a placebo effect alone. These results therefore support the role of parenteral nutrition in optimising the condition of malnourished patients with chronic radiation enteritis prior to surgery (v.i.).

As discussed previously in Section 1.3, the surgical treatment of chronic radiation enterocolitis is difficult. Obstruction of the small intestine, which may be partial or complete, is the most frequent serious manifestation of chronic radiation enterocolitis. Episodes of partial obstruction of the small intestine frequently respond to conservative measures (Smith & DeCosse 1986). When complete small intestinal obstruction occurs, resection and primary anastomosis may be appropriate for patients with single discrete areas of involvement, but the majority have more generalized radiation damage and should be treated by complete gastrointestinal bypass of the area (Wobbes et al 1984; Smith & DeCosse 1986). Patients who present with acute perforation secondary to radiation damage to the small intestine require prompt but conservative surgical treatment with the avoidance of primary anastomosis (Smith & DeCosse 1986). Exteriorization of the involved segments appears to be the optimal procedure in this situation (Hatcher et al 1985), although a further operation is required to reconstitute the alimentary tract. Enteric fistulae should be managed conservatively initially, but rarely close spontaneously (Smith & DeCosse 1986). Complete gastrointestinal bypass without extensive resection of the residual small intestine is the best surgical approach, since mortality is lessened and the chance of recurrent fistulae is reduced (Smith et al 1984).

Conclusions

There have been no comprehensive studies of the long-term effects of therapeutic pelvic irradiation on gastrointestinal function and in most cases treatment of sequelae

is often unsatisfactory and has not been evaluated adequately. The surgical treatment of intestinal obstruction, bleeding and fistula formation is fraught with difficulties and even after apparently successful surgery, persistent symptoms are common.

1.8 EFFECTS OF THERAPEUTIC IRRADIATION ON ANORECTAL FUNCTION.

1.8.1 Acute effects

Prevalence

Acute proctitis manifested clinically as diarrhoea, tenesmus and bleeding per rectum is an invariable consequence of pelvic irradiation (Rubin & Casarett 1968b). In a recent prospective study of the effects of pelvic radiotherapy on anorectal symptoms and rectal morphology, urgency of defaecation and to a lesser extent faecal incontinence, were also found to be common, occurring in 90% and 30% of patients respectively (Sedgwick et al 1994).

Animal studies

There have been no studies of the effects of irradiation on anorectal function in animals.

Human studies

It is well recognized that pelvic irradiation affects both anorectal and intestinal function (Kinsella & Bloomer 1980). Although it has been postulated that the local irritant effect of radiation on the rectal mucosa contributes to symptoms by stimulating motility (Moss & Brand 1979), there have been no clinical studies which have adequately evaluated the acute effects of pelvic irradiation on anorectal motility. The lack of human studies is not surprising partly because of the methodological difficulties of anorectal manometry in patients likely to have frequent, voluminous bowel actions and also because of the need to study small intestinal function simultaneously in order to not to confound the effects of pelvic irradiation on the anorectum with those on the small intestine. Possibly because of these difficulties, the

the only study of the acute effects of pelvic irradiation on anorectal function (Birnbaum et al 1992) included anorectal manometry and transrectal ultrasound, before and 4 weeks following irradiation only, but not during pelvic irradiation The subjects in this study were 20 patients with rectal carcinoma, all of whom received 45.00 Gy external beam radiation therapy in 1.80 Gy increments to the pelvis, but the anal sphincter was in the field of radiation in only half of them. In view of this, and also because the measurements were performed at a time when anorectal symptoms would have been resolving (Sedgwick et al 1994), it is perhaps not surprising that there were no significant changes in maximal squeeze and resting anal pressures, or sphincter length at 4 weeks after pelvic irradiation when compared to baseline. The only parameter of anorectal function to change significantly was the minimal sensory threshold to rectal distention which was higher four weeks following irradiation. This observation was attributed to oedema and inflammation in the rectal mucosa.

In contrast, the effects of pelvic irradiation on the rectal mucosa are well documented in two prospective studies (Gelfand et al 1968, Sedgwick et al 1994). In the more recent study by Sedgwick et al (1994), assessments of anorectal symptoms (questionnaire), sigmoidoscopy (macroscopic appearances) and histology (anterior and posterior rectal wall biopsies) were performed in nine patients before, during and up to twelve weeks after pelvic irradiation for urological malignant disease (five patients had bladder carcinoma and four had prostatic carcinoma). Stool frequency increased in all patients from a mean of 1.7/day to 5.0/day at four weeks during radiation treatment, associated with tenesmus, urgency of defaecation and faecal incontinence. Macroscopically, the rectal mucosa in all patients was noted to be hyperaemic and oedematous with persistent ulcers at the sites of previous biopsies, two and four weeks during radiation therapy. Histological assessment of rectal biopsies showed mucosal changes characterised by crypt cell damage, inflammatory cell infiltrate and loss of crypts. There was no relationship between the severity of symptoms, and sigmoidoscopic or histological measurements. Although virtually all

symptoms had resolved by twelve weeks after pelvic irradiation, in two of 7 patients, sigmoidoscopic and histological abnormalities were still evident. These persistent abnormalities apparently contrast with the early return to "normality" in small intestinal biopsies after abdominal irradiation (Trier & Browning 1966). This discrepancy may reflect the higher radiation doses used by Sedgwick et al (1994), compared with Trier & Browning (1966), or a reduced regenerative capacity of rectal compared with small intestinal mucosa after irradiation. It is likely that mucosal damage and oedema in the rectal wall contribute to symptoms during pelvic irradiation.

Treatment

Although a low residue diet and anti-diarrhoeal agents, such as lomotil and loperamide, have been shown to be effective in alleviating diarrhoea during pelvic irradiation (Bounous et al 1975; Chapaux et al 1978; Geginat et al 1978), it is unclear from these studies whether the improvment resulted from the intestinal or rectal component of diarrhoea, or both, since only symptoms were evaluated. Loperamide is an effective treatment in patients with diarrhoea and incontinence of various aetiologies (Read et al 1982). As it also delays small intestinal transit (Kachel et al 1986), it is rational treatment for diarrhoea of both rectal and small intestinal origin. There is a theoretical risk that the resulting smaller volume, but harder consistency stools will increase the likelihood of mucosal bleeding. For this reason in clinical practice, a stool softener such as docusate sodium is sometimes prescibed with antidiarrhoeal medication.

Conclusions

Damage to the rectal mucosa occurs frequently during pelvic irradiation, but the severity of mucosal changes does not correlate with anorectal symptoms. Although it is recognized that disturbances of anorectal function contribute to the

symptomatology of pelvic irradiation, the acute effects of pelvic irradiation on anorectal function have not been adequately evaluated.

1.8.2 Chronic effects

Prevalence

The results of two retrospective surgical series of the effects of radiation on the gastrointestinal tract indicate that the rectum is involved in 65-80% of cases, either alone or in conjunction with other pelvic organs (DeCosse et al 1969; Wellwood & Jackson 1973). The increased susceptibility of the rectum to radiation injury has been attributed to its fixed anatomical position in the pelvis, compared with more mobile pelvic organs such as the small bowel (Varma et al 1985). The prevalence of anorectal dysfunction following pelvic irradiation is unknown, although faecal urgency with or without incontinence is recognised to occur "frequently" (Hatcher et al 1985).

Human studies

Although three studies have evaluated anorectal function following pelvic irradiation, only two have reported abnormalities. In the first of the two studies with reported changes, ten men with anorectal symptoms between two and five years after pelvic irradiation for carcinoma of the prostate had evaluations of the following parameters of anorectal function: symptoms (questionnaire), morphology (sigmoidoscopy and double contrast barium enema), and rectal volumes and pressures at threshold, constant and maximal tolerable rectal sensations, and rectal compliance (anorectal manometry), (Varma et al 1985). Anorectal manometry was performed using continuous high compliance balloon inflation by means of a peristaltic pump at a constant rate, thus enabling accurate calculation of rectal volumes, whilst monitoring rectal pressures by incorporating a microtransducer within the balloon and connecting the assembly to a chart recorder. There was a marked reduction in rectal volumes and compliance in the patients when compared to the age matched controls despite the absence of obvious structural changes such as strictures on double contrast barium

enemas. Because some parameters of anorectal function, such as maximum tolerable volume and rectal compliance, correlated with symptomatic and sigmoidoscopic scores, it was suggested that there was a causal relationship between manometric abnormalities and symptoms. The study did not assess anal sphincteric function, i.e., the potentially pivotal role of disordered internal and/or external sphincter function in the genesis of anorectal symptoms, such as faecal incontinence was not evaluated. For example, in a study of "idiopathic" faecal incontinence, weakness of the external anal sphincter (EAS) occurred in 90% of patients and internal anal sphincter(IAS) weakness was found in more than 30% (Sun et al 1992a). Furthermore, impaired rectal sensation, which occurs in about 50% of patients with idiopathic incontinence, is associated with abnormal IAS relaxation. Although in a subsequent study Varma et al (1986) assessed anal sphincteric function in the same 10 patients, and reported dysfunction of the IAS (as evidenced by reduced anal canal pressure and shortened physiological sphincter length), but not the EAS, the methodology employed was suboptimal. For example, the recording system consisted of a precalibrated water-filled microballoon connected to an external transducer introduced into the rectum 6 cm from the anal verge and rectal pressures were recorded by the station withdrawl technique. It is now recognized that anorectal manometry performed without multiple closely spaced recording sites and simultaneous measurement of the electrical activities of the EAS and IAS, does not allow the reciprocal relationship in activity of the EAS and IAS to be evaluated and makes interpretation of the manometric profiles difficult (Read & Sun 1989). Although in the study of Varma et al (1986) the "squeeze" pressure of the EAS was not reduced in the patients compared with the control subjects, the critical issue of whether it can compensate for IAS relaxation in response to rectal distension, rectal contraction or increases in intra-abdominal pressure, has not been addressed. Rectal biopsies was not included in the experimental protocol in either of the studies by Varma et al (1985; 1986), histological material was obtained from eight other patients who had undergone resection of the rectum for radiation injury and who had received doses of radiation similiar to the ten patients

who underwent anorectal manometry. In these patients there was marked damage to the myenteric plexus, associated with smooth muscle hypertrophy. It was suggested these changes were responsible for the manometric abnormalities observed in the other patients. Since patients who require surgery have more severe radiation damage, the extrapolation of histological findings based on resected bowel to other situations is inappropriate. However, this study provides evidence that radiation can damage the myenteric plexus.

The last of the three studies which have evaluated the effects of irradiation on anal sphincteric function has major flaws in its design (Birnbaum et al 1994). Ten of the twenty patients who had received pelvic external beam radiotherapy to a dose of 45.00Gy or more for rectal carcinoma and who had anal manometry performed before and four weeks following pelvic irradiation (see Section 1.8.1 Acute effects, Human Studies, for details), underwent a further evaluation at 14 - 42 months after completion of radiotherapy. The anal sphincter was within the maximally irradiated area in only three patients, and four of the ten patients had undergone resection of the rectosigmoid colon with double-stapled "low colorectal anastomosis". Since the maximum radiation dose to the anal sphincter in the patients was at least 20% lower compared with that in the patients in the previous studies (Varma et al 1985; Varma et al, 1986), it was not surprising that no significant changes in maximum squeeze or resting anal pressures, sphincter length and minimal sensory threshold were demonstrated.

Animal studies

There have been no animal studies relating to the chronic effects of irradiation on anorectal function.

Treatment

The limited insights into the pathophysiology of chronic radiation rectal injury resulting from the studies of Varma et al (1985; 1986) in human subjects have implications for the treatment of symptoms, such as frequency and urgency of defaecation and faecal incontinence. For example, the rationale for reducing bulk in the diet is based on the finding of reduced rectal compliance. Urgency of defaecation may also respond to the calcium channel blocker, nicardipine given orally, which has been shown to reduce the rectal sensory threshold for desire to defaecate in patients with irritable bowel syndrome (Sun et al 1990a). A study of patients with chronic diarrhoea of diverse aetiologies associated with faecal incontinence (unrelated to irradiation) showed that loperamide not only reduces stool frequency, stool weight and improves stool consistency, but also lessens episodes of urgency of defaecation and faecal incontinence (Read et al 1982). The significant improvment in continence with loperamide was accompanied by increases in maximum basal sphincter pressure and the rectal volume required to inhibit internal anal sphincter tone, suggesting that loperamide has direct effects on the anal sphincter.

There is a lack of studies assessing medical treatment of chronic proctitis. Since mucosal changes similiar to ulcerative colitis, varying in severity from hyperaemia and telangiectasia to frank ulceration and necrosis, have been reported following pelvic irradiation (Gilinsky et al 1983), steroid enemas (Cunningham 1980; Gilinsky et al 1983) and sulphasalazine are often recommended. Reports of the efficacy of these measures have been anecdotal, however (Goldstein et al 1976). A randomised double blind study compared two treatments, oral sulphasalazine with rectal steroids versus rectal sucralfate plus placebo (Kochhar et al 1991). Patients were assessed by symptom score and endoscopy before and four weeks after entry into the trial by two assessors. Improvement clinically and endoscopically was noted with both treatments compared with baseline observations. When clinical and endoscopic criteria were compared between the two treatments, there was a significantly better symptomatic

response to rectal sucralfate and oral placebo compared with oral sulphasalazine and rectal steroids, although there was no difference in endoscopic appearances between the two groups. Potential sources of bias in this study include the lack of a genuine control arm and an analysis which was based on patients who completed the trial, rather than intention to treat. Further randomised studies are therefore required to verify these observations.

Radiation proctitis can lead to intractable or massive haemorrhage, requiring repeated hospital admissions and blood transfusions (Gilinsky et al 1983). The recent report of the use of dilute endoluminal formalin, applied directly to areas of haemorrhagic proctitis (Seow-Choen et al 1993), appears promising but has not yet been evaluated in a trial setting.

Surgery may be necessary if conservative treatment of rectal stricture or bleeding fails. The choice of surgical procedure is controversial. Defunctioning colostomy and resection with colo-anal anastomosis have both been advocated (Anseline et al 1981; Hatcher et al 1985).

Conclusions

Although anorectal manometric studies have provided some insights into the chronic effects of pelvic irradiation on anorectal function, the prevalence of disordered anorectal function has not been determined. Previous reports of reduced rectal volumes, decreased rectal compliance and anal sphincteric dysfunction require confirmation with multiport anorectal manometry and concurrent electromyography of the EAS and IAS. The relationships between manometric abnormalities and symptoms remains to be established and as a result of this, rational treatment of sequelae is at present not possible.

Summary

Although alterations in a number of aspects of gastrointestinal function have been documented as a result of mediastinal and abdominal irradiation, the natural history of these changes and the aetiology of common sequelae such as dysphagia, nausea and diarrhoea remain poorly defined. As a result of these deficiencies, treatment of these sequelae is often unsuccessful. Most previous studies have focussed on evaluation of specific aspects of gastrointestinal function and many suffer from major methodological inadequacies. Transient mucosal abnormalities are still widely believed to be responsible for gastrointestinal symptoms during irradiation although, in general, their severity correlates poorly with both symptoms and functional changes. The potential contribution of disordered motility to the pathophysiology of radiation damage of the gastrointestinal tract has been inadequately addressed. If abnormal motility contributes to the sequelae of radiation therapy, there is the potential for more specific pharmacological treatment. Although randomised studies have validated the efficacy of some of treatment strategies, in general these have provided limited insights into pathophysiology because in most cases only effects on symptoms have been assessed.

In the oesophagus, the motor abnormalities underlying the delayed transit reported during mediastinal irradiation have not been evaluated. The use of precise techniques of oesophageal manometry is essential to document the effects of mediastinal irradiation on oesophageal function.

Disordered gastric motility may contribute to symptoms such as nausea and vomiting, but there have been no studies of gastric motility or gastric emptying using accurate and physiological tests either during or after abdominal irradiation.

Malabsorption of bile acids, fat, lactose, secretory changes and proctocolitis may all contribute to diarrhoea after irradiation, but these various mechanisms have not been

studied comprehensively in patients irradiated for curable abdominal malignant diseases. There is suggestive evidence that diarrhoea and malabsorption may result from more rapid small intestinal and colonic transit, because of disordered motility. The development of accurate and specific diagnostic tests, such as the estimation of whole body retention of orally ingested isotopically labelled bile acid and vitamin B12, has allowed small intestinal absorptive function to be studied more effectively. The recent use of radioisotopically labelled standard test meals containing non-absorbable carbohydrate and radioopaque markers allows simultaneous measurement of gastric emptying, small intestinal and total gut transit. Since faster small intestinal transit may contribute to diarrhoea as well as malabsorption of nutrients and bile acid, studies of absorption are optimally combined with those of intestinal transit.

There is a need for more sensitive tests to detect gastrointestinal damage due to irradiation, particularly to the small intestine, earlier. The results of recent studies suggest that measurement of intestinal permeability may be useful in relation to this. The treatment of most complications of chronic radiation enteritis, particularly diarrhoea, is often unsatisfactory probably because the pathogenesis is poorly understood. If more rapid intestinal transit is a major aetiological factor in diarrhoea and malabsorption, pharmacological therapies to slow it may be beneficial.

CHAPTER 2

Assessment of the effects of radiation on gastrointestinal function

The interpretation and validity of limited data relating to the effects of radiation on the gastrointestinal tract is difficult because the methodology used in previous studies has often been suboptimal and restricted to specific aspects of gastrointestinal function. In this chapter, the advantages and limitations of the various methods available for studying those aspects of gastrointestinal function known to be affected by mediastinal, abdominal and pelvic irradiation are first discussed. The techniques used in the experiments undertaken by the author are then listed at the end of each section. Finally, the presentation of the individual studies in succeeding chapters is summarised.

2.1 INVESTIGATION OF OESOPHAGEAL MOTOR FUNCTION

The oesophagus transports food from the pharynx to the stomach. The entry of food into the pharynx elicits a swallow reflex. This is a coordinated pattern of relaxation and contraction of the pharyngeal muscles, upper oesophageal sphincter, oesophageal body and lower oesophageal sphincter (Diamant & El-Sharkawy 1977). Contraction of the pharyngeal muscles occurs at the same time as the upper oesophageal sphincter relaxes. Relaxation of the upper oesophageal sphincter is transient, preventing regurgitation of food into the pharynx. The food bolus is then propelled down the oesophagus by a primary peristaltic contraction which is mediated centrally and originates in the pharynx (Christensen 1976). Before the peristaltic contraction reaches the distal oesophagus, the lower oesophageal sphincter relaxes for a few seconds and then contracts once the peristaltic wave has passed. Residual material is cleared from the lower half of the oesophagus by secondary peristaltic contractions, which are local neural reflex responses to distension.

Disordered oesophageal transit reflects either mechanical obstruction to the passage of the food bolus or disruption of the coordinated sequence of contractile activity of the oesophagus - so-called motility disorders. Clinically, the investigation of oesophageal swallowing disorders begins with a carefully taken history and is followed by a barium swallow and/or upper gastrointestinal endoscopy to exclude mechanical obstruction. Investigation of oesophageal motility, which may include radionuclide scintigraphy and oesophageal manometry, is undertaken last.

2.1.1 Clinical assessment

Swallowing disorders originating in the oesophagus are characterised by food or fluids "sticking" after the initiation of swallowing and may be associated with pain on swallowing (odynophagia). Three features crucial to the assessment of the aetiology of oesophageal dysphagia are: 1) the type of food causing oesophageal symptoms, 2) whether the dysphagia is intermittent or progressive and 3) whether there is associated heartburn and regurgitation (Castell & Donner 1987). For example, mechanical causes of obstruction in patients, such as strictures, are associated with dysphagia for solid food initially, whilst neuromuscular disorders are associated with dysphagia for either solids or liquids. Progressive mechanical obstruction is indicative of oesophageal stricture and, if preceded by a history of chronic heartburn and/or regurgitation, suggests peptic stricture associated with reflux oesophagitis.

2.1.2 Barium swallow

An air-barium contrast study is the investigation of first choice in the evaluation of swallowing disorders to identify structural abnormalities such as strictures (Castell 1989). Oesophageal motility changes can also be studied using barium swallows and fluoroscopy (Seaman & Ackerman 1957, Goldstein et al 1975). The radiological changes documented are however, qualitative and sequential studies are usually precluded because of the exposure to ionising radiation associated with fluoroscopy. Modern radiological studies of the oesophagus include videorecording of the images,

which not only allows independent assessment by another observer, but makes sequential studies possible since the radiation dose with videorecording systems is less than that with rapid sequence filming. Intermittent disorders of oesophageal motility may still be missed with this technique since prolonged oesophageal studies are at present not feasible.

2.1.3 Upper gastrointestinal endoscopy

Although used as the first line investigation in some centres (Castell 1989), upper gastrointestinal endoscopy is usually performed after an air contrast barium swallow. This enables radiologically detected structural lesions, such as strictures, to be directly visualised and biopsies to be taken if appropriate. Injury to the oesophageal mucosa either as a result of gastro-oesophageal reflux or mediastinal irradiation can also be documented both visually and by histological assessment of biopsies.

2.1.4 Oesophageal scintigraphy

Oesophageal scintigraphy allows the transit of radionuclide labelled boluses to be quantified under physiological conditions (Blackwell 1989). Since the whole body radiation burden to the subject is less than a single plain abdominal X-ray, these methods are suitable for sequential studies. The technique depends on following the transit of a radio-labelled liquid and/or solid bolus by means of a gamma camera linked to a computer. The subject is usually examined in the supine position for liquid swallows and while sitting for solid boluses. Although it has not been shown that solid swallows provide more clinical information than liquid boluses, additional information is provided by studying both types of boluses since clinical disorders of swallowing, with the possible exception of achalasia, may affect swallowing of solids and liquids differently. By estimating the radioactivity in the oesophagus as a whole, total transit time can be calculated. The oesophagus may also be subdivided into multiple areas and time-activity curves for different regions can be generated. Delayed oesophageal transit resulting from an absence of oesophageal peristalsis or incoordinate activity can be

distinguished from the time-activity curves (Blackwell et al 1983; DeCaestecker 1986), (Figs 2.1a,b). Like barium radiology, oesophageal scintigraphy, may miss intermittent disorders of oesophageal propulsion, because of the relatively short duration of each study. Other disadvantages of the technique relate to technical and clinical aspects which lead to difficulties in interpretation and may limit its accuracy and value. While incomplete or rapid double swallowing can confound interpretation of the data this problem can be minimised by practice swallows with unlabelled water. The oblique entry of the oesophagus into the stomach has to be allowed for when the distal region of the oesophagus is drawn, otherwise a portion of "scatter" from the gastric fundal pool is included. Hiatus hernia even after fundoplication often delays distal oesophageal clearance (Blackwell 1989). This difficulty can be overcome by prior knowledge of the clinical history, as well as radiological and endoscopic findings. It is still possible to measure oesophageal transit in those cases of hiatus hernia who have not had fundoplication, by excluding the hernia from the distal region of interest. Gastro-oesophageal reflux may result in apparent prolongation of total transit time, but can be differentiated from disorganized oesophageal contractions by scrutiny of the time-activity curves and qualitative review of the sequential images (Blackwell 1989). Reflux will be accompanied by a reduction in activity over the gastric fundus, and an increase in the oesophagus.

2.1.5 Oesophageal manometry

This is the most direct method of assessing oesophageal motor function in humans (Dent 1989). Recordings are associated with negligible risk, and do not involve radiation exposure, their duration being limited by the tolerance of the patient and the investigator. Oesophageal manometry has its disadvantages. Recording equipment although less expensive than scintigraphic or radiological equipment, still represents a substantial financial investment. The technique is invasive and performance of technically adequate manometric recordings and interpretation of findings requires considerable knowledge and training. Currently derivation of parameters for sphincter

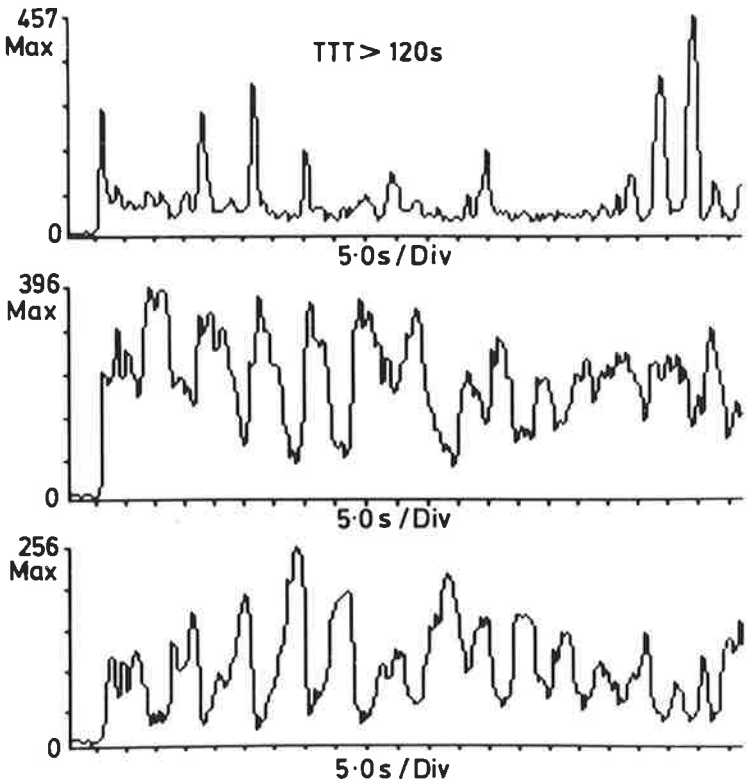


Figure 2.1a Radionuclide time activity curves showing "to and fro" movement of isotope between distal and middle oesophagus. Radioactivity counts in proximal, middle and distal thirds of oesophagus on vertical axis; time in seconds on horizontal axis. *(Reproduced with permission DeCaestecker et al 1986).*

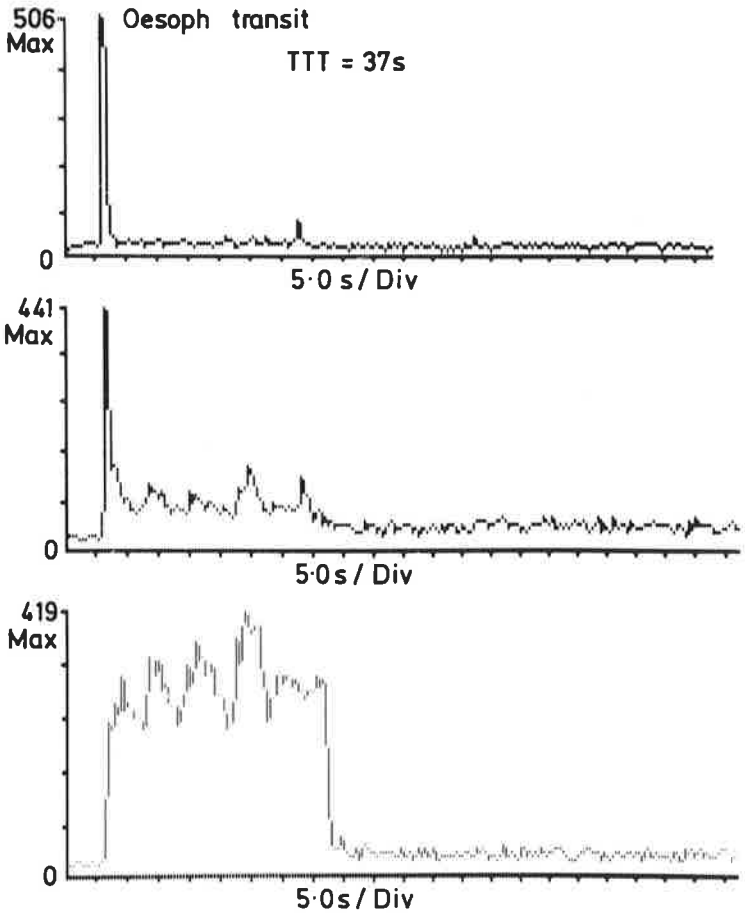


Figure 2.1b Radionuclide time activity curves demonstrating distal static retention for less than 40 seconds. Axes as for Figure 2.1a. *(Reproduced with permission DeCaestecker et al 1986).*

function and oesophageal body peristalsis is dependent mainly on manual analysis, although computerised methods are being developed. It is labour intensive and time consuming. Whether manometry is performed by perfused side hole catheters connected to external transducers or by intraluminal tranducers is largely an issue of cost with the latter technique being more expensive. Although intraluminal transducers have the theoretical advantages of being more physiological in not requiring perfusion and also less prone to technical failure, these drawbacks do not outweigh the increased costs incurred especially as intraluminal transducers are more easily damaged. On the other hand, the manometric approach to monitoring oesophageal sphincteric function is crucial to obtaining accurate data. Focal manometric sensors can lead to falsely high sphincter pressures during swallowing since peristaltic shortening of the oesophagus has been shown to displace the lower oesophageal sphincter(LOS) into the stomach (Dodds et al, 1974). The reflex control of the LOS is of greater physiological and clinical significance than its basal LOS pressure, and only a sleeve sensor tolerant of movement in the longitudinal axis allows effective monitoring of basal LOS pressure and reflex responses (Dent, 1976), (Fig. 2.2).

2.1.6 Combined oesophageal manometry and scintigraphy

As a screening test for disorders of swallowing, oesophageal scintigraphy is not sensitive enough to detect disorders associated with abnormalities in peristaltic waveform and amplitude, but with normal peristaltic progression, such as in patients with high-amplitude peristalsis (nutcracker oesophagus) and hypertensive lower oesophageal sphincter (Holloway et al 1989). On the other hand, oesophageal manometry which quantifies both peristaltic pressures and the rate of propagation is the most sensitive method for diagnosing hypertensive or "nutcracker" oesophagus and diffuse oesophageal spasm (Dent 1989). It is therefore advantageous to combine the two techniques in screening tests of disorders of swallowing and also to enable the motor abnormalities of regional disorders of oesophageal transit to be documented concurrently.

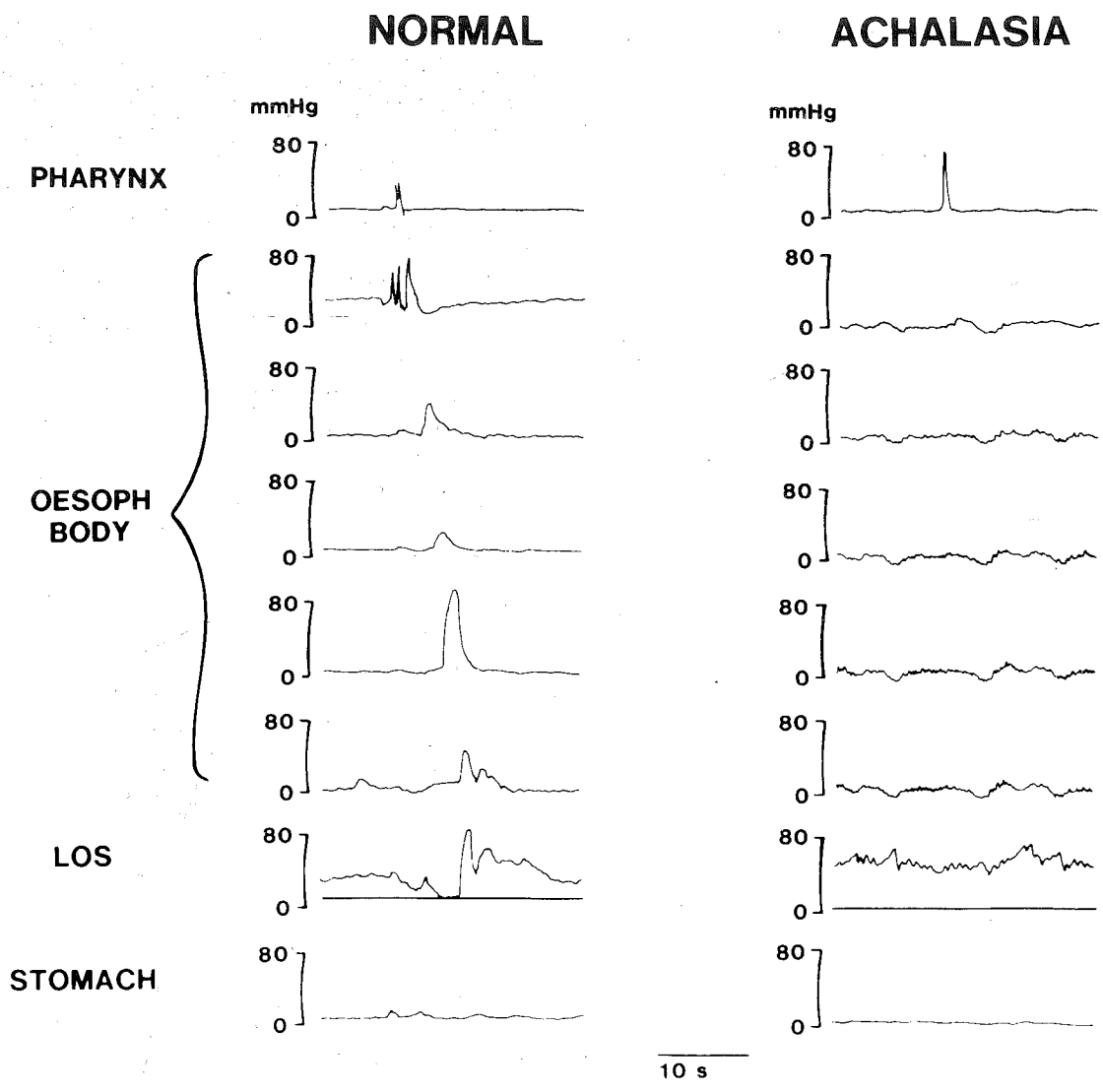


Figure 2.2 Motor responses to a single swallow in a normal subject and a patient with acalasia. The orderly progression of the peristaltic wave and complete relaxation to basal intragastric pressure (horizontal line on lower oesophageal sphincter (LOS) tracing) contrast with aperistalsis and lack of LOS relaxation in the acalasic patient. *(Reproduced with permission Dent 1989).*

Symptoms (questionnaire), mucosal changes (endoscopy score) and oesophageal motility (combined manometry and scintigraphy) were evaluated in the study conducted by the author relating to the effects of mediastinal irradiation on oesophageal function (Chapter 3).

2.2 INVESTIGATION OF GASTRIC MOTILITY

Disordered gastric motility may be associated with symptoms such as nausea, vomiting, abdominal discomfort, early satiety, "dumping" and diarrhoea (Horowitz & Dent 1991). Such symptoms are non specific, and mucosal lesions as well as gastric or proximal small intestinal obstruction must be excluded by barium swallow and/or endoscopy.

Gastric motor function can be assessed by 1) measurement of gastric emptying, 2) manometry, 3) electrogastrography (EGG).

2.2.1 Measurement of gastric emptying

Gastric emptying can be evaluated by either (a) non-radionuclide methods or (b) radionuclide methods such as scintigraphy and radioisotopic breath testing (Table 2.1)

Table 2.1 Methods of Gastric Emptying Measurement (Adapted from Horowitz et al 1985a with permission)

Non-radionuclide
Radiology
Ultrasound
Intubation and aspiration of gastric contents
Absorption kinetics of orally adminstered solutes
Applied potential tomography/epigastric impedance
Magnetic Resonance Imaging
Radionuclide
Scintigraphy
Radioisotopic breath test

(a) Non-radionuclide methods

Radiology

Contrast studies with liquid barium sulphate are only able to detect gross abnormalities of gastric emptying since the volume of barium in the stomach cannot be determined and the use of barium sulphate is in any case non physiological. In addition, the higher radiation exposure compared with scintigraphy makes it an unsuitable technique for serial studies.

Although an abdominal X-ray 6 hrs after ingestion of radio-opaque markers (such as pieces of radio-opaque tubing) has been reported to be a sensitive technique for assessing gastric emptying of non-digestible solids (Feldman & Smith 1987), the passage of markers out of the stomach is almost certainly related to the occurrence of phase 3 of the interdigestive migrating motor complex in the antrum and is therefore not a reflection of gastric emptying per se.

Ultrasound

Ultrasound examination has the advantages of being non-invasive, and since it does not involve radiation exposure can be repeated on separate occasions. However, even with modern high resolution real-time ultrasound equipment, ultrasound is not sufficiently accurate for it to be recommended as an alternative to scintigraphy (Horowitz & Dent 1991).

Intubation and aspiration of gastric contents

The disadvantages of this technique are the technical complexity, limitations on the nature of the meal that can be studied and the invasiveness of the procedure. The presence of an intestinal tube may also affect gastric motility (Fone et al 1991).

Absorption kinetics of orally administered drugs

These depend on the minimal gastric absorption of many orally adminstered drugs such as acetoaminophen (paracetamol) and alcohol (Heading et al 1973; Horowitz et al 1989). The rate of absorption of the drug is therefore a measure of the rate of gastric emptying (Nimmo 1976). Determination of the rate of gastric emptying by measurement of blood concentrations of intestinal absorbed solutes is however unsatisfactory when precise measurement of gastric emptying is required.

Applied potential tomography/impedance epigastrography

These techniques depend on changes in electrical resistivity or impedance to determine the volume of simple liquid meals remaining in the stomach (Avill et al 1987; Baxter et al 1988). The advantages are that they are non-invasive, do not involve the use of ionising radiation and that the equipment used is portable and inexpensive. The disadvantages are that gastric emptying of solid meals cannot be reliably evaluated and gastric acid secretion must be inhibited pharmacologically during measurements, since resistivity changes when acid is secreted (Baxter et al 1988).

Magnetic resonance imaging

By incorporating a gadolinium complex in a liquid meal magnetic resonance imaging can be used to measure both gastric emptying and gastric secretion (Schwizer et al 1992). A three dimensional image of the stomach and its contents is obtained by performing multiple transaxial T1-weghted images. Magnetic resonance imaging is very expensive and requires equipment with limited availability.

(b) Radionuclide methods

Scintigraphy

Radionuclide measurement of gastric emptying is non-invasive, accurate and, since the radiation exposure is less than that associated with an abdominal x-ray, the technique is acceptable in most cases for both single and sequential studies. Radionuclide markers,

most often Tc-99m because of low cost and wide availability, are incorporated into liquid, solid or mixed liquid and solid meals. All tests assume that the gastric emptying of the nuclide adequately represents the behaviour of the test meal , and since the liquid and solid phases of a mixed solid and liquid meal empty at different rates, the precise identification of each phase is necessary for the accurate definition of the emptying of either phase, or of the total meal (Heading et al 1976; Meyer et al 1976). Emptying of solid food is biphasic: an initial lag phase before food enters the duodenum is followed by an emptying phase which approximates a linear pattern. The overall emptying pattern of liquids is non-linear with a slope that decreases with time and often approximates a monoexponential pattern. Liquid emptying is characteristically faster for the first few minutes than the subsequent rate (Heading et al 1976). Gastric emptying of liquids and solid meals may be measured in two separate tests, but this is relatively inefficient approach, particularly as many gamma camera systems can detect two nuclides of different energies (Tc-99m sulphur colloid as a solid marker and In-113m-DPTA (diethylenetriaminepenta-acetic acid) as a liquid marker in the same meal) (Christian et al 1983). There is little information about the appropriate test meal for the optimum detection of differences between health and disease, but it is generally accepted that it should be palatable and representative of an ordinary meal (usually 250-500 ml in volume) (Christian et al 1980; Moore et al 1988). There is a strong temptation to use small volume, bland meals because these are less likely to lead to vomiting during the test and in normal subjects the majority of the meal empties from the stomach in a relatively short time period, but non-nutrient liquids, such as water, which do not stimulate mechanisms which retard gastric emptying, should not be used. If it is only possible for a single isotope to be used a marker for the solid components of a meal is probably preferable since volume and gravity are major determinants of gastric emptying of isotonic, or low nutrient liquids. Adequate gamma-emitting markers are now available for the major components of an ordinary meal, i.e. digestible solid, non-digestible solid, oil and liquid components (Horowitz et al 1985a; Cunningham et al 1991). The abdominal distribution of radioactivity is usually measured by a gamma

camera linked to a computer. By drawing a region-of-interest around the stomach, recognisable by its characteristic shape, changes in counts within the region reflecting the amount of food retained in the stomach can be monitored at regular intervals (Fig. 2.3). Time-activity curves characterising gastric emptying can be constructed and parameters of gastric emptying described (Fig. 2.4).

It is now possible not only to quantify gastric emptying of solid and liquid meals simultaneously (Horowitz et al 1985a), but also to measure gastric emptying concurrently with oesophageal, small intestinal and colonic transit (Read 1989). The disadvantages of scintigraphy are the relative expense, limited availability of equipment and the relatively long time (3-4 hrs) it takes to acquire and process each study. There are also several methodological difficulties which may limit the sensitivity and specificity of radionuclide gastric emptying tests (Horowitz et al 1985a). In particular, movement of radionuclide within the stomach leads to variation in the counts detected because of the different thicknesses of tissue between the stomach and the camera for which corrections must be made (Collins et al 1983). External gamma counting also cannot measure the volume of gastric secretion within or emptied from the stomach. This unknown quantity of gastric secretion dilutes both solid and liquid markers progressively.

Radioisotopic breath testing

The indirect measurement of solid and liquid gastric emptying by detection of radiolabelled carbon dioxide has recently been reported (Ghoos et al 1993; Maes et al 1994). This technique is relatively simple amd yields gastric emptying times which correlate well with those obtained by scintigraphy. For example, C-14 octanoic acid bound to egg is hydrolysed in the duodenum, rapidly absorbed and oxidised in the liver to yield C-14 carbon dioxide. The radiation dose is only about 1% of conventional scintigraphic techniques. Breath testing is therefore likely to be used in the future as a screening test for delayed gastric emptying.

Figure 2.3 Scintiphotograph showing irregular region of interest enclosing stomach, which contains technetium Tc 99m-labelled chicken liver. This method permits selective quantification of gamma emissions for this area. *(Reproduced with permission Horowitz et al 1985a).*

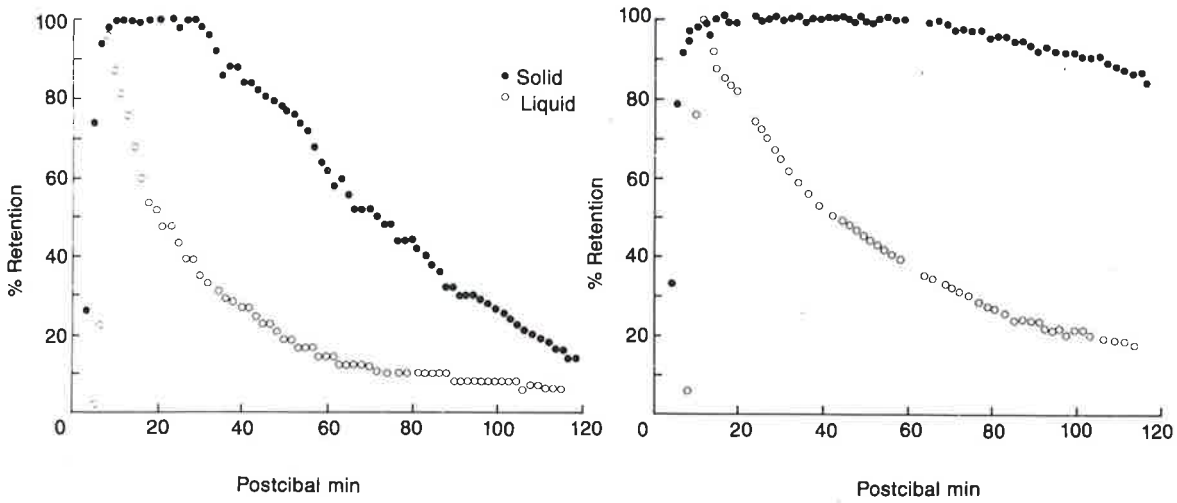


Figure 2.4 Left, Representative histograms for digestible solid (technetium Tc 99m-labelled chicken liver mixed with ground beef) and liquid (indium In 113m-labelled pentetic acid mixed in 150 mL of 10% dextrose) in control subject, showing percentage of retention of isotope against time. Pattern of solid emptying is characterised by lag period, before food leaves the stomach, followed by linear emptying phase. Emptying of liquid meal is more rapid than that of solid meal and has nonlinear pattern, with slope that decreases with time. Right, Solid and liquid emptying curves (identical test meal) in diabetic patient with symptomatic gastroparesis. There is marked delay in both solid and liquid emptying compared with control subject. *(Reproduced with permission Horowitz et al 1985a).*

2.2.2 Manometry

Gastropyloroduodenal manometry, using either minature intraluminal transducers or external transducers linked to multiple lumen manometric catheters to measure pressures, have yielded considerable insights into the physiology of normal gastric emptying and the pathophysiology of disordered gastric emptying (Horowitz & Dent 1991). Its use has so far been as a research tool and its clinical role remains to be defined. The disadvantages of the technique are that it can be uncomfortable for the patient, especially if the catheter is to remain in position for a long time and considerable knowledge is required to perform and interpret studies. Its limitations are that some types of gastric contractions do not produce any change in intragastric pressure and so will not be detected by this method (Fone et al, 1990).

2.2.3 Electrogastrography (EGG)

EGG measures the electrical control activity (ECA) which originates from the pacemaker on the upper greater curve of the stomach and determines the frequency of contractions of the stomach musculature distal to it by means of surface electrodes attached to the skin. While EGG gives an indication of function of the gastric pacemaker (Smout et al 1980; Dubois 1989), the occurrence of contractions, which depends on rapid electrical depolarizations or spikes of the muscle, so-called electrical response activity cannot be monitored (Sun et al 1995). Apart from being technically demanding, EGG has the limitation the occurrence of gastric contractions can only be inferred from the recorded ECA.

In the author's studies (Chapters 4, 5, 6 and 7), gastric emptying following ingestion of a nutrient liquid meal containing the non-absorbable carbohydrate, lactulose was evaluated scintigraphically.

2.3 INVESTIGATION OF SMALL INTESTINAL ABSORPTION

2.3.1 Bile acid absorption

The two primary bile acids, cholic and chenodeoxycholic acid are synthesized in the liver and excreted conjugated to either glycine or taurine in the bile. The glycine and taurine conjugates of cholic and chenodeoxycholic acid are stored and concentrated in the gall bladder between meals. Food intake causes the gall bladder to contract and empty its contents into the duodenum through the common bile duct. When present at a critical concentration, bile salt molecules form micelles which are responsible for the detergent action of bile necessary for the absorption of fat and fat soluble vitamins in the intestine. In the terminal ileum bile salts are actively reabsorbed and returned to the liver via the portal venous system. This cycle, repeated several times a day, has been called the enterohepatic circulation (EHC) of bile salts. About 95% of the conjugated bile salts secreted by the liver are absorbed, chiefly by active transport through the mucosa of the terminal ileum. Bile salts are deconjugated during their passage through the small intestine. This process, which is dependent on enzymatic bacterial action, is completed in the colon with the formation of the secondary bile acids, lithocholic and deoxycholic acid. Deoxycholic and, to a lesser extent, lithocholic acid are reabsorbed in the colon, conjugated and recycled by the primary bile acids, so that no more than 2% of the bile acid pool is normally lost in the faeces with each EHC.

Bile acid absorption can be studied by (a) C-14 cholylglycine breath test, (b) faecal excretion of C-14 taurocholate, (c) radioimmunoassay of glycine conjugates of cholic and chenodeoxycholic acid, (d) Whole body/whole abdominal retention of the Se-75 labelled conjugated bile acid, Seleno-75 Homocholic acid-taurine (Se-75 Hcat).

(a) <u>C-14 cholylglycine breath test</u>

A tracer dose of C-14 cholylglycine is given in a test meal which mixes with the endogenous cholylglycine pool and under normal conditions is almost completely reabsorbed by the terminal ileum and returned to the liver. In terminal ileal disease and

short bowel syndrome, the labelled bile salt is less well absorbed, allowing increased amounts to pass into the colon where bacterial deconjugation and hydrolysis releases C-14 labelled carbon dioxide. The latter is absorbed by the colonic mucosa and excreted in the lungs where increased amounts can be detected in the breath. Without simultaneous measurement of faecal C-14 activity, the C-14 cholylglycine breath test is associated with a high incidence of false positive and negative results for bile acid malabsorption (Heaton 1977). However, even when combined with measurements of faecal C-14 activity, the C-14 cholylglycine breath test does not accurately reflect bile acid absorption because some of the label is passively absorbed since it is in the glycine moiety.

(b) Faecal excretion of C-14 taurocholate

Measurement of faecal C-14 activity following oral adminstration of C-14 taurocholate provides direct evidence of bile acid malabsorption. However, as it may require collection of stools over several days and analysis of an aliquot of each day's collection (Roda et al 1977), it has never been widely employed as a routine clinical test of bile acid absorption.

(c) Radioimmunoassay of glycine conjugates of cholic and chenodeoxycholic acid

Efficient hepatic clearance of bile acids from the portal venous system between meals normally ensures that fasting serum bile acid concentrations are low. After meals, however, serum bile acid concentrations increase slightly in normal subjects and markedly in patients with liver disease (Roovers et al 1968). In subjects with normal liver function, the post-prandial rise in conjugates of the primary bile acid, cholic acid can be used as a quantitative estimate of bile acid absorption, assuming constant hepatic fractional clearance of bile acids (La Russo et al 1974). Fractional hepatic clearance has been shown to be constant over a wide range of bile acid loads in animals (Erlinger et al 1977) and the value of serum bile acids in diagnosing bile acid malabsorption established (Aldini 1982). However, as glycine conjugated bile acid can be absorbed by

passive diffusion in the jejunum and colon (Hislop et al 1967) and following deconjugation in the colon, absorbed by passive non-ionic diffusion, radioimmunoassay of glycine conjugated bile acid does not accurately reflect ileal absorption.

(d) Whole body/whole abdominal retention of SeHcat

Selena-75 Homocholic acid taurine (SeHcat) has been shown to be absorbed from the gut and secreted into the bile at the same rate as the naturally occurring bile acid, cholic acid (Boyd et al 1981; Merrick et al 1982). Since it is a taurine conjugate and has a much lower pKa than glycine conjugates, it cannot be absorbed by passive non-ionic diffusion. Very little bacterial deconjugation of this synthetic bile acid occurs in humans (Ferraris et al 1986). Therefore, SeHcat is closer to fulfilling the criteria for the ideal test substance for ileal function (Fromm & Hofmann 1971; Fromm et al 1973) than the C-14 cholylglycine breath test and measurement of serum levels of glycine conjugates of cholic acid. SeHcat also contains the gamma emitting nuclide Se-75 thus making external counting possible, either in a whole body counter (Yeoh et al 1984) or abdominally by removing the lead collimator from a conventional gamma camera (Thaysen et al 1982). This obviates the need for faecal collection which is an important drawback in measuring faecal C-14 activity following a tracer dose of C-14 taurocholate. Furthermore, since external counting in the whole body monitor is performed 7 days after oral adminstration of the tracer dose, enterohepatic circulation amplifies the effects of quite small changes in absorption efficiency. For example, since each bile acid molecule completes on average about five circuits of enterohepatic circulation per day and has a greater than 95% chance of being absorbed on each circuit, after 7 days, 17.5% of the original activity will still be retained if absorption efficiency is 95%, but only 8.5% is retained if absorption efficiency is 93%(Merrick et al 1985). Although measurements of the 7 day retention of SeHcat by whole body counting and a gamma camera have been shown to correlate with a linear correlation coefficient of 0.96 (Hames et al 1984), the sensitivity of the SeHcat test is reduced if the time interval

between the administration of the dose and counting is less. For example, the sensitivity of the 5 day SeHcat retention by gamma camera measurement is probably inadequate for detecting borderline bile acid malabsorption (Thaysen et al 1982).

An advantage of whole body counting over the whole abdominal counting method is that SeHcat and Co-58 vitamin B12 can be given together to evaluate bile acid and vitamin B12 absorption simultaneously (Yeoh et al 1984; Ludgate & Merrick 1985).

2.3.2 Vitamin B12 absorption

Vitamin B12 is derived from meat and dairy products in the diet. The minimum daily requirement is 2 micrograms, but since the total body stores are 4 milligrams (half of which are in the liver), if intake or absorption were to cease abruptly, it takes between 3-6 years for a normal individual to become deficient in vitamin B12. Vitamin B12 is absorbed by active transport in the terminal ileum only after it has formed a complex with intrinsic factor, a mucoprotein secreted by parietal cells in the gastric mucosa. The active transport mechanism in the terminal ileum is easily saturated and the percentage absorption falls as the total adminstered dose rises, from 75% of an oral dose of 0.5 microgram to about 50% of a 1 microgram dose (Chanarin 1969). Pharmacological doses of vitamin B12 are absorbed across the intestinal mucosa by diffusion, but this mechanism does not play an important role under normal physiological conditions.

Malabsorption of vitamin B12 may result from failure of production of intrinsic factor (as in pernicious anaemia) removal or disease of the terminal ileum, bacterial destruction of the vitamin before it is absorbed (as in blind loop syndrome) or competition for absorption (as by the fish tapeworm, Diphyllobothrium latum).

Vitamin B12 is a complex organo-metallic compound containing cobalt which can be labelled with radioisotopes. In clinical practice absorption tests of vitamin B12 depend on labelling of the vitamin with cobalt (Co)-57 and/or (Co)-58. After an oral tracer dose

of vitamin B12, the following methods can be used to evaluate vitamin B12 absorption: (a) faecal excretion, (b) urinary excretion (Schilling's test), (c) hepatic uptake, (d) assessment of plasma radioactivity and (e) whole body counting.

(a) Faecal excretion method

The amount of vitamin B12 absorbed is calculated by subtracting the radioactivity recovered from the faeces from that in the ingested oral dose. This method is not commonly used because of difficulties in obtaining complete collectons of stools and potential radiation hazards to personnel.

(b) Urinary excretion method (Schilling's test)

A large intramuscular dose of vitamin B12 is given 1-2h after an oral tracer dose of Co-57 vitamin B12 designed to saturate plasma and tissue binding sites, and the absorbed vitamin B12 is excreted in the urine. The amount of administered radioactivity recovered from the urine is dependent on the amount of the oral dose absorbed, since the free vitamin is filtered by the glomerulus and there is no tubular absorption or secretion. A low recovery may be due to malabsorption, renal failure, incomplete urinary collection, administration of a large parenteral dose of vitamin B12 within 3 days of the test or ingestion of a meal high in vitamin B12 content shortly before or after the tracer dose. An accurate timed collection of urine is less critical in the dual isotope technique which by employing simultaneous adminstration of Co-58 vitamin B12 and Co-57 vitamin B12-intrinsic factor, allows separate counting of the isotopes and enables a ratio of their activities to be derived as well as total activity of each isotope, both of which are important for diagnosis (Allen 1982). It also enables malabsorption due to lack of intrinsic factor in pernicious anaema to be identified since this results in reduced recovery of Co-58, but normal recovery of Co-57 and a high Co-57/Co-58 ratio, whilst in other causes of malabsorption the ratio of Co-57/Co-58 is normal even though the percentage recovery of both isotopes in the urine is low.

(c) Hepatic uptake method

An estimate of the amount of labelled vitamin B12 absorbed and deposited in the liver is made by surface counting (Chanarin 1969). However, inaccuracies arise because the subject has to be in exactly the same position for subsequent counts and the estimate is unreliable in the presence of liver disease.

(d) Assessment of plasma radioactivity

8-12 hrs after an oral dose, radioactivity is measured in a blood sample. The disadvantage of this technique is that it is semi-quantatative (Chanarin 1969).

(e) Whole body counting method

Radioactivity retained in the body is measured 7 days after an oral tracer dose of Co-58 Vitamin B12. This is potentially the most accurate method, but requires specialised equipment. Its accuracy and reproducibility has been demonstrated (Finlayson et al 1969).

2.3.3 Lactose absorption

Lactose, a disaccharide present in milk and dairy products is normally hydrolysed into its constituent monosaccharides glucose and galactose by the enzyme lactase which is present in the brush border of the intestinal mucosa where the highest concentrations are found in the jejunum. Glucose and galactose are then actively transported into the mucosal cell to be absorbed. The rate of hydrolysis of lactose is relatively slow and limits its absorption, in contrast to sucrose where absorption is limited by the rate of glucose transport across the cell.

A deficiency of the enzyme lactase can arise either primarily, after weaning, (most commonly in populations of African and Asian origin), or secondarily to intestinal disease (commonly acute infections). This results in failure of lactose absorption. Unabsorbed lactose acts as an osmotic load in the colon and may result in diarrhoea,

abdominal colic and distension. A history of dietary intolerance is, however, seldom obtained since subjects avoid milk and milk products (Horowitz et al, 1987). Bacterial fermentation of the unabsorbed lactose results in excess hydrogen production which can be detected in the breath (Newcomer et al, 1975).

The definitive diagnosis of lactase deficiency requires a biopsy specimen from the small intestine and enzyme assay. Since there is a gradient of activity along the small bowel in normal and lactase deficient subjects, the site of biopsy needs to be standardized (Newcomer & McGill 1966). Owing to these difficulties, indirect methods of detecting lactase deficiency are preferred. These methods depend on changes in the blood concentration of digestive products of lactose (glucose and galactose), or the breath concentration of either hydrogen or C-14 labelled carbon dioxide (derived from tissue oxidation of absorbed C-14 labelled lactose). The following indirect methods of determining lactose absorption are available: (a) C-14 lactose breath test, (b) the lactose hydrogen breath test.

(a) C-14 lactose breath test

C-14 labelled lactose is given by mouth together with 50g lactose. The C-14 lactose is hydrolysed to C-14 glucose which is then oxidised to C-14 labelled carbon dioxide by tissue enzymes and excreted in the breath. Breath samples are collected in ethanolic hyamine and the radioactivity of trapped C-14 labelled carbon dioxide determined by liquid scintillation spectroscopy. The C-14 lactose breath test thus measures hydrolysis of lactose and absorption of glucose. It suffers from the disadvantage that unabsorbed lactose reaching the colon is degraded to C-14 labelled carbon dioxide by bacteria and this bacterial derived C-14 labelled carbon dioxide is also excreted in the breath. It is not as sensitive as the lactose hydrogen breath test and also suffers from the drawback of requiring the adminstration of a radionuclide with a long physical half life, even though dose calculations indicate that the radiation hazard is negligible. Furthermore, metabolic diseases such as diabetes may be associated with a decreased rate of conversion of

absorbed C-14 glucose to C-14 labelled carbon dioxide (Newcomer et al, 1975).

(b) Lactose hydrogen breath test

This method of detecting lactase deficiency depends on bacterial digestion of unabsorbed lactose in the colon releasing hydrogen which is detected in the breath. In one prospective study comparing various indirect methods of detecting lactase deficiency, the lactose hydrogen breath test correctly identified all 25 patients who were lactase deficient and there were no false positive results (Newcomer et al 1975). In population studies, however, it may miss a small proportion of subjects (>5%) who have no hydrogen in their breath after ingesting non-absorbable carbohydrate (Shearman & Finlayson 1989).

Close attention to detail relating to the collection and analysis of the breath samples is necessary in order to ensure the quality of the results. Adverse factors affecting quality of the breath samples include extraintestinal factors such as cigarette smoking, hyperventilation and hydrogen production by oropharyngeal bacteria (Thompson et al 1985). The transient rise in exhaled breath hydrogen soon after ingestion of the carbohydrate test meal attributed to oropharyngeal bacteria can be largely eliminated by a bacterial mouthwash and avoidance of carbohydrate consumption after test meal ingestion (Thompson et al 1986). An early rise in breath hydrogen may also occur from the passage into the caecum, soon after meal ingestion, of carbohydrate retained in the ileum from previous meals (Read et al 1985). By avoiding non- absorbable carbohydrate on the evening preceding the test, a low basal hydrogen can be ensured (Perman et al 1984). Most antibiotics, by reducing bacterial flora in the colon, and laxatives/enemas decrease hydrogen production and are preferably avoided for at least 48h before the test meal. Variations in the breath sample quality resulting from the collection of end expiratory breath samples affect the sensitivity of the test, but can be corrected by normalization of hydrogen values using simultaneous measurement of oxygen, carbon dioxide or nitrogen (Newcomer 1984). Although Newcomer et al

(1978) adopted an upper normal limit for breath hydrogen of 20 ppm at 2 hours, this criterion reduces the sensitivity of the test. With 30 minute sampling of breath any sustained rise in breath hydrogen above baseline of > 10 ppm is considered an abnormal result, indicative of lactose malabsorption (Horowitz et al, 1987).

2.3.4 Fat absorption

Dietary fat, which constitutes approximately 40% of the calorie intake, is made up predominantly of triglycerides, but also contains phospholipid, cholesterol and other sterols. Triglycerides form over 98% of dietary lipids and consist of glycerol which is esterified to three long chain fatty acids with 16-18 carbon atoms. A small but variable proportion of so called medium chain triglycerides have fatty acids with only 6-10 carbon atoms and are absorbed differently. Since fat absorption studies only satisfactorily quantify long chain triglycerides, the absorption of medium chain triglycerides, phospholipid, cholesterol and other sterols will not be considered further. Insoluble long chain triglycerides are converted by a complex sequence of steps into a form that can be taken up into mucosal cells. This involves (i) emulsification in the gastric antrum and duodenum to produce stable lipid particles with a large surface area, (ii) hydrolysis of triglycerides within the duodenum primarily by pancreatic lipase to monoglycerides and fatty acids, (iii) solubilization with conjugated bile acid polymolecular aggregates to form mixed micelles which increase the surface area of lipid particles thereby facilitating absorption. (iv) Uptake by the mucosal cells so that the fatty acids themselves become the substrate for the re-constitution of triglyceride and (v) incorporation into chylomicrons, which are particles of triglyceride enclosed by phospholipid, protein and free cholesterol to (vi) transport away from the mucosa in the lymphatic channels of the lamina propria. A physiological abnormality at any of these steps may result in impairment of absorption of dietary triglyceride, over 95% of which is normally absorbed.

The following tests of fat absorption are available (a) I-131 labelled trioleate in the blood or faeces, (b) Chemical estimation of fat in the faeces.

(a) I-131 labelled trioleate in the blood or faeces

Estimation of blood radioactivity (Reeves et al 1965) after a tracer dose of I-131 labelled trioleate avoids the need for faecal collection as a means of determining fat absorption. Unfortunately, blood radioactivity correlates poorly with fat absorption (Shearman & Finlayson 1989). Estimation of faecal radioactivity (Dalla Palma 1968) after oral ingestion of I-131 labelled trioleate is unreliable compared to fat estimation by the chemical method (Shearman & Finlayson 1989).

(b) Chemical estimation of fat in the faeces

This enables fat absorption to be quantified indirectly by measuring fat excretion in the stool (van de Kamer et al 1949). It depends on an accurate timed (72 h) collection of faeces and measurement of the fatty acid liberated from triglyceride derived from the diet and intestinal contents (desquamated mucosa, secretions and bacteria). Fatty acids of chain lengths of less than 10 carbon atoms are not measured satisfactorily. Therefore, for patients receiving medium chain triglycerides (MCT), unabsorbed MCT in the stool are not measured. Other limitations of this method include the need to ingest a diet containing 70-100 g fat/day, which may not be practical. Low readings may reflect infrequent bowel actions in some patients and incomplete stool collections in others.

In the author's studies (Chapters 4, 5, 6 and 7), absorption of: (i) bile acid and vitamin B12 was assessed by whole body retention of SeHcat and Co-58 vitamin B12, (ii) lactose by the hydrogen breath test and (iii) fat by chemical estimation of faecal fat.

2.4 INVESTIGATION OF SMALL INTESTINAL, COLONIC/TOTAL GUT TRANSIT.

The passage of food through the stomach, small intestine and colon is normally regulated to optimise digestion and absorption. For example, acceleration of gastric emptying results in poor mixing of food with pancreatico-biliary secretions and may impair digestion. Acceleration of small bowel transit by reducing the contact time between food and the intestinal absorptive epithelium may result in malabsorption (Johansson 1975; Holgate & Read 1983), whilst delayed small bowel transit may also impair absorption by causing bacterial overgrowth. In the colon, rapid transit of intestinal luminal contents may limit the capacity to salvage water and electrolytes.

2.4.1 Small intestinal transit

Small intestinal transit can be studied by the following techniques: (a) small bowel barium meal, (b) breath hydrogen analysis/plasma sulphapyridine measurement, (c) radionuclide gastrointestinal transit and (d) combined breath hydrogen analysis and radionuclide transit.

(a) Small bowel barium meal

Measuring the transit of barium through the small intestine is not physiological (Embring & Mattson, 1966) and probably not representative of the passage of food. Mixing the food with barium gives a more accurate index of the rate of entry of food residues into the colon (Mattson et al 1960). However, this involves fluoroscopy and/or multiple abdominal films resulting in unacceptably high levels of radiation exposure, particularly in sequential studies. The relatively large amounts of barium required may also interfere with the normal rate of passage of food (Read et al 1986). The other drawback of radiological techniques is that it gives only a semi-quantitative estimate of intestinal transit.

(b) Breath hydrogen analysis/plasma sulphapyridine measurement

Determining the breath hydrogen response to the non-absorbable carbohydrate, lactulose has been shown to provide an accurate measure of the mouth to caecum transit time (Bond & Levitt 1975; Read et al 1980). On its own, the reproducibilty is relatively poor, but this can be improved by adding lactulose to a liquid nutrient meal (LaBrooy et al 1983). However, the breath hydrogen test only adequately assesses the arrival of the head of the meal in the caecum and cannot quantify the transit time of the entire meal (Malagelada et al 1984) and, unless the lactulose is given intraduodenally cannot determine the individual effects of gastric emptying and small intestinal transit (Caride et al 1984).

Orocaecal transit can also be quantified by measurement of plasma sulphapyridine using spectrophotometry after the oral administration of salicylazosulphapyridine. After ingestion the majority of salicylazosulphapyridine reaches the colon intact, where its azo bond is split by bacterial enzymes yielding sulphapyridine and 5-aminosalicylic acid (Kellow et al, 1986).

(c) Radionuclide gastrointestinal transit

Scintigraphic techniques for determining small intestinal transit, in contrast to radiological methods, entail minimal radiation exposure. Tracer doses of radionuclide are used to label solid and/or liquid meals (Malagelada et al 1984; Read et al 1986) and this enables gastrointestinal transit to be quantified accurately and more physiologically than with radiological techniques (Caride et al 1984). Gastric emptying, small intestinal transit and colonic filling can now be evaluated simultaneously following ingestion of a radioisotopically labelled test meal by quantifying its progress through the gastrointestinal tract by means of a gamma camera linked to a computer (Malagelada et al 1984; Read et al 1986). Regions-of-interest can be drawn round the stomach and the colon and time activity curves of gastric emptying, colonic filling and, by inference, small intestinal residence derived (Caride et al 1984; Read et al 1986). Parameters of

intestinal transit, independent of gastric emptying can be calculated including mean intestinal transit and small intestinal residence (Read et al 1986).

(d) Combined breath hydrogen and radionuclide small intestinal transit

The rationale of combining breath hydrogen and scintigraphy in the assessment of orocaecal transit is based on two observations. Firstly, a small proportion of subjects (<5%) have no hydrogen in their breath after ingesting non-absorbable carbohydrate (Shearman & Finlayson 1989), and secondly the assessment of first arrival of the meal in the caecum scintigraphically can be problematic since the location of the caecum is uncertain in up to 36% of subjects (Caride et al 1984).

2.4.2 Colonic/total gut transit

Colonic/Total gut transit can be assessed by either (a) radio-opaque marker techniques and/or (b) radioisotopic methods.

(a) Radio-opaque marker techniques

These depend on the ingestion of inert, non-absorbable radio-opaque markers which have a specific gravity similiar to gut contents and subsequent evaluation of the distribution of the markers in the colon by plain abdominal radiology (Mantelli et al 1978) or quantification of their excretion in the faeces (Hinton et al 1969). Faecal quantification is simple and can be performed by an untrained technician but suffers from a number of disadvantages, including the inconvenience and potential inaccuracies of stool collections lasting up to 5 days. Although whole gut transit can be evaluated by analysis of a single stool, the method requires ingestion of several different radio-opaque markers over 3 consecutive days (Cummins & Wiggins 1976) and its accuracy is restricted to a range of one to four days. Both the one radio-opaque marker/multiple stool measurements and the different radio-opaque markers/single stool measurements assesses mouth to anus transit and give no indication of segmental transit times within the large intestine, which is necessary to characterise localised disorders of colonic

motility (Mantelli et al 1978; Watier et al, 1983). However, by including plain abdominal radiology following ingestion of the radio-opaque markers, segmental colonic transit can be calculated either using daily abdominal films (Arhan et al 1981), or a single abdominal film taken on the fourth day after ingestion of three different markers (Metcalf et al 1987). Even though the radiation dose of a single film technique has been reduced to about 25% of that of a conventional abdominal x-ray, the accuracy of the technique is limited. For example, rapid colonic transit could cause all the markers to be lost in the faeces before the time of abdominal radiography and, conversely, in subjects with slow transit, all markers could still be present on the single abdominal film at four days.

(b) Radioisotopic methods

The progress of radioisotopes through the colon can be measured using a gamma camera linked to a computerised recording and processing system. In contrast to X-ray methods, continuous observation of the radionuclide in the large bowel for long periods is possible, without unacceptable radiation exposure. Not only can various intestinal regions be studied simultaneously but also the transit of both solids and liquids evaluated by using different radionuclide labels (Proano et al 1991). In addition, by appropriate choice of a suitable liquid radioisotopic marker, such as diethylenetriaminepenta-acetic acid (DPTA), satisfactory images can be obtained with a volume of marker that is small enough not to influence colonic transit when instilled into the caecum (Krevsky et al 1986). Scintigraphy is thus a safer, more physiological and accurate method of evaluating colonic transit compared with radio-opaque marker techniques. However, it is expensive, requiring access to a nuclear medicine department and trained technicians. In addition, there are methodological problems associated with the delivery of the radionuclide markers to the large bowel which limit its applicabilty. The isotope is usually injected into the colon via a tube that has either been swallowed (Krevsky et al 1986) or inserted by means of a colonoscope (Lambert et al 1988), although it is now possible to deliver the radionuclide to the colon by ingesting a coated

capsule incorporating the isotope marker which then disperses at the pH of the ileum (Proano et al 1990). The latter approach, by making it possible to image the unprepared colon without the use of intubation or bowel preparation of any kind is more physiological. Whole gut transit can be evaluated either by following the progress of a swallowed I-131 capsule by a scintillation counter (Kirwan & Smith 1974) or by gamma camera scintigraphy using resin particles labelled with Tc-99m and In-111, to quantify gastric emptying and small bowel transit, and colonic transit respectively (Stivland et al 1991). Gamma camera scintigraphy is more accurate, particularly in subjects with diarrhoea, since scintillation counters cannot scan as wide an area as gamma cameras. Not surprisingly, whole gut transit determined by a scintillation counter following ingestion of the I-131 capsule correlates poorly with total gut transit asssessed by recovery of ingested radio-opaque markers in the faeces in patients with diarrhoea (Kirwan & Smith 1974).

In the experiments performed by the author relating to the effects of abdominal and pelvic irradiation on gastrointestinal function (Chapters 4 ,5, 6 and 7), gastric emptying and small intestinal transit were evaluated by combined breath hydrogen analysis and scintigraphy of a radio-isotopically labelled liquid nutrient meal containing the non-absorbable carbohydrate, lactulose and radio-opaque markers. The latter were used to determine whole gut transit by radiological quantification in a three day collection of faeces (Read et al 1980).

2.5 INVESTIGATION OF SMALL INTESTINAL PERMEABILITY

The permeabilty of the intestine is defined as that property of the intestinal wall which modifies the permeation of solute across or into the intestine. Low molecular weight solutes such as mannitol and monosaccharides including rhamnose diffuse across the cell membrane through polar regions or "aqueous pores" incorporated into the membrane structure (Solomon et al 1984). Larger hydrophilic molecules such as ethylenediamine-tetra-acetic acid (EDTA) and lactulose do not permeate across cell

membranes and presumably diffuse across the mucosa by an intercellular route (Axon & Creamer 1975).

Methods of assessing intestinal permeabilty determine either the larger pathway such as the Cr-EDTA absorption test or both pathways such as the double sugar (lactulose/rhamnose) absorption test. In addition, both Cr-51 EDTA and lactulose/rhamnose absorption tests can be combined.

(a) Cr-51 EDTA absorption test

This test is based on the urinary recovery of an orally adminstered dose of Cr-51 EDTA and therefore only tests the intercellular pathway. The reproducibility of the test has been shown to depend on the duration of urine collection, being best for a full 24 hour colllection (Bjarnson et al 1983). The disadvantages of this method of determining intestinal permeability are that its accuracy is dependent on a number of factors such as a timed complete collection of urine, normal renal function and normal gastrointestinal transit (Brunetto et al 1990). Ingestion of alcohol, aspirin and other non-steroidal anti-inflammatory drugs influences the results (Aarbakken 1989).

(b) Double sugar(lactulose/rhamnose) absorption test

The differential sugar absorption test assesses both pathways for non-mediated absorption of water soluble molecules (Pounder et al 1983). In the presence of mucosal disease, the urinary recovery of the disaccharide, lactulose is increased whilst that of the monosaccharide, rhamnose is decreased. Since the urinary recovery of an oral dose is expressed as a ratio of the two sugars, the effect of variations in factors such as renal function and gastrointestinal transit is minimised. A deficiency of this test is that if absorption of both sugars is increased, or decreased to the same extent, the ratio remains the same.

(c) Combined Cr-51 EDTA and lactulose/rhamnose absorption test

Although the value of combining the two techniques of assessing intestinal permeability has not been investigated, it may help interpret equivocal results with either technique alone. For example, mucosal disease associated with rapid intestinal transit may result in normal or reduced Cr-51 EDTA absorption test but may be detected by a rise in the ratio in the two sugars, lactulose/rhamnose in the double sugar absorption test.

In the author's studies (Chapters 4, 5, 6 and 7), intestinal permeability was determined by both Cr-51 EDTA and lactulose/rhamnose absorption tests.

2.6 INVESTIGATION OF ANORECTAL FUNCTION

The anorectum is involved in two major functions: control of defaecation and the preservation of continence. These functions depend on the coordinated activity of the rectum and anal sphincters, and are influenced by rectal sensation, colonic motility and the consistency of the stool.

Defaecation is a stereotyped sequence of actions usually initiated by a conscious mechanism and involving a number of pelvic reflexes that are controlled and coordinated by a centre in the brain stem (Read & Sun 1989). Faeces are propelled into the rectum by propagated colonic contractions. If the stool is large enough, the resulting rectal distension induces a desire to defaecate. This sensation is usually associated with a rectal contraction and a relaxation of the internal anal sphincter (IAS) which serves to push the stool down into the proximal anal canal, increasing the defaecatory urge. If conditions are appropriate, the subject sits or squats, contracts the diaphragm, the abdominal muscles and the levator ani, whilst relaxing the external anal sphincter (EAS) and possibly the puborectalis. The latter actions open up the anorectal angle and faeces is extruded. Once defaecation has started, it can continue with no conscious effort presumably as a result of propagated colonic contractions.

Continence to faeces is usually mantained by the resistance of the anal sphincters. Under resting conditions and during slow rectal distension, this is effected largely by tonic contraction of the IAS with some tonic contribution of the EAS (Haynes & Read 1982; Sun et al 1990b). However, the IAS may be unable to maintain continence during rapid rectal distension, rectal contraction and increases in intra-abdominal pressure, because rapid rectal distension and contraction induce reflex relaxation of the IAS (Duthie, 1975), and increases in intraabdominal pressure may be sufficient to overwhelm resting IAS pressure. Under these conditions, continence is preserved by contraction of the EAS. Contraction of the puborectalis occurs simultaneously with that of the EAS and assists in maintaining continence by making the anorectal angle more acute. Rectal and anal sensation, via intrinsic and extrinsic reflexes, are important in modulating motor activity and mediating motor reflexes that underly both faecal continence and defaecation.

Anorectal motor function can be assessed by: (a) defaecography, (b) anorectal manometry and (c) neurophysiological tests.

2.6.1 Defaecography

This is a radiological technique which records on videotape the changes which takes place in the anorectum and the movements of the pelvic floor at rest, and during defaecation. Although structural abnormalities in the anorectum such as, rectocoele, rectal intussusception and rectal mucosal prolapse, have been identified at defaecography, their relationship to disorders of defaecation is uncertain since these abnormalities are also found in normal people without symptoms (Stevenson 1988). Although no preparation of the patient is needed for the examination, defaecography suffers from a number of disadvantages including the time required for the investigation and the necessity for sophisicated radiological equipment. In addition, since it involves exposure to ionising radiation, the technique is not suitable for sequential studies.

2.6.2 Anorectal manometry

The identification of abnormalities of internal and external anal sphincter function by manometric techniques is only possible if pressures are recorded at multiple closely spaced sites within the anal canal (Fig. 2.5). This is because the two muscles often exhibit reciprocal activity; hence the EAS contraction that occurs, for example, during rectal distension, can mask IAS relaxation in the distal anal channels, but not in the proximal channels. Interpretation of the manometric profiles is greatly facilitated by simulataneous recording of the EAS and IAS, allowing changes in pressure caused by activity of these muscles to be identified (Read & Sun 1989).

2.6.3 Neurophysiological tests

Damage to the innervation of the EAS can be localised to the pudendal nerve by demonstrating prolongation of pudendal nerve terminal motor latency. Prolongation of pudendal nerve terminal motor latency does not provide any indication of the strength and hence the functional capacity of the external sphincter, particularly in response to rectal distension and increases in intra-abdominal pressure. Moreover, pudendal neuropathy is a normal accompaniment of ageing, particularly in females, and its demonstration does not exclude a greater role of other factors, such as loss of rectal sensation or impaired internal sphincter function (Lauberg & Swash 1989).

More centrally located neurogenic lesions of the EAS can be diagnosed by measuring the external sphincter responses to cerebral and spinal stimulation or by recording cerebral potentials evoked by perineal or rectal stimulation. Such lesions are however, rare and may be suspected on the basis of the combined manometric, electrophysiological and sensory testing in any case (Read & Sun 1989).

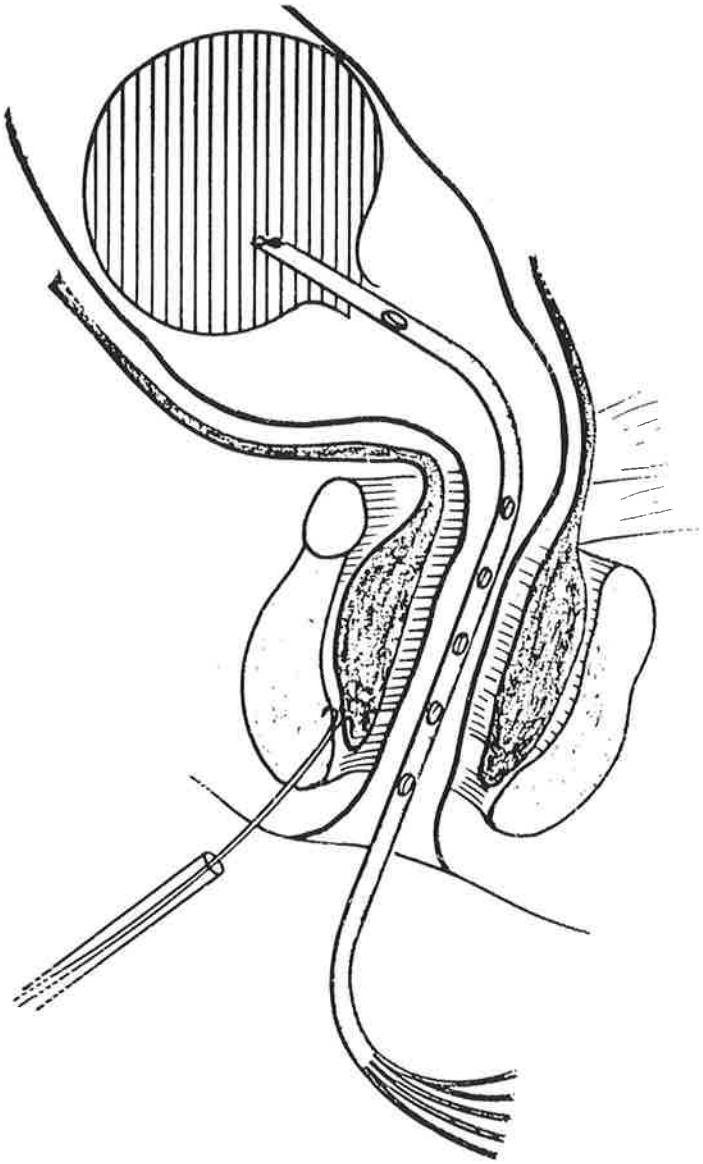


Figure 2.5 A diagram of the probes used to measure anorectal pressures and the electrical activity of the IAS and EAS. Attached to the rectal end of the anorectal manometer is an inflatable balloon which enables rectal sensation and changes in anorectal pressures to varying degrees of rectal distension to be measured. An index of rectal compliance ($\Delta V/\Delta P$) can then be derived.
(Reproduced with permission Read & Sun 1989).

In the study relating to the effects of pelvic irradiation on anorectal function performed by the author, symptoms (questionnaire) and anorectal function (multiport manometry with sensory testing and concurrent electromyography) and endorectal ultrasound of the IAS, were evaluated (Chapter 8).

The following studies of the effects of radiation on gastrointestinal function were performed:

I. A prospective study of the acute and subacute effects of mediastinal irradiation on oesophageal function (Chapter 3).

II. A retrospective study of the chronic effects of pelvic irradiation for carcinoma of the cervix on gastrointestinal function (Chapter 4).

III. A prospective study of the acute, subacute and chronic effects of pelvic and abdominal irradiation on gastrointestinal function (Chapter 5).

IV. A retrospective study of the chronic effects of abdominal irradiation for seminoma of the testis on gastrointestinal function (Chapter 6).

V. A double blind placebo controlled study of the effects of loperamide-N-oxide on gastrointestinal function in chronic radiation enteritis (Chapter 7).

VI. A retrospective study of the effects of pelvic irradiation on anorectal function (Chapter 8).

In the chapters which follow, the details of the methodology used for each study will be described briefly following presentation of the subject selection criteria and the experimental protocol. Finally the results and their significance are discussed. Since identical methodology was used to assess various aspects of gastrointestinal function in studies II, III, IV and V, details of the techniques used will only be presented in the description of study II (Chapter 4).

CHAPTER 3

The effects of mediastinal irradiation on oesophageal function (Gut 1995; in press)

3.1 INTRODUCTION

Dysphagia and substernal burning are almost inevitable during the course of therapeutic mediastinal irradiation for intrathoracic malignant diseases and may be severe enough to interrupt treatment (Roswit et al 1972). The resulting prolongation in the course of treatment may compromise the chance of cure (Roswit et al 1972; Perez et al 1980). The pathogenesis of these sequelae however, is poorly understood; in particular, it is uncertain whether symptoms arise as a result of oesophageal mucosal damage or disordered oesophageal motility. Mucosal damage has been documented in two prospective studies (Nicolopoulos et al 1985; Soffer et al 1994), but its severity does not correlate with symptoms. Delayed oesophageal transit reported in patients undergoing mediastinal irradiation also correlates poorly with oesophageal symptoms (LaManna et al 1985). However, there have been no manometric studies to correlate possible changes in oesophageal transit with motilty. The aim of this study, therefore was to investigate prospectively the relationships among oesophageal symptoms, mucosal damage and motility changes in patients undergoing therapeutic mediastinal irradiation for non-oesophageal malignancy.

3.2 METHODS

8 patients (5 female, 3 male) - median age 68 yrs (53-85 yrs), median body weight 75.9 kg (62-120.9 kg) and median body mass index (BMI) 26.2 (21.7-42.8) undergoing mediastinal irradiation for potentially curable carcinoma of the lung (4 patients), Hodgkin's lymphoma (1 patient) and breast carcinoma (3 patients) were studied. Characteristics of the patients and radiation dosimetry are summarised in Table 3.1.

Table 3.1: Characteristics of the Patients

Patient Number	Age (y)	Body Weight (kg)	Body Mass Index	Diagnosis	Radiation Dose Gy/No of fractions/d	Radiation Field Size (cm x cm)	Symptom Score During (Before) Radiation
1	82	70.0	22.8	Carcinoma (L) Lung	30 Gy/15F/20d 20 Gy/10F/13d 10 Gy/5F/6d	15.5 x 16.0 12.5 x 10.0 10.0 x 9.0	4(1)
2	85	63.5	22.2	Carcinoma (R) Lung	30 Gy/15F/28d 30 Gy/15F/28d	15.0 x 16.5 12.0 x 11.0	3(0)
3	58	120.9	42.8	Carcinoma (L) Breast	50 Gy/25F/34d	22.0 x 3.4	2(0)
4	69	92.2	31.7	Hodgkin's Lymphoma	35 Gy/20F/29d 9.1 Gy/6F/7d 7.5 Gy/5F/10d	25.0 x 29.0 14.0 x 15.5 12.0 x 9.0	4(0)
5	67	71.8	29.1	Carcinoma (R) Breast	50 Gy/25F/32d	22.0 x 32.0	0(0)
6	53	80.0	23.4	Carcinoma (L) Lung	30 Gy/15F/23d 10 Gy/15F/7d 20 Gy/10F/13d	15.5 x 16.0 10.5 x 11.0 10.5 x 8.0	3(0)
7	65	85.5	33.4	Carcinoma (L) Breast	50 Gy/25F/34d	12.5 x 28.0	5(3)
8	75	62.0	21.7	Carcinoma (R) Lung	44 Gy/22F/31d 16 Gy/8F/11d	14.5 x 13.0 10.0 x 11.0	3(0)

Patients with a history of oesophageal surgery or disordered oesophageal motility and those patients with oesophageal involvement by the malignant process as demonstrated by endoscopy and/or barium swallow were excluded. No patients received concurrent chemotherapy. The study was approved by the Research Ethics Committee of the Royal Adelaide Hospital and informed consent was obtained from each patient.

Each patient was assessed by symptom questionniare, barium swallow, endoscopy and combined radionuclide scintigraphy and oesophageal manometry before irradiation, during the last week of irradiation (4-6 weeks after commencement of treament) and 6-8 weeks following the completion of irradiation. The various assessments were performed within 1 week of each other.

Symptom questionnaire

The following symptoms were assessed at the start of each series of measurements: dysphagia, odynophagia, heartburn and regurgitation. Heartburn and regurgitation was also included in the questionnaire as pre-existing reflux oesophagitis was not an exclusion criteria and could contribute to the morbidity of mediastinal irradiation. Dysphagia, odynophagia and regurgitation were scored as: 0 = symptom absent; 1 = mild, requiring minor modification of diet; 2 = moderate, requiring modification to liquid diet only; 3 = severe, preventing intake of either solids or liquids(LaManna et al 1985; Nicolopoulos et al 1985). Heartburn was also graded on a similiar basis: 0 = symptom absent; 1 = mild, not requiring medication; 2 = moderate, requiring medication; 3 = severe, not responsive to medication. The total score for all symptoms (maximum 12) was calculated. The body weight was also recorded at the start of each series of tests. Height was recorded only on entry into the study.

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed using fibreoptic or video endoscopes. Assessment was by a single observer (Dr R Holloway) using previously defined visual

criteria: 0 = no changes, 1 = mild erythema, 2 = obvious inflammatory changes including marked erythema and submucosal swelling, 3 = friabilty, 4 = ulceration (Nicolopoulos et al 1985). Biopsies for histological assessment were performed only if visual abnormalities were present. The single observer was not informed of the phase of the study of each patient at the time of endoscopy.

Combined oesophageal manometry and scintigraphy

Oesophageal manometry was performed using a multi-lumen manometric assembly. A sleeve sensor (Dent 1976) recorded lower oesophageal sphincter (LOS) pressure. A side hole 1 cm beyond the distal end of the sleeve recorded intragastric pressure. Additional side holes at the proximal margin of the sleeve and at 4, 8 and 12 cm proximally recorded pressure in the oesophageal body. A side hole in the hypopharynx monitored swallowing. The position of each side hole as well as the mid-point of the sleeve was marked by a radioactive cobalt marker. The sleeve, gastric and oesophageal lumens were perfused with degassed distilled water at 0.5 ml/min by a pneumohydraulic capillary infusion pump (Arndorfer et al 1977). The pharyngeal side hole was perfused at 0.13 ml/min. Each lumen was connected to an external pressure transducer (Transpac, Abbott Laboratories/Hospital Products Division, North Chicago, Illinois 60064), whose output was recorded on a multichannel chart recorder at a paper speed of 5 mm/sec.

The assembly was passed via an anaesthetised nostril and positioned so that the sleeve straddled the LOS. The patients were then positioned supine and allowed to adapt over a period of 15 min. Each patient then undertook a series of 10 dry and 10 water swallows (5 ml bolus) with an interval of at least 20 sec between successive swallows. After the unlabelled swallows, the patients then sat up with their backs to a gamma camera. The manometric assembly was repositioned so that the side hole of the proximal margin of the sleeve was sited 2 cm above the proximal margin of the LOS. The position of the cricoid cartilage was marked by a labelled cobalt marker and a 5 min

recording of the catheter and cobalt marker made to establish the positions of the markers for subsequent analysis. Each patient then swallowed, in triplicate, 10 g boluses of cooked hamburger meat labelled with 6 MBq Tc-99m. The patient was asked to chew the bolus, swallow it with one swallow and then to perform dry swallows at 30 sec intervals until the bolus was seen to enter the stomach or a total of 5 minutes had elapsed. Images of the entire oesophagus from the pharynx to the gastric fundus were acquired starting in 1 sec frames for the first 150 sec and 3 sec frames for the remaining time.

After assessment of solid transit, the patients then lay down supine. Transit of liquids was assessed using 5 ml water boluses labelled with 9 MBq Tc-99m. Labelled swallows were taken in triplicate. Each bolus was swallowed in a single swallow and subsequent dry swallows taken at 30 sec intervals until the bolus had cleared the oesophagus or 2 min had elapsed. Scintigraphic images were acquired in 0.5 sec frames starting 10 sec before the labelled bolus was swallowed.

Data analysis

Oesophageal manometry

The manometric tracings of the unlabelled liquid and labelled solid and liquid swallows were analysed for oesophageal contraction amplitude, peristaltic success and the level of peristaltic failure for the index swallow (Figs 3.1a, 3.1b). Peristaltic failure was deemed to occur when a contraction wave less than 10mm Hg was seen at one or more oesophageal recording sites, or synchronous contractions at two or more recording sites (Schoeman & Holloway 1994). For the unlabelled liquid swallows, the mean of the 10 swallows in each patient was first calculated. The mean values of the individual patients pre, during and after irradiation were derived by pooling the available swallows, because technical probelms, such as fragmentation of the bolus in the mouth rendered the swallow sequence unanalysable in some instances.

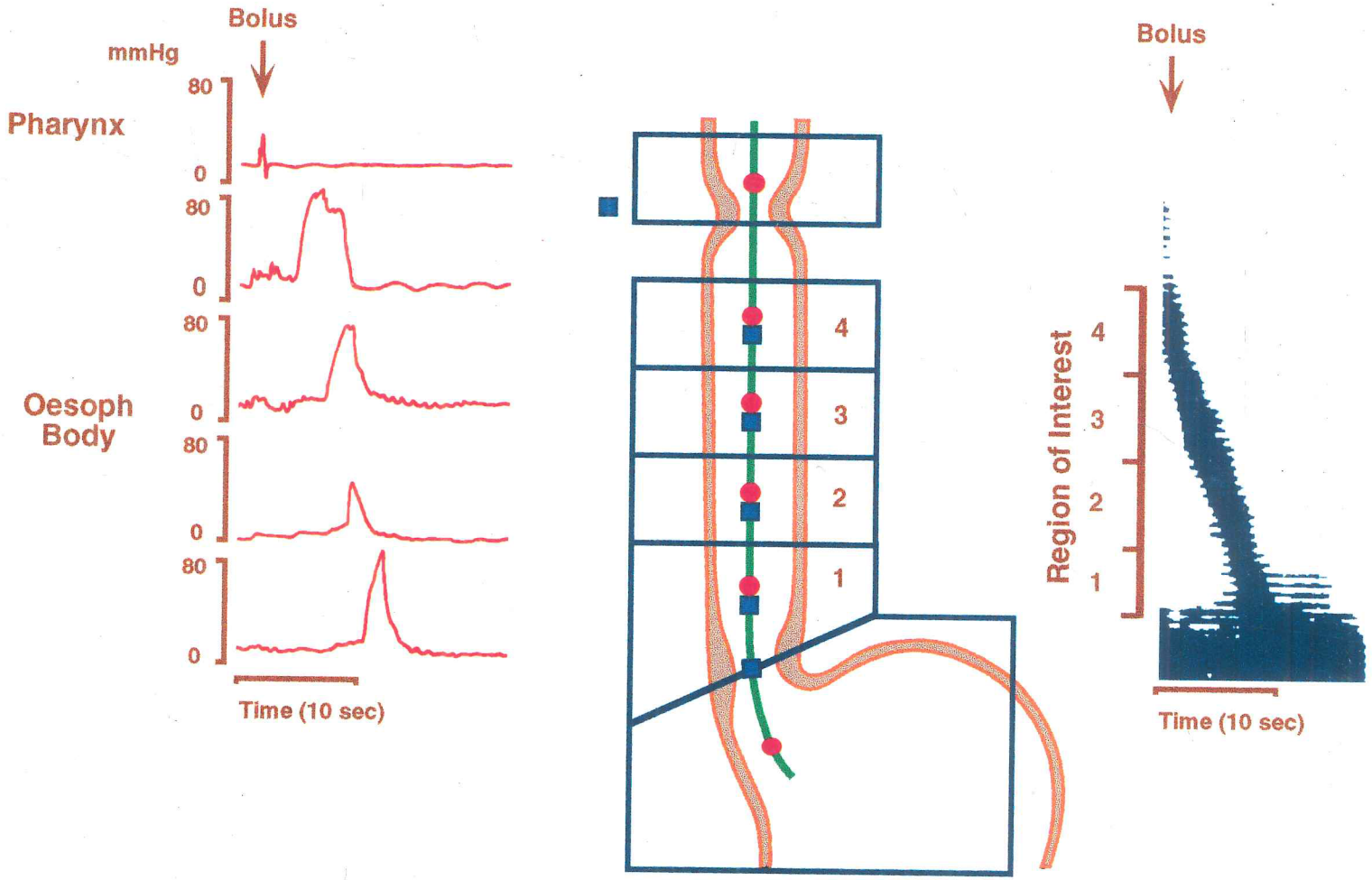


Figure 3.1a Concurrent oesophageal manometry and radionuclide transit showing normal oesophageal motility (left) and transit of a liquid bolus (right). In the middle, the location of the oesophageal, pharyngeal and intragastric ports is shown in red, the location of the mid-point of each region of interest in the oesophageal body centred on a cobalt marker in blue.

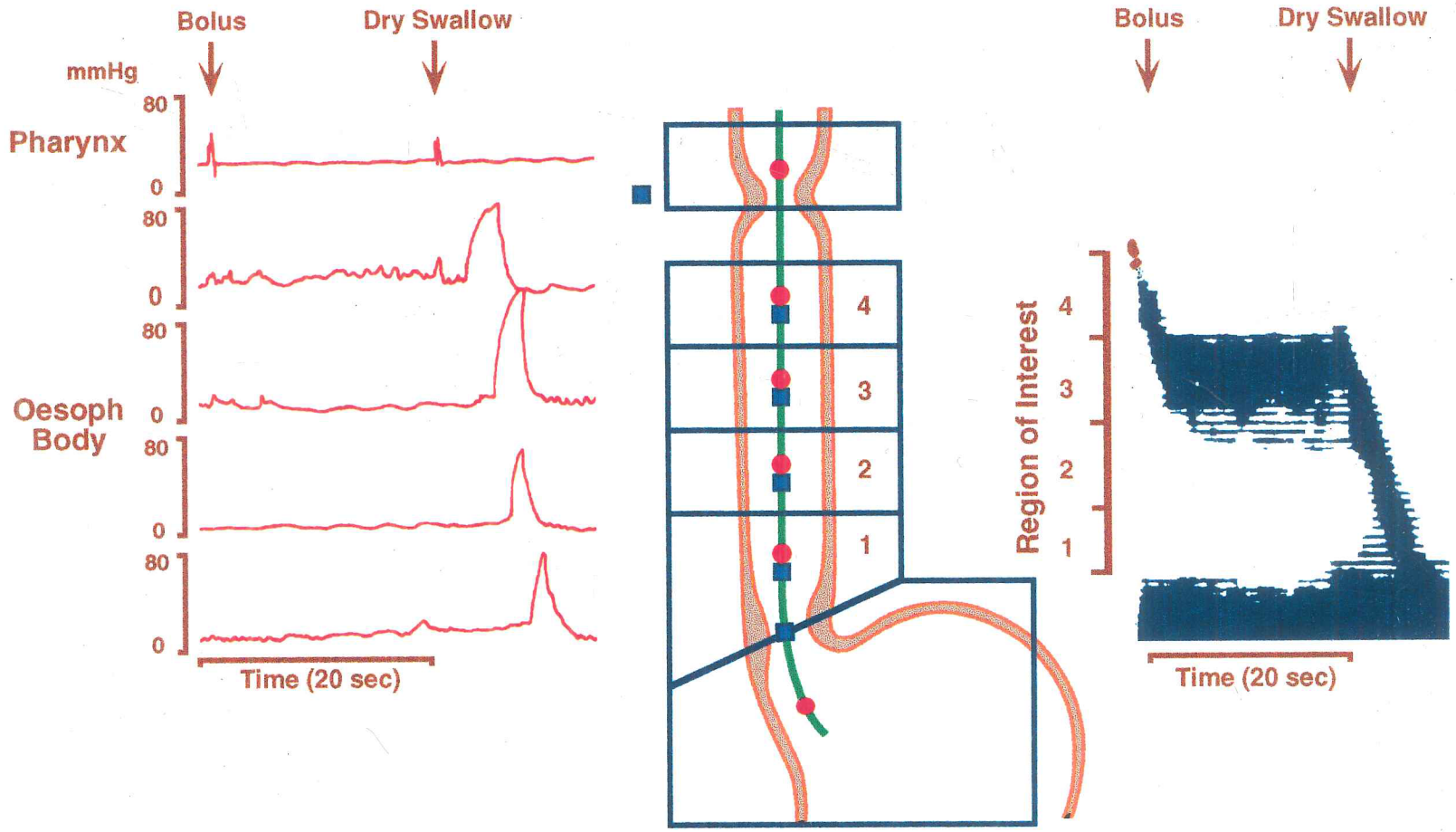


Figure 3.1b Concurrent oesophageal manometry and radionuclide transit showing failed oesophageal peristalsis (left) associated with hold-up of a liquid bolus (right). For explanation of the middle diagram see Figure 3.1a.

Scintigraphy

Solid and liquid swallows were replayed as a composite image and displayed on a screen. Using the cricoid marker, the marker at the mid-point of the sleeve sensor and the isotope in the gastric fundus to define the proximal and distal limits of the oesophagus, the oesophagus was divided into four regions of interest of equal length each with a side-hole manometric recording site at its mid-point . Pharyngeal and gastric regions of interest were also constructed. Time-activity curves for each region were then generated (Blackwell et al 1983), (Figs. 3.1a, 3.1b). Total transit time, was defined as the time period between clearance of the bolus from the pharyngeal segment to clearance from the distal oesophageal segment. Clearance from each segment was deemed to have occurred when the activity of the labelled bolus had dropped to 10% of its peak value. Bolus transit was classified as hold-up if transit time was more than15 seconds for liquids and greater than 20 seconds for solids (Holloway et al 1989) (Fig. 3.1b). For total transit, the mean values for both solid and liquid swallows pre, during and post irradiation were derived by pooling all available triplicate swallow data for individual patients. The percentage of hold-ups of both labelled solid and liquid boluses was also calculated from the pooled available individual swallow measurements.

Statistical analysis

Symptom and endoscopy scores before, during and post irradiation were analysed using the non-parametric rank sum test (Koch 1969) and linear regression analysis. The manometric and scintigraphic data obtained from various phases of the experiment were compared, using analysis of variance for multiple comparisions (ANOVA). As the distributions of both symptom and endoscopy scores were skewed, these parameters are shown as median values and interquartile ranges. Manometric and scintigraphic data are shown as mean values ± SEM. A p value of < 0.05 was considered significant in all analyses.

3.3 RESULTS

Symptoms

Before irradiation, all but 2 patients (patients 1 and 7) both of whom had heartburn with/without regurgitation), were free of symptoms. In contrast, all but 1 patient (patient 5) experienced odynophagia and/or dysphagia during mediastinal irradiation (Table 3.1). The two patients (patients 1 & 7) who had pre-existing reflux reported a worsening of their symptoms. There was no significant weight loss in the group as a whole. One patient (patient 2), with locally advanced lung cancer, however lost 6 kg weight during irradiation. Except for the patients with pre-existing reflux symptoms, all oesophageal symptoms had resolved 6-8 weeks following completion of irradiation.

Endoscopy

Before irradiation, endoscopy was normal in all but one patient (patient 7) who had two streaks of erythema approximately 1 cm in length just proxiaml to the oesophago-gastric junction, consistent with pre-existing reflux oesophagitis.

During radiation therapy, endoscopic abnormalities were found in three patients (patients 1,3 & 8). In patients 1 & 8, neither of whom had mucosal lesions pre-irradiation, the changes consisted of patchy mucosal ulceration in the proximal oesophagus. Histological examination of biopsies of these mucosal lesions showed changes consistent with radiation effect. Patient 3 was noted to have candidiasis in the distal oesophagus. Interestingly, the mucosal changes noted before irradiation at the oesophago-gastric junction of Patient 7 were no longer visible.

The endoscopic abnormalities noted in all three patients during mediastinal irradiation resolved completely 6-8 weeks after its completion. There was no correlation between the severity of oesophageal symptoms and endoscopic lesions.

Scintigraphy

(i) Liquid bolus

Before irradation, mean transit time was within normal limits (Table 3.2) although 23% of the swallows were classified as having held-up. During and post-irradiation, neither the percentage of swallows which were held-up nor mean transit times changed significantly.

(ii) Solid bolus

In contrast to the liquid swallows, 63% of the solid sequences pre-irradiation were characterised as held up and resulted in prolongation of mean transit time for solids (defined as greater than 20 secs). During and after irradiation, no significant changes in percentage of hold-up of solid swallows or mean transit times were observed.

Manometry

(i) Unlabelled swallows

No significant changes in the manometric parameters were observed during or post-irradiation compared with those measured pre-irradiation (Table 3.2).

(ii) Liquid bolus

Before irradiation, the transit sequences with bolus hold-up were associated with either peristaltic failure (33.3%) or hypotensive contractions (16.7%), at or above the level of hold-up. During and post-irradiation, however, none of the manometric parameters changed significantly (Table 3.2).

(iii) Labelled solid swallows

Before irradiation, the major pattern of motility associated with hold-up was peristaltic failure, accounting for 58.3% of the sequences; 33% were associated with hypotensive contractions. The remainder of the sequences were associated with normal peristalsis. During irradiation, the manometric measurements did not change significantly. In contrast, after irradiation, peristaltic transit time increased ($p < 0.01$).

Table 3.2: Results in patients at Baseline (Pre), 4-6 Weeks After Starting Radiation (During) and 6-8 Weeks Following Completion of Radiation (Post)

Parameter	Pre	During	Post
Symptom Score[a]	0.0 (0-0.5)	3.0* (2.5-4.0)	0.0 (0-0.5)
Endoscopy Score[a]	0.0 (0-0)	0.0 (0-1.5)	0.0 (0-0)
Oesophageal Scintigraphy			
(i) Liquid:			
Transit Time (sec)[b]	11.0 ± 1.6	10.3 ± 1.4	13.1 ± 2.8
Hold-up (% tests)	23	13	21
(ii) Solid:			
Transit time (sec)[b]	47.4 ± 11.4	51.3 ± 10.2	44.6 ± 7.8
Hold-up (% tests)	63	78	75
Oesophageal Manometry			
(i) Unlabelled:			
Total transit (sec)	6.3 ± 0.4	7.0 + 0.4	6.4 + 0.3
Contraction Amp (mm Hg)	62.4 ± 14.0	65.6 + 13.7	72.2 + 17.5
Peristaltic failures (% tests)	48.0	49.0	41.0
(ii) Labelled liquid:			
Total transit (sec)[b]	6.5 ± 0.6	6.1 ± 0.5	6.7 ± 0.4
Contraction Amp (mm Hg)[b]	51.5 ± 5.1	63.6 ± 9.2	69.2 ± 8.2
Peristaltic failures (% tests)	50	66.67	52.17
(iii) Labelled Solid:			
Total transit (sec)[b]	6.1 ± 0.5	7.0 ± 0.7	9.0** ± 1.0
Contraction Amp (mm Hg)[b]	47.4 ± 7.9	49.7 ± 5.1	64.8 + 12.2
Peristaltic failures (% tests)	81.8	69.6	61.9

*$p < 0.001$, **$p < 0.01$, ANOVA

[a]median (interquartile range), [b]mean ± SEM

3.4 DISCUSSION

This is the first comprehensive study of the effects of mediastinal irradiation on oesophageal function and also the first to examine critically its effects on oesophageal motility. Previous studies have either focussed on symptoms and mucosal changes (Nicolopoulos et al 1985; Soffer et al 1994), or on symptoms and oesophageal transit (LaManna et al 1985).

We have confirmed previous observations that symptoms referable to oesophageal dysfunction are almost inevitable during mediastinal irradiation (Roswit et al 1972). Unlike a previous study (Soffer et al 1994), however, there was in general, no associated weight loss in our patients. This is likely to be attributable to differences in the characteristics of the patient group. In our study only those patients who were potentially curable were included, in contrast to the previous study in which the majority of patients were treated with palliative intent and therefore were likely to have metastatic disease (Soffer et al 1994).

The demonstration of macroscopic oesophageal mucosal abnormalities in only 3 out of 8 patients is consistent with the findings of previous studies (Nicolopoulos et al 1985; Soffer et al 1994). The mucosal changes were mild, confined to the proximal oesophagus or associated with candidiasis in the distal oesophagus and did not correlate with the severity of oesophageal symptoms. However, biopsies were not obtained in patients with no visual evidence of oesophageal damage.

It has previously been suggested that oesophageal symptoms in patients undergoing mediastinal irradiation may reflect disordered oesophageal motility (Soffer et al 1994). We found no evidence to support this concept, there being no significant change in motility or transit associated with radiation therapy. The absence of changes of oesophageal transit conflict with the only other prospective study of oesophageal motor function during mediastinal irradiation (LaManna et al 1985). The discrepant findings

can be attributed to differences in the patient selection criteria and methodology between the studies. In the previous study (LaManna et al 1985), patients with structural lesions such as strictures causing mechanical obstruction were not excluded and these abnormalities could have contributed to the observed prolongation of oesophageal transit. It is also possible that the assessment of scintigraphic oesophageal transit in the previos study was influenced by rapid double swallows, which are known to induce abnormal peristaltic responses (Vanek & Diamant 1987), and the inclusion of sequences associated with a fragmented bolus.

The absence of significant changes in oesophageal transit and motility despite the development of oesophageal symptoms in virtually all patients has a number of possible explanations. The inclusion in our sudy of three patients with breast carcinoma who received a calculated radiation dose to the oesophagus of approximately a third of the other patients, may theoretically have contributed to our negative findings. However, this appears unlikely since despite the lower radiation doses, two of the three patients had oesophageal symptoms during mediastinal irradiation. Second, it is possible that mediastinal irradiation caused subtle changes in oesophageal motility that were not detected, either because of the relatively small number of patients studied, or inadequate sensitivity of the measurements used. Although we only studied eight patients, the data analysis for each phase of the protocol was based on a total of sixteen individual patient swallows. It is unlikely therefore that a Type II statistical error could have occurred under these circumstances. Although the overall sensitivity of concurrent oesophageal radionuclide scintigraphy and manometry in detecting changes in oesophageal motor function has not been formally assessed by longitudinal studies, the overall sensitivity of radionuclide transit and manometry in detecting oesophageal dysmotility has been reported as 75% and 83% respectively (DeCaestecker et al 1986) and it is acknowledged that the diagnostic yield of concurrent studies is higher (Blackwell 1989).

Third, small changes in oesophageal function may have been masked by underlying abnormalities in oesophageal function. The relatively high percentage of hold-ups of solid and peristaltic failures of both liquid and solid swallows observed in our patients pre-irradiation is possibly a function of their advanced age, since data in younger subjects from our laboratory indicate that the prevalence of these abnormalities is much lower (Tippett et al 1994). Although a younger group of patients may have shown changes in oesophageal motor function during radiation therapy, we do not believe that this data would be representative of the typical population of patients currently subjected to mediastinal irradiation, given the increasing use of chemotherapy instead of radiation for Hodgkin's lymphoma. The significance of our observation that the manometric transit of solid slowed following irradiation is uncertain, since it occurred when oesophageal symptoms had resolved.

The most likely explanation for the development of symptoms in the absence of changes in oesophageal transit and motility is that oesophageal symptoms are the result of exaggerated mucosal sensitivity consequent to mediastinal irradiation. This increased perception of stimuli in the absence of motility changes has been demonstrated in other parts of the gastrointestinal tract (Mearin et al 1991; Accarino et al 1992). Increased mucosal sensitivity as a result of mediastinal irradiation could lead to the perception of previously asymptomatic bolus hold-up. This hypothesis, however, awaits specific investigation.

CHAPTER 4

A retrospective study of the effects of pelvic irradiation for carcinoma of the cervix on gastrointestinal function (Int J Radiat Oncol Biol Phys 1993;26:229-237)

4.1 INTRODUCTION

Pelvic irradiation is frequently used in the curative treatment of carcinoma of the cervix and other abdominal or pelvic malignancies. During the course of pelvic irradiation, acute radiation enteritis characterized by diarrhoea with or without abdominal cramps is almost inevitable (Yeoh & Horowitz 1987). While it is recognized that chronic radiation enteritis is a clinically important sequel to radiation treatment, the prevalence of chronic radiation enteritis is uncertain. Retrospective surgical series (DeCosse et al 1969; Schofield et al 1983) suggest a prevalence of 5-15%, but do not include patients who have died or were lost to follow-up in the prolonged interval between treatment and the development of symptoms. One retrospective medical series indicates that in about 70% of female patients, pelvic radiotherapy is associated with a chronic increase in stool frequency (Newman et al 1973). It is likely, therefore, that the majority of patients do not seek medical attention until the occurrence of a serious complication such as bleeding, stricture, or fistula formation and that an increased frequency of bowel actions is the most frequent symptom of chronic radiation enteritis.

While the histological abnormalities associated with chronic radiation enteritis are well documented (Wellwood & Jackson 1973), the effects of radiation on gastrointestinal function and the pathogenesis of diarrhea due to chronic radiation enteritis is poorly understood. Abnormalities in gastrointestinal absorption (Dalla Palma 1968; Stryker et al 1978; Stryker & Demers 1979) and transit (Frankendal & Junghagen 1974) have been documented in some patients but to date there has been no comprehensive study of

gastrointestinal function in patients who had received abdominal or pelvic irradiation.

We have now evaluated various aspects of gastrointestinal function in a randomly selected cohort of patients treated with pelvic irradiation for carcinoma of the cervix between 1-6 years previously.

4.2 METHODS

Subjects

30 randomly selected patients who had completed pelvic irradiation for carcinoma of the cervix 1-6 years previously were studied. The study group was derived from 90 consecutive patients treated for carcinoma of the cervix with pelvic irradiation, with or without surgery by two radiation oncologists (EKY &ASA) in the years 1985-1990. 43 of these patients had died and in at least 28 of these cases, death was related to recurrent malignant disease. Patients who have had gastrointestinal surgery, apart from uncomplicated appendicectomy, were excluded. Other criteria for exclusion were inflammatory bowel disease, pernicious anaemia, evidence of hepatic and renal function (any biochemical parameter for hepatic function exceeding twice the normal range and/or plasma creatinine > 0.12 mmol/l), and a constant requirement for medication (such as anti-cholinergics, anti-depressants or non steroidal anti-inflammatory drugs) which could influence gastrointestinal motility, or interfere with the assessment of the intestinal permeability. 2 patients had previous bowel resection for complications of radiation enteritis and were not eligible for the study. 2 patients were lost to follow-up. The remaining 43 patients were all invited to participate in the study of whom 30 agreed and 13 declined. One of the patients who refused to be studied had been previously told that she had radiaton enteritis.

30 patients [median age 60 yr (27-81 yr), median body weight 63 kg (39-91 kg) and median body mass index (BMI) 25 (16-41)] were therefore studied. Significant intestinal stricture was excluded in all cases by a radiological small bowel series. 19 of

these patients had radiation treatment alone and 11 patients had radiation treatment either before of after surgery. Characteristics of the patient group and details of radiation treatment are shown in Table 4.1.

18 normal volunteers [11 female, 7 male, median age 45 yr (19-75 yr), median body weight 75 kg (45-109 kg) and median body mass index (BMI) 26.0 (17.8-38.7)] who had no history of gastrointestinal disease and were not taking any medication were also studied.

All but three of the patients and all but one of the control subjects was Caucasian.The control subjects were younger than the patients ($p < 0.05$). Body weight was greater in control subjects compared with the patients ($p < 0.05$), but there were no significant difference in BMI between the two groups.

Protocol

Each of the patients and normal volunteers underwent the same tests of gastrointestinal function.

Measurements

The following measurements of gastrointestinal function were assessed in the patients and control subjects: (a) Gastrointestinal symptoms (questionnaire) (b) Absorption of: i) bile acid and vitamin B12, ii) lactose, iii) fat, and measurement of stool weight (c) Gastrointestinal transit: gastric emptying, small intestinal transit and whole gut transit and (d) Intestinal permeability.

Because of methodological practicalities, absorption of bile acid and vitamin B12 was determined before the measurements of gastrointestinal transit and intestinal permeability was measured last.

TABLE 4.1: Characteristics of the patient group

Patient	†FIGO Stage	Age (Yr)	Body Weight (Kg)	Body Mass Index	Treatment	Radiation Dose * Gy/No. of Fractions/Days	Size of Radiation Field + (cm x cm)
1	IIIa	67	69	26.0	Radiation Alone	44.95 Gy/25 F/32 Days (25 Gy to Point 'A'/52 hr)	16.5 x 18.5
2	IIb	58	74	24.2	Radiation Alone	44.00 Gy/22 F/32 Days (25 Gy to Point 'A'/46 hr)	18.5 x 16.0
3	Ib	45	67	22.5	Radiation Alone	50.00 Gy/25 F/36 Days (25 Gy to Point 'A'/45 hr)	18.0 x 20.0
4	IIb	65	62	22.7	Radiation Alone	45 Gy/25 F/39 Days (25 Gy to Point 'A'/54 hr)	17.5 x 15.5
5	IIb	43	65	23.3	Radiation Alone	44 Gy/22 F/33 Days (26 Gy to Point 'A'/49 hr)	17.0 x 18.0
6	Ib	73	85	40.8	Radiation Alone	30 Gy/10 F/12 Days (30 Gy to Point 'A' x2/64/59 hr)	16.0 x 15.0
7	IIb	61	83	29.7	Surgery & Radiation	50 Gy/25 F/3 Days (20 Gy to Vaginal Vault/39 hr)	17.0 x 18.0
8	IIb	48	87	30.9	Radiation Alone	50 Gy/25 F/33 Days (25 Gy to Point 'A'/48 hr)	18.5 x 20.5
9	Ib	72	55	19.0	Radiation Alone	44 Gy/23 F/36 Days (30 Gy to Point 'A'/48 hr)	16.0 x 14.0

Table 4.1 continued

Patient	†FIGO Stage	Age (Yr)	Body Weight (Kg)	Body Mass Index	Treatment	Radiation Dose * Gy/No. of Fractions/Days	Size of Radiation Field + (cm x cm)
10	IIb	71	68	25.6	Radiation Alone	45 Gy/25 F/38 Days (25 Gy to Point 'A'/40 hr)	17.0 x 16.5
11	IIb	65	70	25.7	Radiation Alone	46 Gy/25 F/37 Days (26 Gy to Point 'A'/50 hr)	15.0 x 20.0
12	IIb	70	58	25.2	Surgery & Radiation	50 Gy/25 F/37 Days (20 Gy Vaginal Mould/33 hr)	17.5 x 17.5
13	IIb	43	78	28.0	Radiation Alone	44 Gy/22 F/30 Days (25 Gy to Point 'A'/40 hr)	17.0 x 17.5
14	Ib	58	39	16.3	Surgery & Radiation	45 Gy/25 F/35 Days 14.4 Gy/8 F/32 Days	16.0 x 15.0 11.5 x 10.0
15	IIb	53	50	20.8	Radiation Alone	44 Gy/22 F/30 Days (25 Gy to Point 'A'/46 hr)	15.0 x 14.5
16	IIb	76	64	27.8	Radiation Alone	46 Gy/23 F/36 Days (25 Gy to Point 'A;/60 hr)	19.0 x 15.0
17	Ib	39	61	25.4	Surgery & Radiation	45 Gy/25 F/38 Days	18.5 x 16.5
18	Ib	68	55	24.4	Surgery & Radiation	45 Gy/25 F/40 Days (15 Gy to Vaginal Vault/28 hrs)	16.0 x 15.5

Table 4.1 continued

Patient	†FIGO Stage	Age (Yr)	Body Weight (Kg)	Body Mass Index	Treatment	Radiation Dose * Gy/No. of Fractions/Days	Size of Radiation Field + (cm x cm)
19	IIb	77	50	21.7	Surgery & Radiation	45 Gy/25 F/36 Days 20 Gy/10 F/14 Days	15.5 x 16.0 10.0 x 7.5
20	IIa	27	59	24.6	Radiation Alone	45 Gy/25 F/41 Days (25 Gy to Point 'A'/34 hr)	17.5 x 17.5 16.5 x 15.5
21	IIa	61	91	37.0	Surgery & Radiation	(60 Gy Vaginal Mould/84 hr)	
22	IIb	47	59	20.9	Radiation & Surgery	45 Gy/25 F/34 Days	18.0 x 19.5
23	IIb	58	54	19.9	Radiation Alone	44 Gy/22 F/31 Days (21 Gy/10 F/13 Days)	17.5 x 18.0 13.0 x 12.0
24	IIb	66	51	19.9	Radiation Alone	50 Gy/25 F/56 Days (20 Gy to Point 'A'/50 hr)	15.0 x 17.0 16.0 x 16.0
25	Ib	50	80	26.1	Surgery & Radiation	50 Gy/25 F/36 Days	16.0 x 19.0
26	Ib	52	75	29.3	Surgery & Radiation	50 Gy/25 F/36 Days (20 Gy Vaginal Mould/24 hr)	15.0 x 19.5
27	IIa	64	45	18.3	Radiation Alone	50 Gy/25 F/48 Days (20 Gy to Point 'A'/43 hr)	15.5 x 16.5

Table 4.1 continued

Patient	†FIGO Stage	Age (Yr)	Body Weight (Kg)	Body Mass Index	Treatment	Radiation Dose * Gy/No. of Fractions/Days	Size of Radiation Field + (cm x cm)
28	Ib	55	72	27.1	Radiation Alone	50 Gy/24 F/36 Days (25 Gy to Point 'A'/39 hr)	16.0 x 19.0
29	IIb	81	62	25.2	Radiation Alone	44 Gy/22 F/33 Days 20 Gy/10 F/14 Days	16.0 x 18.0 10.0 x 10.0
30	Ib	42	62	22.2	Surgery & Radiation	50 Gy/25 F/36 Days	17.0 x 21.0

* For each patient, external beam dose (from a Phillips SL75-20 linear accelerator) given first and except for patient 6 and 28, the dose increment is 1.80-2.00 Gy prescribed as a minimum tumor dose given 5x/week. Intracavitary radiation doses are given in parentheses and are prescribed to Manchester Point 'A' unless otherwise stated in which cases doses are prescribed to the outer surface of vaginal mould. Selectron applicators were used for intracavitary radiation therapy.

\+ Sizes given are for AP-PA fields only. Most patients had treatment with a 4 field technique. Except for patient 6 (who received 2 intracavitary insertions), no shielding of central pelvic structures was employed.

† International Federation of Gynecology and Obstetrics

(a) Gastrointestinal symptoms

The following symptoms were assessed by questionnaire on entry into the study: nausea, vomiting, abdominal pain and frequency of bowel actions (number of bowel actions per week). Except for frequency of bowel actions, each symptom was scored according to the following classification: 0 = Symptoms absent, 1 = Mild; symptoms could be ignored if the subject did not think about it, 2 = Moderate; symptoms could not be ignored but did not influence daily activities, 3 = Severe; symptoms influenced daily activities (Horowitz et al 1985b). The total score (Maximum 9) was calculated. The number of bowel actions and their consistency in the three day faecal collection performed for measurement of fat excretion and the presence or absence of faecal incontinence was recorded.

A questionnaire was also used to record dietary intake of milk products and fat and the presence or absence of intolerance to milk and milk products (symptoms of nausea, abdominal bloating, abdominal cramps or diarrhoea) after each subject had been enrolled into the study. Intake of dairy foods was expressed as calcium intake/week and fat intake classified as 1 = low, 2 = medium or 3 = high (Angus & Eisman 1988).

(b) Absorption studies

i) Bile acid and vitamin B12 absorption

On day 1, following a light breakfast at 0700h, one capsule of Co-58 Vitamin B12 (Co-58 B12), (Amersham International) containing 30kBq Co-58 was ingested orally with 30ml water at 0900h. The photo-peak counts corresponding to the 808 keV photon energy of Co-58 and the 265 keV photon energy of Se-75 (to correct for down scatter from the higher energy Co-58 window into the lower energy Se-75 window) were recorded from a whole body counter with a moving circular gantry of four diametrically opposing sodium iodide crystal detectors of 12.5 cm diameter each and the spectrum stored in a multichannel analyser. At 0930h one capsule of Se-75 Hcat (Amersham International) containing 37kBq Se-75 was then swallowed with 30 ml water. 4h later

the number of counts in both the Co-58 and Se-75 photo peak windows were determined. This figure, after correction for room background counts (and Compton scatter from the Co-58 into the Se-75 photo peak windows), was considered to represent 100% whole body retention. At 0900h 7 days later the counts in both Co-58 and Se-75 photo peak windows were again measured. This number, after correction for room background counts, radionuclide decay and Compton scatter was used to derive the percentage whole body retention of bile acid and vitamin B12 (Yeoh et al 1984).

ii) Lactose absorption

The evening meal preceding the test day was consumed before 7pm and consisted of absorbable carbohydrates eg., meat/rice with or without salad. A list of forbidden non-absorbable carbohydrates was given to the subject who was instructed to fast from 10pm the evening before until after the test was over. Smoking was not permitted an hour before and during the test

On the morning of the test, the subject was first given an antibacterial mouthwash of 1% chlorhexidine following which a basal end expiratory breath sample was taken. At 0900h 50 g lactose dissolved in 200 ml water was then ingested and subsequent breath samples taken at least every 30 min for up to 4 h. All breath samples were analysed for hydrogen concentration using a chromatographic method capable of detecting concentrations as low as 1ppm (Robb & Davidson 1983). The results were normalized to correct for variations in breath sample quality using simultaneous measurements of oxygen, carbon dioxide and nitrogen (Newcomer 1984). A sustained peak in breath hydrogen greater than 10 parts per million was taken to indicate malabsorption of lactose (Horowitz et al 1987). Symptoms such as nausea, abdominal bloating, cramps , or diarrhoea were recorded during and the day after the performance of the test.

iii) Fat absorption

The subjects were placed on a normal diet estimated to contain 50-150 g fat. A three day collection of faeces was arranged to coincide with the start of the radioisotopically labelled liquid nutrient test meal used for measuring gastrointestinal transit (v.i.). Each bowel motion was collected in a plastic bag which was used to line a specially constructed metal rim designed to fit onto a conventional toilet bowl. The plastic bag was then tied and labelled with the date and time of the specimen. It was then placed in a pre-weighed tin, and when the three day collection was completed weighed again. The number of radio-opaque markers in each labelled bowel action was determined by orthogonal x-rays to determine whole gut transit (v.i.). The consistency of each bowel action and its wet weight were noted. The entire three day collection was then pooled and homogenized by adding a known volume of water and the weight of the homogenate calculated. An aliquot was taken, placed in a pre-weighed glass cylinder and boiled with concentrated hydrochloric acid. The liberated fatty acids was then extracted in chloroform, dried and weighed (van de Kamer et al 1949 modified for extraction of fatty acids in chloroform). The result was then calculated as follows and expressed in mmol fat/3days:

Wt of faeces = (Wt of tin + faeces) - (Wt of tin)

Wt of homogenate = (Wt of faeces + Wt of water added)

Wt of aliquot of homogenate = (Wt of aliquot + cylinder) - Wt of cylinder

$$\frac{\text{Wt of dried extract x Wt of homogenate}}{\text{Wt of aliquot of homogenate}} \times 5.28 = \text{Total fat, mmol/3d}$$

(c) Gastrointestinal transit

Data acquisition

At 0830 h, following an overnight fast from 2200 h the evening before the test, each subject ingested 200 ml water containing 10 g lactulose (Duphalac-Duchar, Holland), 20 g dextrose, 40 MBq Tc-99m sulphur colloid and 50 cylindrical radio-opaque plastic

markers (sections of tubing 4mm x 2mm) (Read et al 1980) over two minutes. The subject then lay supine under a large field of view gamma camera linked to a PDP-11 computer. A cobalt marker was placed at the anterior superior iliac crest to aid alignment of images. Data were acquired for approximately 5 h. For the first 30 min after meal completion, data were sampled every minute, followed by 3 min frames for the remainder of the study. End-expiratory breath samples were taken at 10-15 min intervals following ingestion of the meal for breath hydrogen analysis. During the study the subject was allowed to sit up, or walk around briefly if they wished every 60 min.

Regions of interest were initially drawn around the stomach and ascending colon. This task was greatly facilitated by replaying the entire series of scans backwards in time so that the ascending colon which was well defined by the radionuclide in the later scans (Fig 4.1) can be located in the earlier scans (Malagelada et al 1984). The images in the earlier scans were then aligned, the cobalt marker sited at the anterior superior iliac crest serving as an additional anatomical landmark (Read et al 1986). Regions-of-interest were then drawn to define the caecum, tranverse and descending colon as well as a suitable background region at the periphery of the images and the alignment of the images in these later scans completed. As previously reported (Malagelada et al 1984) cases of genuine overlap of the terminal ileum and caecum were rare and occurred in less than 10% of studies as it was possible not only to look at the images backwards but also to verify the arrival of the radionuclide in the colon from the breath hydrogen data. In those studies where the terminal ileum was not able to be separated from the caecum confidently, the region-of-interest in the ascending colon was drawn with the lower limit at mid-ascending colon as previously described (Caride et al 1984). The counts in each region were then corrected for radionuclide decay and background and normalised to the maximum count in the stomach and colon as a whole. Time activity curves of gastric emptying and colonic filling were generated by a series of least squares fit to the data points using two of the following mathematical functions:

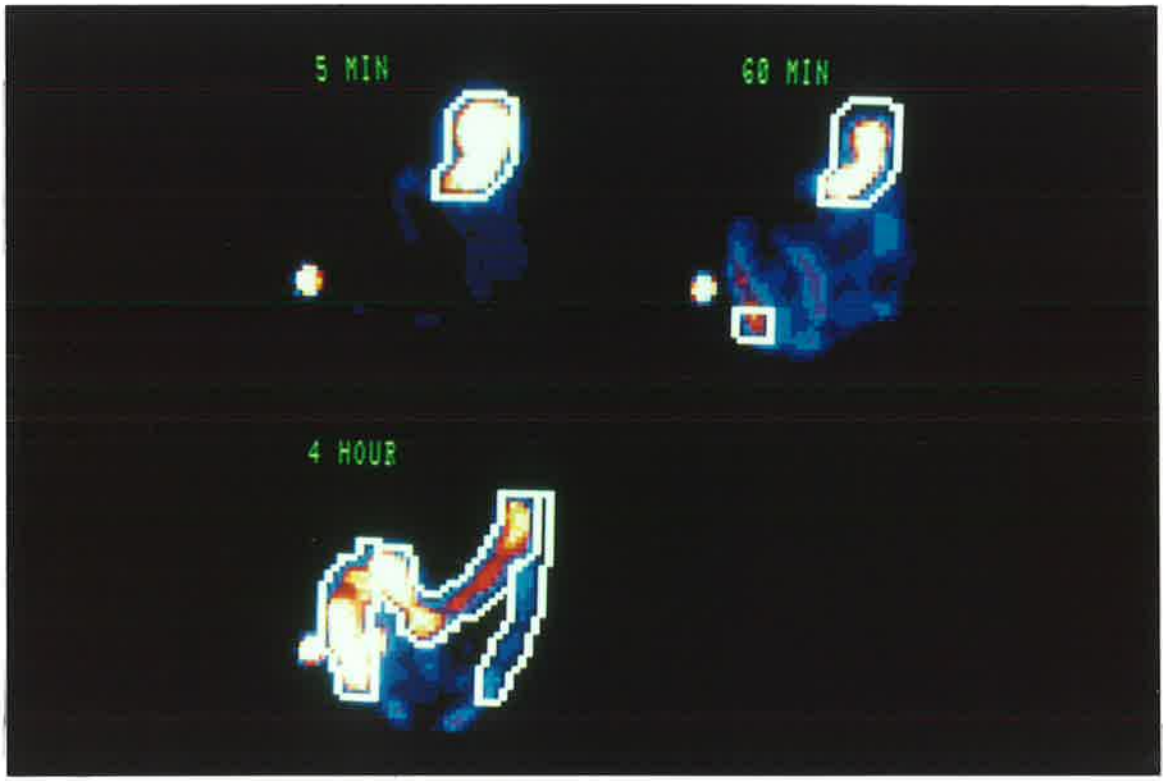


Figure 4.1 Abdominal scintiphotograph showing the intraabdominal distribution of a liquid technetium Tc 99m-labelled lactulose nutrient meal at various time intervals after ingestion. The ascending colon which is easily identifiable in the scintiphotograph at 4hr post ingestion aids in the locating the caecum at 60 min.

(1)	linear,	$f(t,a,b) = a + b.t$
(2)	exponential,	$f(t,a,b)\ a \times e^{b.t}$
(3)	logarithmic,	$f(t,a,b) = a+b.\ln(t)$
(4)	power,	$f(t,a,b) = a+t^{b}$
(5)	modified power,	$f(t,a,b) = 2^{-(a \times t)^{b}}$,

where f = activity, t = time, e = exponent, ln = logarithm to base 10, and a and b = constants.

It was found that almost invariably, the exponential function gave the best fit to the gastric emptying data whilst the linear function provided the best fit for the colonic filling data (Figs 4.2 & 4.3). By a process of computer subtraction, time activity curves characterising small intestinal residence were subsequently derived (Fig 4.4). Time zero was considered the time of completion of the test meal. A sustained rise in breath hydrogen concentrations = or > 5 ppm (determined by gas chromatography) was considered to represent the arrival of the meal at the caecum (Read et al 1986).

For gastric emptying the lag phase before any radionuclide emptied from the stomach and the 50% emptying time were determined (Collins et al 1983). For small intestinal transit the following parameters were determined:- (1) start of colonic filling (arrival of the head of the meal assessed scintigraphically and by breath hydrogen measurements) (Caride et al 1984), (2) small intestinal transit (start of colonic filling minus the lag phase for gastric emptying), (3) small intestinal residence (area under derived small intestinal transit time activity curve), (4) time for 50% colonic filling (Read et al, 1986, Malagelada et al, 1984). Whole gut transit was determined radiographically by the first arrival of radio-opaque marker(s) in the faeces and the time when 50% or more of the radio-opaque markers were in the stool (Read et al 1980).

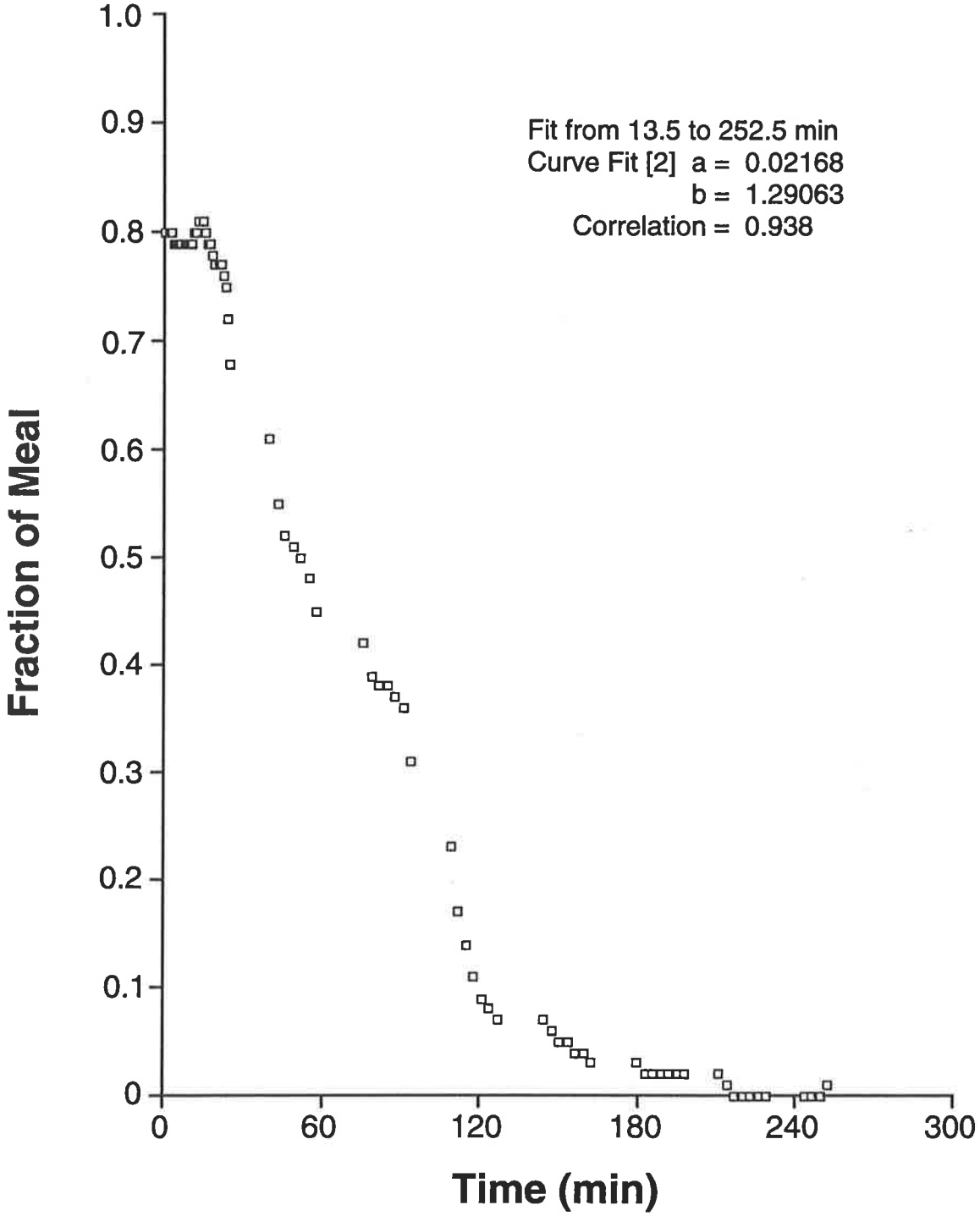


Figure 4.2 Computer derived histogram showing the fraction of liquid radio-labelled nutrient meal (200 ml water containing 10 g lactulose, 20 g dextrose and Tc 99-m sulphur colloid) left in the stomach plotted against time in minutes since ingestion of the meal in a patient.

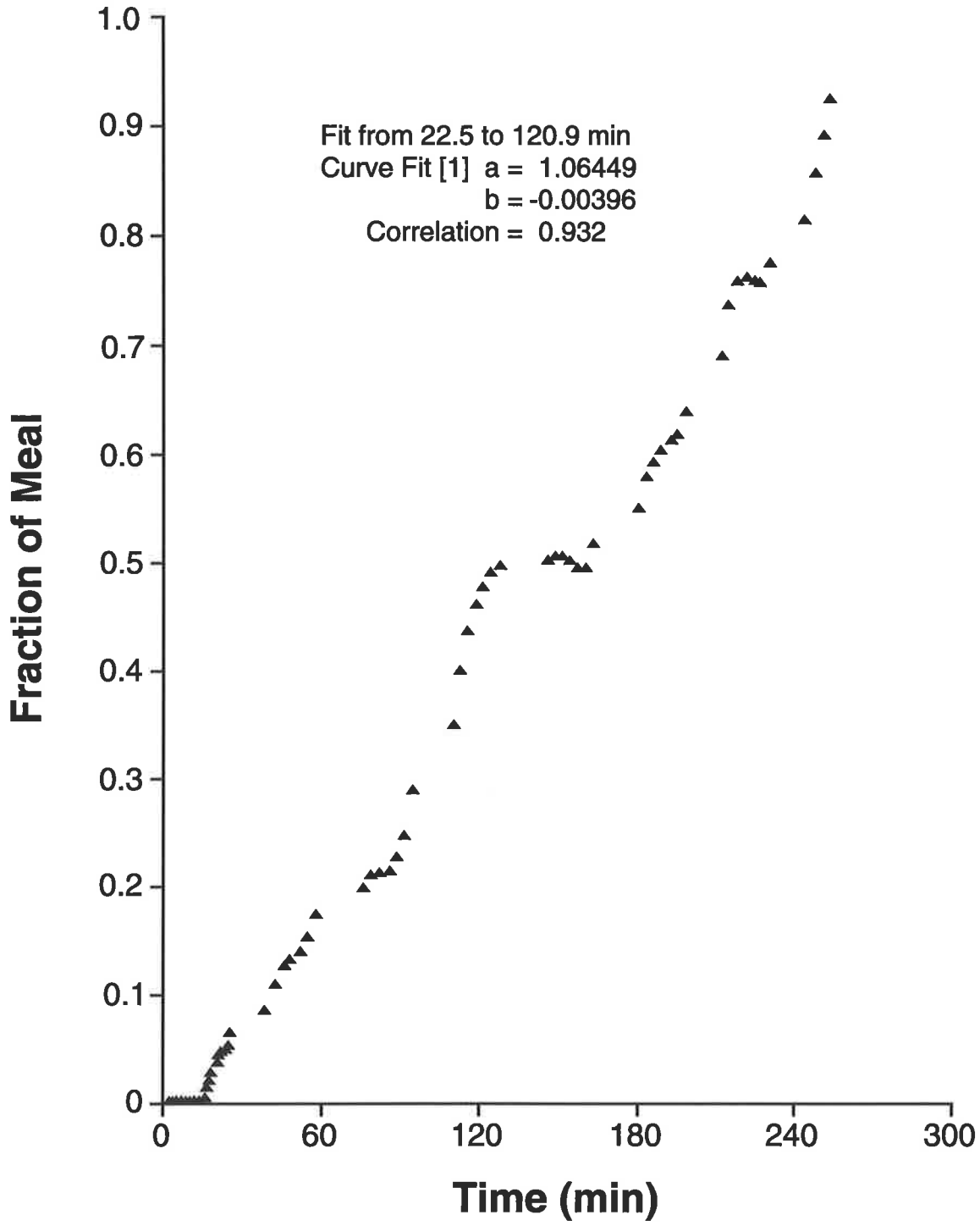


Figure 4.3 Computer derived histogram showing the fraction of radio-labelled liquid nutrient meal in the colon of the same patient as in Figure 4.2 plotted against time.

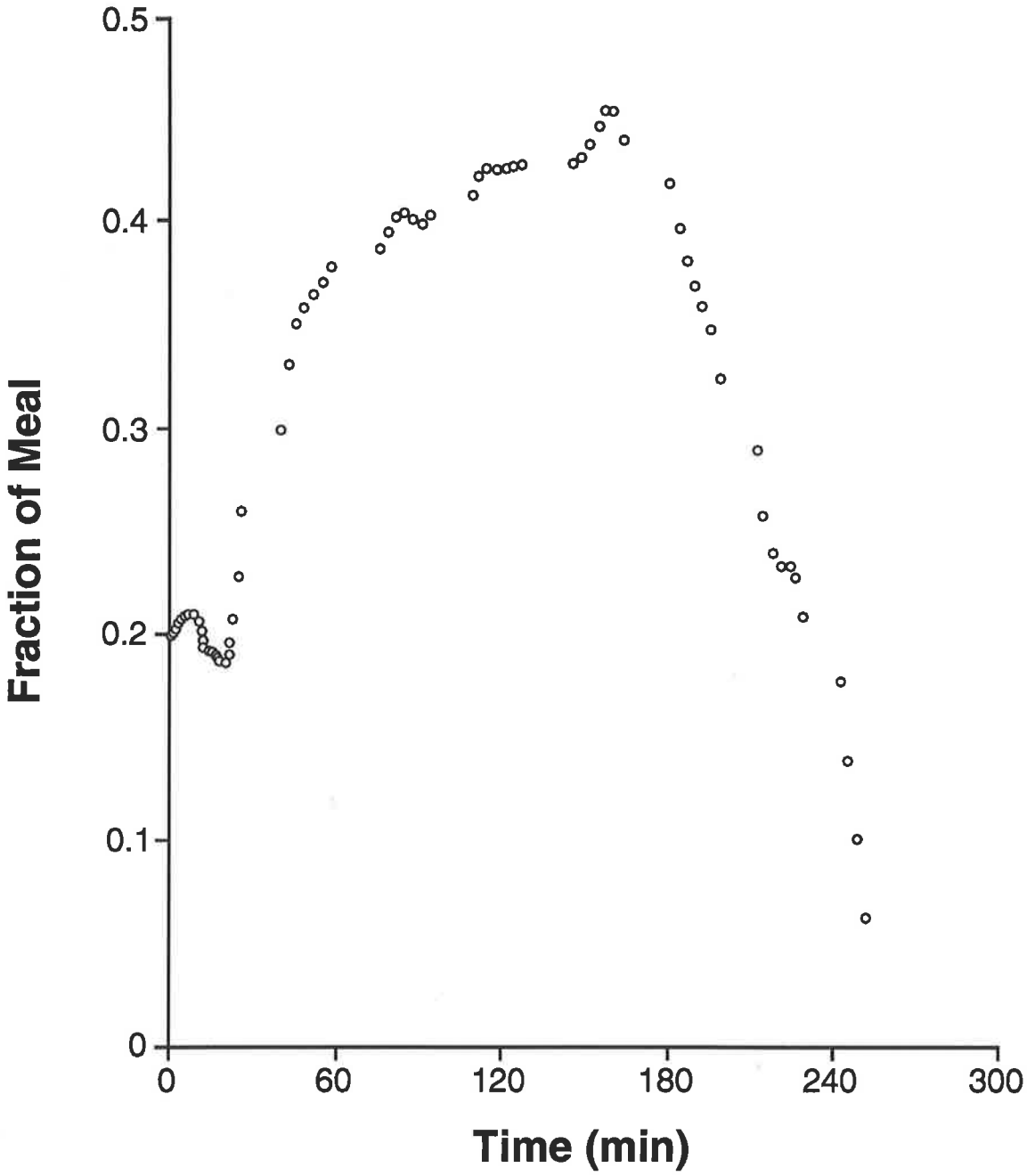


Figure 4.4 Computer derived histogram representing small intestinal residence (area under derived small intestinal time activity curve) in the same patient as in Figure 4.2.

(d) Intestinal permeability

i) Cr-EDTA absorption test

Each subject was initially asked to collect their urine for 24 h prior to the test. At 0930, following an overnight fast (from 2400 h), the subject ingested 2-10 ml of a stock solution of chromium-51 labelled ethylenediamine- tetra-acetic acid (Cr-EDTA) (Australian Atomic Energy Commission Code No CRIMI) containing 750 kBq of Cr-51, followed by 300 ml water. Fasting was maintained for a further 2 h, after which a normal diet was permitted. Subjects were instructed to take no alcohol and aspirin and to collect urine for the next 24 h. The entire 24 h collection was then counted in a large volume counter ('ECKO' Dual 2"). The pre-Cr-EDTA dose was also counted, to correct for any background activity derived from the Se-75 from the bile acid absorption test. The percentage urinary recovery of the orally adminstered dose was then calculated as follows:

$$\text{Subject counts} = \frac{\text{Subject dose (ml)}}{\text{Std dose (ml)}} \times \text{nett Std count}$$

$$\% \text{ Urinary excretion} = \frac{\text{nett urine counts}}{\text{Subject counts}} \times 100$$

Std (Standard) count was determined by the stock solution and diluting to 2.5 litres water in a urine collection bottle and counting under identical conditions as the urine collection in the large volume counter. All samples were counted within 36 hours from commencement of the study (Hetzel et al 1986).

ii) Differential sugar absorption test

After an overnight fast (from 2400 h), each subject was asked to urinate and then given 22.6 g glucose, 5 g lactulose and 1 g L-rhamnose in 100 ml of distilled water and instructed to collect urine over the next 5 h. Thirty min after ingestion of the test solution the patient was encouraged to drink water and was allowed a normal diet after 3 h. The volume of urine was noted. A 1 ml sample was estimated for urea content and

the concentrations of lactulose and rhamnose determined by high performance thin layer chromatography in a 2 ml aliqout of urine (Menzies et al 1979). Lactulose-rhamnose ratios were calculated using the following formula:

$$\frac{\text{Lactulose conc}}{\text{Urea correct Rhamnose conc}} \times \frac{1}{5}$$

Stastistical analysis

The Mann-Whitney test was used to compare patient data to that obtained in the control subjects. Linear regression analysis was also used to evaluate the data. The Chi-squared test was used to evaluate changes in lactose absorption. A p value < 0.05 was considered significant in all analyses.

4.3 RESULTS

All patients and control subjects completed the study protocol. One lactulose/rhamnose intestinal permeability measurement (patient 20) was lost. Table 4.2 summarises the results of the measurements in the patients and control subjects. Most patients had relatively few gastrointestinal symptoms, although the prevalence of symptoms was greater ($p < 0.001$) in the patients than in the control subjects. Stool frequency was not significantly different between the two groups, although in five patients the frequency of bowel actions/week was greater than the control range (Fig. 4.5) and stool frequency/week before the commencement of radiation was 7 (2-32) compared to 10 (4-26) after radiotherapy ($p < 0.001$). Six patients suffered from fecal incontinence. Stool weight was slightly less in the patients compared with the controls ($p < 0.05$). Bile acid ($p < 0.001$) and vitamin B12 ($p < 0.01$) absorption were less in the patients compared with the control subjects (Fig. 4.6). Bile acid absorption was below the control range in 14 patients. Fecal fat excretion was less ($p < 0.05$) in the patients. There was a marked increase ($p < 0.01$) in lactose malabsorption in the patients. Although only one patient gave a history of milk intolerance, dietary calcium intake was lower ($p < 0.05$) in those patients with lactose malabsorption (2870 mg/wk (73-6899)) when compared

TABLE 4.2 Measurements of gastrointestinal function in patients and in control subjects *

Parameter	Control subjects	Patients	p value
Number of subjects	18	30	
Calcium Intake (mg/wk)	3155 (65-9486)	3170 (73-14350)	N.S.
Gastrointestinal symptoms			
Score	0 (0-1)	0 (0-8)	<0.001
Stool frequency/wk	8 (3-14)	10 (4-26)	N.S.
Stool frequency/3d	4 (2-10)	4 (2-9)	N.S.
Stool wt/3d (g)	507 (308-1190)	355 (120-745)	<0.01
Absorption			
SeHCAT (%)	23 (9-64)	9 (0-61)	<0.001
Co-58 Vit B12 (%)	81 (29-99)	69 (37-96)	<0.01
Fecal fat (mmol/3d)	53 (20-80)	39 (11-164)	<0.05
Lactose malabsorption (no)	2	13	<0.01
Gastrointestinal transit			
Gastric emptying			
Lag phase (min)	0.5 (0.5-8)	0.5 (0.5-5.5)	<0.001
50% emptying (min)	65 (27-99)	45 (13-71)	<0.01
Small intestinal transit			
Start colonic filling (min)	57 (23-117)	30 (9-73)	<0.001
50% colonic filling (min)	178 (88-295)	126 (61-204)	<0.001
Small intestinal transit (min)	52 (22-114)	29 (6-66)	<0.001
Small intestinal residence (AUC)	39 23-58)	31 (10-51)	<0.01
Whole gut transit			
First marker (hr)	27 (7-48)	24 (7-72)	N.S.
50% markers (hr)	33 (18-72)	46 (10-72)	N.S.
Intestinal Permeability			
Cr-51 EDTA (%)	1.5 (0.7-4.1)	2.2 (0.6-7.3)	N.S.
Lactulose/Rhamnose (ratio)	0.095 (0.04-0.29)	0.10 (0.02-0.25)	N.S.

* Data are median values and ranges (analysis by Mann-Whitney U test).

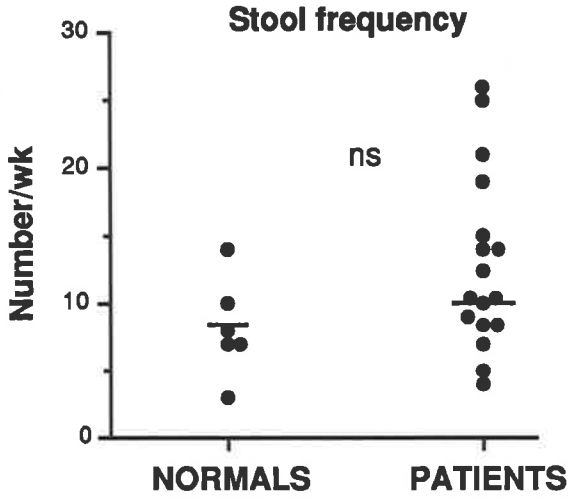


Fig 4.5 Stool frequency in patients and control subjects. The median values are shown

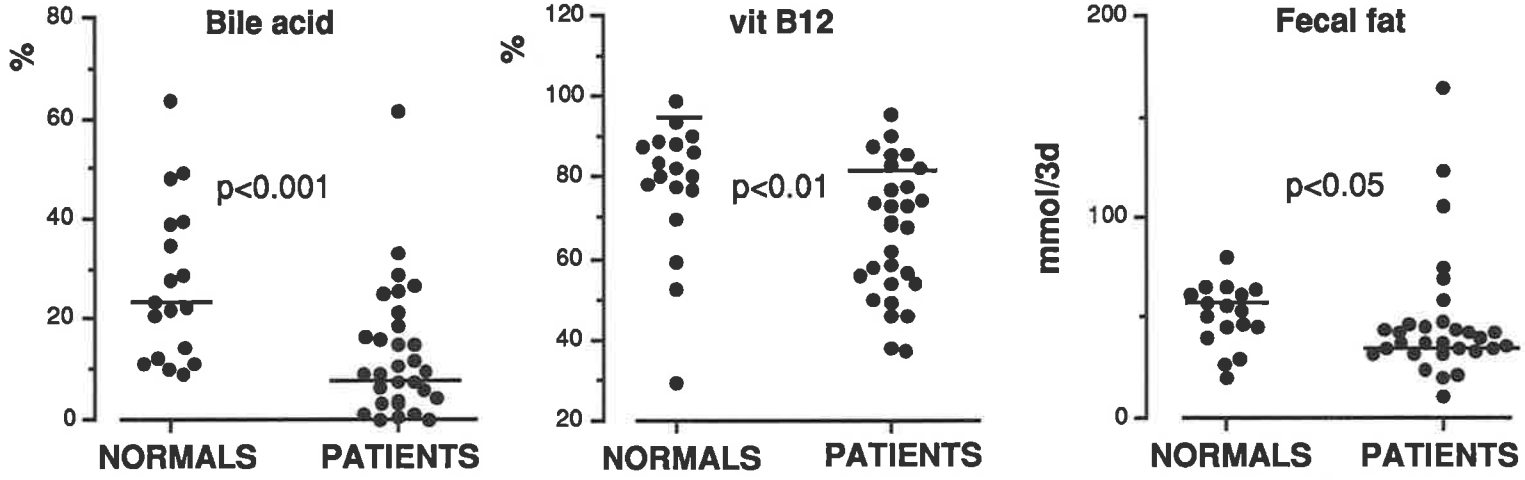


Fig 4.6 Bile acid and Vitamin B12 absorption and fecal fat excretion in patients and control subjects. The median values are shown.

to the remainder of the group (4995 mg/wk (1548-14350)). Gastric emptying ($p < 0.01$) and small intestinal transit ($p < 0.01$) were faster in the patients than in control subjects. There was no significant difference between the two groups in whole gut transit, although this was faster than the control range in two patients (Fig. 4.7). There was no difference in intestinal permeability between the two groups. Either bowel frequency, bile acid absorption, vitamin B12 absorption or orocecal transit was outside the control range in 19 of the 30 patients.

In the control group, there was a significant relationship between bile acid absorption and whole gut transit ($r=0.48$, $p < 0.05$ for both 1st and 50% markers). In the patients, bile acid absorption was related to both whole gut transit ($r=0.40$, $p < 0.05$ for 1st markers and $r=0.48$, $p < 0.01$ for 50% markers) and stool weight ($r=0.50$, $p < 0.01$). Orocecal transit ($r=-0.42$, $p < 0.05$) and whole gut transit for 1st marker ($r=-0.45$, $p < 0.05$) were related to stool frequency (Fig. 4.8). Stool weight was related to whole gut transit for 50% markers ($r=0.54$, $p < 0.01$). Intestinal permeability to Cr-51 EDTA was related to small intestinal transit ($r=0.37$, $p<0.05$) and whole gut transit for 1st markers ($r=0.48$, $p < 0.01$).

There was no significant relationship between measurements of gastrointestinal function and either total radiation dose or the age of the patient. Vitamin B12 absorption was related ($r=0.41$, $p < 0.05$) to the time since completion of radiation treatment. There were no differences in the measurements between patients who received radiation treatment alone and those who had radiation treatment with surgery (Table 4.3).

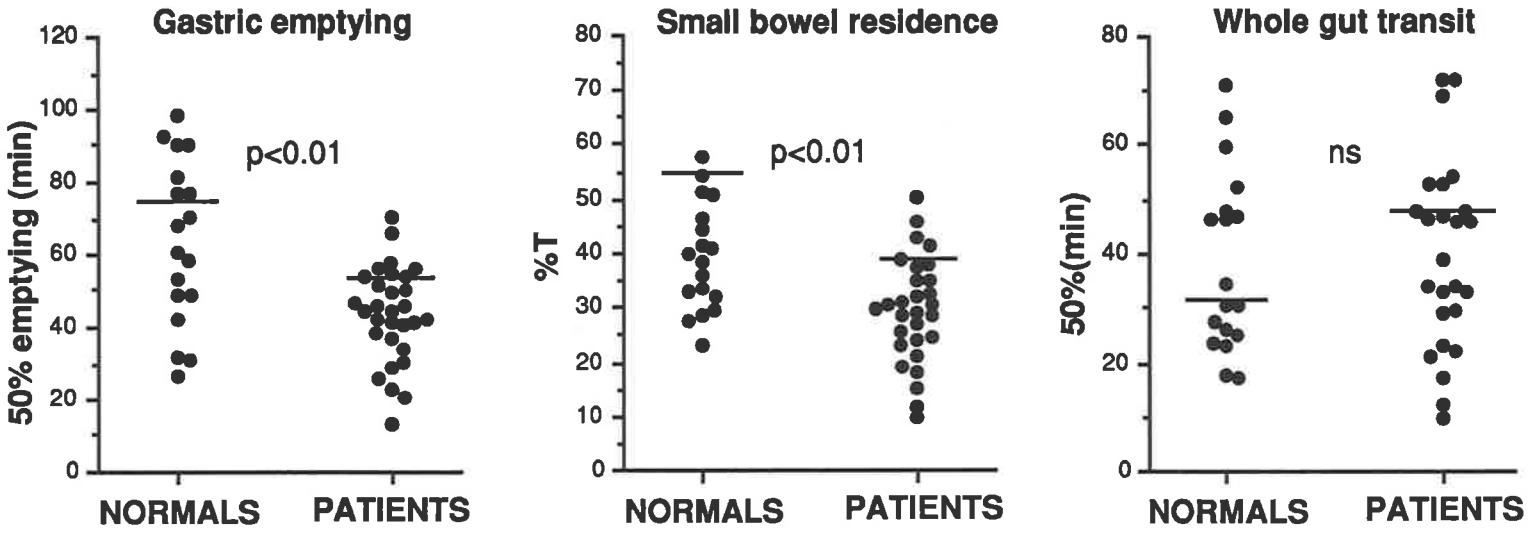


Fig 4.7. Gastric emptying (50% emptying time), small intestinal transit (AUC) and whole gut transit (50% markers) in patients and control subjects. The median values are shown.

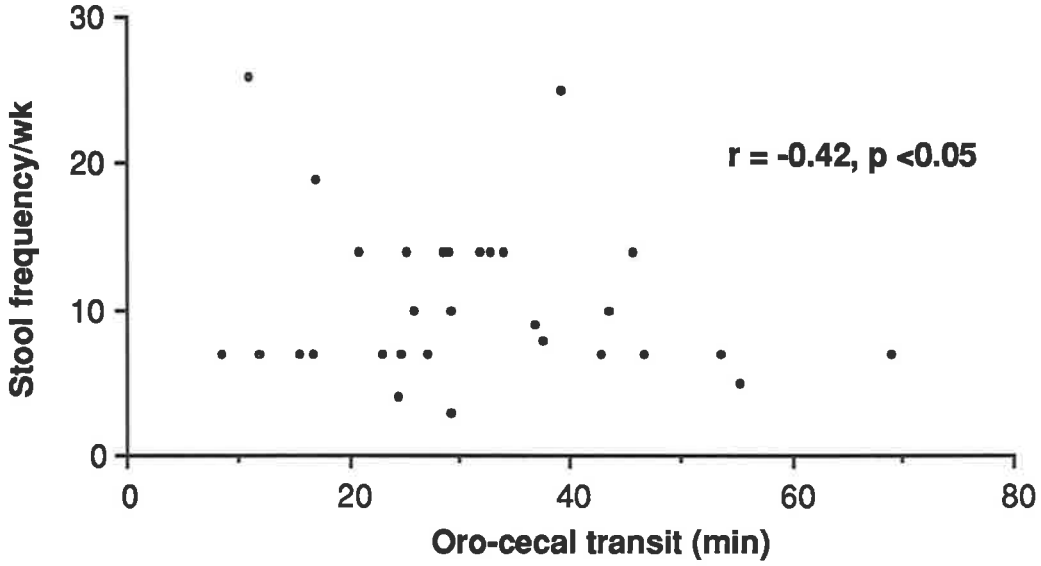


Fig 4.8 Relationship between orocaecal transit time and stool frequency in 30 patients who had received pelvic irradiation (r=-0.42 p<0.05)

TABLE 4.3 Measurements of gastrointestinal function in patients who had pelvic radiotherapy only and those who had received both surgery and pelvic radiotherapy *

Parameter	Pelvic irradiation	Surgery and pelvic irradiation	p value
Number of subjects	19	11	
Gastrointestinal symptoms			
Score	0 (0-8)	1 (0-3)	N.S.
Stool frequency/wk	10 (4-26)	9 (7-21)	N.S.
Stool frequency/3 d	4 (2-8)	5 (3-9)	N.S.
Stool wt/3d (g)	325 (120-710)	413 (229-745)	N.S.
Absorption			
SeHCAT (%)	9 (0-61)	12 (0-25)	N.S.
Co-58 Vit B12 (%)	68 (38-86)	73 (37-96)	N.S.
Fecal fat (mmol/3d)	37 (11-122)	40 (21-164)	N.S.
Lactose malabsorption (no)	8	7	N.S.
Gastrointestinal transit			
Gastric emptying			
Lag phase (min)	0.5 (0.5-3.5)	0.5 (0.5-5.5)	N.S.
50% emptying (min)	42 (20-58)	46 (13-71)	N.S.
Small intestinal transit			
Start colonic filling (min)	30 (9-56)	32 (13-73)	N.S.
50% colonic filling (min)	129 (64-204)	126 (61-180)	N.S.
Small intestinal transit (min)	27 (8-55)	34 (5-65)	N.S.
Small intestinal residence (AUC)	31 (13-51)	31 (10-38)	N.S.
Whole gut transit			
First marker (hr)	23 (7-72)	26 (10-48)	N.S.
50% markers (hr)	48 (13-72)	34 (10-72)	N.S.
Intestinal Permeability			
Cr-51 EDTA (%)	2.0 (0.6-7.3)	2.3 (0.6-4.9)	N.S.
Lactulose/Rhamnose (ratio)	0.1 (0.02-2.05)	0.07 (0-0.63)	N.S.

* Data are median values and ranges (analysis by Mann-Whitney U Test).

4.4 DISCUSSION

The results of our study suggest that abnormal gastrointestinal function is essentially an inevitable long-term sequel of pelvic radiation used in the treatment of carcinoma of the cervix and that the prevalence of chronic radiation enteritis has been generally underestimated in surgical series which have focused on "significant" injury (DeCosse et al 1969; Schofield et al,1983). While acknowledging the limitations of a retrospective study, and in particular the possibility of selection bias, (12 patients refused to be studied and at least one of these had been found to have radiation enteritis) virtually all (29/30) patients had at least one abnormal test of gastrointestinal function. The difference in age between the patients and control subjects is unlikely to have had a significant influence on our results. Consistent with the study by Newman *et al.* 1973, although the frequency of bowel actions was above the normal range in only 5 patients, the majority (19/30) of patients reported an increased frequency of bowel actions, compared to that which existed before the initiation of radiation treatment. The lower stool weight and fecal fat excretion in the patients is likely to primarily reflect differences in dietary habits between the two groups, as evidenced by the lower intake of dairy products in the patients with lactose malabsorption. It is also possible that in some patients concurrent radiation proctitis caused rectal irritability (as suggested by the presence of fecal incontinence) and contributed to a stool weight which was lower than predicted from stool frequency i.e. small volume, but multiple stools.

The abnormalities in bile acid and vitamin B12 and, possibly, lactose absorption may reflect either mucosal damage, or a reduction in the time available for nutrient absorption as a result of more rapid intestinal transit. While bacterial overgrowth may occur in patients with chronic radiation enteritis as a result of stricture formation (Beer et al 1985), this was not evident in any of our patients - stricture formation was excluded by barium follow through studies and there was no early rise in breath hydrogen concentrations during the measurement of intestinal transit (Read et al 1984).

While it has been suggested that the small intestinal mucosa recovers within two weeks of the completion of radiation therapy this point is controversial (Stryker et al 1977; Yeoh et al 1984). The possibility that abnormalities in intestinal motor function may result from radiation damage has been recognized (Yeoh et al 1984; Otterson et al 1988) as damage to intestinal smooth muscle is well documented (Rubin & Casarett 1968b). There is, however, little information about the chronic effects of irradiation on gastrointestinal transit. Our results indicate that pelvic irradiation increases the rate of gastric emptying and small intestinal transit. The observed changes in gastric emptying were somewhat surprising. The stomach is outside the pelvic radiation field and, in any case, delayed gastric emptying is a recognized, but probably rare, complication of high dose abdominal irradiation (Layer et al 1986). The terminal ileum appears to have a major role in the regulation of both gastric emptying and small intestinal transit of nutrients (Kinsman & Read 1984; Read et al 1984; Holgate & Read 1985). It is possible that damage to mucosal receptors in the small intestine, particularly in the terminal ileum, could contribute to faster small intestinal transit and gastric emptying.

Surgery has been reported to be a risk factor for radiation enteritis (LoIudice et al 1977) although this is controversial (Kinsella & Bloomer 1980). The failure to demonstrate an adverse influence of surgery in our study may be because in all but one (no. 20) of the patients who received combined treatment the total radiation dose to the pelvis was less than 60 Gy, whereas most of the patients who received radiotherapy alone had more than 70 Gy. In addition the number of subjects that we studied was relatively small.

Medical therapy of diarrhea due to chronic radiation enteritis has been largely empirical and there have been no adequate controlled studies. Antidiarrheal agents, broad spectrum antibiotics, cholestyramine, sulphasalazine and oral corticosteroids have all been used but anecdotal experience suggests that satisfactory control of diarrhea is rarely achieved (Goldstein et al 1976; Heusinkveld et al 1978). The rationale for use of

these treatments are that small intestinal bacterial overgrowth, bile salt malabsorption and active intestinal inflammation are contributory factors to diarrhea in such cases. Most studies have focused on surgical approaches to complications such as stricture and fistula formation. The demonstration of a high prevalence of lactose malabsorption after radiation treatment suggests that simple avoidance of milk or milk products may relieve symptoms in some patients. The absence of a clear history of milk intolerance in such patients is not surprising (Horowitz et al 1987). Bile salt binding agents such as cholestyramine are likely to be beneficial in patients with malabsorption of bile acid (Heusinkveld et al 1978). Our study suggests that measurement of bile acid absorption may be the most sensitive screening test for radiation enteritis, as this was abnormal in about 50% of our patients. A high prevalence of bile acid malabsorption has been reported in patients with otherwise unexplained diarrhea and it has been claimed that this is predictive of improvement with cholestyramine (Merrick et al 1985). Another therapeutic approach to the treatment of diarrhea associated with radiation enteritis may be by slowing small intestinal transit. We have reported that loperamide-N-oxide, a peripheral opiate agonist precursor, improves bile acid absorption, slows small intestinal and whole gut transit and is effective in treating diarrhea in such patients (Chapter 7). Our study suggests that evaluations of lactose and bile acid absorption and small intestinal transit should be included in the evaluation of patients who suffer diarrhoea after radiation therapy and that the results of these investigations may dictate the choice of therapy.

The observed changes in gastrointestinal function occurred despite the use of relatively sophisticated techniques for planning and delivery of radiation treatment, such as dedicated computerized axial tomographic planning, multiple radiation fields, customized beam blocks and high energy linear accelerators. Somewhat paradoxically the incidence of radiation bowel disease appears to have increased in recent years (Allen-Mersh et al 1986; Schofield et al 1986; Galland & Spencer 1987) and this has been attributed to changes in long established methods, in particular the modifications

in both intracavitary and external radiation techniques which occurred concurrently in many centers (Sherrah-Davies 1985; Allen-Mersh et al 1986; Yeoh & Spittle 1986).

CHAPTER 5

The effect of pelvic and abdominal irradiation on gastrointestinal function: a prospective longitudinal study

(Am J Med 1993;95: 397-406)

5.1 INTRODUCTION

Acute radiation enteritis, manifested principally as diarrhea, with or without abdominal cramps, is almost inevitable when radiation is used to treat curable pelvic or intra-abdominal malignant disease. Nausea and vomiting are also common symptoms, particularly when the whole abdomen is irradiated (Yeoh & Horowitz, 1987). In approximately 20% of patients undergoing pelvic irradiation, the severity of diarrhea leads to an interruption of the planned course of treatment and may reduce the chance of cure (Yeoh & Horowitz 1987; Amdur et al 1990; Fyles et al 1992). Although diarrhea usually decreases in severity within six weeks of the completion of abdominal or pelvic irradiation treatment, limited data suggest that the majority of patients experience an increased frequency of bowel actions in the long-term (Newman et al 1973). Chronic radiation enteritis, with its attendant complications of stricture and fistula formation, is a major cause of both morbidity and mortality (Kwitko et al 1982; Beer et al 1985).

The pathophysiology of diarrhea and other gastrointestinal symptoms associated with acute and chronic radiation enteritis is poorly understood and controversial (Yeoh & Horowitz 1987). The majority of studies relating to this topic have significant limitations (Newman et al 1973; Kinsella & Bloomer 1980; Beer et al 1985) and previous prospective studies have focussed on specific aspects of gastrointestinal function (Yeoh & Horowitz 1987). Probably as a result of this, treatment approaches are frequently unsuccessful (Kinsella & Bloomer 1980). In an attempt to better define both the short and long-term effects of irradiation on gastrointestinal function we have

performed a prospective study of a number of aspects of gastrointestinal function in patients undergoing radiation therapy for curable pelvic and intra-abdominal malignant disease before, during and at various time intervals following the completion of radiation therapy.

5.2 METHODS

Subjects

27 patients [23 female, 4 male, median age 62 yr (37-82 yr), median body weight 69.7 kg (39-95 kg) and median body mass index (BMI) 25.6 (18.1-40.8)] with potentially curable malignant diseases were studied. Patients had either radiation treatment alone (16 patients) or radiation treatment following gynaecological surgery (11 patients). The operations performed were: hysterectomy (1), hysterectomy and salphingo-oophorectomy (4), hysterectomy, salphingo-oophorectomy and omentectomy (5) and nephrectomy (1). 17 patients received pelvic irradiation alone and 10 patients received abdominal as well as pelvic irradiation. No patients received chemotherapy. Characteristics of the patients are shown in Table 5.1. Exclusion criteria for the patients in this study are as detailed in Chapter 4, Section 4.2 Methods. No patient was given vitamin B12, or other vitamin supplements or antibiotics.

18 normal volunteers [11 female, 7 male, median age 45 yr (19-75 yr), median body weight 75 kg (45-109 kg) and median body mass index (BMI) 26.0 (17.8-38.7)] who had no history of gastrointestinal disease and were not taking any medication were also studied.

All but one of the patients and all but one of the control subjects was Caucasian. The control subjects were younger than the patients ($p < 0.05$), but there were no significant differences in body weight or BMI between the two groups.

TABLE 5.1: Characteristics of the patient group

Patient Number	Age (Yr)	Body Weight (Kg)	Body Mass Index	Diagnosis	Radiation Dose* Gy/No of Fractions/Days	Size of Radiation Field† (cm x cm)
Pelvic Irradiation only						
1	67	69	26.0	Carcinoma of Cervix	44.95 Gy/25 F/32 Days (25 Gy to Point 'A'/52 hr)	16.5 x 18.5
2	58	74	24.2	Carcinoma of Cervix	44.00 Gy/22 F/32 Days (25 Gy to Point 'A'/46 hr)	18.5 x 16.0
3	45	67	22.5	Carcinoma of Cervix	50.00 Gy/25 F/36 Days (25 Gy to Point 'A'/45 hr)	18.0 x 20.0
4	65	62	22.7	Carcinoma of Cervix	45 Gy/25 F/39 Days (25 Gy to Point 'A'/54 hr)	17.5 x 15.5
5	43	65	23.3	Carcinoma of Cervix	44 Gy/22 F/33 Days (26 Gy to Point 'A'/49 hr)	17.0 x 18.0
6	73	85	40.8	Carcinoma of Cervix	30 Gy/10 F/12 Days (30 Gy to Point 'A' x2/64/59 hr)	16.0 x 15.0
7	72	68	29.4	Carcinoma of Cervix	50 Gy/25 F/35 Days (20 Gy to Vaginal Vault/54 hr)	14.5 x 19.0
8	61	83	29.7	Carcinoma of Cervix	50 Gy/25 F/3 Days (20 Gy to Vaginal Vault/39 hr)	17.0 x 18.0

Table 5.1 continued

Patient Number	Age (Yr)	Body Weight (Kg)	Body Mass Index	Diagnosis	Radiation Dose* Gy/No of Fractions/Days	Size of Radiation Field† (cm x cm)
9	48	87	30.9	Carcinoma of Cervix	50 Gy/25 F/33 Days (25 Gy to Point 'A'/48 hr)	18.5 x 20.5
10	72	55	19.0	Carcinoma of Cervix	44 Gy/23 F/36 Days (30 Gy to Point 'A'/48 hr)	16.0 x 14.0
11	71	68	25.6	Carcinoma of Cervix	45 Gy/25 F/38 Days (25 Gy to Point 'A'/40 hr)	17.0 x 16.5
12	82	70	25.6	Carcinoma of Cervix	45 Gy/25 F/36 Days 20 Gy/10 F/15 Days	18.0 x 17.5 9.5 x 12.5
13	65	70	25.6	Carcinoma of Cervix	46 Gy/25 F/37 Days (26 Gy to Point 'A'/50 hr)	15.0 x 20.0
14	68	70	24.2	Endometrial Carcinoma	50 Gy/25 F/33 Days (20 Gy Vaginal Mould/34 hr)	16.5 x 15.5
15	71	82	29.1	Endometrial Carcinoma	50 Gy/25 F/36 Days (20 Gy Vaginal Mould/47 hr)	15.5 x 16.5
16	59	90	37.5	Endometrial Carcinoma	50 Gy/25 F/41 Days (20 Gy Vaginal Mould/29 hr)	15.5 x 17.5

Table 5.1 continued

Patient Number	Age (Yr)	Body Weight (Kg)	Body Mass Index	Diagnosis	Radiation Dose* Gy/No of Fractions/Days	Size of Radiation Field† (cm x cm)
17	62	79	32.0	Endometrial Carcinoma	48.6 Gy/27 F/42 Days (20 Gy Vaginal Mould/24 hr)	16.5 x 19.5
Pelvic and Abdominal Irradiation						
18	37	65	20.1	Seminoma L Testis	30.00 Gy/20 F/29 Days	14.5 x 40.0
19	63	95	29.3	Seminoma L Testis	30.00 Gy/20 F/32 Days	18.0 x 35.5
20	75	50	20.0	Ovarian Carcinoma	25.00 Gy/20 F/25 Days 25.40 Gy/13 F/21 Days	31.5 x 38 16.5 x 15.5
21	52	72	27.1	Non-Hodgkin's Lymphoma	21 Gy/14 F/19 Days 20 Gy/10 F/23 Days	19.5 x 40 18.5 x 24
22	39	87	28.4	Non-Hodgkin's Lymphoma	34.50 Gy/23 F/27 Days 5.40 Gy/3 F/2 Days	19.5 x 40 18.5 x 24
23	58	79	30.9	Ovarian Carcinoma	30.00 Gy/22 F/40 Days 20.40 Gy/11 F/14 Days	22.0 x 35.5 14.0 x 29.0
24	51	59	24.0	Endometrial and Ovarian Carcinoma	22.50 Gy/20 F/25 Days 22.50 Gy/10 F/11 Days (25.00 Gy Vaginal Mould/55 hr)	28.0 x 39.5 16.0 x 16.0

Table 5.1 continued

Patient Number	Age (Yr)	Body Weight (Kg)	Body Mass Index	Diagnosis	Radiation Dose Gy/No of Fractions/Days	Size of Radiation Field (cm x cm)
25	37	58	20.1	Seminoma R Testis	30.00 Gy/20 F/31 Days	15.0 x 35.0
26	66	61	25.7	Endometrial Carcinoma	22.44 Gy/22 F/31 Days 37.60 Gy/20 F/28 Days	28.0 x 36.0 14.0 x 13.0
27	38	39	18.1	Ovarian Carcinoma	22.44 Gy/22 F/44 Days 21.60 Gy/12 F/17 Days	22.5 x 36.0 13.5 x 14.0

* Intracavitary radiation doses where applicable are given in parentheses and are prescribed to Manchester Point 'A' unless otherwise stated in which cases are prescribed to the surface of vaginal mould.

† Sizes given are for anterior/posterior fields only.

Protocol

Various aspects of gastrointestinal function were evaluated, before the start of radiation therapy (baseline or first series), 3-4 weeks after the commencement of radiation treatment (second series), 6-8 weeks after the completion of radiation treatment (third series), 12-16 weeks after the completion of radiation (fourth series) and 1-2 years (fifth series) after completion of radiation treatment, in the patients.

Control subjects underwent the same measurements of gastrointestinal function once.

Measurements

The following measurements of gastrointestinal function were assessed in the patients and control subjects: (a) Gastrointestinal symptoms (questionnaire) (b) Absorption of: i) bile acid and vitamin B12, ii) lactose, iii) fat, and measurement of stool weight (c) Gastrointestinal transit: gastric emptying, small intestinal transit and whole gut transit and (d) Intestinal permeability. In those subjects undergoing sequential measurements of vitamin B12 and bile acid absorption, although the intervals between evaluations was at least 4 weeks, a correction for patient background counts was made by first counting the residual counts in both the Co-58 and Se-75 photo peak windows prior to the adminstration of the subsequent doses of Co-58 B12 and Se-75 Hcat. Otherwise, an identical protocol for measurements of gastrointestinal function as outlined in Chapter 4, Section 4.2 Methods, was observed.

Measurement of intestinal permeability was not included in the 4th series of tests. A radiological small bowel series (using barium sulphate) was performed in all patients between 1 and 2 years after the completion of radiation treatment. Plasma biochemical parameters of hepatic function, glucose and creatinine were measured during the first, second and fifth series of tests.

Stastistical analysis

Different series of measurements in the patients were analysed using the non-parametric rank sum test (Koch 1969) and linear regression analysis. The Mann-Whitney U test was used to compare patient data with that obtained in the control subjects. The Chi-squared test was used to evaluate changes in lactose absorption. A p value of < 0.05 was considered significant in all analyses.

5.3 RESULTS

All 27 patients completed at least two series of measurements. One patient withdrew from the study after completing the second series of measurements, leaving 26 patients who completed the third series. One patient died from recurrent malignancy and one patient developed intestinal obstruction after completing the 3rd series of measurements, leaving 24 patients who completed the fourth series. Four more patients died from recurrent malignant disease and two patients withdrew after completing the fourth series of measurements, and 18 patients therefore completed all five series of measurements. Liver function tests, plasma glucose and plasma creatinine remained within the normal range in all patients.

One gastrointestinal transit measurement (patient 1) was lost in the first series owing to technical factors. One SeHCAT measurement (patient 26), one Cr-51 EDTA measurement (patient 25) and three fecal fat measurements (patients 1, 6 and 7) were lost in the second series. Two Cr-51 EDTA measurements were lost in the third series. No measurements were missing from the fourth series. One Cr-51 EDTA measurement (patient 22) was lost in the fifth series.

Comparison between baseline measurements (Series 1) in patients and control subjects

Table 5.2 summarises the results of the baseline or 1st series of measurements in the patients and the 18 control subjects. Stool weight and the frequency of bowel actions were slightly greater in the control subjects compared with the patients ($p < 0.05$ for both). Gastrointestinal symptoms were greater in the patients ($p < 0.01$). Intestinal permeability to lactulose-rhamnose was marginally less in the patients compared with the control subjects ($p<0.05$). There were no other significant differences in any of the other measurements of gastrointestinal function between the patients and the control subjects. There was no significant difference between patients who received pelvic irradiation alone, and those who received both pelvic and abdominal irradiation.

In the control group there was a significant relationship between bile acid absorption and whole gut transit ($r=0.48$, $p<0.05$ for both first marker and 50% markers). In the patients, bile acid and vitamin B12 absorption were both inversely related to stool frequency ($r=-0.40$, $p<0.05$ and $r=-0.43$, $p<0.05$ respectively). Bile acid absorption was also related to whole gut transit ($r=0.65$, $p<0.001$ for 1st marker and $r=0.49$, $p < 0.01$ for 50% markers). Stool weight was inversely related to whole gut transit for the first marker ($r=-0.44$, $p<0.05$).

Comparison between measurements at baseline (Series 1) and 3-4 weeks after commencement of irradiation (Series 2)

Table 5.3 summarises the results of the 1st and 2nd series of measurements in the patients. Stool frequency and weight were greater during radiation treatment (Figure 5.1) ($p<0.01$). Bile acid and vitamin B12 absorption decreased ($p<0.001$) and fecal fat excretion increased ($p<0.05$). There was a striking increase ($p<0.01$) in the prevalence of lactose malabsorption during radiation treatment. This was not due to intestinal bacterial overgrowth, as there was not an early rise in breath hydrogen concentrations after oral lactulose used in the gastrointestinal transit measurements (i.e. in all cases

TABLE 5.2 Results in control subjects and in patients before the commencement of radiation (Series 1) and 1-2 years after radiation (Series 5)•

Parameter	Control subjects	Patients (Series 1)	(Series 5)
Number of subjects	18	27	18
Gastrointestinal symptoms			
Score	0(0-1)	0(0-5) **	0(0-3) ***
Stool frequency/wk	8(3-14)	7(2-17) *	10(4-26)
Stool frequency/3d	4(2-10)	3(1-8)	4(2-9)
Stool wt/3d (g)	507(308-1190)	355(123-1105) *	428(120-805) *
Absorption			
SeHCAT (%)	23(9-64)	23(4-66)	12(0.5-61) *
Co-58 Vit B12 (%)	81(29-99)	77(32-91)	63(17-86) **
Fecal fat (mmol/3d)	53(20-80)	44(9-98)	51(16-262)
Lactose malabsorption (no)	2	3	4
Gastrointestinal transit			
(i) Gastric emptying			
Lag phase (min)	0.5(0.5-8)	0.5(0.5-17)	0.5(0.5-4) ***
50% emptying (min)	65(27-99)	59(15-128)	49(13-88) *
(ii) Small intestinal transit			
Start colonic filling (min)	57(23-117)	67(17-118)	28(13-46) ***
50% colonic filling (min)	178(88-295)	183(95-328)	137(64-204) **
Small intestinal transit (min)	55(22-114)	63(14-117)	26(12-45) ***
Small intestinal residence (AUC)	39(23-58)	40(20-56)	27(13-51) **

Table 5.2 cont'd

Parameter	Control subjects	Patients (Series 1)	(Series 5)
(iii) Whole gut transit			
First marker (h)	26.5(6.5-48)	26(8-72)	24(7-72)
50% markers (h)	32.5(17.5-71)	47(21-72)	48(7-72)
Intestinal Permeability			
Cr-51 EDTA (%)	1.5(0.7-4.1)	1.8(0.8-5.3)	2.3(0.96-7.3)
Lactulose/Rhamnose (ratio)	0.095(0.04-0.29)	0.06(0.02-0.23) *	0.095(0.02-0.3)

• Data are median values and ranges (analysis by Mann-Whitney U test)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ cf control subjects

TABLE 5.3: Results in patients at base-line (Series 1), 3-4 weeks after commencement of radiation (Series 2)• and 6-8 weeks (Series 3), 12-16 weeks (Series 4) and 1-2 years (Series 5) after the completion of radiation•

Parameter	Series 1	Series 2	Series 3	Series 4	Series 5
Number of subjects	27	27	26	24	18
Gastrointestinal symptoms					
Score	0(0-5)	1(0-7) **	0(0-3)	0(0-3)	0(0-3) *
Stool frequency/wk	7(2-17)	17(5-52) ***	10(4-26) ***	10(4-26) **	10(4-26) ***
Stool frequency/3d	3(1-8)	7(2-21) ***	4(2-15) *	4(2-11) *	4(2-9)
Stool wt/3d (g)	355(123-1105)	590(175-1865) **	373(85-1155)	408(140-1175)	428(120-805)
Absorption					
SeHCAT (%)	23(4-66)	7(0-96) ***	17(0-59) *	20(0-60)	12(0.5-61) *
Co-58 Vit B12 (%)	77(32-91)	47(2-96) ***	65(46-90)	66(6-85) *	63(17-86)
Fecal fat (mmol/3d)	44(9-98)	56(21-138) *	45(6-88)	48(12-162)	51(16-262)
Lactose malabsorption (no)	3	16 **	6	4	4
Gastrointestinal transit					
(i) Gastric emptying					
Lag phase(min)	0.5(0.5-17)	0.5(0.5-11)	0.5(0.5-34)	0.5(0.5-13)	0.5(0.5-4) *
50% emptying (min)	58(15-128)	60(25-240)	64(15-100)	53(17-172)	49(13-88)
(ii) Small intestinal transit					
Start colonic filling (min)	67(17-118)	33(19-64) ***	28(11-72) ***	35(18-71) **	28(13-46) ***
50% colonic filling (min)	183(95-328)	144(72-284) ***	136(76-208) ***	157(55-212) **	137(64-204) ***
Small intestinal transit (min)	63(14-117)	33(8-63) **	25(3-71) ***	33(8-70)	26(12-45) **
Small intestinal residence (AUC)	40(20-56)	26(13-45) ***	29(17-43) ***	32(6-49) **	27(13-51) **

Table 5.3 cont'd

Parameter	Series 1	Series 2	Series 3	Series 4	Series 5
(iii) Whole gut transit					
First marker (h)	26(8-72)	18(5-36) *	24(10-62)	29(7-62)	24(7-72)
50% markers (h)	47(21-72)	29(11-72)	36(10-72)	50(22-72)	48(7-72)
Intestinal Permeability					
Cr-51 EDTA (%)	1.8(0.8-5.3)	2.0(0.4-5.9)	1.8(0.9-4.5)	Not done	2.3(0.96-7.3)
Lactulose/Rhamnose (ratio)	0.06(0.02-0.23)	0.1(0.02-0.23) **	0.075(0.01-0.28)	Not done	0.095(0.02-0.30) **

- Data are median values and ranges (analysis by non-parametric rank sum test - as per Koch (20))

* $p < 0.05$. ** $p < 0.01$, *** $p < 0.001$ cf Series 1

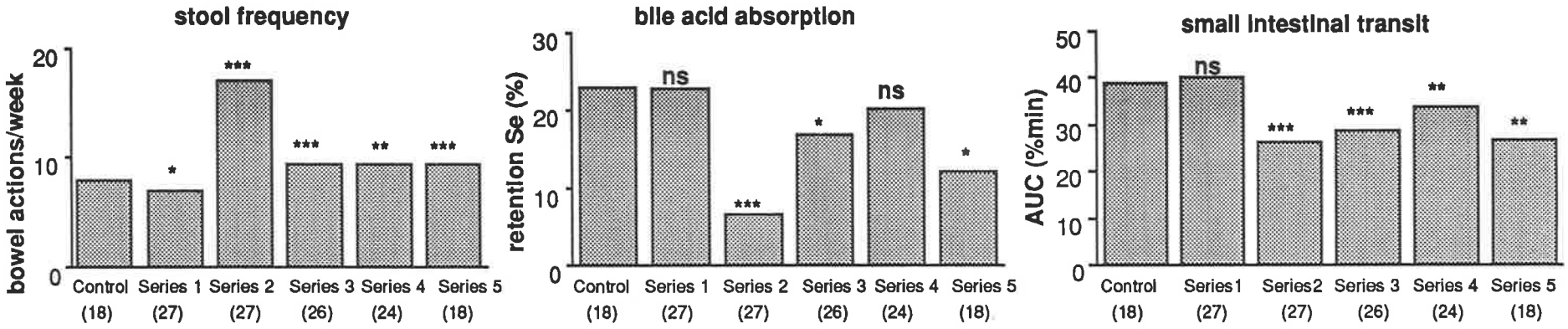


Figure 5.1 Stool frequency, bile acid absorption and small intestinal transit in control subjects and patients before (Series 1), during (Series 2), 6-8 weeks after (Series 3), 12-16 weeks after (Series 4) and 1-2 years after (Series 5) radiation treatment. The number of control subjects and patients studied is shown in parentheses. Data are shown as median values for control subjects and patients * $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to baseline data for patients.

there was a close correlation between scintigraphic arrival of the head of the meal at the cecum and the rise in breath hydrogen concentrations) and it is unlikely that the small difference in median age between the patients and the control subjects nor the racial difference (only 1 patient was non-Caucasian) can account for such a high prevalence of lactose malabsorption in the patients. There was no difference in gastric emptying. Small intestinal ($p<0.01$) and whole gut transit ($p<0.05$) were more rapid during radiation treatment. Intestinal permeability, measured by the Cr-51 EDTA test did not change during treatment, but permeability, as evaluated by the lactulose/rhamnose ratio, increased significantly.

When compared to the control subjects stool frequency was greater ($p<0.01$), absorption of vitamin B12 ($p<0.001$), bile acid ($p<0.001$) and lactose ($p<0.05$) were less and small intestinal ($p<0.001$) and whole gut transit ($p<0.01$) were faster in the patients (data not shown). Although there was no significant difference in fecal fat excretion between patients and controls, it was greater than the control range in 4 of the patients.

During radiation treatment, bile acid absorption and the time for 50% colonic filling were related ($r=0.61$, $p<0.001$). Vitamin B12 absorption was related to the time for 50% colonic filling, small intestinal residence and whole gut transit to 50% markers ($r=0.41$, $p<0.05$; $r=0.46$, $p<0.05$; and $r=0.40$, $p<0.05$ respectively) and inversely to stool frequency ($r=-0.54$, $p<0.01$). There was a direct relationship between stool frequency and stool weight ($r = 0.44$, $p<0.05$).

Stool frequency each week was higher ($p<0.01$) in patients who received pelvic irradiation alone (21 (8 - 52)) than in patients who received both pelvic and abdominal irradiation (8 (5 - 21)). Whole gut transit was faster ($p<0.05$) in patients who received both pelvic and abdominal radiotherapy (data not shown).

Comparison between measurements at baseline (Series 1) and 6-8 weeks after irradiation (Series 3)

Table 5.3 compares the results at baseline (Series 1) and 6-8 weeks after radiation (Series 3) in the patients. At 6-8 weeks the number of bowel actions was greater ($p<0.001$), although there was no difference in stool weight. Bile acid absorption ($p<0.05$) was less, but there was no difference in vitamin B12, or lactose absorption, or fecal fat excretion. Small intestinal transit ($p<0.001$) was faster, but there was no significant difference in whole gut transit or intestinal permeability.

6-8 weeks after completion of radiation, bile acid absorption was related to whole gut transit ($r=0.66$, $p<0.001$ for 1st markers and $r=0.54$, $p<0.01$ for 50% markers). Stool weight was inversely related to whole gut transit ($r=-0.42$, $p<0.05$ for 1st marker and $r=-0.61$, $p<0.001$ for 50% markers).

Comparison between measurements at baseline (Series 1) and 12-16 weeks after irradiation (Series 4)

Table 5.3 summarises the results at baseline (Series 1) and 12-16 weeks after irradiation (Series 4). Stool frequency ($p<0.01$) was greater, vitamin B12 ($p<0.05$), but not bile acid absorption was lower and small intestinal residence was less ($p<0.01$) 12-16 weeks after irradiation. At this time bile acid absorption correlated with whole gut transit ($r=0.54$, $p<0.01$ for first markers and $r=0.44$, $p<0.05$ for 50% markers). Stool frequency was inversely related to whole gut transit for 50% markers ($r=-0.57$, $p<0.05$). Stool weight was also inversely related to whole gut transit ($r=-0.56$, $p<0.05$ for first marker and $r=-0.41$, $p<0.05$ for 50% markers) and directly related to stool frequency ($r=0.54$, $p<0.001$).

Comparison between measurements at baseline (Series 1) and 1-2 years (Series 5) after irradiation

Table 5.3 compares the results at baseline (Series 1) with those obtained 1-2 years

(Series 5) after irradiation. Bowel frequency was greater ($p<0.001$) bile acid absorption was less ($p<0.05$) and small intestinal transit was faster ($p<0.01$) at 1-2 years (Figure 5.1). The number of bowel actions was greater than at baseline in 11 of the 18 patients. The double sugar test, but not the Cr-51 EDTA permeability test was marginally greater compared with baseline ($p<0.01$).

At 1-2 years after completion of radiation treatment, absorption of bile acid ($p<0.05$) and vitamin B12 ($p<0.01$) were less and gastric emptying ($p<0.05$) and small intestinal transit ($p<0.001$) were faster in the patients, when compared with the normal subjects (Table 5.2). Although fecal fat excretion was not significantly different between patients and controls, it was above the control range in 4 of the patients. In 16 of the 18 patients at least one parameter of gastrointestinal function was abnormal (outside the range in the control subjects). There was no evidence of stricture on the radiological small bowel series in any patient.

At 1-2 years bile acid absorption was related to whole gut transit for the 1st marker ($r=0.59$, $p<0.01$) and inversely to stool frequency ($r=-0.48$, $p<0.05$). Stool frequency was inversely related to whole gut transit for 1st marker ($r=-0.59$, $p<0.01$). Stool weight correlated directly with stool frequency ($r=0.62$, $p<0.01$) and inversely with whole gut transit to 50% markers ($r=-0.69$, $p<0.001$).

Stool weight was greater (481 (448-805) g vs 335 (120-745) g $p<0.05$) and whole gut transit less (24 (7-27) h vs 53 (33-72) h, $p<0.01$) in the patients who had received both abdominal and pelvic irradiation, when compared to those who received pelvic irradiation alone. Symptom score (0(0-3) vs 0(0-1), $p<0.001$) and stool frequency (5(4-9) vs 3 (2-5) $p<0.001$) and fecal fat excretion (88(16-262) mmol vs 43 (24-122) mmol, $p<0.05$) were greater in the patients who had surgery and radiation therapy when compared to those who were treated with radiation therapy alone.

5.4 DISCUSSION

Our study indicates that abnormal gastrointestinal function is essentially an inevitable long-term sequel in patients who receive pelvic, with or without, abdominal irradiation. The diarrhea of acute radiation enteritis was associated with decreased absorption of bile acid, vitamin B12, lactose and fat and more rapid small intestinal and whole gut transit The decrease in absorption may reflect mucosal injury, particularly to the terminal ileum (Trier & Browning 1966; Stryker et al 1978; Stryker & Demers 1979). However, faster intestinal transit, by reducing the time available for nutrient absorption, may also contribute to malabsorption and diarrhea (Read et al 1980). This latter possibility is supported by the observed relationship between both bile acid and vitamin B12 absorption and intestinal transit. The increased intestinal permeability, measured by the ratio of the two sugars lactulose and rhamnose, during radiation therapy is likely to be due to mucosal damage. Although the lactulose/rhamnose and Cr EDTA tests evaluate different pathways, an increase in permeability to chromium-51 EDTA may not have been apparent because of more rapid intestinal transit (Brunetto et al 1990). The cause of the more rapid intestinal transit during radiotherapy is uncertain, but both single large doses, and fractionated doses of radiation has been shown to alter intestinal motility in animals (Summers et al 1970; Otterson et al 1988). Fractionated doses of abdominal radiation result in an increased frequency of giant migrating contractions and retrograde giant contractions in the small intestine (Otterson et al 1988). It is possible that the faster small intestinal transit observed during radiation treatment may reflect impaired function of mucosal receptors which regulate small intestinal transit of nutrients (Kinsman & Read 1984; Read et al 1984; Holgate & Read 1985).

Our findings in relation to acute radiation enteritis have potentially important therapeutic implications. The high prevalence of lactose malabsorption suggests that diarrhea caused by acute radiation enteritis may respond to the avoidance of milk and milk products. Our results also support the use of elemental diets during radiation therapy (Bounous et al 1975), since absorption of these constituents is less likely to be

compromised. While we did not evaluate the effect of radiation on intestinal secretion, a useful therapeutic approach to the treatment of diarrhea during abdominal and pelvic radiotherapy may be to slow intestinal transit and this may explain the apparent efficacy of the peripheral opiate agonist, loperamide (Chapaux et al 1974). The demonstrated malabsorption of bile acid in many cases provides a rationale for the use of agents such as cholestyramine. Our study suggests that small intestinal bacterial overgrowth is not a major factor in diarrhea associated with acute radiation enteritis.

There is relatively little information in relation to prevalence of chronic radiation enteritis. Several retrospective surgical series have suggested that the incidence of "significant" damage is only 5-15% (DeCosse et al 1969; Schofield et al 1983). However, these studies have considerable limitations, particularly as they do not include patients who died, or were lost to follow-up in the prolonged interval between treatment and the onset of symptoms. Our study demonstrates that the incidence of gastrointestinal dysfunction following radiation treatment has been generally underestimated and supports the hypothesis that the majority of patients with chronic radiation enteritis do not seek medical help until the occurrence of a severe complication, such as stricture, perforation or anaemia due to blood loss (Yeoh & Horowitz 1987). Following the completion of abdominal and pelvic radiotherapy median stool frequency decreased, but remained increased even at 1-2 years. At 1-2 years small intestinal transit was faster and absorption of bile acid, was reduced and both abnormalities may contribute to diarrhea. The persistent increase in stool frequency is consistent with a retrospective study (Newman et al 1973) in which an increase in the frequency of bowel actions was reported in 12 of 17 patients who had received pelvic radiotherapy for gynecological malignancy. The abnormalities in bile acid and vitamin B12 and, in some cases, lactose absorption may again reflect mucosal damage and/or more rapid intestinal transit. Although it has been suggested that small bowel mucosal damage occurring during radiation therapy is reversible within a few weeks (Trier & Browning 1966) we and others (Chapter 7; Beer et al 1985) have

found a high prevalence of lactose malabsorption in patients with diarrhea due to chronic radiation enteritis. The changes in absorption which we have demonstrated persist for longer than the time for histological recovery of the intestinal mucosa after irradiation (Trier & Browning 1966). It is therefore probable that changes in intestinal transit (particularly in the small intestine) contribute to diarrhea and malabsorption. While vitamin B12 malabsorption has been demonstrated in some patients with chronic radiation enteritis (Ludgate & Merrick 1985), our results support previous evidence that bile acid absorption is a more sensitive test of terminal ileal function than vitamin B12 absorption (Fromm et al 1973). Bacterial overgrowth may occur in patients with chronic radiation enteritis (Beer et al 1985), but this did not appear to be a significant factor in the present study, possibly because of the absence of stricture formation. Although only two thirds of the original cohort of 27 patients were studied 1-2 years after completion of radiation therapy, this is unlikely to have significantly influenced the results. Similarly, the relatively small difference in median age between the patients and the control subjects is unlikely to be important. The observed higher stool frequency and fecal fat excretion in patients who received surgery, is consistent with the suggestion that the latter may increase the risk of radiation bowel injury (Kinsella & Bloomer 1980).

The rectum, sigmoid colon and terminal ileum appear to be particularly at risk from pelvic radiotherapy (Wellwood & Jackson 1973;Schofield et al 1983). While the histological features of chronic radiation enteritis, characterized by obliterative endarteritis of the small vessels in the intestinal wall, submucosal oedema and lymphatic dilatation are well documented (Wellwood & Jackson 1973), there is little information about the pathophysiology of diarrhea due to chronic radiation enteritis (Beer et al 1985; Yeoh & Horowitz 1987). It has been suggested that diarrhea reflects malabsorption due to either infiltration of the mucosa by inflammatory cells and luminal narrowing of the submucosal arterioles (Carr et al 1984), or intestinal bacterial overgrowth (Ludgate & Merrick 1985). The possibility that abnormalities in intestinal motor function due to

radiation damage may be important has also been recognized (Yeoh et al 1984; Otterson et al 1988). Although it is clear that damage to the intestinal smooth muscle may result from irradiation (Rubin & Casarett, 1968b) and that abdominal radiation may be complicated by chronic gastroparesis (Layer et al 1986), we are unaware of any studies of intestinal motor function in chronic radiation enteritis in either animals or humans.
The sustained increase in stool frequency, but not stool weight has a number of possible explanations. Dietary changes inevitably occur in patients with chronic diarrhea and in our study, were likely to be associated with a reduced intake of dairy products, because of lactose malabsorption, possibly contributing to the normal fecal fat excretion. It is also likely that in some patients concurrent radiation proctitis contributed to a stool weight which was lower than predicted from stool frequency. In this regard anorectal manometric measurements would be of interest, but were not performed because of the extensive nature of our investigative protocol. The value of rectal biopsy in such cases is likely to be limited (Newman et al 1973).

Medical therapy of diarrhea due to chronic radiation enteritis has been largely empirical and there have been no adequate controlled studies. Antidiarrheal agents, broad spectrum antibiotics, cholestryamine, sulphasalazine and oral corticosteroids have all been used but anectdotal experience suggests that satisfactory control of diarrhea is rarely achieved (Goldstein et al 1976; Heusinkveld et al 1978; Schofield et al 1983). Most studies have focused on surgical approaches to complications such as stricture and fistula formation. The demonstration of lactose malabsorption in a number of patients following the completion of treatment has important implications for the treatment of diarrhea. Simple avoidance of milk or milk products may relieve symptoms in some patients. Bile salt binding agents such as cholestyramine are likely to be beneficial in patients with malabsorption of bile acid (Heusinkveld et al 1978). A high prevalence of bile acid malabsorption has been reported in patients with otherwise unexplained diarrhea and it has been claimed that this is predictive of improvement with cholestyramine (Merrick et al 1985). Another therapeutic approach to the treatment of

diarrhea associated with radiation enteritis may be by slowing small intestinal transit. We have reported that loperamide-N-oxide, a peripheral opiate agonist precursor, improves bile acid absorption, slows small intestinal and whole gut transit and is effective in treating diarrhea in such patients (Chapter 7).

The observed persistent changes in gastrointestinal function occurred despite the use of relatively sophisticated techniques for planning and delivery of radiation treatment, such as dedicated computerized axial tomographic planning, multiple radiation fields, customized beam blocks and high energy linear accelerators. More specialized techniques reported to improve tolerance of pelvic irradiation were not employed (Green 1983; Shanahan et al 1990). While it would be of interest to document the impact of such specialized techniques on gastrointestinal function, somewhat paradoxically there is evidence that the incidence of radiation bowel disease has increased in recent years, as a result of changes in long established techniques (Schofield et al 1986; Galland & Spencer 1987). For example, although the use of radium has now been changed to safer isotopes such as cesium and cobalt, this has also entailed new or modified applicators, altered dose rates and changes in the number of treatments.

CHAPTER 6

A retrospective study of the effects of abdominal irradiation for seminoma of the testis on gastrointestinal function (J Gastroenterol Hepatol 1995; 10:125-130)

6.1 INTRODUCTION

Damage to the intestine is a generally underestimated cause of morbidity when radiation is used in the curative treatment of abdominal or pelvic malignancy (Newman et al 1973; Beer et al 1985). We have recently reported that when pelvic irradiation is used in the treatment of carcinoma of the cervix abnormal gastrointestinal function is essentially an inevitable long term sequela (Chapter 4). Abdominal irradiation is commonly used as an adjunct to surgery in the curative treatment of seminoma of the testis and other abdominal malignancies and it is well recognised that short-term symptoms such as nausea, vomiting and diarrhoea occur frequently as a result of such treatment (Priestman et al 1987; Yeoh et al 1993). Although chronic gastroparesis has been reported as a sequel to abdominal irradiation, there is little information about the long-term effects of abdominal irradiation on gastrointestinal function (Layer et al 1986). Effects of irradiation are likely to be dependent on the duration of treatment, the dose given and the amount and region of intestine exposed (Strockbine et al 1970; Wharton et al 1977; Withers et al 1977; Bourne et al 1983). The dose of radiation given for the treatment of carcinoma of the cervix is greater than that used in the treatment of seminoma, although the treatment of seminoma employs a larger radiation field. The issue of whether the use of irradiation in the treatment of seminoma is associated with significant long-term morbidity is of critical importance in view of recent studies that indicate that abdominal irradiation may be avoidable in up to 85% of patients (Peckham et al 1987; Duchesne et al 1990).

We have now evaluated various aspects of gastrointestinal function in a randomly selected cohort of patients treated with abdominal irradiation for seminoma of the testis between 2 and 10 years previously.

6.2 METHODS

Subjects

The study group comprised 15 patients [median age 39 yr (25-70) yr, median body weight 81 kg (65-137 kg) and median body mass index (BMI) 25 (20-42)] who were randomly selected from a total cohort of 63 patients who had been treated for Stage I seminoma of the testis, with abdominal (para-aortic nodal) and ipsilateral pelvic nodal irradiation between 1981 and 1990 at the Royal Adelaide Hospital. Of these 63 patients, 3 had died (1 of recurrent disease, 2 of unrelated causes) and 7 were lost to follow-up. Characteristics of the patient group are shown in Table 6.1. The median time since the completion of radiation treatment was 5 years (2-10 years). Six of the 15 patients had right sided seminoma and in one patient the seminoma was bilateral. The exclusion criteria for the patients in this study are as detailed in Chapter 4, Section 4.2 Methods. Significant intestinal stricture was also excluded in all cases by a radiological small bowel series. All of the patients and all but one of the control subjects was Caucasian.

The same 18 normal volunteers as in the retrospective study of the chronic effects of irradiation for carcinoma of the cervix on gastrointestinal function (Chapter 4, Section 4.2 Methods) served as control subjects.

There were no significant differences in age, body weight and BMI between the two groups.

Protocol

Each of the patients and normal voluteers underwent the same measurements of gastrointestinal function as detailed in Chapter 4, Section 4.2 Methods.

TABLE 6.1 Characteristics of the patient group

Patient Number	Age (Yr)	Body Weight (Kg)	Body Mass Index	Treatment	Radiation Dose* Gy/No of Fractions/Days	Size of Radiation Field+ (cm x cm)
1	40	65	20.1	Para-aortic and left pelvis	30 Gy/20 F/29 Days	14.5 x 40
2	65	95	29.3	Para-aortic and left pelvis	30 Gy/20 F/32 Days	18.0 x 35.5
3	25	77	23.0	Para-aortic and left pelvis	30 Gy/20 F/35 Days	13.5 x 39
4	39	84	28.1	Para-aortic and pelvis	30 Gy/20 F/28 Days	23.0 x 36.5
5	33	71	22.4	Para-aortic and right pelvis	30 Gy/20 F/29 Days	16.0 x 36.5
6	27	81	24.2	Para-aortic and left pelvis	30 Gy/20 F/29 Days	16.0 x 38
7	37	72	24.1	Para-aortic and right pelvis	40 Gy/20 F/35 Days	11.5 x 25
8	70	85	24.8	Para-aortic and right pelvis	37.8 Gy/22 F/45 Days	16.0 x 40
				Right kidney bed boost	14 Gy/7 F/8 Days	10.5 x 14

Table 6.1 continued

Patient Number	Age (Yr)	Body Weight (Kg)	Body Mass Index	Treatment	Radiation Dose* Gy/No of Fractions/Days	Size of Radiation Field+ (cm x cm)
9	68	89	29.4	Para-aortic and left pelvis	30 Gy/20 F/33 Days (30 Gy to Point 'A'/48 hr)	14.0 x 28
10	36	68	24.9	Para-aortic and left pelvis	30 Gy/20 F/30 Days	12.0 x 30
11	46	95	26.9	Para-aortic and right pelvis	30 Gy/18 F/24 Days	11.0 x 31
12	35	73	22.5	Para-aortic and left pelvis	29.3 Gy/20 F/26 Days	12.5 x 37.5
13	45	137	42.3	Para-aortic and right pelvis	34.9 Gy/24 F/36 Days	15.0 x 34
14	35	85	23.5	Para-aortic and right pelvis	40 Gy/25 F/50 Days	15.0 x 40
15	39	79	25.5	Para-aortic and left pelvis	40 Gy/25 F/39 Days	15.0 x 38

* For each patient, the dose increment is 1.50-2.00 Gy prescribed as a minimum tumour dose given 5x/week.

\+ Sizes given are for maximum field dimensions. Shielding blocks were customized for each patient.

Stastistical analysis

Data were evaluated using the Mann-Whitney test and linear regression analysis. The Chi-squared test was used to evaluate changes in lactose absorption. Values outside the control range were considered abnormal. A p value < 0.05 was considered significant in all analyses.

6.3 RESULTS

The lactose absorption and intestinal permeability tests were not done in two of the patients. The 13 remaining patients and all of the control subjects completed the study protocol.

Table 6.2 summarises the results of the measurements in the patients and control subjects. Although most patients had relatively few upper gastrointestinal symptoms, the prevalence of symptoms was greater ($p < 0.01$) than in the control subjects. Stool frequency was not significantly different between the two groups, but in two patients it was greater than the control range. In the patients there was a non-significant trend for an increase in stool frequency/week when compared to before the commencement of radiation (7 (5-32) bowel actions/wk vs 11 (7-32) bowel actions/wk ($p=0.058$). There was no significant difference in stool weight or faecal fat excretion between the patients and control subjects, but faecal fat excretion was greater than the control range in 3 of the patients. There was also no significant difference in dietary calcium intake, or the prevalence of lactose malabsorption between the two groups. Bile acid and vitamin B12 absorption did not differ between patients and controls, but in one patient with right sided seminoma bile acid absorption was below the control range. Gastric emptying was faster in the patients ($p<0.01$) and in seven of the patients the 50% gastric emptying time was less than the control range. There was no difference in small intestinal transit, whole gut transit, or intestinal permeability between the two groups. Despite the absence of statistically significant differences at least one parameter of gastrointestinal function was abnormal in 11 of the 15 patients.

TABLE 6.2 Measurements of gastrointestinal function in patients and in control subjects *

Parameter	Control subjects	Patients	p value
Number of subjects	18	15	
Calcium intake (mg/wk)	3155(65-9486)	5030(17-13650)	N.S.
Gastrointestinal symptoms			
Score	0(0-1)	1(0-7)	<0.01
Stool frequency/wk	8(3-14)	7(4-21)	N.S.
Stool frequency/3d	4(2-10)	3(1-8)	N.S.
Stool wt/3d (g)	507(308-1190)	470(165-948)	N.S.
Absorption			
SeHCAT (%)	23(9-64)	22(8-51)	N.S.
Co-58 Vit B12 (%)	81(29-99)	75(56-94)	N.S.
Faecal fat (mmol/3d)	53(20-80)	62(16-124)	N.S.
Lactose malabsorption (no.)	2	3	N.S. **
Gastrointestinal transit			
Gastric emptying			
Lag phase (min)	0.5(0.5-8)	0.5(0.5-8.5)	N.S.
50% emptying (min)	65(27-99)	30(10-87)	<0.01
Small intestinal transit			
Start colonic filling (min)	57(23-117)	39(22-98)	N.S.
50% colonic filling (min)	178(88-295)	153(105-252)	N.S.
Small intestinal transit (min)	55(22-114)	38(21-97)	N.S.
Small intestinal residence (AUC)	39(23-58)	41(23-75)	N.S.
Whole gut transit			
First marker (h)	27(7-48)	23(12-55)	N.S.
50% markers (h)	33(18-72)	37(22-55)	N.S.
Intestinal Permeability			
Cr-51 EDTA (%)	1.5(0.7-4.1)	2.0(1.2-3.6)	N.S. **
Lactulose/Rhamnose (ratio)	0.095(0.04-0.29)	0.04(0-0.43)	N.S. **

* Data are median values and ranges (analysis by Mann-Whitney U test)

** Result based on 13 of 15 patients

Patients who had right sided seminoma (7 patients including the patient with bilateral seminoma) had a greater frequency of bowel actions/week when compared to those with left sided seminoma (14(5-21) vs 7(4-18), $p<0.05$). Apart from this there were no other significant differences between the two patient groups. When the group with right sided seminoma (7 patients) was compared to the control subjects, symptom score was greater ($p<0.01$) and there was a trend ($p=0.06$) towards faster gastric emptying in the patients. Symptom score was greater ($p<0.05$) and gastric emptying faster ($p<0.01$) in the 8 patients with left sided seminoma when compared to the control subjects.

In the control group, there was a significant correlation between bile acid absorption and whole gut transit ($r=0.48$, $p < 0.05$ for both 1st and 50% markers). In the patients, stool frequency was inversely related to whole gut transit for 1st markers ($r=-0.51$, $p<0.05$) and directly related to both stool weight ($r=0.63$, $p < 0.01$) and faecal fat excretion ($r=0.71$, $p<0.01$).

6.4 DISCUSSION

The results of this study show, contrary to commonly held belief, that treatment of seminoma of the test with abdominal irradiation is frequently associated with long-term effects on gastrointestinal function. Although a modest increase in the prevalence of upper gastrointestinal symptoms and more rapid gastric emptying were the only parameters of gastrointestinal function which were statistically different from the control subjects, other measurements were clearly abnormal in individual patients. For example, faecal fat excretion was abnormal in three of the 15 patients, stool frequency was increased in two patients, one patient had more rapid small intestinal transit and in 11 of the 15 patients at least one parameter was abnormal. It is therefore likely that a greater number of significant differences would have been apparent if a greater number of patients was studied.

The demonstration of faster gastric emptying in our patients was surprising, particularly in view of a report of gastroparesis as a complication of abdominal irradiation for seminoma (Layer et al 1986). The mechanical controls of gastric emptying are still poorly understood. The traditional concept that tonic contraction of the gastric fundus has the major control over liquid emptying (Hinder & Kelly 1977) has been challenged by observations which have shown that transpyloric flow of liquids is mainly pulsatile (Houghton et al 1988). The pylorus appears to be important in the control of nutrient emptying by acting as a brake (Heddle et al 1989). Small intestinal receptors exert feedback on this mechanism so that emptying of nutrients is normally tightly regulated (McHugh & Moran 1979; Brener et al 1983). The cause of the more rapid gastric emptying after abdominal irradiation is uncertain but may reflect changes in proximal gastric or pyloric motor function, or defective small intestinal feedback mechanisms. Effects on gastric motor function may well be dose-dependent, as the radiation dose given in our study was substantially less than in the previous report (Layer et al 1986). It is also uncertain whether more rapid gastric emptying contributes to the increased prevalence of upper gastrointestinal symptoms in these patients.

The relatively subtle changes in gastrointestinal function observed in this study contrast with the marked abnormalities that exist in most patients who have received pelvic irradiation for treatment of carcinoma of the cervix (Chapter 4). This is not surprising. The radiation doses used in this study were substantially less than those employed in our previous report (Chapter 4, 30Gy (29.3-51.8) vs 69 Gy (30-75), $p < 0.001$) and the terminal ileum was outside the radiation field in those patients with left sided seminoma. It is of interest that stool frequency was greater in those patients who had right sided seminoma.

We have suggested previously (Chapters 4 and 5) that more precise characterisation of the abnormalities in gastrointestinal function associated with chronic radiation enteritis

may allow therapy to be targeted more effectively. For example, lactose malabsorption should be treated by avoidance of milk products (a history of lactose intolerance is seldom obtained) and bile salt binding agents such as cholestyramine may be beneficial in patients with bile acid malabsorption (Heusinkveld et al 1978). Another therapeutic approach to the treatment of diarrhoea associated with chronic radiation enteritis may be by slowing intestinal transit (Chapter 7).

Our results do not allow a definitive conclusion as to whether irradiation should be avoided if at all possible in the treatment of Stage I seminoma (Peckham et al 1987; Duchesne et al 1990). However, with the demonstration that a policy of close surveillance following orchidectomy produces an equivalent long term survival to immediate post-operative radiation therapy for Stage I seminoma of the testis (Peckham et al 1987; Duchesne et al 1990) the morbidity of treatment, even if relatively minor, assumes a new significance.

CHAPTER 7

Gastrointestinal function in chronic radiation enteritis - the effects of loperamide-N-oxide (Gut 1993;34:476-482)

7.1 INTRODUCTION

Chronic radiation enteritis is now recognised to be a frequent and clinically important sequel of abdominal and pelvic irradiation treatment for malignant disease (Newman et al 1973; Ludgate & Merrick 1985; Schofield et al 1986; Galland & Spencer 1987; Yeoh & Horowitz 1987). Diarrhea with or without abdominal cramps is the most common symptom (Newman et al 1973). Although intestinal stricture and associated bacterial overgrowth are well recognised in chronic radiation enteritis, in most cases the pathophysiology of diarrhea is uncertain. While changes in intestinal absorption and motility unrelated to bacterial overgrowth have been implicated in the aetiology of diarrhea (Newman et al 1973; Ludgate & Merrick 1985; Yeoh et al 1984; Yeoh & Horowitz 1987; Chapter 5) there has been no comprehensive evaluation of gastrointestinal function in chronic radiation enteritis. Perhaps partly as a result of this, present approaches to treatment have been often empirical (Galland & Spencer 1987; Yeoh & Horowitz 1987).

The aim of our study was to evaluate various aspects of gastrointestinal function in patients with diarrhea due to chronic radiation enteritis and the effects of treatment with the peripheral opiate agonist precursor loperamide-N-oxide.

7.2 METHODS

Subjects

20 patients [16 female, 4 male, median age 73 yr (42-90 yr), median body weight 65 kg (54-114) and median body mass index (BMI) 25.1 (18.8-31.4)] with persistent diarrhoea 3-22 years after therapeutic pelvic irradiation for carcinoma of the genitourinary tract (see Table 7.1 for individual patient characteristics) were studied.

TABLE 7.1 Characteristics in the patient group

Patient Number	Age (Yr)	Body Weight (Kg)	Body Mass Index	Diagnosis	Radiation Dose Gy/No of Fractions/Days	Radiation Field Size - Cm x Cm
1	68	69.2	25.6.	Carcinoma of Cervix	44.95 Gy/25 F/32 Days (25 Gy to Pt 'A' Intra-Cavitary)	16.5 x 18.5
2	80	71.9	24.8	Carcinoma of Prostate	59.76 Gy/30 F/51 Days	15.5 x 17.5
3	80	72.5	24.7	Carcinoma of Prostate	62.15 Gy/31 F/44 Days	15.5 x 19.0
4	63	58.8	27.7	Carcinoma of Cervix	No Details Available (Treated in Chile)	
5	76	62.5	27.6	Endometrial Carcinoma	46 Gy/23 F/31 Days	17.5 x 15.5
6*	79	66.0	23.5	Endometrial Carcinoma	50 Gy/25 F/41 Days (20 Gy Vaginal Mould)	17.5 x 18.0
7	85	58.0	23.6	Carcinoma of Cervix	46 Gy/23 F/33 Days (20 Gy to Pt 'A' Intra-Cavitary)	16.0 x 16.5
8	90	54.0	21.3	Carcinoma of Cervix	50 Gy/25 F/3 Days (20 Gy to Pt 'A' Intra-Cavitary)	15.0 x 16.0
9	70	54.0	22.5	Carcinoma of Cervix	34 Gy/17 F/27 Days (45 Gy to Pt 'A' Intrac-Cavitary)	14.0 x 15.0
10	42	62.0	22.2	Carcinoma of Cervix	50 Gy/25 F/36 Days	17.0 x 21.0
11	63	67.0	28.3	Endometrial Carcinoma	50 Gy/25 F/32 Days	15 x 28.5 (Abdomen) 15 x 17.5 (Pelvis Only)
12	73	67.0	25.9	Carcinoma of Cervix	50 Gy/25 F/39 Days	14 x 19.5
13*	73	65.0	21.2	Carcinoma of Prostate	64 Gy/32 F/47 Days	13.0 x 19.5 (Pelvis) 8.5 x 9.5 (Prostate)
14	72	59.0	22.5	Carcinoma of Cervix	50 Gy/30 F/45 Days	15.0 x 14.0
15	78	70.0	29.2	Endometrial Carcinoma	46.8 Gy/26 F/39 Days (20 Gy Vaginal Mould)	15.5 x 17.0
16	73	54.0	21.4	Carcinoma of Ovary	50 Gy/26 F/39 Days	15.0 x 18.0
17	81	74.0	25.3	Carcinoma of Prostate	64 Gy/32 F/45 Days	15.0 x 14.5
18	63	57.0	18.8	Carcinoma of Ovary	49.9 Gy/25 F/35 Days	15.0 x 20.0
19	48	114.0	51.4	Carcinoma R Fallopian Tube	55 Gy/30 F/40 Days	15.0 x 20.0
20	57	80.0	28.4	Endometrial Carcinoma	50 Gy/25 F/35 Days	Not Available

* Patients withdrew from study

Persistent diarrhoea was defined as a chronic doubling of the frequency of defaecation before irradiation and a minimum frequency of 14 bowel actions a week. The exclusion criteria for patients in this study are as detailed in Chapter 4, Section 4.2 Methods. Significant intestinal stricture were also excluded in all cases by a radiological small bowel series.

The same18 normal volunteers as detailed in Chapter 4, Section 4.2 served as control subjects.

All but three of the patients and all but one of the control subjects was Caucasian. The control subjects were younger than the patients ($p < 0.05$). Body weight was greater in control subjects compared with the patients ($p < 0.05$), but there were no significant difference in BMI between the two groups.

Protocol

Each of the 20 patients was given in double-blind randomised order, loperamide oxide tablets (Janssen Pharmaceutica Beerse, Belgium) in a dose of 3 mg twice daily by mouth (0800h and 2000h) and placebo (identical tablets without loperamide oxide) for 14 days, separated by a wash-out period of 14 days. Between days 3 and 14 after starting either loperamide oxide or placebo, each patient underwent measurements of a number of aspects of gastrointestinal function.

Each patient had a complete blood examination, multiple biochemical analysis of plasma and ECG when admitted into the study and at the end of each phase of the study. Any adverse effects potentially related to the trial medication were also documented at the end of each phase of the study.

The control subjects did not receive either placebo or loperamide oxide tablets but underwent an identical series of measurements of gastrointestinal function on one occasion.

Measurements

The following measurements of gastrointestinal function were assessed in the patients and control subjects: (a) Gastrointestinal symptoms (questionnaire) (b) Absorption of: i) bile acid and vitamin B12, ii) lactose, iii) fat, and measurement of stool weight (c) Gastrointestinal transit: gastric emptying, small intestinal transit and whole gut transit and (d) Intestinal permeability. In those subjects undergoing sequential measurements of vitamin B12 and bile acid absorption, although the intervals between evaluations was at least 4 weeks, a correction for patient background counts was made by first counting the residual counts in both the Co-58 and Se-75 photo peak windows prior to the adminstration of the subsequent doses of Co-58 B12 and Se-75 Hcat. Otherwise, an identical protocol for measurements of gastrointestinal function as outlined in Chapter 4, Section 4.2 Methods, was observed.

Statistical analysis

Data were evaluated using the Wilcoxon rank sum test (paired measurements), the Mann-Whitney U test (unpaired measurements) (Conover 1980), the Chi-squared test, and linear regression analysis. A p value of < 0.05 was considered significant.

7.3 RESULTS

18 out of 20 patients completed the study. The two patients who withdrew (numbers 6 and 13) felt they could no longer cope with the program of evaluations of gastrointestinal function required in the protocol. No significant adverse effects were reported and no significant changes in haematological, biochemical and electrocardiographic parameters were documented. One scintigraphic assessment of gastric emptying and intestinal transit (in patient 5), one urine collection for the double sugar lactulose/rhamnose permeability test (patient 10) and one faecal fat estimation (in patient 11) were lost. In consequence only 17 paired measurements were used in some cases for the comparison between placebo and loperamide oxide phases of the study.

Comparison between control subjects and patients during placebo treatment

Table 7.2 summarises the results for the patients during the placebo phase of the study and the control subjects. There was no evidence of small intestinal bacterial overgrowth in the patients i.e. no early rise in breath hydrogen concentrations after oral lactose or lactulose. Both the number of bowel actions per week (assessed by diary) and stool frequency per 3 days (assessed by 3 day faecal collection) were greater in the patients compared with the control group ($p<0.001$). There was no significant difference in stool weight. Except for the frequency of bowel actions there was no difference in gastrointestinal symptoms between the patients and controls. Bile acid absorption was markedly reduced in the patients ($p<0.001$), but there was no significant difference between the two groups in vitamin B12 absorption. Faecal fat excretion was less in the patients ($p<0.01$). Dietary intake of dairy products was lower ($p<0.02$) and fat intake also tended to be less ($p=0.09$) in the patients. 10 patients had lactose malabsorption, compared to 2 of the control subjects ($p<0.05$). Of the patients with lactose malabsorption only 2 had a history of gastrointestinal intolerance to milk, or milk products. Despite this dietary intake of dairy products was less in patients with lactose malabsorption than the remainder of the group (213g (0-4940) vs 2354g (320-8190) $p<0.05$). Gastrointestinal symptoms after the lactose load were reported by 4 patients. There was no significant difference in gastric emptying between the two groups, but small intestinal transit ($p<0.001$) and whole gut transit ($p<0.05$) were faster in the patients than in the control subjects. There was no significant difference in intestinal permeability between the two groups. In the control group there was a significant correlation ($r=0.48$, $p<0.05$) between bile acid absorption and whole gut transit (first radioopaque marker and 50% markers). In the patients stool frequency/3d was inversely related to bile acid absorption ($r=-0.49$, $p<0.05$). Otherwise there were no significant relationships between the frequency of bowel actions, or stool weight and other parameters of gastrointestinal function in either the patients, or the control subjects.

TABLE 7.2 Results in patients during the placebo phase of the study and in control subjects*

Parameter	Control	Patients (Placebo)	p value
Number of subjects	18	18	
Calcium intake (mg/wk)	3155(65-9486)	1475(0-8190)	<0.02
Gastrointestinal symptoms			
Score	0(0-1)	0(0-3)	N.S.
Bowel actions/wk	8(3-14)	19(9-53)	<0.001
Stool frequency/3d	4(2-10)	7(2-14))	<0.001.
Stool wt/3d (g)	507(308-1190)	450(186-1275)	N.S.
Absorption			
SeHCAT (%)	22.8(9.2-63.6)	3.3(0.0-45.7)	<0.001.
Co-58 Vit B12 (%)	81.4(29.4-98.9)	74.3(45.1-100)	N.S.
Faecal fat (mmol/3d)	53(20-80)	33(11-65)	<0.01.
Lactose malabsorption (no)	2	10	<0.05.
Gastrointestinal transit			
Gastric emptying			
Lag phase (min)	0.5(0.5-7.5)	0.5(0.5-3.5)	N.S.
50% emptying (min)	65(27-99)	55(1-160)	N.S.
Small intestinal transit			
Start colonic filling (min)	57(23-117)	29(14-73)	<0.001
50% colonic filling (min)	178(88-295)	125(83-208)	<0.001
Small intestinal transit (min)	52(22-114)	28(14-68)	<0.001
Small intestinal residence (AUC)	39.2(23.2-57.7)	27.4(18.6-46.8)	<0.01
Whole gut transit			
First marker (h)	26.5(6.5-48)	21.5(6-45)	<0.05
50% markers (h)	32.5(17.5-71)	28.5(10-72)	N.S.
Intestinal Permeability			
Cr-51 EDTA (%)	1.49(0.70-4.06)	1.99(0.091-8.25)	N.S.
Lactulose (mmol/l)	0.93(0.14-16.3)	0.60(0.04-9.8)	N.S.
Rhamnose (mmol/l)	1.85(0.33-48.3)	1.91(0.23-52.2)	N.S.
Lactulose/Rhamnose (ratio)	0.095(0.04-0.29)	0.060(0.03-0.25)	N.S.

* Data are median values and ranges (analysis by Mann-Whitney U test)

Effects of loperamide oxide

Table 7.3 summarises the results during placebo and the loperamide oxide phases of the study. Loperamide oxide decreased stool frequency ($p<0.001$) and weight ($p<0.01$). After treatment with loperamide oxide the number of bowel actions was still greater in the patients when compared to the control subjects ($p<0.05$), but stool weight was less ($p<0.01$) (Table 7.4). Bile acid absorption was increased markedly by loperamide oxide ($p<0.01$) (Figure 7.1) and, after treatment, was not significantly different from the control group (Table 7.4). Somewhat surprisingly, treatment with loperamide oxide was associated with a small, but significant decrease ($p<0.05$) in vitamin B12 absorption. Loperamide oxide did not affect faecal fat excretion, but during treatment with loperamide oxide there was an inverse relationship between bile acid absorption and faecal fat excretion ($r=-0.63$, $p<0.01$). There was no difference between the two groups in the lag phase, but the time for 50% gastric emptying was less during treatment with loperamide oxide ($p<0.01$) and gastric emptying was faster in patients after treatment with loperamide oxide ($p<0.05$) than in control subjects (Table 7.4). In contrast, loperamide oxide delayed both small intestinal ($p<0.01$) and whole gut ($p<0.01$ first marker, $p<0.05$ 50% markers) transit. During treatment with loperamide oxide, small intestinal transit and whole gut transit were not significantly different from the control group (Table 7.4). There were significant relationships between stool weight and both whole gut transit ($r=-0.58$, $p<0.01$) and stool frequency ($r=0.45$, $p<0.05$) during treatment with loperamide oxide. Intestinal permeability, as assessed by the Cr-51 EDTA test, was greater ($p<0.01$) after treatment loperamide-oxide, but there was no difference in the absorption of lactulose/rhamnose (Table 7.3). Cr-51 EDTA absorption was related to small bowel residence during both the placebo and loperamide oxide phases ($r>0.45$, $p<0.05$).

TABLE 7.3 Results in patients during placebo and loperamide phases*

Parameter	Placebo	Loperamide oxide	p value
Number of subjects	18	18	
Gastrointestinal symptoms			
Score	0(0-3)	0(0-3)	N.S.
Bowel actions/wk	19(9-53)	13.5(6-39)	<0.001
Stool frequency/3d	7(2-14)	5(1-10)	<0.05
Stool wt/3d (g)	450(186-1275)	260(63-1170)	<0.01
Absorption			
SeHCAT (%)	3.3(0.0-45.7)	20.5(0.0-65.4)	<0.01
Co-58 Vit B12 (%)	74.3(45.1-100)	62.8(37.7-90.9)	<0.05
Faecal fat (mmol/3d)	33(11-65)	35(9-68)	N.S.
Lactose malabsorption (no)	10	7	N.S.
Gastrointestinal transit			
Gastric emptying			
Lag phase(min)	0.5(0.5-3.5)	0.5(0.5-9.5)	N.S.
50% emptying (min)	55(1-160)	39(1-135)	<0.01
Small intestinal transit			
Start colonic filling (min)	29(14-73)	37.5(14-135)	<0.01
50% colonic filling (min)	125(83-208)	164(83-269)	<0.001
Small intestinal transit (min)	28(14-68)	37(13-134)	<0.01
Small intestinal residence (AUC)	27.4(18.6-46.8)	41.8(26.4-62.5)	<0.001
Whole gut transit			
First marker (h)	21.5(6-45)	28.5(10.5-72)	<0.01
50% markers (h)	28.5(10-72)	58.5(10.5-72)	<0.05
Intestinal Permeability			
Cr-51 EDTA (%)	1.99(0.091-8.25)	2.70(0.16-6.8)	<0.01
Lactulose (mmol/l)	0.60(0.04-9.8)	0.41(0.07-9.83)	N.S.
Rhamnose (mmol/l)	1.91(0.23-52.2)	2.60(0.54-21.3)	N.S.
Lactulose/Rhamnose (ratio)	0.06(0.03-0.25)	0.06(0.01-0.28)	N.S.

* Data are median values and ranges (analysis by Wilcoxon test)

TABLE 7.4 Results in patients during treatment with loperamide oxide and control subjects*

Parameter	Control	Loperamide oxide	p value
Number of subjects	18	18	
Gastrointestinal symptoms			
Score	0(0-1)	0(0-3)	N.S.
Bowel actions/wk	8(3-14)	13.5(6-39)	<0.05
Stool frequency/3d	4(2-10)	5(1-10)	<0.05
Stool wt/3d (g)	507(308-1190)	260(63-1170)	<0.01
Absorption			
SeHCAT (%)	22.8(9.2-63.6)	20.5(0-65.4)	N.S.
Co-58 Vit B12 (%)	81.4(29.4-98.9)	62.8(37.7-90.9)	<0.01
Faecal fat (mmol/3d)	53(20-80)	35(9-68)	<0.05
Lactose malabsorption (no)	2	7	N.S.
Gastrointestinal transit			
Gastric emptying			
Lag phase(min)	0.5(0.5-7.5)	0.5(0.5-9.5)	N.S.
50% emptying (min)	65(27-99)	39(1-135)	<0.05
Small intestinal transit			
Start colonic filling (min)	57(23-117)	37.5(14-135)	N.S.
50% colonic filling (min)	178(88-295)	164(83-269)	N.S.
Small intestinal transit (min)	52(22-114)	37(13-134)	N.S.
Small intestinal residence (AUC)	39.2(23.2-57.7)	41.8(26.4-62.5)	N.S.
Whole gut transit			
First marker (h)	26.5(6.5-48)	28.5(10.5-72)	N.S.
50% markers (h)	32.5(17.5-71)	58.5(10.5-72)	N.S.
Intestinal Permeability			
Cr-51 EDTA (%)	1.49(0.7-4.06)	2.70(0.16-6.8)	<0.05
Lactulose (mmol/l)	0.93(0.14-16.3)	0.41(0.07-9.83)	N.S.
Rhamnose (mmol/l)	1.85(0.33-48.3)	2.60(0.54-21.3)	N.S.
Lactulose/Rhamnose (ratio)	0.095(0.04-0.29)	0.060(0.01-0.28)	N.S.

* Data are median values and ranges (analysis by Mann-Whitney U test.

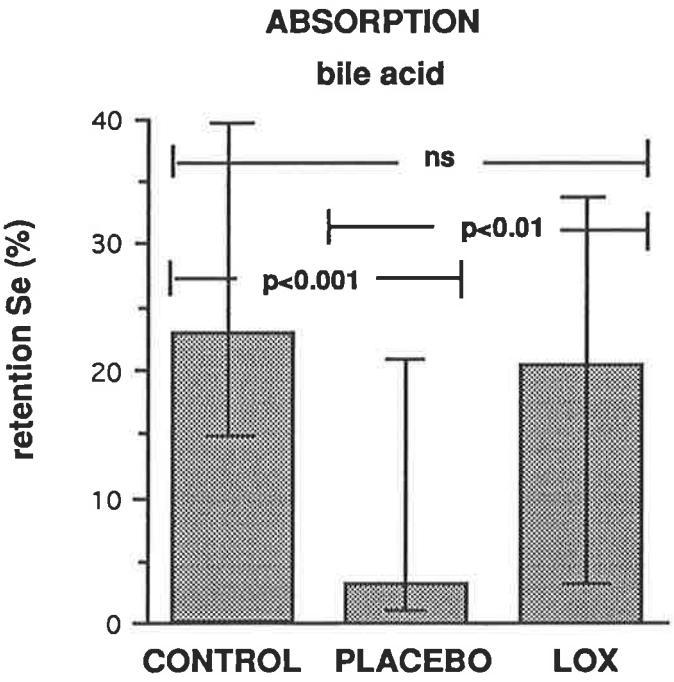


Figure 7.1 Absorption of bile acid in control subjects and patients with radiation enteritis during treatment with placebo and loperamide oxide (Lox). Data are shown as median values and interquartile ranges.

7.4 DISCUSSION

During the course of abdominal and/or pelvic irradiation, acute radiation enteritis manifest as diarrhea with or without abdominal cramps, is almost inevitable (Yeoh et al 1984; Yeoh & Horowitz 1987). The prevalence of chronic radiation enteritis, defined as persistence of symptoms beyond 3 months after completion of radiation treatment, is however uncertain (Yeoh & Horowitz 1987). Several retrospective surgical series suggest that the incidence of "significant" damage is only 5-15% (DeCosse et al 1969; Schofield et al 1983). These studies have, however, considerable limitations, particularly as they do not include patients who died, or were lost to follow-up in the prolonged interval between treatment and the onset of symptoms. In contrast, a sustained increase in bowel frequency was noted in 12 of 17 unselected women who had received pelvic radiotherapy for gynaecological malignancy 1-26 years previously (Newman et al 1973). It therefore appears probable that the incidence of chronic radiation enteritis has been generally underestimated (and may be more than 50%), that increased bowel frequency is the most frequent symptom of chronic radiation enteritis and that the majority of patients with chronic radiation enteritis do not seek medical help until the occurrence of a severe complication, such as stricture, perforation or anaemia due to blood loss (Yeoh & Horowitz 1987). There is some evidence that the incidence of radiation bowel disease has increased in recent years, as a result of changes in long established techniques (Schofield et al 1986; Galland & Spencer 1987). For example, although the use of radium has now been changed to safer isotopes such as cesium and cobalt, this has also entailed new or modified applicators, altered dose rates and changes in the number of treatments.

The rectum, sigmoid colon and terminal ileum appear to be particularly at risk from pelvic radiotherapy (Ludgate & Merrick 1985). While the histological features of chronic radiation enteritis, characterized by obliterative endarteritis of the small vessels in the intestinal wall, submucosal oedema and lymphatic dilatation are well documented (Wellwood & Jackson 1973), there is little information about the pathophysiology of

diarrhea due to chronic radiation enteritis (Ludgate & Merrick 1985; Yeoh & Horowitz 1987). It has been suggested that diarrhea reflects malabsorption due to either infiltration of the mucosa by inflammatory cells and luminal narrowing of the submucosal arterioles (Carr et al 1984), or intestinal bacterial overgrowth (Ludgate & Merrick 1985). The possibility that abnormalities in intestinal motor function may be important has also been recognised (Yeoh et al 1984; Otterson et al 1988). In the first comprehensive study of intestinal function in patients with diarrhea due to chronic radiation enteritis, we have demonstrated a high prevalence of abnormalities in intestinal transit and absorption. Both small intestinal and whole gut (mainly colonic) transit, were faster in the patients than the control subjects. Bile acid absorption was reduced in many of the patients (although vitamin B12 absorption was usually normal) and 10 patients had malabsorption of lactose. All of these factors may theoretically contribute to diarrhea. These observations were not due to intestinal stricture or bacterial overgrowth. The relatively small difference in median age between the patients and the control subjects is unlikely to be important. The observation that despite increased stool frequency, stool weight was not greater in the patients is likely to reflect dietary changes, which inevitably occur in patients with a long history of diarrhea. Intake of dairy products was less in the patients and probably contributed to the normal faecal fat excretion. It is also possible that in some patients concurrent radiation proctitis caused rectal irritability and contributed to a stool weight which was lower than would be predicted from stool frequency.

The SeHCAT test has made intestinal bile acid malabsorption much more easy to detect (Merrick et al 1985; Ferraris et al 1986). A high prevalence of bile acid malabsorption has been reported in patients with otherwise unexplained diarrhea (Merrick et al 1985; Sciarretta et al 1987) and it has been suggested that this is of pathogenetic importance and predictive of improvement with cholestyramine (Merrick et al 1985). Our observation of a high prevalence of bile acid malabsorption in patients with chronic radiation enteritis is consistent with the results of a previous study (Ludgate & Merrick

1985). While vitamin B12 malabsorption has been demonstrated in some patients (Ludgate & Merrick 1985), it is recognised that bile acid absorption is a more sensitive test of terminal ileal function than vitamin B12 absorption (Fromm et al 1973). The reduced bile acid absorption is likely to reflect damage to the terminal ileal mucosa. It should, however, be recognised that more rapid intestinal transit, by reducing the time available for absorption could contribute to decreased bile acid absorption and diarrhea (Yeoh et al 1984; Schiller at al 1987; Sciarretta et al 1987). In particular, the terminal ileum appears to have an important role in the regulation of small intestinal transit (Read et al 1984). The lactose malabsorption demonstrated in 10 patients most likely reflects mucosal damage, as small intestinal bacterial overgrowth was essentially excluded and all of the patients were Caucasian. A high prevalence of lactose malabsorption has been reported previously in patients with chronic radiation enteritis who required parenteral nutrition (Beer et al 1985). The observation that lactose malabsorption is a common long-term effect of abdominal and/or pelvic irradiation is important and consistent with findings of a prospective study conducted by our group which suggests that mucosal damage in acute radiation enteritis does not recover in many patients (Chapter 5). It is not surprising that a history of milk intolerance was seldom obtained in patients with lactose malabsorption, although dietary intake of dairy products was reduced (Horowitz et al 1987).

We have demonstrated for the first time that small intestinal and whole gut transit is faster in patients with chronic radiation enteritis. Both single large doses, and fractionated doses of radiation have been shown to alter small intestinal motility in animals (Summers et al 1970; Otterson et al 1988). Fractionated doses of abdominal radiation increase the frequency of giant migrating contractions and retrograde giant contractions (Otterson et al 1988). We and others have reported that both small intestinal and total gut transit is faster in acute radiation enteritis (Yeoh et al 1984, LaManna et al 1985). Although there is unequivocal evidence of damage to the intestinal smooth muscle in chronic radiation enteritis (Rubin & Casarett 1968b), we

are unaware of any studies of intestinal motor function in chronic radiation enteritis in either animals or humans.

Medical therapy of diarrhea due to chronic radiation enteritis has been largely empirical and there have been no adequate controlled studies (Yeoh & Horowitz 1987). Antidiarrheal agents, broad spectrum antibiotics, cholestyramine, sulphasalazine and oral corticosteroids have all been used (Goldstein et al 1976; Heusinkveld et al 1978; Schofield et al 1986), but anectdotal experience suggests that satisfactory control of diarrhea is rarely achieved. Most series have focused on surgical approaches to complications such as stricture and fistula formation. The results of our study indicate that loperamide-N-oxide is effective in the treatment of diarrhea associated with chronic radiation enteritis.

Loperamide-N-oxide is a peripheral opiate agonist precursor, which is converted to loperamide in the intestinal lumen (Lavrijsen et al 1984) and liver (Niemegeers et al 1986). Loperamide-N-oxide is itself inactive and has negligible affinity for opiate receptors (Gommeren & Leysen 1988). Plasma levels of loperamide after oral administration of loperamide-oxide are two-fold lower than the equivalent oral doses of loperamide (Van De Velde et al 1987) resulting in a two-fold increase in the already high safety margin of loperamide (Van De Velde et al 1987; Van De Velde et al 1988). At the same time anti-diarrheal efficacy is maintained, since a dose of even 1 mg of loperamide oxide has been shown to be effective in a randomised double blind study of acute diarrhea in adults (Van Den Eynden et al 1995). As a result of the gradual activation of loperamide oxide, associated with lessened absorption of loperamide into the systemic circulation, it has been suggested that the incidence of adverse effects such as constipation may be less (Van De Velde et al 1988).

Previous studies (Chapaux et al 1974; Geginat et al 1978) which suggest that loperamide may be effective in the treatment of diarrhea associated with acute radiation

enteritis provide no insights into the mechanisms of efficacy, as only symptoms were evaluated. Other studies indicate that loperamide may prolong intestinal transit, normalize intestinal fluid and electrolyte movement and increase anal sphincter tone (Read et al 1982; Schiller et al 1984; Basilisco et al 1985; Kachel et al 1986). Treatment of diarrhea associated with chronic radiation enteritis with loperamide oxide was associated with significant changes in stool frequency and volume, gastrointestinal transit, intestinal absorption and permeability. Stool frequency and volume decreased and bile acid absorption increased after treatment with loperamide oxide. We are unable to explain why vitamin B12 absorption decreased during treatment with loperamide oxide, but can only comment that the magnitude of the change was relatively small. Loperamide oxide increased the rate of gastric emptying, but slowed both small intestinal and whole gut transit. Intestinal permeability to Cr-51 EDTA, but not lactulose/rhamnose was increased by loperamide oxide. The beneficial effects of loperamide oxide on stool frequency, bile acid absorption and intestinal permeability are likely to reflect the slowing of small intestinal and colonic transit (Schiller et al1984). The fact that permeability as evaluated by the double sugar test was not increased by loperamide oxide is consistent with this hypothesis, as results of this test are independent of intestinal transit (Brunetto et al 1990). An effect of loperamide-oxide on intestinal secretion cannot be excluded as this was not examined (Geginat et al 1978). The faster gastric emptying after treatment with loperamide oxide is not unexpected (Cann et al 1982)· This effect is likely to reflect the absence of central opiate properties of loperamide, compared to other opiates, such as morphine which slow gastric emptying. Although the majority of our patients had minimal upper gastrointestinal symptoms and normal gastric emptying, the effect of loperamide on gastric emptying may be beneficial in some patients with chronic radiation enteritis, as chronic gastroparesis is a recognised sequel to abdominal irradiation (Layer et al 1986).

CHAPTER 8

A retrospective study of the effects of pelvic irradiation on anorectal function (manuscript submitted for publication)

8.1 INTRODUCTION

Pelvic irradiation is being increasingly used in the curative treatment of malignant diseases such as carcinoma of the cervix and uterine corpus (Sher & Bauer 1990). During pelvic irradiation, gastrointestinal symptoms are inevitable (Yeoh et al 1984). Symptoms referable to anorectal dysfunction, including faecal incontinence are common (Sedgwick et al 1994). Sedgwick et al (1994) reported that urgency of defaecation and faecal incontinence occurred in 90% and 30% of patients undergoing pelvic radiotherapy, respectively. We (Chapter 5) and others (Newman et al 1973) have reported that although gastrointestinal symptoms usually improve following the completion of pelvic irradiation, there is often a persistent increase in the frequency of defaecation, associated with decreased absorption of nutrients and rapid small intestinal transit (Chapter 5). In contrast stool weight is characteristically not increased in the long term (Chapters 4 and 5). We therefore postulated that the cause for the discrepancy between stool frequency and faecal weight is radiation-induced anorectal injury (Chapters 4 and 5). In support of this concept, two studies of the chronic effects of pelvic irradiation on anorectal function reported a reduction in rectal volumes and compliance associated with reduced basal anal (predominantly due to internal anal sphincter contraction) but normal squeeze pressures (predominantly due to external anal sphincter contraction (Varma et al 1985; Varma et al 1986). However, in these studies, only patients with symptoms were evaluated and the prevalence of disordered anorectal function after pelvic irradiation has not been determined. Furthermore, measurement of anorectal pressures in these studies was performed using single channel recordings, and it is now recognised that optimal investigation of anal sphincteric function requires multiple closely spaced recording sites and simultaneous recordings of the electrical

activities of the external and internal anal sphincters (Read & Sun 1989). Although it is now possible to quantify the dimensions of the anal sphincters by ultrasonography (Sun et al 1992b), the effects of pelvic irradiation on anal sphincteric morphology have not been evaluated.

We have now assessed various aspects of anorectal function, using multiport anorectal manometry with concurrent electromyography and ultrasonography of the anal sphincters, in a randomly selected cohort of patients treated with pelvic irradiation 5-10 years previously for curable gynaecological malignant diseases.

8.2 METHODS

Subjects

The study group was derived from the remaining 25 of an initial cohort of 30 female patients with carcinoma of the cervix and three patients treated for endometrial carcinoma who participated in two previous studies of the effects of pelvic irradiation on gastrointestinal function (Chapters 4 and 5). Of the total of 33 patients who had completed pelvic or pelvic and abdominal irradiation between five and ten years previously, six patients had died and two had been lost to follow-up since completing the previous studies. All of the twenty-five remaining patients had no evidence of recurrent malignant disease and were invited to participate in the current study. Ten of these refused and at least two of these had chronic radiation proctitis, as evidenced by intermittent episodes of rectal bleeding. None of the 15 patients who participated, median age 67 yr (47-84), median body weight 62 kg (45-82) and median body mass index (BMI) 24.4 (18.3-29.1) had a history and clinical signs suggesting spinal injury or generalised neuropathy nor a constant requirement for medication (such as anti-cholinergics, tricyclic anti-depressants or prokinetic agents) which could influence gastrointestinal motility. Characteristics of the patient group and details of radiation treatment are shown in Table 8.1. Patients had either radiation treatment alone (10 patients) or radiation treatment following gynaecological surgery (five patients). The

Table 8.1 - Characteristics of the Patient Group

Patient No	Age (y) at treat-ment	Age (y) at follow-up	Body Weight (kg)	Body Mass Index	Diagnosis	Treat-ment ǂ	Radiation Dose* Gy/No of fractions/d	Radiation Field Size (cm x cm)	Radiation Technique+	Radiation Beam Energy & Modality
1	55	63	74	24.2	Carcinoma of Cervix	R	44 Gy/22F/32 Days (25 Gy to Point 'A'/46 hr)	18.5 x 16.0 12.0 x 16.0	AP-PA and LATS	10 MV PHOTONS
2	69	76	76	25.6	Carcinoma of Cervix	R	45 Gy/25F/38 Days (25 Gy to Point 'A'/40 hr)	17.0 x 16.5 13.0 x 16.5	AP-PA and LATS	10 MV PHOTONS
3	49	57	59	24.0	Endometrial and Ovarian Carcinoma	S+R	22.50 Gy/20F/25 Days 22.50 Gy/10F/11d (25 Gy to Vaginal Vault/55 hr)	28.0 x 39.5 16.0 x 16.0 13.0 x 16.0	AP-PA (Abdomen) AP-PA and LATS (Pelvis)	4 MV PHOTONS
4	59	67	45	18.3	Carcinoma of Cervix	R	50 Gy/25F/48 Days (20 Gy to Point 'A'/43 hr)	15.5 x 16.5	AP-PA ONLY	10 MV PHOTONS
5	61	70	70	25.7	Carcinoma of Cervix	R	46 Gy/25F/37 Days (26 Gy to Point 'A'/50 hr)	15.0 x 17.5 12.5 x 17.5	AP-PA and LATS	10 MV PHOTONS
6	68	76	82	29.1	Endometrial Carcinoma	S+R	50 Gy/25F/36 Days (20 Gy to Vaginal Vault/47 hr)	15.5 x 16.5 13.0 x 16.5	AP-PA and LATS	10 MV PHOTONS

Table 8.1 - Continued

Patient No	Age (y) at treat-ment	Age (y) at follow-up	Body Weight (kg)	Body Mass Index	Diagnosis	Treat-ment ∓	Radiation Dose* Gy/No of fractions/d	Radiation Field Size (cm x cm)	Radiation Technique	Radiation Beam Energy & Modality
7	75	84	62	25.2	Carcinoma of Cervix	R	44 Gy/22F/33 Days 20 Gy/10F/14 Days	16.0 x 18.0 11.5 x 18.0 6.0 x 10.0 10.0 x 10.0	AP-PA and LATS AP-PA and LATS	4 MV PHOTONS
8	38	47	61	25.4	Carcinoma of Cervix	S+R	45 Gy/25F/38 Days (15 Gy to Vaginal Vault/29 hr)	18.5 x 16.5 10.5 x 16.5	AP-PA and LATS	10 MV PHOTONS
9	40	47	78	28.0	Carcinoma of Cervix	R	44 Gy/22F/30 Days (25 Gy to Point 'A'/40 hr)	17.0 x 17.5 12.5 x 17.5	AP-PA and LATS	4 MV PHOTONS
10	45	53	80	26.1	Carcinoma of Cervix	S+R	50 Gy/25F/36 Days	16.0 x 19.0 16.0 x 19.0	AP-PA and LATS	10 MV PHOTONS
11	40	49	67	22.5	Carcinoma of Cervix	R	50 Gy/25F/36 Days (25 Gy to Point 'A'/45 hr)	18.0 x 20.0	AP-PA ONLY	10 MV PHOTONS
12	64	71	55	24.4	Carcinoma of Cervix	S+R	45 Gy/25F/39 Days (15 Gy to Vaginal Vault/28 hrs)	16.0 x 15.5 10.0 x 15.5	AP-PA and LATS	4 MV PHOTONS

Table 8.1 - Continued

Patient No	Age (y) at treat-ment	Age (y) at follow-up	Body Weight (kg)	Body Mass Index	Diagnosis	Treat-ment ‡	Radiation Dose* Gy/No of fractions/d	Radiation Field Size (cm x cm)	Radiation Technique	Radiation Beam Energy & Modality
13	62	71	62	22.7	Carcinoma of Cervix	R	45 Gy/25F/39 Days (25 Gy to Point 'A'/54 hr)	17.5 x 15.5 12.0 x 15.5	AP-PA and LATS	10 MV PHOTONS
14	60	69	51	19.9	Carcinoma of Cervix	R	50 Gy/25F/56 Days (20 Gy to Point 'A'/50 hr	15.0 x 17.0	AP-PA ONLY	10 MV PHOTONS
15	54	62	54	19.9	Carcinoma of Cervix	R	44 Gy/22F/31 Days (21 Gy/10F/13 Days)	17.5 x 18.0 11.0 x 18.0 13.0 x 12.0 10.5 x 12.0	AP-PA and LATS AP-PA and LATS	10 MV PHOTONS

* For each patient, external beam therapy was given first, the radiation dose increment having been 1.80-2.00 Gy prescribed as a minimum tumor dose delivered 5x/week. Intracavitary radiation then followed and radiation doses (in parentheses) were prescribed to Manchester Point 'A' unless otherwise stated in which cases doses were prescribed to the outer surface of vaginal mould and delivered by a Selectron low dose rate automated after loading unit.

\+ Except for patients 4, 11 and 14, external beam irradiation to the pelvis was delivered using a four field isocentric technique, anterior-posterior, posterior-anterior (AP-PA) and lateral fields (LATS). The lower border of the AP-PA field extended below the lower border of the obturator foramen in all cases. No shielding blocks were used in the lateral fields.

‡ R = Radiotherapy alone. S+R = Surgery plus radiotherapy.

operations performed were either total abdominal hysterectomy and bilateral salpingo-oophorectomy (four patients; patients 3, 6, 10 and 12) or total abdominal hysterectomy alone (one patient; patient 8). None of the patients who had hysterectomy had pelvic node dissection. Patients 10 and 12 had adenocarcinoma of the endocervical canal, not distinguishable from endometrial carcinoma preoperatively and patient 8 had abdominal hysterectomy for severe recurrent cervical dysplasia, but was found to have invasive squamous cell carcinoma. The median interval since completion of pelvic irradiation in the patients studied was eight years (range 7-9 years) (Table 8.1).

Nine healthy female volunteers, median age 63 yr (41-70), median body weight 70 kg (60-88) and median body mass index (BMI) 25.7 (20-33) who had no significant gastrointestinal symptoms and were not on medication that could influence gastrointestinal motility were also studied. There were no differences in age, body weight and BMI between the patients and the control subjects. Obstetric history (number of babies, and number of patients who had large babies (>4 kg) and forceps deliveries) also did not differ between the two groups (Table 8.2).

Protocol

Each of the patients and normal volunteers underwent measurements of the following aspects of anorectal function:- (a) symptoms, (b) anorectal manometry with concurrent electromyography of the anal sphincters and (c) anal ultrasound. The study protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

Table 8.2: Anorectal symptoms including bowel habits and obstetric parameters in patients and normal subjects

Parameters	Faecal incontinence			Urgency of defaecation	Symptom score[+]	No of bowel actions/wk[+]	No of babies[+]	No with large babies	No who had forceps delivery
Subjects	Diurnal	Nocturnal	Both						
Patients	3/15	1/15	1/15	10/15**	3*(0-8)	13(3-28)	3(0-12)	4/15	3/15
Normals	0/9	0/9	0/9	1/9	0(0)	7(7-14)	3(0-4)	2/9	2/9

[+] Median (Range)

* $p < 0.001$ ** $p < 0.01$ compared to normals

Measurements

Anorectal symptoms including bowel habit

The following symptoms were assessed by questionnaire on entry into the study:- faecal incontinence (diurnal and nocturnal), urgency of defaecation and bowel frequency (number of bowel actions/week). The frequency of faecal incontinence (diurnal and nocturnal) and urgency of defaecation was scored as follows: 0 = < 1 episode/week, 1 = ≤ 3 episodes/week, 2 = ≥ 3 episodes/week, 3 = ≥ 1 episode/day. The severity of urgency of defaecation was scored as: 0 = symptom absent, 1 = mild; symptom could be ignored if patient did not think about it, 2 = moderate; symptom could not be ignored, but did not influence daily activities, 3 = severe, symptom influenced daily activities (Horowitz et al 1985b). The severity of faecal incontinence, both diurnal and nocturnal was scored as: 0 = absence of faecal incontinence, 1 = predominantly incontinent of flatus, 2 = incontinence necessitating the wearing of a pad, 3 = incontinence necessitating a change of pad more than once a day (Pescatori et al 1992). The total score of anorectal symptoms (maximum 18) was calculated.

Anorectal manometry with concurrent electromyography of the anal sphincters

Each subject was encouraged to empty the rectum before the test if they felt the need to do so and a rectal examination was performed to confirm that the rectum was empty. Measurements were performed with the subject in the left lateral position with the hips flexed to a 90 degree angle. A manometric probe with an external diameter of 4 mm and consisting of a 5-lumen silicone tube with a sleeve sensor was inserted into the rectum (Orkin et al 1991). When correctly positioned, manometric side-holes were situated in the anal canal, approximately 0.5 cm from the anal verge, and in the rectum at 4 cm and 8 cm. The sleeve sensor was placed in the anal canal. The side holes were perfused with water at a rate of 0.6 mL/min by a low compliance pressurised perfusion system (Royal Adelaide Hospital, Biomedical Engineering Department), and pressures were measured by pressure transducers (Transpac, Abbott Laboratories/Hospital Products Division, North Chicago, Illinois 60064) that were situated in each perfusion line and

connected via amplifiers to a multichannel chart recorder (Grass Instrument Co., Quincy, Massachusetts USA). A latex balloon was tied to the probe 10 cm from the anal verge. The pressure within the balloon was measured by a water-filled, non perfused transducer.

The electrical activity of the sphincters was recorded using bipolar electrodes consisting of two wire columns situated at the back of the sleeve (Orkin et al 1991). The signals were then filtered using 0.3-3 Hz and 10-40 kHz frequencies respectively, in order to differentiate internal anal sphincter (IAS) and external anal sphincter (EAS) electrical activity (Sun et al 1990c). The activity of the IAS was represented on the raw electromyography record as a regular oscillation at a frequency of between 10 and 24 oscillations per minute which increased in amplitude as the activity of the muscle increased and vice versa. The integrated activity of the EAS was represented as an elevation above the base line (Sun et al 1990b).

Anorectal pressures were recorded under resting conditions for at least 20 minutes to ensure that steady state pressures were measured. The subject was then instructed to contract her anal sphincter maximally for a period of 20 seconds on three separate occasions, a minute apart. Following this, the rectal balloon was inflated serially with 10, 20, 40, 60 and 100 ml of air (the subject was not aware of the nature or grade of the stimulus). Each inflation was maintained for one minute and, after deflation, at least one minute was allowed before the next inflation. During each inflation the subject was asked to report subjective sensations and to indicate the duration of the sensation on a chart using an event marker. The minimum volume at which the balloon was perceived and when a sensation of gas in the rectum (wind), a desire to defaecate and pain were experienced, were recorded. The pre inflation, post inflation and residual pressures in each channel at these times were noted (Sun et al 1992a) The slope of the rectal pressure/volume relationship from 0 to 100 mL was determined (Sun et al 1990b). After a further rest period of 10 minutes the subject was instructed to increase intra-

abdominal pressure by blowing up a party balloon on three occasions separated by at least one minute.

Anal Ultrasound

With the subject in the supine position, a 7.5 MHz rotating ultrasonographic scanner of outer diameter 1 cm (Bruel and Kjaer, Naerum, Denmark) was inserted just inside the anal margin. The subject was asked to relax as much as possible. The IAS showed as a distinct, hypoechoic circular ring in relation to mucosa, submucosa and longitudinal muscle (Sun et al 1992b). Cross-sectional images were obtained at several sites in the anal canal and both the IAS and EAS were measured at their maximum thickness. The mean thickness of the IAS and EAS at respective sites were calculated from measurements made at eight equidistant points around the anal canal (Sun et al 1992b).

Statistical Analysis

The Mann Whitney U test was used to compare symptom score, sensory data, thickness of the IAS and EAS between the patients and healthy subjects. Anal sphincter basal and squeeze pressures, pressures in response to rectal distension and increases in intra-abdominal pressure were analysed by using Student's unpaired t test, as these data were normally distributed. Differences in rectal sensory perception between the two groups was analysed using the log rank test since the subject was not tested again once the rectal volume at which the desire to defaecate was reached. Analysis of variance (ANOVA) was used to evaluate the pressure/volume relationships. Linear regression analysis was used for anorectal symptom score, bowel habit, basal pressures and those generated in response to voluntary squeeze and rectal distension, as well as the pressure/volume ratios with serial rectal balloon distension. A p value < 0.05 was considered significant in all analyses.

8.3 RESULTS

Anorectal symptoms including bowel habit

Total symptom score was greater ($p = < 0.001$) in the patients, (Table 8.2). Urgency of defaecation was the most frequent symptom, occurring in the ten out of the 15 patients (67%). Four of these patients also had faecal incontinence (27% overall prevalance).

In eight of the 10 patients with faecal urgency, this symptom resulted in changes in life-style, such that these patients were either housebound or could only go out if there was a toilet nearby.

Although there was no significant difference in the frequency of defaecation between patients and normal subjects (Table 8.2), in four patients the number of bowel actions/week was greater than the control range. Three of these four patients also suffered urgency of defaecation.

In the patients, total anorectal symptom score was directly related to the number of bowel actions/week ($r = 0.602$, $p < 0.05$), (Figure 8.1).

Anorectal Manometry

Basal minimum pressures at 4 cm from the anal verge were lower in the patients than the controls ($p = 0.05$) and there was a trend for lower basal maximum pressures at the same site ($p = 0.07$). Although resting anorectal pressures at other sites were not significantly different between the two groups, basal minimum and/or basal maximum pressures at the anal ports was below the control range in five of the 15 patients, all of whom had anorectal symptoms. Squeeze pressures measured at the sleeve sensor and at 4 cm from the anal verge were lower in the patients ($p < 0.05$) (Table 8.3) and were below the control range in five patients.

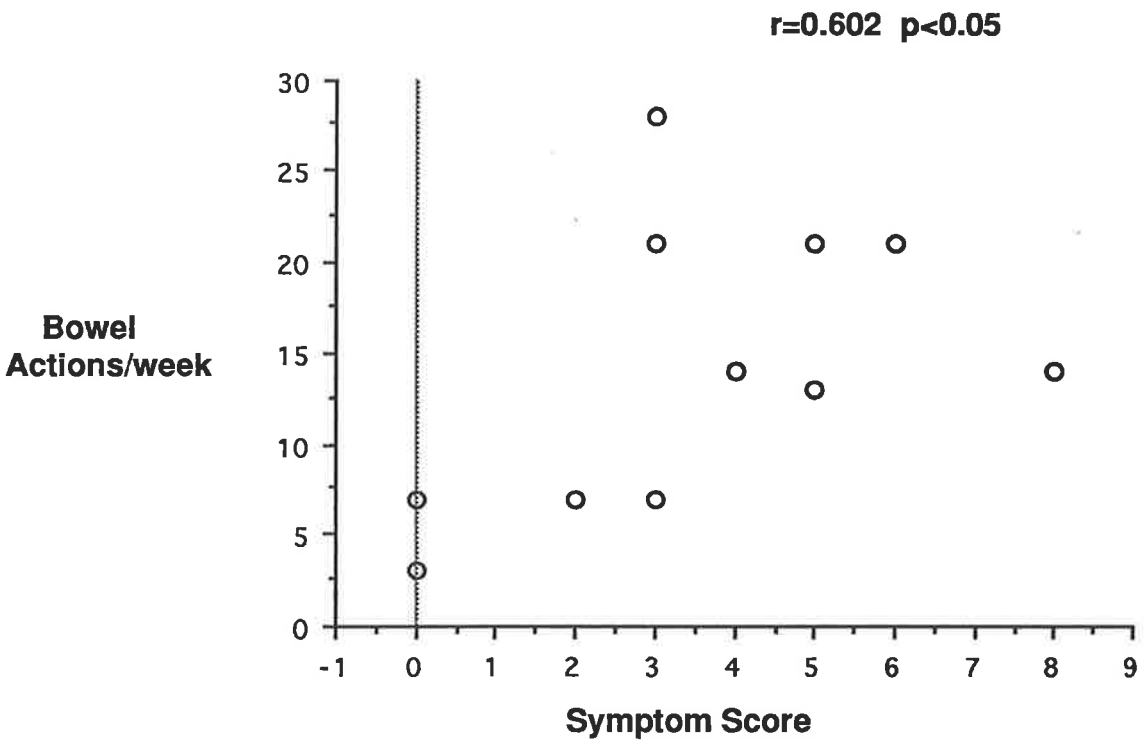


Figure 8.1 Relationship between anorectal symptom score and frequency of bowel actions.

Table 8.3: Maximum thickness of IAS and EAS and anorectal pressures (basal, in response to voluntary squeeze and blowing up a party balloon).**

		NORMAL		PATIENTS		p VALUE
EAS (mm)		8.8	± 0.5	9	± 0.4	0.78
IAS (mm)		2.8	± 0.2	2.3	± 0.2	0.65
B MAX						
(mm Hg)	ANAL 0.5 CM*	64	± 12.5	45.1	± 5.5	0.13
	SLEEVE	58.7	± 6.3	53.3	± 6.2	0.58
	ANORECTAL 4 CM*	22	± 5.8	12.1	± 1.9	0.07
B MIN						
(mm Hg)	ANAL 0.5 CM*	32.2	± 8.2	33.1	± 5.0	0.93
	SLEEVE	44.3	± 5.6	41.5	± 5.9	0.75
	ANORECTAL 4 CM*	14.1	± 3.3	8.1	± 1.0	0.05
VOLUNTARY						
SQUEEZE	ANAL 0.5 CM*	108.2	± 21.6	70	± 10.0	0.08
(mm Hg)	SLEEVE	103	± 10.2	68.1	± 7.2	0.01
	ANORECTAL 4 CM*	26.4	± 4.6	16.3	± 1.8	0.03
	CHANGE EMG ACTIVITY %	6.7	± 1.8	6.2	± 0.8	0.75
BLOWING						
UP A PARTY	ANAL 0.5 CM*	61.8	± 11.6	49.4	± .08	0.35
BALLOON	SLEEVE	70.1	± 7.5	65.6	± 7.8	0.7
	ANORECTAL 4 CM*	35.8	± 3.7	30.5	± 2.2	0.21
	CHANGE EMG ACTIVITY %	3.8	± 1.0	3.4	± 0.5	0.75

* Manometric port distances from anal verge

** Data are mean values ± SEM

In the patients, residual anorectal pressures measured at 0.5 cm from the anal verge in response to rectal distension were less ($p < 0.05$) at volumes 10, 20 and 40 mls (Table 8.4). There was also a trend for lower pressures in the patients at the highest (100 ml) volume ($p = 0.09$).

A significantly higher proportion of patients ($p < 0.05$) perceived the desire to defaecate at lower rectal volumes than the controls (Figure 8.2). The slope of the pressure/volume relationship associated with rectal distension volumes of 20, 40, 60, 100 ml and the overall slope was greater in the patients ($p < 0.05$, < 0.01, < 0.001, < 0.001 and < 0.05 respectively) than the controls suggesting that rectal wall compliance was reduced in the patients (Figure 8.3).

Anorectal pressures in response to an increase in intra-abdominal pressure resulting from blowing a party balloon did not differ between the two groups, but were below the normal range in six of the 15 patients.

There were no differences in external anal sphincteric electrical activity between the patients and normal subjects in response to voluntary squeeze and blowing up a party balloon (Table 8.3).

Either basal pressures, pressures generated in response to rectal distension, voluntary squeeze and blowing up a party balloon were lower than the control range in fourteen of the 15 patients including all ten patients with anorectal symptoms.

There was a non-significant trend for total urgency of defaecation score to be inversely related to pressure-volume ratios associated with 20 and 40 ml rectal distension ($r = -0.21$ and -0.33 respectively, $p > 0.10$ for both).

Table 8.4: Residual anorectal pressures in response to rectal distension (RD), with 10,20,40,60,100 ml**

		NORMAL		PATIENTS		p VALUE
RD 10						
	ANAL 0.5 CM*	47.3	± 10.8	27.7	± 4.1	0.05
	SLEEVE	41.6	± 7.9	30.8	± 4.3	0.2
	ANORECTAL 4 CM*	8.6	± 1.5	8.1	± 0.6	0.77
RD 20						
	ANAL 0.5 CM*	40.2	± 5.9	24.6	± 3.0	0.02
	SLEEVE	34.2	± 7.5	26.7	± 3.4	0.31
	ANORECTAL 4 CM*	10.4	± 1.9	9.1	± 0.7	0.44
RD 40						
	ANAL 0.5 CM*	35.6	± 4.8	23.1	± 3.2	0.04
	SLEEVE	30.2	± 4.7	30.3	± 3.7	0.99
	ANORECTAL 4 CM*	12	± 1.7	10.2	± 0.8	0.3
RD 60						
	ANAL 0.5 CM*	43.5	± 12.0	29.9	± 7.6	0.33
	SLEEVE	31.1	± 6.0	30.9	± 4.0	0.98
	ANORECTAL 4 CM*	17	± 2.5	12.8	± 1.3	0.12
RD 100						
	ANAL 0.5 CM*	43.8	± 11.8	20.1	± 6.3	0.09
	SLEEVE	30.5	± 6.9	35.5	± 5.7	0.59
	ANORECTAL 4 CM*	13.7	± 2.5	19	± 6.6	0.49

* Manometric port distances from anal verge

** Data are mean values ± SEM

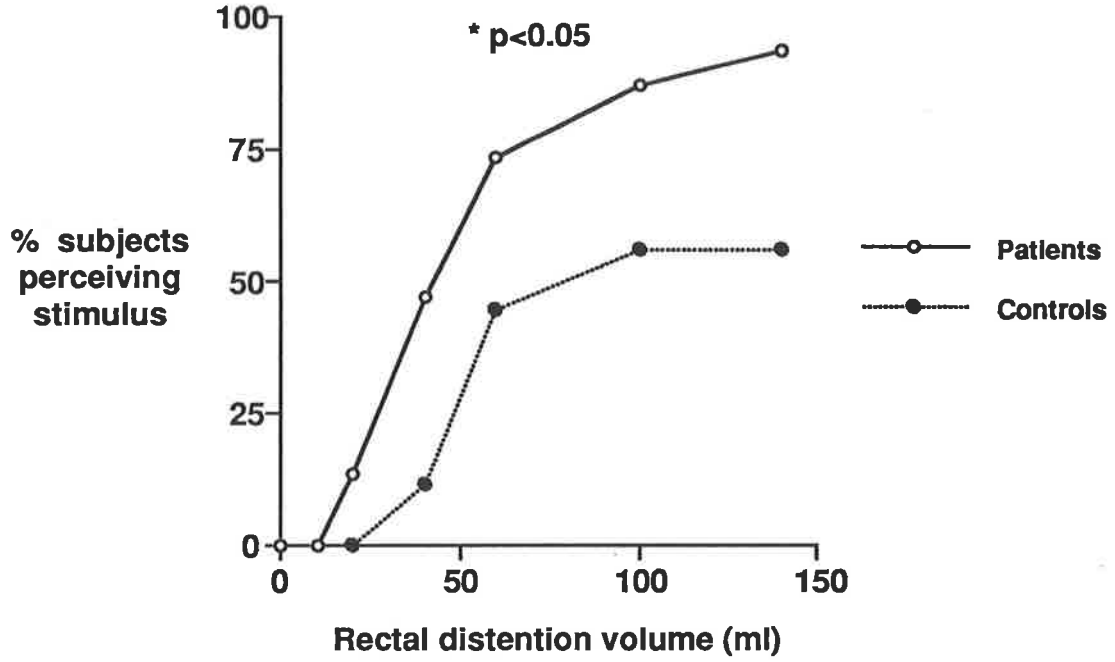


Figure 8.2 Rectal volumes at which patients and normal subjects felt desire to defaecate

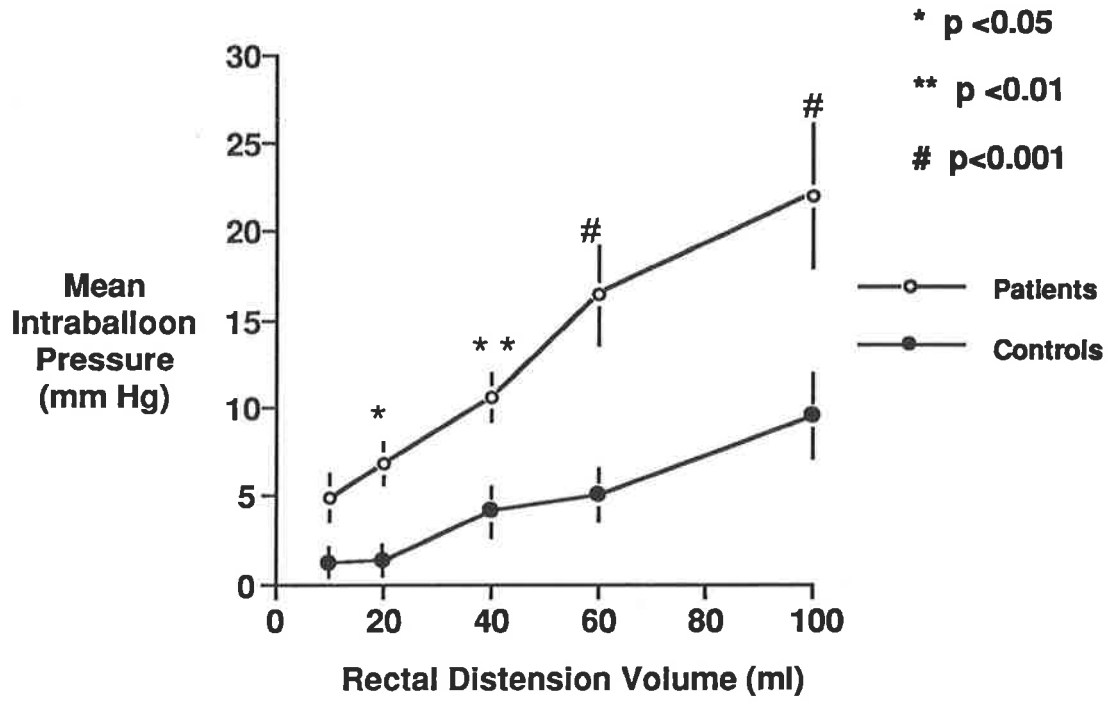


Figure 8.3 Pressure/volume relationship in patients and normal subjects associated with rectal distension. The overall slope of the pressure/volume graphs is greater for the patients compared with controls ($p<0.05$).

Anorectal ultrasound

Although IAS thickness was less than the control range in 4 of the 15 patients including three of the patients with anorectal symptoms there were no significant difference in mean IAS thickness between the two groups. There was no difference in thicknesses of the EAS and IAS in patients with and without urgency of defaecation.

8.4 DISCUSSION

Although retrospective surgical series have suggested that there is a high prevalence of rectal injury following pelvic radiation therapy (DeCosse et al 1969; Wellwood & Jackson 1973), the prevalence of anorectal dysfunction has hitherto not been evaluated. Whilst acknowledging the limitations inherent in a retrospective study, and in particular a potential selection bias, (10 patients refused to be studied and at least two of these had radiation proctitis), 10 out of the 15 (67%) patients studied suffered urgency of defaecation and this was associated with faecal incontinence in four of them (27%). In 8 of the 10 patients, these symptoms were of sufficient severity to result in changes in lifestyle. Our observations indicate that disordered anorectal function occurs frequently - at least one anorectal manometric parameter was outside the control range in 14 of the 15 patients, and that these abnormalities are heterogenous. In particular, anorectal symptoms were associated with increased rectal sensory perception, decreased basal anorectal pressures, decreased external anal sphincteric pressures and increased stiffness of the rectal wall.

Maintenance of faecal continence is dependent upon the combination of normal rectal sensation and anorectal motor function, ordered colonic motility and appropriate faecal consistency. Under resting conditions and during slow rectal distension, continence is maintained largely by the tonic contraction of the IAS with some contribution from tonic contraction of the EAS (Haynes & Read 1982; Sun et al 1990b). During rapid rectal distension or rectal contraction, and increases in intra-abdominal pressure during straining, continence is maintained by reflex contraction of the EAS which is closely

linked to rectal sensation (Sun & Read 1989b; Sun et al 1990c). Faecal incontinence may thus result from increased colorectal motility, reduced strength of the IAS or EAS, decreased rectal compliance, impaired rectal sensation, or a combination of these factors (Sun et al 1989a; Sun et al 1989b; Sun & Read 1990; Sun et al 1990c; Sun et al 1990d; MacDonnagh et al 1992; Sun et al 1992a).

Previous studies have given limited insights into the pathophysiology of anorectal dysfunction following pelvic irradiation (Varma et al 1985; Varma et al 1986). Although reported reductions in rectal volumes and compliance may account for urgency of defaecation, the techniques used in these studies were suboptimal and only patients with symptoms were evaluated (Varma et al 1985; Varma et al 1986). Furthermore, the critical issues of whether faecal continence can be maintained in response to rectal distension, rectal contraction or increases in intra-abdominal pressure were not addressed.

This is the first study to document the effects of pelvic irradiation on anorectal function using multiport anorectal manometry and concurrent electromyography of the anal sphincters. Anorectal pressures at both the rectum and anal canal are recorded concurrently which facilitates the interpretation of manometric profiles, particularly as the anorectal catheter used in the study incorporates a sleeve sensor which is tolerant of axial movement (Orkin et al 1991). By monitoring pressures throughout the anal canal the sleeve sensor reduces the need for closely spaced ports within the canal and minimizes the effects of axial movement on measurements. The incorporation of bipolar electrodes into the sleeve allows concurrent recording of the electrical activities of the anal sphincters. Like Varma et al (1985), we found that rectal sensory thresholds were reduced in the patients and even though we did not formally measured rectal compliance, the observed increase in the slope of the pressure/volume relationships in the patients is consistent with reduced rectal compliance (Varma et al 1985). In contrast to Varma et al (1986), maximum basal anal pressures in our patients did not differ

significantly from the controls but minimum basal pressures were slightly less, compatible with reduced internal sphincter function. The novel observation of a substantial reduction in "squeeze" pressures implies weakness of the external anal sphincter. This concept is supported by the observation of lower residual anal pressures during rectal distension in the patients. The absence of a significant difference at higher volumes, can be attributed to the failure of many patients to tolerate higher rectal volumes, so that a reduced number of pressure measurements at these volumes were obtained (three patients were unable to tolerate 60 ml rectal distension and a further three could not tolerate 100 ml rectal distension). Varma et al (1986) attributed the lower basal anal but normal voluntary squeeze pressures observed in their patients to dysfunction of the IAS, but their observations were based on single channel recordings obtained using the pull-through technique without concurrent electromyography of the anal sphincters. It is now recognised that without multiport anorectal manometry and concurrent electromyography of the anal sphincters, the reciprocal relationship between the activities of the IAS and EAS cannot be appreciated particularly in response to threats to faecal incontinence (Read & Sun 1989). Our data suggest that dysfunction of the EAS rather than the IAS may be primarily responsible for faecal incontinence in our patients. The absence of a significant correlation between faecal incontinence and the residual pressure in response to distension is likely attributable to the relatively small number of patients with faecal incontinence.

Although our patients were all female, the observed differences in function of the EAS are most unlikely to be related to birth trauma, particularly as there was no difference in obstetric history between the patients and the control subjects. The anatomical substrate underlying the EAS damage is likely to be myogenic, since there were no differences in EMG activity in the patients compared with normal subjects. Although generally regarded as relatively radioresistant, damage to striated and smooth muscle has been documented in other parts of the gastrointestinal tract following irradiation (Rubin & Casarett 1968b; Seaman & Ackerman 1957). It should be recognised that a neurogenic

component to the dysfunction of the EAS cannot be excluded since neurophysiological studies, such as measurement of pudendal nerve conduction were not performed (Kiff & Swash 1984). However, severe pudendal nerve damage appears unlikely as there was no difference in morphology of the anal sphincters, as assessed by anal ultrasonography between the patients and normal subjects. It is also unlikely that hysterectomy with or without salpingo-oophorectomy (in five of the 15 patients) could have been responsible for the observed abnormalities of anorectal function since our patients had faecal urgency and incontinence rather than constipation which may be a complication of hysterectomy (Smith et al 1990; Prior et al 1992).

Our observations have implications for the treatment of persistent anorectal symptoms following pelvic irradiation. The demonstrated reduction in rectal compliance supports a role for low residue diets. Urgency of defaecation may also potentially respond to the calcium channel blocker, nicardapine, which when given orally has been shown to increase the rectal threshold for desire to defaecate in patients with irritable bowel syndrome (Sun et al 1990a). The weakness of the EAS may potentially respond to loperamide which has been reported to increase maximum squeeze as well as basal anal sphincter pressures in patients with incontinence of diverse aetiologies (Read et al 1982). We have reported previously that these patients have more rapid intestinal transit (Chapters 4 and 5) which is likely to contribute to faecal urgency and incontinence. Loperamide has been shown to slow intestinal transit in patients with diarrhoea associated with chronic radiation enteritis (Chapter 7).

CHAPTER 9

Summary and conclusions

Introduction

In this final chapter, the major insights into the effects of mediastinal, abdominal and pelvic irradiation on gastrointestinal function gained as a result of the studies described in this thesis are initially summarised, followed by a discussion of the implications of these observations.

9.1 AIM OF STUDIES

The broad hypothesis addressed in this thesis is that alterations in gastrointestinal motor function are important in the aetiology of some of the sequelae of mediastinal, abdominal and pelvic irradiation particularly symptoms such as dysphagia, nausea, diarrhoea and faecal incontinence. The aims of the six studies were in three inter-related areas viz., to determine (i) the acute and subacute effects of therapeutic irradiation on oesophageal, gastric and intestinal function, (ii) the chronic effects of therapeutic irradiation on gastric, intestinal, and anorectal function and (iii) the effects of a potential treatment of diarrhoea due to chronic radiation enteritis, loperamide-N-oxide on gastrointestinal function.

While this represents the most comprehensive evaluation of the effects of therapeutic irradiation on gastrointestinal functions performed to date, the design of the studies was in most cases less than optimal. In particular, ethical considerations and patient acceptabilty inherent in research on human subjects limited the range of measurement techniques. With the exception of the studies on oesophageal and anorectal function, evaluations of various aspects of gastrointestinal function employed non-invasive techniques. While the latter is likely to have been pivotal to the high patient compliance with the experimental protocols, particularly the longitudinal study of the effects of

abdominal and pelvic irradiation on gastrointestinal function, a number of issues could not be addressed. For example, the motor correlates of the faster small intestinal transit observed both during and after abdominal and pelvic irradiation remains to be characterised because small intestinal manometry was not performed. Conversely, in studies in which more invasive techniques such as manometry were used as in the evaluation of the effects of mediastinal irradiation on oesophageal function, recruitment of subjects was more difficult and a smaller number of subjects was studied, increasing the risk of a type II statistical error (see Chapter 3, Section 3.4 Discussion). It should be recognised that the potential for selection bias is inherently greater in retrospective studies than those which are conducted prospectively, although this probelm was minimised in all four retrospective studies, by the selection of patients on a random basis using pre-determined inclusion and exclusion criteria and by the fact that most subjects agreed to participate.

9.2 SUMMARY OF RESULTS

Although gastrointestinal symptoms are an inevitable consequence of therapeutic mediastinal, abdominal and pelvic irradiation, the relationship between symptoms and both motor function and luminal transit appears to vary throughout the gastrointestinal tract.

In the study on the effects of mediastinal irradiation on oesophageal function (Chapter 3), the severity of symptoms such as dysphagia and odynophagia did not correlate with mucosal changes which in most cases were mild. Since concurrent radionuclide scintigraphy and oesophageal manometry did not demonstrate altered transit or motility it is probable that oesophageal symptoms during mediastinal irradiation reflect altered mucosal sensitivity. However, the possibility that changes in oesophageal motor function contribute to symptoms has not been excluded. Our patients were relatively old and, probably because of this, there was a higher prevalence of oesophageal motor abnormalities before the initiation of mediastinal irradiation. It is possible that if patients

had been younger, abnormalities in oesophageal motor function may have been evident, especially as it is clear that oesophageal dysmotility may occur as a result of mediastinal irradiation (Seeman et al 1992).

During the course of abdominal irradiation there was no change in gastric emptying of a nutrient liquid, although a number of patients experienced symptoms such as nausea and abdominal pain. Similiarly, in patients several years after completing abdominal irradiation while there was a modest acceleration of gastric emptying of liquids, there was no significant relationship between gastric emptying and gastrointestinal symptoms (Chapter 6, Section 6.3 Results). These observations are not surprising since there is in general a poor correlation between rates of gastric emptying and upper gastrointestinal symptoms (Horowitz & Fraser 1994). While it is possible that abnormalities in gastric emptying may have been apparent with the use of other test meals (e.g. solid, high fat) it is likely that upper abdominal symptoms, both during and after radiation therapy, are not due to disordered gastric emptying itself. This is not to exclude a role for disordered motility in the aetiology of symptoms - both gastric motility and myoelectrical activity may be abnormal when the rate of gastric emptying is within the normal range (Koch et al 1989; Horowitz & Dent 1991). It is also possible that abnormal sensory feedback from the stomach and small intestine contributes to symptoms (Horowitz & Dent 1991; Coffin et al 1994; Edelbroeck et al 1994).

Diarrhoea during abdominal and pelvic irradiation is associated with widespread abnormalities in gastrointestinal function. Although these improve with time, bowel frequency was still increased at two years after the completion of abdominal irradiation and this was associated with persistently decreased bile acid absorption and faster small intestinal transit (Chapter 5, Table 5.3). The observations that both during and after abdominal and pelvic irradiation, vitamin B12 and bile acid absorption were inversely related to bowel frequency and directly related to whole gut transit suggests a causal relationship between the frequency of bowel actions, intestinal absorptive capacity and

gastrointestinal transit.

Anorectal symptoms following pelvic irradiation are associated with increased mucosal sensitivity, increased rectal wall stiffness and external anal sphincteric dysfunction. Disordered anorectal motility occurs frequently - even though there were no statistically significant relationships between anorectal motilty and symptoms, one or more measurements of anorectal function was abnormal in fourteen of fifteen patients, including all ten with symptoms. The apparently mild anorectal dysfunction sustained by patients following pelvic irradiation may well be easily overwhelmed by threats to faecal continence, particularly in view of the more rapid intestinal transit demonstrated in these patients.

9.3 PREVALENCE OF GASTROINTESTINAL DYSFUNCTIONS AND IMPLICATIONS FOR THERAPY

The observed differential effects of therapeutic radiation on transit, motility and symptoms in different parts of the gastrointestinal tract have important implications for therapy.

9.3.1 Acute effects of radiation

As discussed, during mediastinal and abdominal irradiation, it is likely that increased mucosal sensitivity contributes to upper gastrointestinal symptoms and this issue should be addressed in future studies. Should this hypothesis prove to be correct, therapy should ideally be targeted at the mechanism(s) responsible for disordered sensory feedback. Modulation of sensory input can be directed either peripherally at the level of the enteric nervous system, or centrally, at spinal or supraspinal levels. An example of modulation of the peripheral sensory input is the use of ondansetron in the treatment of vomiting resulting from abdominal irradiation. As discussed in Chapter 1, Section 1.6.1 Acute effects (Animal studies), the 5 HT-3 antagonist, ondansetron reduces vagal afferent fibre discharge in ferrets (Andrews & Davidson, 1990). Such

targeted therapy for dysphagia is not yet available, but the clinical observation that local anaesthetic gels such as viscous lignocaine are frequently effective, suggests that more specific measures to reduce abnormal sensory feedback are likely to be successful in this area.

The observed relationships among diarrhoea, nutrient malabsorption and intestinal transit during abdominal and pelvic irradiation suggest that slowing intestinal transit may not only control diarrhoea but also improve nutrient absorption. This is likely to be responsible for the clinical observation that anti-diarrhoeal agents which slow intestinal transit, such as opiate agonists and diphenoxylate, are frequently successful in improving patient tolerance to abdominal and pelvic irradiation by reducing stool frequency, improving stool consistency and preventing significant weight loss (Chapaux et al 1978; Stryker et al 1979).

As discussed in Chapter 1, Section 1.8.2 Chronic effects (Treatment), opiate agonists such as loperamide may also benefit symptoms attributable to anorectal dysfunction, such as urgency of defaecation and faecal incontinence, during pelvic irradiation. Loperamide has been reported to be effective in patients with faecal incontinence of diverse aetiologies by directly influencing anal sphincteric function (Read et al 1982). However, it should be recognised that by changing stools to a harder consistency, opiate agonists may theoretically increase the risk of rectal bleeding during pelvic irradiation.

9.3.2 Chronic effects of radiation

It has been suggested previously that disordered gastrointestinal motility may contribute to symptoms after therapeutic irradiation (Layer et al 1986; Seeman et al 1992). The demonstration of faster gastric emptying after abdominal irradiation does not however, imply a causal relationship, particularly as it did not correlate with symptoms and the magnitude of the mean difference was relatively small. Therapy directed towards

slowing gastric emptying is therefore not likely to improve symptoms. Rational therapy for chronic upper abdominal symptoms following therapeutic irradiation must await further studies to define their pathogenesis. If abnormal sensory feedback is confirmed as an important factor, pharmacological manipulation of sensory conduction, either peripherally or centrally is possible.

Both the longitudinal and retrospective studies of the effects of abdominal and pelvic irradiation on gastrointestinal function demonstrate that disordered intestinal function is a common long term effect of therapeutic irradiation. As discussed in Chapter 5, Section 5.4 Discussion, following abdominal and pelvic irradiation, stool frequency remained persistently increased in the majority of patients up to two years after completion of radiation therapy and this was associated with reduced bile acid absorption and faster small intestinal transit. It is logical to suggest that slowing of intestinal transit may improve diarrhoea and nutrient absorption. The observed effects of the loperamide precursor, loperamide-N-oxide on gastrointestinal function and symptoms in chronic radiation enteritis are consistent with this concept. However, it should be recognised that the possibilty that loperamide has an anti-secretory effect was not evaluated in this study.

The author's study establishes that anorectal dysfunction is also a common long term sequela of pelvic irradiation. As discussed in Chapter 8, Section 8.3 Results (Anorectal manometry), both sensory and motility changes contribute to symptomatology. The mechanism(s) underlying the sensory and motor changes require clarification before targeted therapy is possible.

9.4 POTENTIAL MECHANISMS UNDERLYING GASTROINTESTINAL SYMPTOMS

Current understanding of the aetiology of gastrointestinal symptoms is limited. In general terms, symptoms may result from abnormal motor activity or abnormal sensory function (or a combination of the two).

9.4.1 Disordered gastrointestinal motility

In the last two decades, the concept has emerged that disordered gastrointestinal motility is responsible in many cases for common gastrointestinal symptoms such as dysphagia, nausea, abdominal pain, diarrhoea and faecal incontinence, particularly when the latter occur in the absence of demonstrable structural abnormalities.

Gastrointestinal smooth muscle contractions are controlled by a number of mechanisms which include pacemakers that are physically very close but probably distinct from smooth muscle, by the enteric nervous system (the so-called "gut brain") and the central nervous system. These control mechanisms work in concert to produce motor patterns that are tailored to the regional needs of the gastrointestinal tract. Whilst in some cases these regulatory mechanisms are solely concerned with movement of luminal content (e.g. in the oesophagus and anorectum), those in the stomach and intestine also subserve the need for simultaneous processing of the luminal contents. For example, in the small intestine to allow optimal nutrient absorption and mixing with digestive enzymes, a complex system of control of motility is required which is sensitive to the physical and chemical nature of the luminal contents. Although a complete understanding of the neural controls of intestinal motility is yet to be achieved, the major mechanisms and the neurotransmitters involved are apparent (Costa et al 1987; Stark & Szurszewski 1992). Within the ganglia of the myenteric and submucous plexuses of the gut wall, motor-, inter- and sensory neurones interact to achieve control in the basic patterns of intestinal motility. Enteric motor neurons may affect smooth muscle activity causing inhibition (mainly via release of nitric oxide, vasoactive intestinal polypeptide (VIP), or adenosine triphosphate (ATP)), or excitation (mainly via release of acetyl choline (ACh) or substance P) (Stark & Szurszewski 1992). The temporal and spatial organisation of smooth muscle contractions generated by the enteric nervous system may be modulated or overridden by extrinsic neural influences via vagal and spinal innervation (mainly via release of ACh or noradrenaline respectively, e.g. Kawahara et al 1994).

Gastrointestinal hormones may act as systemic or local modulators of motility (Weisbrodt 1987). Systemic modulation of small intestinal motility has been shown for motilin and cholecystokinin (Weems et al, 1985) and suggested for peptide YY (Sheikh 1991). A local function for cholecystokinin has also been demonstrated (Blackshaw & Grundy 1990).

Disordered gastrointestinal motility resulting from dysfunction of one or more of these regulatory mechanisms may potentially lead to gastrointestinal symptoms as well as delayed or accelerated luminal transit. As discussed in Chapter 6, Section 6.4 Discussion, changes in proximal stomach and pyloric motor function may contribute to the observed accelerated gastric emptying and higher prevalence of upper gastrointestinal symptoms in patients following therapeutic abdominal irradiation.

Although the accelerated luminal transit associated with diarrhoea during and after abdominal and pelvic irradiation is probably multifactorial involving disordered motility, impaired absorption and possibly excessive intestinal secretion, it is likely that the various factors interact at the level of the enteric nervous system to cause a pattern of intestinal motility that induces more rapid intestinal transit. While it is likely that the amplitude of intestinal contractions will be increased, it should be recognised that the motor correlates of normal transit in the small intestine and colon have not been clearly defined (Schemann & Ehrlein 1986; Siegle & Ehrlein 1988), in particular the relative roles of non lumen and lumen occlusive contractions (Furukawa et al 1994). As in the stomach, the temporal and spatial organisation of contractions will be an important determinant of flow (Horowitz & Dent 1994). In considering possible mechanisms of this effect, it is of interest that the majority of diarrhoeal disorders associated with active intestinal secretion involve irritants or toxins and mediatiors of inflammatory or allergic responses which also cause propagated intestinal contractions. Furthermore, it has been shown that secretion induced by inflammatory mediators such as histamine and prostaglandins can be partially blocked by neurotoxins or anticholinergic agents

(Lundgren, 1988). The concept of diarrhoea being a primary motility disorder applies even to diarrhoea initiated by` malabsorption of nutrients. For example, in conditions causing terminal ileal dysfunction including pelvic irradiation, impaired bile acid and fatty acid absorption leads to reflex colonic secretion and propulsion (Mekhjian et al 1971; Karlstrom 1986). The demonstration that secretion induced by bile and fatty acids can be inhibited by neurotoxins also suggests involvement of the enteric nervous system (Field et al 1989).

Similiarly, as discussed in Chapter 8, Section 8.4 Discussion, anorectal symptoms such as faecal incontinence are likely to reflect damage to the mechanism(s) regulating colonic motility and anal sphincteric function.

9.4.2 Disordered sensory feedback

Recent studies suggest that an alteration in visceral pain threshold, especially that for distension, may characterise and link so-called functional gastrointestinal disorders including non-cardiac chest pain, non-ulcer dyspepsia and irritable bowel syndrome (Ritchie 1973; Whitehead et al 1980; Richter et al 1986; Kellow et al 1988; Kellow et al 1990; Lemann et al 1991; Mearin et al 1991; Coffin et al 1994). Alterations in the threshold for stimulation of gut-wall receptors, modulation in the conduction of the sensory input, or conscious perception at a central level could all explain visceral hypersensitivity. Abnormal gastrointestinal motility could in theory be a secondary phenomenon produced by central or reflex stimulation. For example, patients with non-cardiac chest pain with or without disordered oesophageal motility, have lower pain thresholds for oesophageal balloon distension compared with healthy controls (Richter et al 1986). It is therefore possible that patients may more readily experience dysphagia and odynophagia during mediastinal irradiation as a result of lowered sensory thresholds, whether or not oesophageal motility is abnormal. The observed reduction in the rectal balloon volume at which there was a desire to defaecate in patients following pelvic irradiation closely parallels the observations of increased sensory perception to

rectal balloon distension in patients with irritable bowel syndrome (Ritchie 1973; Whitehead et al 1980). Afferent information from the gastrointestinal tract is carried by both the vagus and the spinal sympathetic nerves. Although both central autonomic and higher cortical functions modulate the processing of visceral afferent information from the gastrointestinal tract and could thereby influence symptoms, it is probably more likely that gut inflammation resulting from irradiation alters visceral afferent function at the level of the enteric nervous system.

Alterations in the sensory response to gastric distension may also account for symptoms during abdominal irradiation, similiar to the observations reported in patients with non-ulcer dyspepsia (Lemann et al 1991; Mearin et al 1991; Coffin et al 1994). In the most recent study of patients with non-ulcer dyspepsia (Coffin et al 1994), visceral hypersensitivity was found to be restricted to the stomach and not triggered by duodenal distension, although patients with non-ulcer dyspepsia showed defective gastric relaxation responses to duodenal distension. Abdominal irradiation could also contribute to visceral hypersensitivity by modulating the response of small intestinal chemoreceptors and mechanoreceptors to the presence of nutrients in the small intestinal lumen (Horowitz & Dent 1991; Edelbroek et al 1994).

9.4.3 Relationship between disordered sensation and motility

Altered sensitivity of the intestinal afferent and efferent pathways to physiological stimuli, such as those related to meals, may contribute to abnormal motility and increased transit in radiation enteritis in a manner analogous to the increased sensitivity to normal motor events shown by patients with diarrhoea-predominant irritable bowel syndrome (Kellow et al 1991).

Although there is little information about postprandial patterns of motility evoked by different stimuli along the small intestine, the concept has emerged that sensory mechanisms within the small intestinal lumen sample the chemical and mechanical

properties of the contents and in turn trigger programmed patterns of motor activity (Weisbrodt 1987). Although the presence of fat and carbohydrate in the ileum both slow gastric emptying and jejunal transit (Read et al 1984), intraluminal stimulation with mechanical stimuli such as distension (Weisbrodt 1987) and reflux of material from the colon (Kruis et al 1985) both increase motor activity which appears to be propulsive. The sensitivity of the intestinal motor pathways to intraluminal stimuli suggests that dysfunction of mucosal sensory mechanisms could result in changes in motor activity and transit in radiation enteritis.

A largely unexplored mechanism for neural control of motility is the local release of neuropeptides from stimulated vagal and spinal sensory endings, known as axon reflexes. These sensory endings may be activated by a variety of mechanical and chemical stimuli (Blackshaw et al 1987; Blackshaw & Grundy 1990; Blackshaw & Grundy 1993a; Blackshaw & Grundy 1993b) and release transmitters including substance P, calcitonin gene related peptide (CGRP) amd VIP onto gut and vascular smooth muscle. The latter may cause contraction or relaxation (Holzer 1988). Much evidence for this mechanism has stemmed from the use of sensory neurotoxins such as capsaicin and resiniferatoxin, which when given acutely selectively activate extrinsic sensory endings at low doses, and when administered chronically in high doses or during prolonged exposure in vitro cause sensory degeneration (Marsh et al 1987). Axon reflexes are thought to be particularly important in inflammation, such as that which occurs in association with gastrointestinal mucosal damage during mediastinal, abdominal and pelvic irradiation.

The recent development of specific antagonists for gastrointestinal hormones such as loxiglumide (Meyer et al 1987; Anvari et al 1994) should allow further delineation of hormonal function in the modulation of intestinal motility. A local function of, for example, cholecystokinin and serotonin released from the neuroendocrine cells in the mucosa changes the activity of sensory neurones (Blackshaw & Grundy 1990;

Blackshaw & Grundy 1993a). These cells may therefore function as "taste cells" (Newson et al 1982). It is now widely believed that such a mechanism may be involved in the triggering of the intestinal peristaltic reflex, and could play a role in the mediation of gastrointestinal sensations such as fullness and nausea.

9.5 PRIORITIES IN FUTURE STUDIES

9.5.1 Animal studies

There is an urgent need to develop appropriate animal models to study the mechanisms of acute and chronic gastrointestinal motor dysfunction. Although the morphological effects of a range of single radiation doses have been well documented in a number of species, there is a paucity of data using modern techniques to evaluate the effects of irradiation on gastrointestinal motility. As discussed in Chapter 1, existing data is conflicting, partly because most previous studies have employed single, large, radiation doses and suboptimal techniques, but also because it was not generally realised that motility changes can occur within hours of the first radiation exposure. For example, it is now apparent that even with the relatively small dose increments used in conventional fractionated clinical radiation therapy the frequency of giant migrating contractions and retrograde giant contractions in the small intestine of dogs increases significantly as early as the day of the first fractionated radiation treatment, long before morphological abnormalities are apparent (Otterson et al 1988). The effects of these motility changes on intestinal transit remain to be confirmed since gastrointestinal transit was not measured. Because of technical limitations, few studies have attempted to relate transit to specific motor patterns, even though such a correlation is of fundamental importance to an understanding of normal and disordered nutrient absorption. In particular, there has been a lack of concurrent measurement of intraluminal pressure and transit on a second by second basis. The significance of the spatial pressure pattern profile responsible for movement of luminal contents has also not been fully appreciated because pressures have not been measured at multiple, closely spaced, points. Appropriate in-vivo studies of the mechanisms of small intestinal motor dysfunction

which address these issues are at present not technically feasible.

In order to gain the best insight into changes in control mechnisms of intestinal motility, in vitro studies involving isolation of a segment of intestine in an organ bath is necessary. This also allows accurate physiological measurements and removes the influence of anaesthetics and fluctuating levels of circulating hormones. Evaluation of receptor mediated events is possible with a range of antagonists and agonists which cannot be achieved in vivo due to slow metabolism or toxicity of compounds. The recent development of an in-vitro preparation of rat small intestine which is arterially perfused with a fluorocarbon solution has the advantage over in-vitro preparations perfused with Krebs' biocarbonate buffer in that it remains viable for several hours and does not show histological evidence of mucosal hypoxic injury (Bercik et al, 1994). The latter is of particular importance in studying a disease where abnormalities in mucosal sensory mechanisms may relate to changes in motility. This preparation may therefore allow correlation of motility patterns with movement of intraluminal contents in radiation induced motor dysfunction (Otterson et al 1988).

9.5.2 Human studies

Whilst targetted pharmocotherapy for some of the sequelae of therapeutic irradiation of the gastrointestinal tract must await clarification of the neural, hormonal and myogenic mechanisms underlying gastrointestinal symptoms, priorities in clinical studies are in the following areas: (i) evaluation of the potential role of abnormal sensory feedback in the genesis of gastrointestinal symptoms as a result of therapeutic mediastinal and abdominal irradiation, (ii) characterisation of the motor patterns underlying the accelerated intestinal transit observed during and after abdominal and pelvic irradiation, (iii) definition of the relative roles of neural and myogenic mechanisms in motor dysfunction following abdominal and pelvic irradiation, (iv) evaluation of novel approaches to reduce the risk of radiation injury to the gastrointestinal tract. Each of these priorities and possible approaches to their investigation will now be briefly

discussed.

(i) The role of abnormal sensory feedback in the genesis of upper gastrointestinal symptoms resulting from mediastinal irradiation could be further investigated by initially evaluating sensory perception in response to intraoesophageal balloon distension (Richter et al 1986; Mehta et al 1995) and gastric or intestinal distension using an electronic barostat (Coffin et al 1994).

(ii) The motor patterns underlying accelerated intestinal transit during and after abdominal irradiation on humans would optimally be evaluated by concurrent manometry and scintigraphic assessment of transit. Currently because of technical limitations, manometry using multiple recording ports is only possible for one particular region so that the effects of therapeutic irradiation on motility and transit in different regions will require separate experiments.

(iii) Definition of the relative roles of neural and myogenic mechanisms underlying gastrointestinal dysfunction requires in-vivo electrophysiological studies. Technical limitations restrict the use of this approach at present to the measurement of the latency of conduction of the external pudendal nerve (Kiff & Swash, 1984) and its relationship with anorectal manometric parameters.

(iv) Investigation of novel approaches to reduce the risk of radiation injury to the gastrointestinal tract would include (a) more precise identification of individuals at increased risk of radiation injury to the gastrointestinal tract by large scale multi-centre prospective longitudinal studies correlating putative risk factors with outcome. It is possible that there may be subsets of patients who are genetically predisposed to radiation damage. For example, carriers of the ataxia telangiectasia gene, who comprise 5% of the cancer population, have increased radiosensitivity when compared with normal individuals (Chen et al 1978).

Alternative modalities of therapy if available, e.g. surgery for early cervical carcinoma, should be the treatment of choice for such patients. When therapeutic irradiation is the only curative modality, it is possible that tumours from these individuals may also show increased radiosensitivity and therefore require a lower radiation dose to eradicate, (b) techniques designed to reduce the amount of the gastrointestinal tract in the high dose radiation field, such as bladder distension to displace the small intestine out of the pelvic radiation field, and so-called "conformal therapy". Although the relatively simple technique of bladder distension during therapeutic pelvic radiation has been reported to reduce the prevalence of diarrhoea (Green 1983; Gallagher et al 1986), no controlled studies have been done to confirm this. The successful exploitation of bladder distension to displace small intestinal loops out of the pelvic radiation field is predicated by these loops remaining free mobile which is not the case in many patients, as small bowel loops may be stuck in the pelvis (Green 1975). Conformal therapy, which attempts to minimise the irradiation of normal tissue by a combination of minimising patient movement and using individually shaped lead blocks, is currently being used in an attempt to reduce the long term morbidity of pelvic irradiation for prostatic carcinoma on relatively fixed parts of the gastrointestinal tract such as rectum. The application of this concept which has been facilitated by the advent of three dimensional computer planning programs, may prove to be beneficial for patients with fixed loops of small intestine in the pelvis.

Appendix

PUBLICATIONS RESULTING FROM THE STUDIES REPORTED IN THIS THESIS

Scientific Papers

1. Yeoh EK, Horowitz M. Radiation enteritis. Surg Gynecol Obstet 1987; 165:373-376.
2. Yeoh EK, Horowitz M, Russo A, Muecke T, Ahmad A, Robb T, Chatterton B. A retrospective study of the effects of pelvic irradiation for carcinoma of the cervix on gastrointestinal function. Int J Radiat Oncol Biol Phys 1993a; 26:229-237.
3. Yeoh EK, Horowitz M, Russo A, Muecke T, Robb T, Chatterton B. Gastrointestinal function in chronic radiation enteritis - effects of loperamide-N-oxide. Gut 1993b; 34:476-482.
4. Yeoh EK, Horowitz M, Russo A, Muecke T, Robb T, Maddox A, Chatterton B. Effect of pelvic irradiation on gastrointestinal function: A prospective longitudinal study. Am J Med 1993c; 95:397-406.
5. Yeoh EK, Horowitz M, Russo A, Muecke T, Robb T, Chatterton B. The effects of abdominal irradiation for seminoma of the testis on gastrointestinal function. J Gastroenterol Hepatol 1995; 10:125-130.
6. Yeoh EK, Holloway RH, Russo A, Tippett M, Bermingham H, Chatterton B, Horowitz M. Effects of mediastinal irradiation on oesophageal function. Gut 1995 (in press).

Abstracts

1. Yeoh EK, Horowitz M, Maddox A, Chatterton B, Robb T, Davidson G, Shearman DJC. Changes in gastrointestinal function in acute radiation enteritis. Gastroenterology 1987; 92:1704.

2. Yeoh EK, Horowitz M, Maddox A, Chatterton B, Robb T, Davidson G, Shearman DJC. Acute changes in gastrointestinal function after abdominal irradiation. Aust NZ J Med 1987; 17:473.

3. Yeoh EK, Horowitz M, Maddox A, Chatterton B, Robb T, Davidson G, Shearman DJC. Changes in gastrointestinal function in acute radiation enteritis. Aust NZ J Med 1987; 17:507.

4. Yeoh EK, Horowitz M, Maddox A, Wishart J Muecke T, Gaffney R, Robb T, Davidson G, Chatterton B, Shearman D. Acute effects of abdominal irradiation on gastrointestinal function. Gastroenterology 1988; 94:A510.

5. Yeoh EK, Horowitz M, Maddox A, Wishart J Muecke T, Gaffney R, Robb T, Davidson G, Chatterton B, Shearman D. Effects of abdominal irradiation on gastrointestinal function. Gastroenterology 1989; 96:A560.

6. Yeoh EK, Horowitz M, Russo A, Muecke T, Robb T, Chatterton B. effects of loperamide-N-oxide on gastrointestinal function in chronic radiation enteritis. Gastroenterology 1991; 100:A264.

7. Yeoh EK, Horowitz M, Russo A, Muecke T, Ahmad A, Chatterton B. Prevalence of chronic radiation enteritis after pelvic irradiation. Gastroenterology 1992; 102:A411.

8. Yeoh EK, Horowitz M, Russo A, Muecke T, Ahmad A, Chatterton B. Gastrointestinal function after abdominal or pelvic irradiation. Gastroenterology 1993; 104:A463.

9. Yeoh EK, Holloway R, Horowitz M, Russo A, Tippett M, Bermingham H, Chatterton B. Effects of mediastinal irradiation on esophageal function. Gastroenterology 1995;108:A264.

Bibliography

Aabakken L 1989. Cr-51 Ethylenediaminetetraacetic acid absorption test: Methodological aspects. Scand J Gastroenterol 24:351-358.

Accarino AM, Azpiroz F, Malagelada JR 1992. Symptomatic responses to stimulation of sensory pathways in the jejunum. Am J Physiol 263:G673-G677.

Adrian TE, Savage AP, Bacarese-Hamilton AJ, Wolfe K, Besterman HS, Bloom SR 1986. Peptide abnormalities in gastrointestinal diseases. Gastroenterology 90:379-384.

Aldini R, Roda A, Festi D, Mazzella G, Morselli Am, Sama C, Roda E, Scopinaro N, Barbara L 1982. Diagnostic value of serum primary bile acids in detecting bile acid absorption. Gut 23;829-834.

Allen RH 1982. Cobalamin (Vitamin B12) absorption and malabsorption. Viewpoints Dig Dis 14;17-20.

Allen-Mersh TG, Wilson EJ, Hope-stone HF, Mann CV 1986. Has the incidence of radiation-induced bowel damage following treatment of uterine carcinoma changed in the last 20 years? J Roy Soc Med 79:387-390.

Ambrus JL, Ambrus CM, Lillie DB, Johnson RJ, Gastpar H, Kishel S 1984. Effect of sodium meclofenamate on radiation induced esophagitis and cystitis. J Med 15:81-91.

Amdur RJ, Parsons JT, Fitzgerald LT, Millon RR 1990. The effect of overall treatment time on local control in adenocarcinoma of prostate treated with radiation therapy. Int J Radiat Oncol Biol Phys 19: 1377-1382.

Andersson H, Isaksson B, Sjogren B 1974. Fat-reduced diet in the symptomatic treatment of small bowel disease. Gut 15:351-359.

Andrews PLR, Hawthorn J 1987. Evidence for an extra-abdominal site of action for the 5-HT3 receptor antagonist BRL 24924 in the inhibition of radiation-evoked emesis in the ferret. Neuropharmacology 26:1367-1370.

Andrews PLR, Davidson HIM 1990. Activation of vagal afferent terminals by the 5-HT3 receptor in the anaesthetised ferret. J Physiol 422:92P(Abstract).

Andrews PLR, Davis CJ, Bingham S, Davidson HIM, Hawthorn J, Maskell L 1990. The abdominal visceral innervation and the emetic reflex: pathways, pharmacology and plasticity. Can J Physiol Pharmacol 68:325-345

Andrews PLR, Rapeport WG, Sanger GJ 1988. Neuropharmacology of emesis induced by anti-cancer therapy. Trends Pharmacol Sci 9:334-341.

Angus RM, Eisman JA 1988. Osteoporosis: the role of calcium intake and supplement. Med J Aust 148:630-633.

Anseline PF, Lavery IC, Fazio VW, Jagelman DG, Weakley FL 1981. Radiation injury to the rectum. Evaluation of surgical treatment. Ann Surg 194:716-724.

Anvari M, Malbert C, Horowitz m, Jamieson GG 1994. Loxiglumide abolishes the effects of intraduodenal oleic acid on gastric motility and emptying in the pig. Neurogastroenterol Motil 6:181-187.

Arhan P, Devroede Gh, Jehannin B, Lanza M, Faverdin Cl, Dornic C, Persoz B, Tetreault L, Perey B Pellerin D 1981. Segmental colonic transit time. Dis Colon Rectum 24:625-629.

Arndorfer RC, Stef JJ, Dodds WJ, Lineham JH, Hogan WJ 1977. Improved infusion system for intraluminal oesophageal manometry. Gastroenterology 73:23-27.

Atweh SF, Kuhar MJ 1977. Autoradiographic localization of opiate receptors in rat brain. I. Spinal cord and lower medulla. Brain Res 124:53-67.

Avill R, Mangnall YF, Bird NC, Brown BH, Barber DC, Seagar AD, Johnson AG, Read NW 1987. Applied potential tomography. A new non-invasive technique for measuring gastric emptying. Gastroenterology 92:1019-1026.

Axon ATR, Creamer B 1975. The exsorption characteristics of various sugars. Gut 16:99-104.

Azpiroz F, Malagelada JR 1985. Intestinal control of gastric tone. Am J Physiol 249:G501-509.

Barc ZM, Alexander P, 1961. Fundamentals of Radiobiology, 2nd edition. Pergamon Press, New York:411.

Barton MB, Keane TJ, Gadalla T, Maki E 1992. The effect of treatment time and treatment interruption on tumour control following radical radiotherapy of laryngeal cancer. Radiother Oncol 23:137-143.

Basilisco G, Bozzani A, Camboni G, Recchia M, Quatrini M, Conte D, Penagini R, Bianchi PA 1985. Effect of loperamide and naloxone on mouth-to-caecum transit time evaluated by lactulose hydrogen breath test Gut 26: 700-703.

Baxter AJ, Mangnall YF, Loj GH, Brown B, Barber DC, Johnson AG, Read NW 1988. Evaluation of applied potential tomography as a new non-invasive gastric secretion test. Gut 9:1730-1735.

Beer WH, Fan A, Halsted CH 1985. Clinical and nutritional implications of radiation enteritis. Am J Clin Nutr 41:85-91.

Belli JA, Dicus GJ, Bonte FJ 1967. Radiation response of mammalian tumor cells. I. Repair of sublethal damage in vivo. J Natl Cancer Inst 38:673-682

Bercik P, Armstrong D, Fraser R, Dotoit P, Emde C, Primi MP, Blum AL, Kuchera P 1994. Origin of motility patterns in isolated arterially perfused rat intestine. Gastroenterology 106:649-657.

Birnbaum EH, Dreznik Z, Myerson RJ, Lacey DL, Fry RD, Kodner IJ, Fleshman JW, 1992. Early effect of external beam radiation therapy on the anal sphincter: A study using anal manometry and transrectal ultrasound. Dis Colon Rectum 35:757-761.

Birnbaum EH, Myerson RJ, Fry RD, Kodner IJ, Fleshman JW, 1994. Chronic effects of pelvic radiation therapy on anorectal function. Dis Colon Rectum37:909-915.

Bjarnason I, Peters TJ, Veall N 1983. A persistent defect in intestinal permeability in coeliac disease demonstrated by a Cr-51 labelled EDTA absorption test. Lancet (i):323-325.

Blackwell JN 1989. Oesophageal scintigraphy. In: Read NW Ed., Gastrointestinal Motility Which Test? Wrightson Biomedical Publishing Ltd, Petrsfield:53-61.

Blackwell JN, Hannan WJ, Adam RD, Heading RC 1983. Radionuclide studies in the detection of oesophageal dysmotility. Gut 24:421-426.

Blackshaw LA, Grundy D 1990. Effects of cholecystokinin (CCK-8) on two classes of gastroduodenal vagal afferent fibre. J Auton Nerv Syst 31:191-202.

Blackshaw LA, Grundy D 1993a. Effects of 5-hydroxytryptamine (5HT) on the discharge of vagal mucosal afferent fibres in the upper gastrointestinal tract of the anaesthetised ferret. J Auton Nerv Syst 45:41-50.

Blackshaw LA, Grundy D 1993b. Effects of 5-hydroxytryptamine (5HT) on the discharge of vagal mechanoreceptors and motility in the upper gastrointestinal tract of the anaesthetised ferret. J Auton Nerv Syst 45:51-59.

Blackshaw LA, Grundy D, Scratcherd T, 1987. Vagal afferent discharge from gastric mechnoreceptors during contraction and relaxation of the ferret corpus. J Auton Nerv Syst 18:19-24.

Bond JH, Levitt MD 1975. Investigation of small bowel transit time in normal subjects utilising pulmonary hydrogen measurements. J Lab Clin Med 86:546-555.

Bosaeus I, Andersson H, Nystrom C 1979. Effect of a low fat diet on bile salt excretion and diarrhoea in the gastrointestinal radiation syndrome. Acta Radiol Oncol 18:460-464.

Bouckaert A 1968. Tracer study of gastro-intestinal transit in abdomen-irradiated rats. Rad Biol Ther 9:567-572

Bounous G, Le Bel E, Shuster J, Gold P, Tahan Wt, Bastin E 1975. Dietary protection during radiation therapy. Strahlentherapie 149:476-483.

Bourne RG, Kearsley JH, Grove WD, Roberts SJ 1983. The relationship between early and late gastrointestinal complications of radiation therapy for carcinoma of the cervix Int J Radiat Oncol Biol Phys 9:1445-1450.

Boyd GS, Merrick MV Monks R, Thomas IL 1981. Se-75 labelled bile acid analogues, new radiopharmaceuticals for investigating the enterohepatic circulation. J Nucl Med 22;720-725.

Brenner W, Hendrix TR, McHugh PR 1983. Regulation of gastric emptying of glucose. Gastroenterology 85:76-82.

Brizzee KR 1956. Effect of localised brain stem lesions and supradiaphragmatic vagotomy on X-radiation emesis in the monkey. Am J Physiol 187:567-570.

Brown MS, Buchanan RB, Karran SJ 1980. Clinical observations on the effects of elemental diet supplementation during irradiation. Clin Radiol 31:19-20.

Brunetto AL, Pearson ADJ, Gibson R, Bateman DN, Rashid MU, Laker MF 1990. The effect of pharmocological modification of gastric emptying and mouth-to-caecum transit time on the absorption of sugar probe molecules of intestinal permeability in normal man. Eur J Clin Invest 20:279-284.

Cann PA, Read NW, Holdsworth CD 1982. Loperamide improves dyspeptic symptoms and accelerates gastric emptying in patients with irritable bowel syndrome. Gut 25:A437(Abstract).

Caride VJ, Prokop EK, Troncale FJ, Buddoura W, Winchenbach K, McCallum RW 1984. Scintigraphic determination of small intestinal transit time: comparison with the hydrogen breath technique. Gastroenterology 86:714-720.

Carr ND, Pullen BR, Hasleton PS, Schofield PF 1984. Microvascular studies in human radiation bowel disease. Gut 25:448-454.

Castell DO 1989. Indications for oesophageal function tests. In: Read NW Ed., Gastrointestinal Motility Which Test? Wrightson Biomedical Publishing Ltd, Petrsfield:9-17.

Castell DO, Donner MW 1987. Evaluation of dysphagia: A careful history is crucial. Dysphagia 2:65-71.

Chanarin I 1969. The megaloblastic anaemias. Blackwell, Oxford.

Chapaux J, Chapaux P, Royer E 1974. Loperamide in patients with radiotherapy-induced diarrhoea. Arzeim-Forsch Drug Res 28:864-866.

Chen PC, Lavin MF, Kidson C 1978. Identification of ataxia telangiectasia heterozygotes, a cancer prone population. Nature 274:484-486.

Chinn HI, Wang SC 1954. Locus of emetic action following irradiation. Proc Soc Exp Biol Med 85:472-477.

Chmelar V, Grossmann V, Hais IM, Deml F 1969. Gastric retention and its changes in mice and rats during the first six days following X-irrradiation. Radiat Res 37:627-635.

Chowhan NM 1990. Injurious effects of radiation on the esophagus.Am J Gastroenterol 85:115-120.

Christensen J 1976. The controls of oesophageal movement. Clinics in Gastroenterology 5:15.

Christian P, Moore J, Sorensen J, Coleman R, Weich D 1980. Effects of meal size and correction technique on gastric emptying time: studies with two tracers and opposed detectors. J Nucl Med 21:883-872.

Christian PE, Datz FL, Sorensen JA, Taylor A 1983. Technical factors in gastric emptying studies. J Nucl Med 21:883-885.

Coffin B, Azpiroz F, Guarner F, Malagelada J-R 1994. Selective gastric hypersensitivity and reflex hyporeactivity in functional dyspepsia. Gastroenterology 107:1345-1351.

Coia LR, Hanks GE 1988. Complications from large field intermediate dose infradiaphargmatic radiation: An analysis of the patterns of care outcome studies for Hodgkin's disease and seminoma. Int J Radiat Oncol Biol Phys 15:29-35.

Collins PE, Horowitz M, Cook DJ, Harding PE, Shearman DJC 1983. Gastric emptying in normal subjects - a reproducible technique using a single scintillation camera and computer system. Gut 24:1117-1125.

Condon JR, South M, Wolverson RL, Brinkley D 1978. Radiation Diarrhoea and cholestyramine. Postgrad Med J 54:838-839.

Conover WJ 1980. Practical non-parametric stastistics, 2nd edition. John Wiley & Sons, New York.

Conrad RA 1951. Effect of X-Irradiation on intestinal motility of the rat. Am J Physiol 165:375-385.

Conrad RA 1956. Some effects of ionising radiation on the physiology of the gastrointestinal tract: a review. Radiat Res 5:167-188.

Cooper JR, Mattsson JL, 1979. Control of radiation-induced emesis with promethazine, cimetidine, thiethylperazine or naloxone. Am J Vet Res 40:1057-1061.

Costa M, Furness J, Llewellyn-Smith I 1987. Histochemistry of the enteric nervous system. In: Johnson LR Ed., Physiology of the gastrointestinal tract. Raven Press, New York:1-40.

Cummings JH, Wiggins HS 1976. Transit through the gut measured by analysis of a single stool. Gut 17:219-223.

Cunningham IGE 1980. The management of radiation proctitis. Aus NZ J Surg 50:172-178.

Cunningham KM, Baker R, Horowitz M, Maddox A, Edelbroek M, Chatterton B 1991. Use of a new radiopharmaceutical, technetium-99m (v) thiocyanate to measure gastric emptying of fat. J Nucl Med 32:878-881.

Dalla Palma L 1968. Intestinal malabsorption in patients undergoing abdominal radiation therapy. In: Sullivan MF Ed., Gastrointestinal Radiation Injury, Excerpta Medica Foundation, Washington DC:261-272.

Danjoux CE, Rider WD, Fitzpatrick PJ 1979. The acute radiation syndrome. A memorial to William Michael Court-Brown. Clin Radiol 30:581-584.

DeCaestecker JS, Blackwell JN, Adam RD, Hannan WJ, Brown J, Heading RC 1986. Clinical value of radionuclide oesophageal transit measurement. Gut 27:659-666.

DeCosse JJ, Rhodes RS, Wentz WB, Reagan JW, Dworken HJ, Holden WD 1969. The natural history and management of radiation induced injury of the gastrointestinal tract. Ann Surg 170:369-384.

Deluca FR, Ragins H 1985. Construction of an omental envelope as a method of excluding the small intestine from the field of postoperative irradiation to the pelvis. Surg Gynecol Obstet 160:365-366.

Dencker H, Johnsson JE, Liedberg G, Tibblin S 1971. Surgical aspects of radiation injury to the small and large intestines Acta Chir Scand 137:692-695.

Dent J 1976. A new technique for continuous sphincter pressure measurement. Gastroenterology 71:263-269.

Dent J 1989. Oesophageal manometry. In: Read NW Ed., Gastrointestinal Motility Which Test. Wrightson Biomedical Publishing Ltd, Petersfield:27-40.

Desjardins AU 1931. Action of roentgen rays and radium on the gastrointestinal tract. Am J Roentgenol 26:151-190,337-370,495-510.

Diamant NE, El-Sharkawy TY 1977. Neural control of esophageal peristalsis. A conceptual analysis. Gastroenterology 72:546-556.

Dodds WJ, Stewart ET, Hogan WJ, Stef JJ, Arndorfer RC 1974. Effect of oesophageal movement on intraluminal oesophageal pressure recording. Gastroenterology 67:592-600.

Doig RK, Funder JF, Weiden S, 1951. Serial gastric biopsy studies in a case of duodenal ulcer treated by deep x-ray therapy. Med J Aust 38:828-830.

Donaldson SS, Jundt S, Ricour C, Sarrazin D, Lemerle J, Schweisguth O 1975. Radiation enteritis in children. Cancer 35:1167-1178.

Donaldson SS, Wesley MN, Ghavimi F, Shils ME, Suskind RM, DeWys WD 1982. A prospective randomised clinical trial of total parenteral nutrition in children with cancer. Med Pediatr Oncol 10:129-139.

Dorval ED, Mueller GP, Eng RR, Durakovic A, Conklin JJ, Dubois A 1985. Effect of ionising radiation on gastric secretion and gastric motility in monkeys. Gastroenterology 89:374-380.

Douglass HO, Milliron S, Nava H, Eriksson B, Thomas P, Novick A, Holyoke ED 1978. Elemental diet as an adjuvant for patients with locally advanced gastrointestinal cancer receiving radiation therapy: a prospectively randomised study. JPEN 2:682-686.

Dubois A 1989. Gastric dysrhythmias: pathophysiologic and etiologic factors. Mayo Clin Proc 64:246-250.

Dubois A, Jacobus JP, Grissom MP, Eng RR, Conklin JJ 1984. Altered gastric emptying and prevention of radiation-induced vomiting in dogs. Gastroenterology 86:444-448.

Duchesne GM, Horwich A, Dearnaley DP, Nicholls J, Jay G, Peckham MJ, Hendry WF 1990. Orchidectomy alone for Stage I Seminoma of the testis. Cancer 65:1115-1118.

Duncan W, Nias AHW 1977. In: Late effects on normal tissues, Clinical Radiobiology, Churchill Livingstone, Edinburgh:127-142.

Duthie HL 1975. Dynamics of the rectum and anus. Clinics in Gastroenterology 4:467-477.

Edelbroek M, Horowitz M, Dent J, Sun WM, Malbert C, Smout A, Akkermans L 1994. Effect of duodenal distension on fasting and postprandial antropyloroduodenal motility in humans. Gastroenterology 106:583-592.

Editorial 1984. Radiation bowel disease. Lancet ii:963-964.

Editorial 1985. Intestinal permeability. Lancet i:256-258.

Embring GI, Mattsson O 1966. An improved radiological contrast medium for the alimentary tract. Acta Radiol Diag 4:105-109.

Engelstad RB 1938. The effect of roentgen rays on the stomach in rabbits. Am J Roentgenol 40:243-263.

Erlinger S, Paupon R, Glasinovic J, Dumont M 1977. Hepatic uptake, storage and biliary transport maximum of bile acids in the dog. Bile acid metabolism in health and disease. In: Proceedings of 4th Bile Acid Meeting, Basel. MTP Press, Lancaster:107-112.

Feldman M, Smith HJ 1987. Effect of cisapride on gastric emptying of indigestible solids in patients with gastroparesis diabeticorum: a comparison with metoclopramide and placebo. Gastroenterology 92: 171-174.

Ferguson A 1981. Diagnosis and treatment of lactose intolerance. Br Med J 283:1423-1424.

Ferraris R, Jazrawi R, Bridges C, Northfield TC 1986. Use of a gamma-labelled bile acid (SeHCAT) as a test of ileal function. Methods of improving accuracy. Gastroenterology 90:29-36.

Field M, Rao MC, Chang EB 1989. Intestinal electrolyte transport and diarrhoeal disease. New Eng J Med 321:800-806.

Finkelstein E 1986. Nifedipine for radiation oesophagitis. Lancet i:1205-1206.

Finlayson NDC, Simpson JD, Tothill P, Samson RR, Girdwood RH, Shearman DJC 1969. Application of whole body counting to the measurement of Vitamin B12 absorption with reference to achlorhydria. Scand J Gastroenterol 4:397-405.

Fisher RS, Malmud LS, Roberts GS, Lobis IF 1977. The lower oesophageal sphincter as a barrier to gastro-oesophageal reflux. Gastroenterology 72: 19-22.

Fitzpatrick PJ, Rider WD 1976. Half body radiotherapy. Int J Radiat Oncol Biol Phys 1:197-207.

Fone DR, Akkermans LMA, Dent J et al 1990. Evaluation of patterns of human antral and pyloric motility with an antral wall motion detector. Am J Physiol 258:G616-G623.

Fone DR, Horowitz M, Heddle R et al 1991. Comparative effects of duodenal and ileal intubation on gastric emptying and postprandial antral, pyloric and duodenal motility. Scand J Gastroenterol 26:16-22.

Ford JH, Dudan RC, Bennett JS, Averette HE 1972. Parenteral hyperalimentation in gynecologic patients. Gynecol Oncol 1:70-75.

Fossa SD, Aass N, Kaalhus O 1989. Long term morbidity after infradiaphragmatic radiotherapy in young men with testicular cancer. Cancer 64:404-408.

Fowler JF, Lindstrom MJ 1992. Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys 22:457-467.

Fox BW, Lajtha LG 1973. Radiation damage and repair phenomena. Br Med Bull 29:16-22.

Fozard JR, Mobarok Ali AT 1978. Blockade of neuronal tryptamine receptors by metoclopramide. Eur J Pharmol 49:109-112.

Frankendahl B 1973. Gastric emptying and small intestinal propulsion in mice following irradiation of the abdomen. Acta Radiol Ther Phys Biol 12:529-540.

Frankendal B, Junghagen P 1974. Gastrointestinal transit time in ovarian carcinoma irradiated with Co-60. Acta Radiol Ther Phys Biol 13:129-140.

Friedman M 1952. Calculated risks of radiation injury of normal tissue in the treatment of cancer of the testis. Proc 2nd Nat Cancer Conf I:390-400.

Fromm H & Hofmann AF 1971. Breath test for altered bile acid metabolism. Lancet ii:621-625.

Fromm H, Thomas PJ, Hofmann AF 1973. Sensitivity and specificity in tests of distal ileal function: prospective comparison of bile acid and vitamin B12 absorption in ileal resection patients. Gastroenterology 64::1077-1090.

Furukawa Y, Cook IJ, Panagopoulos V, McEvoy D, Sharp DJ, Simula M 1994. Relationship between sleep patterns and human colonic motor patterns. Gastroenterology 107:1372-1381.

Fyles A, Keane TJ, Barton M, Simm J 1992. The effect of treatment duration in the local control of cervix cancer. Radiother Oncol 25:273-279.

Gallagher MJ, Brereton HD, Rostock RA, Zero JM, Zekoski DA, Poyss LF, Richter MP, Kligerman MM 1986. A prospective study of treatment techniques to minimise the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. Int J Radiat Oncol Biol Phys 12:1565-1573.

Galland RB, Spencer J 1985. The natural history of clinically established radiation enteritis. Lancet i:1257-1258.

Galland RB, Spencer J 1987. Natural history and surgical management of radiation enteritis. Br J Surg 74:742-747.

Geginat G, Behdjati F, Green E, Kaeferstein D 1978. Study of loperamide in patients with diarrhoea following telecobalt irradiation for malignant abdominal tumors. Strahlenther 154:11-15.

Gelfand MD, Tepper M, Katz LA, Binder HJ, Yersner R, Floch MH 1968. Acute irradiation proctitis in man: development of eosinophilic crypt abscesses. Gastroenterology 54:401-411.

Ghoos Y, Maes B, Geypens B et al, 1993. Measurement of gastric emptying rate of solids by means of carbon-labelled octanoic breath test. Gastroenterology 104:1640-1647.

Gilinsky NH, Burns DG, Barbezat GO, Levin W, Myers HS 1983. The natural history of radiation induced proctosigmoiditis: An analysis of 88 patients. Q J Med 52:40-53.

Goldgraber MB, Rubin CE, Palmer WL, Dobson RL, Massey BW 1954. The early gastric response to irradiation: a serial biopsy study. Gastroenterology 27:1-20.

Goldstein F, Khoury J, Thorton JJ 1976. Treatment of chronic radiation enteritis and colitis with salicylazosulfapyridine and systemic corticosteroids. Am J Gastroenterol 65:201-208.

Goldstein HM, Rogers LF, Fletcher GH, Dodd GD 1975. Radiological manifestations of radiation-induced injury to the normal upper gastrointestinal tract. Radiology 117:135-140.

Gommeren W, Leysen J 1985. In vitro receptor binding and amine uptake inhibition profile of R 58 425 and loperamide (R 18 533)Janssen Preclinical Research Report:N46 505.

Green N 1983. The avoidance of small intestine injury in gynecologic cancer. Int J Radiat Oncol Biol Phys 9:1385-1390.

Green N, Iba G, Smith WR 1975. Measures to minimize small intestine injury in the irradiated pelvis. Cancer 35:1633-1640.

Gunderson LL, Russell AH, Llewellyn HJ, Doppke KP, Tepper JE 1985. Treatment planning for colorectal cancer: radiation and surgical techniques and value of small-bowel films. Int J Radiat Oncol Biol Phys11:1379-1393.

Haddad H, Bounous G, Tahan WT, Devroede G, Beaudry R, Lafond R 1974. Long term nutrition with an elemental diet following intensive abdominal irradiation: report of a case. Dis Col Rect 17:373-376.

Hames TK, Condon BR, Fleming JS, Phillips G, Holdstock G, Smith CL, Howlett PJ, Ackery D 1984. A comparison between the use of a shadow shield whole body counter and an uncollimated gamma camera in the assessment of the seven-day retention of SeHCAT. Br J Radiol 57:581-584.

Hamilton C, Horwich A, Easton D, Peckham MJ 1986. Radiotherapy for Stage I seminoma of the testis: Results of treatment and complications. Radiother Oncol 6:115-120.

Hamilton FE 1947. Gastric ulcer following radiation. Arch Surg 55:394-399.

Hatcher PA, Thomson HJ, Ludgate SN, Small WP, Smith AN 1985. Surgical aspects of intestinal injury due to pelvic radiotherapy. Ann Surg 201: 470-475.

Hauer Jansen M, Sauer T, Devik F, Nygaard K 1983. Late changes following single dose roentgen irradiation of rat small intestine. Acta Radiol Oncol 22:299-303.

Haynes WG, Read NW 1982. Ano-rectal activity in man during rectal infusion of saline: a dynamic assessment of the anal continence mechanism. J Physiol 330:45-56.

Heading RC, Nimmo J, Prescott LF et al 1973. The depedence of paracetamol absorption on the rate of gastric emptying. Br J Pharmacol 47:415-421.

Heading RC, Tothill P, McLoughlin GP, Shearman DJC 1976. Gastric emptying rate measurements in man. A double isotope scanning technique for simultaneous study of liquid and solid components of a meal. Gastroenterology 71:45-50.

Heaton KW 1977. Disturbances of bile acid metabolism in intestinal disease. Cilnics in Gastroenterology 6:69-89.

Heddle R, Collins PJ, Dent J, Horowitz M 1989. Motor mechanisms associated with slowing of the gastric emptying of a solid meal by an intraduodenal lipid infusion. J Gastroenterol Hepatol 4:437-447.

Henriksson R, Franzen L, Littbrand B 1992. Effects of sucralfate on acute and late bowel discomfort following radiotherapy of pelvic cancer. J Clin Oncol 10:969-975.

Hetzel PAS, LaBrooy JT, Bellon M, Davidson GP, Johnson RB, Chatterton BE, Shearman DJC 1986. The Cr-51 EDTA absorption test in coeliac patients treated with a gluten free diet. IRCS med Sci 14:1183-1184.

Heusinkveld RS, Manning MR, Aristizabal SA 1978. Control of radiation-induced diarrhea with cholestyramine. Int J Radiat Oncol Phys Biol 4:687-690.

Hinder RA, Kelly KA 1977. Gastric emptying of solids and liquids. Am J Physiol 233:E335-E340.

Hinton JM, Lennard-Jones JE, Young AC 1969. A new method for studying gut transit times using radioopaque markers. Gut 10:842-847.

Hirschowitz L & Rode J 1991. Changes in neurons, neuroendocrine cells and nerve fibres in the lamina propria of irradiated bowel. Virchows Archiv A Pathol Anat 418:163-168.

Hislop IG, Hofman AF, Schoenfield LJ 1967. Determinants of the rate and site of bile acid absorption in man. J Clin Invest 46:1070-1071 (abstract).

Holgate AM, Read NW 1983. Relationship between small bowel transit time and absorption of a solid meal: Influence of metoclopramide, magnesium sulfate and lactulose. Dig Dis Sci 28:812-819.

Holgate AM, Read NW 1985. Effect of ileal infusion of intralipid on gastrointestinal transit, ileal flow rate and carbohydrate absorption in humans after ingestion of a liquid meal. Gastroenterology 88:1005-1011.

Holloway RH, Lange RC, Plankey MW, McCallum RW 1989. Detection of esophageal motor disorders by radionuclide transit studies. Dig Dis Sci 34:905-912.

Holzer P 1988. Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene related peptide and other neuropeptides. Neuroscience 24:739-768.

Horowitz M, Collins PJ, Shearman DJC 1985a. Disorders of gastric emptying in humans and the use of radionuclide techniques. Arch Intern Med 145:1467-1472.

Horowitz M, Dent J 1991. Disordered gastric emptying: mechanical basis, assessment and treatment. Bailliere"s Clinical Gastroenterology 5(2):371-407.

Horowitz M, Dent J 1994. The study of gastric mechnics and flow: a mad hatter's tea party starting to make sense? Editorial, Gastroenterology 107:302-306.

Horowitz M, Dent J, Fraser R, Sun WM, Hebbard G 1994. Role and integration of mechanisms controlling gastric emptying. Dig Dis Sci 39:12:S7-S13.

Horowitz M, Fraser R 1994. Disordered gastric motility in diabetes mellitus. Diabetologia 37:543-551.

Horowitz M, Harding PE, Chatterton BE, Collins PJ, Shearman DJC 1985b. Acute and chronic effects of Domperidone on gastric emptying in diabetic autonomic neuropathy. Dig Dis Sci 30:1-9.

Horowitz M, Maddox A, Bochner M et al 1989. Relationships between gastric emptyingof solid and caloric liquid meals and alcohol absorption. Am J Physiol 257:G291-G298.

Horowitz M, Wishart J, Mundy L, Nordin BEC 1987. Lactose and calcium absorption in postmenopausal osteoporosis. Arch Intern Med 147:534-536.

Houghton LA, Read NW, Heddle R Horowitz M, Collins PJ, Chatterton B, Dent J 1988. The relationship of the motor activity of the antrum, pylorus and duodenum to gastric emptying of a solid-liquid mixed meal. Gastroenterology 94:1285-1291.

Hulse EV 1966. Gastric emptying in rats after part-body irradiaton. Int J Radiat Oncol Biol Phys 10:521-532.

Jennings F, Arden A 1960. Acute radiation effects in the esophagus. Arch Path 69:407-412.

Johansson C 1975. Studies of gastrointestinal interaction (VII). Characteristics of absorption pattern of sugar fat and protein from composite meals in man. Scand J Gastrenterol 10:33-42.

Joslin CAF, Smith CW, Mallik A 1972. The treatment of cervix cancer using high activity Co-60 sources. Br J Radiol 45:257-270.

Kachel G, Ruppin H, Hagel J, Barina W, Meinhardt M, Domschke W 1986. Human intestinal motor activity and transport: effects of a synthetic opiate. Gastroenterology 90:85-93.

Karlstrom L 1986. Evidence of involvement of the enteric nervous system in the effects of sodium deoxycholate on small intestinal transepithelial fluid transport and motility. Scand J Gastroent 21:321-330.

Kawahara H, Blackshaw LA, Nisyrios V, Dent J 1994. Transmitter mechanisms in vagal afferent-induced reduction of lower oesophageal sphincter (LOS) pressure in the rat. J Auton Nerv Syst 49:69-80.

Kellow J, Eckersley G, Jones M 1991. Enhanced perception of physiological intestinal motility in the irritable bowel syndrome. Gastroenterology 101:1621-1627.

Kellow J, Gill RC, Wingate DC 1990. Prolonged ambulatory recordings of small bowel motility demonstraate abnormalities in the irritable bowel syndrome. Gastroenterology 98:1208-1218.

Kellow J, Phillips S 1987. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology 92:1885-1893.

Kellow J, Phillips SF, Miller LJ, Zinsmeister AR 1988. Dysmotility of the small intestine in irritable bowel syndrome. Gut 29:1236-1243.

Kellow JE, Borody TJ, Phillips SF, Haddad AC, Brown ML 1986. Sulfapyridine appearance in plasma after Salicylazosulfapyridine. Another simple measure of intestinal transit. Gastroenterology 91:396-400.

Kelly KA 1980. Gastric emptying of liquids and solids: roles of proximal and distal stomach. Am J Physiol 239:G71-G76.

Kendall GPN, Thompson DG, Day SJ, Garvie N 1987. Motor responses of the oesophagus to intraluminal distention in normal subjects and patients with oesophageal clearance disorders. Gut 28:272-279.

Kiff ES, Swash M 1984. Normal and delayed distal conduction in the pudendal nerves of patients with idiopathic (anorectal) incontinence. J Neurol Neurosurg Psychiatry 47:820-823.

Kinsella TJ, Bloomer WD 1980. Tolerance of the intestine to radiation therapy. Surg Gynecol Obstet 151:273-284.

Kinsella TJ, Malcolm AW, Bothe A, Valerio D, Blackburn GL 1981. Prospective study of nutritional support during pelvic irradiation. Int J Radiat Oncol Phys Biol 7:543-548.

Kinsman RI, Read NW 1984. Effect of naloxone on feedback regulation of small bowel transit by fat. Gastroenterology 87:335-337.

Kirwan WO, Smith AN 1974. Gastrointestinal transit estimated by an isotope capsule. Scand J Gastroenterol 9:763-766.

Klein HA 1984. Computer aided analysis of radionuclide oesophageal transit studies. J Nucl Med 29:957-964.

Kline JC, Buchler DA, Boone ML, Peckham BM, Carr WF 1972. The relationship of reactions to complications in the radiation therapy of cancer of the cervix. Radiology 105:413-416.

Koch GG 1969. Some aspects of the analysis of "split plot" experiments in completely randomised layouts. J Am Stat Assoc 64:485-505.

Koch KL, Stern RM, Stewart WR, Vasey MW 1989. Gastric emptying and gastric myoelectrical activity in patients with diabetic gastroparesis: effect of long term domperidone. Am J Gastroenterol 84:69-75.

Kochhar R, Patel F, Dhar A, Sharmz SC, Ayyagari S, Aggarwal R, Goenka MK, Gupta BD, Mehta SK 1991. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulphasalazine plus rectal steroids versus rectal sucralfate. Dig Dis Sci 36:103-107.

Korneeva YS 1963. Changes in gastric secretion and motility following X-irradiation of the gastric region. In: Effects of ionizing radiation on the digestive system. Ed IT Kurstin, Elsevier Publishing Company, Amsterdam, London, New York:158-188.

Krevsky B, Malmud LS, D'Ercole F, Maurer AH, Fisher RS 1986. Colonic transit scintigraphy. A physiological approach to the quantitative measurement of colonic transit in humans. Gastroenterology 91:1102-1112.

Kruis W, Azpiroz F, Philips S 1985. Contractile patterns and transit of fluid in canine terminal ileum. Am J Physiol 249:G264-G270.

Kwitko AO, Pieterse AS, Hecker R, Rowland R, Wigg D 1982. Chronic radiation injury to the intestine: a clinico-pathological study. Aust N Z J Med 12:272-277.

LaBrooy SJ, Male P-J, Beavis AK, Misiewicz JJ 1983. Assessment of the reproducibility of the lactulose H-2 breath test as a measure of mouth to caecum transit time. Gut 24:893-896.

LaManna MM, Parker JA, Wolodzko BS, Zekavat PP, Popky GL 1985. Radionuclide esohageal and intestinal transit scintigraphy in patients undergoing radiation therapy. Radiat Med 3:13-16.

Lambert B, Mareno-Osset E, Baillet G, Kolanz R, Snape WJ, Mena I 1988. Evaluation of colonic motility in normal human volunteers: correlation between colonic scintigraphies and manometric studies. In: Schmidt HAE & Csernay L Eds., Nuklearmedizin. Schattauer Verlag, Stuttgart, New York:413-415.

LaRusso NF, Korman MG, Hoffman NE, Hofmann AF 1974. Dynamics of the enterohepatic circulation of bile acids. Postprandial serum concentrations of conjugates of cholic acid in health, cholecystectomized patients, and patients with bile acid malabsorption. N Engl J Med 291:689-692.

Laufer I 1979. Double contrast gastrointestinal radiology with endoscopic correlation. WB Saunders, Philidelphia 79-128.

Lauberg S, Swash M 1989. Effects of aging on the anorectal sphincters and their innervation. Dis Colon Rectum 32:737-742.

Lavrijsen K, Meuldermans W, Hendrickx J Swysen E, Heykants J 1984. The reductive in-vitro metabolism of loperamide-N-oxide by rat liver homogenates, red blood cells and gut contents. Arch Int Pharmadyn Ther 270:174-175.

Layer P, Demol P, Hotz J, Goebell H 1986. Gastroparesis after radiation. Dig Dis Sci 31:377-380.

Lemann M, Dedering JP, Flourie B, Franchisseur C, et al 1991. Abnormal perception of visceral pain in response to gastric distension in chronic idiopathic dyspepsia. The irritable stomach syndrome. Dig Dis Sci 36:1249-1254.

Lindahl F 1970. Intestinal injuries following irradiation for carcinoma of the uterine cervix and vesical carcinoma. Acta Chir Scand 136:725-730.

LoIudice T, Baxter D, Balint J 1977. Effects of abdominal surgery on the development of radiation enteropathy. Gastroenterology 73:1093-1097.

LoIudice TA, Lang JA 1983. Treatment of radiation enteritis: A comparison study. Am J Gastroenterol 78:481-487.

Longstreth GF, Malagelada JR, Kelly K, 1977. Metoclopramide stimulation of gastric motility and emptying in diabetic gastroparesis. Ann Intern Med 86:195-196.

Ludgate SM, Merrick MV 1985. The pathogenesis of post-radiation chronic diarrhoea: measurement of SeHCAT and B12 absorption for differential diagnosis determines treatment. Clin Radiol 36:275-278.

Lundgren O 1988. Nervous control of intestinal transport. Baillieres Clin Gastroenterology 2:85-106.

MacDonald GE, Hoyt LH 1956. Corticotrophin(ACTH) gel in treatment of irradiation enterocolitis. JAMA 161:1381-1383.

MacDonnagh R, Sun WM, Read NW 1992. Anorectal function in patients with superconal spinal cord lesions. Gut 33:1352-1358.

Maes BD, Hiele MI, Geypens BJ, Rutgeers RJ, Ghoos YF, Vantrappen G 1994. Pharmacological modulation of gastric emptying rate of solids as measured by carbon labelled octanoic acid breath test: influence of erythromycin and propantheline. Gut 35:333-337.

Malagelada JR, Rees WDW, Mazzotta LJ, Go VLW 1980. Gastric motor abnormalities in diabetic and postvagotomy gastroparesis: Effect of metoclopramide and bethanechol. Gastroenterology 78:286-293.

Malagelada J-R, Robertson JS, Brown ML, Remington M, Duenes JA, Thomforde GM, Carryer PW 1984. Intestinal transit of solid and liquid components of a meal in health. Gastroenterology 87:1255-1263.

Mantelli H, Devroede Gh, Arhan P, Duguay C 1978. Mechanisms of idiopathic constipation: outlet obstruction. Gastroenterology 75:623-631.

Marsh S, Stansfeld C, Brown D, McCarthy D 1987. The mechanism of action of capsaicin on sensory C-type neurons and their axons in vivo. Neuroscience 23:275-289.

Marty M, Pouillart P, Scholl S, et al, 1990. 5-hydroxytryptamine-3(serotonin) antagonist ondansetrone(GR 38032F) with high dose metoclopramide in the control of cisplatin-induced emesis. N Eng J Med 322:816-821.

Maruyama Y, Van Nagell JR, Utley J, Vider ML, Parker JC 1974. Radiation and small bowel complications in cervical carcinoma therapy. Radiology112:699-703.

Mason GR, Dietrich P, Friedland GW, Hanks GE 1970. The radiological findings in radiation-induced enteritis and colitis: A review of 30 cases. Clin Radiol 21:232-247.

Mattson O, Perman G, Lagerlof H 1960. The small intestine transit time with a physiologic contrast medium. Acta Radiol (Stockh) 54:334-344.

McHugh PR, Moran TH 1979. Calories and gastric emptying: A regulatory capacity with implications for feeding. Am J Physiol 236:R254-R260.

Mearin F, Culcala M, Azpiroz F, Malagelada J-R 1991. The origin of symptoms on the brain-gut axis in functional dyspepsia. Gastroenterology 101:999-1006.

Mehta AJ, De Caestecker JS, Camm AJ, Northfield TC 1995. Sensitization to painful distention and abnormal sensory perception in the esophagus. Gastroenterology 108:311-319.

Mekhjian HS, Phillips SF, Hofmann AF 1971. Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. J Clin Invest 50;1569-1577.

Mennie AT, Dalley VM, Dinneen LC, Collier HOJ 1975. Treatment of radiation-induced gastrointestinal distress with acetylsalicylate. Lancet ii:942-943.

Menzies IS, Laker MF, Pounder R, Bull J, Heyer S, Wheeler PG, Creamer B 1979. Abnormal intestinal permeabilty to sugars in villous atophy. Lancet ii:1107-1109.

Merrick MV, Eastwood MA, Anderson JR, Ross H McL 1982. Enterohepatic circulation in man of a gamma-emitting bile-acid conjugate, 23-Selena-25-Homotaurocholic Acid (SeHCAT). J Nucl Med 23:126-130.

Merrick MV, Eastwood MA, Ford MJ 1985. Is bile acid malabsorption underdiagnosed? An evaluation of accuracy of diagnosis by measurement of SeHCAT retention Br Med J 290:665-668.

Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG 1987. Simplified assessment of segmental colonic transit. Gastroenterology 92:40-47.

Meyer B, Berglinger C, Janssen J et al 1989. Role of cholecystokinin in regulation of gastrointestinal motor functions. Lancet ii:12-15.

Meyer JH, MacGregor IL, Gueller R Martin P, Cavalieri R 1976. Tc-99m - tagged chicken liver as a marker of solid food in the human stomach. Dig Dis Sci 21:296-304.

Miholic J, Vogelsang H, Schlappack O, Kletter K, Szepesi T, Moeschl P 1989. Small bowel function after surgery for chronic radiation enteritis. Digestion 42:30-38.

Miller DG, Ivey M, Young J 1979. Home parenteral nutrition in treatment of severe radiation enteritis. Ann Intern Med 91:858-860.

Moore J, Datz F, Christian P, Greenberg E, Alazraki N 1988. Effect of body posture on radionuclide measurements of gastric emptying. Dig Dis Sci 33:1592-1595.

Morgenstern L, Thompson R, Friedman NB 1977. The modern enigma of radiation enteropathy: sequelae and solutions. Am J Surg 134:166-172.

Morris AI, Turnberg LA 1979. Surreptitious laxative abuse. Gastroenterology 77:780-786.

Moss WT, Brand HB, Battifora H 1979. The cervix. In: Radiation Oncology rationale, technique, results, 5th edition. Mosby, St Louis:453-458.

Nagashima R 1981. Mechanisms of action of sucralfate. J Clin Gastroenterol 3(suppl 2):117-127.

Neal DE, Williams NS, Barker MCJ, King RFGJ. 1984. The effect of resection of the distal ileum on gastric emptying, small bowel tramsit and absorption after proctocolectomy. Br J Surg 71:666-670.

Newcomer AD 1984. Screening tests for carbohydrate malabsorption. J Pediat Gastrenterol Nutr 3:6-8.

Newcomer AD, Hodgson SF, Mcgill DB, Thomas PJ 1978. Lactase deficiency: Prevalence in osteoporosis. Ann Inter Med 89:218-220.

Newcomer AD & McGill DB 1966. Distribution of disacharidase activity in the small bowel of normal and lactase-deficient subjects. Gastroenterology 51:481-488.

Newcomer AD, McGill DB, Thomas PJ, Hofmann AF 1975. Prospective comparison of indirect methods for detecting lactase deficiency. N Engl J Med 293:1232-1236.

Newman A, Katsaris J, Blendis LM, Charlesworth M, Walter LH 1973. Small intestinal injury in women who have had pelvic radiotherapy. Lancet ii:1471-1473.

Newson B, Ahlman H, Dahlstrom A, Nyhus LM 1982. Ultrastructural observations in the rat ileal mucosa of possible epithelial "taste cells" and submucosal sensory neurons. Acta Physiol Scand 114:161-164.

Nicolopoulos N, Mantidis A, Stathopoulos E, Papaodysseas S, Kouvaris J, Varveris H, Papavasiliou 1985. Prophylacyic administration of indomethacon for irradiation esohagitis. Radiother Oncol 3:23-25.

Niemegeers CJE, Awouters F, Lenaerts FM, Artois KSK, Vermeire J 1986. Anti-diarrheal specificity and safety of the N-oxide of loperamide (R 58 525) in rats. Drug Development Research 8:279-286.

Nimmo WS 1976. Drugs , diseases and altered gastric emptying. Clin Pharmacokinet 1:189-203.

Northway MG, Libshitz, HI, Osborne BM, Feldman MS, Mamel JJ, West JH, Szwarc IA 1980. Radiation esophagitis in the opossum: radioprotection with indomethacin. Gastroenterology 78:883-892.

Northway MG, Libshitz HI, West J, Withers HR, Mukhopadhyay AK, Osborne BM, Szwarc IA, Dodd GD 1979. The opossum as an animal model for studying radiation esophagitis. Radiology 131:731-735.

Orkin BA, Hanson RB, Kelly KA, Phillips SF, Dent J 1991. Human anal motility while fasting, after feeding, and during sleep. Gastroenterology 100:1016-1023.

O'Rourke IC, Tiver K, Bull C, Gebski V, Langlands AO 1988. Swallowing performance after radiation therapy for carcinoma of the esophagus. Cancer 61:2022-2026.

Otterson MF, Sarna SK, Lee MB 1992. Fractionated doses of ionizing radiation alter postprandial small intestinal motor activity. Dig Dis Sci 37:709-715.

Otterson MF, Sarna SK, Moulder JE 1988. Effects of fractionated doses of ionizing radiation on small intestinal motor activity. Gastroenterology 95:1249-1257.

Palmer JA, Bush RS 1976. Radiation injuries to the bowel associated with the treatment of carcinoma of the cervix. Surgery 80:458-464.

Papas TN, Debas HT, Chang AM, Taylor IL 1986. Peptide YY release by fatty acids is sufficient to inhibit gastric emptying in dogs. Gastroenterology 91:1386-1389.

Peckham MJ, Hamilton CR, Horwich A, Hendry WF 19987. Surveillance after orchidectomy for stage I seminoma of the testis. Br J Urol 59:343-347.

Pelu G, Vichi GF, Pistocchi F, 1964. La digestione delle sostanze proteiche e dei grassi ed il tempo di transito nei soggeti irradiati sull'addome. Nuntius Radiologicus 30:816-829.

Perez CA, Breaux S, Bedwinek JM, Madoc-Jones H, Camel HM, Purdy JA, Walz BJ 1984. Radiation therapy alone in the treatment of carcinoma of the uterine cervix. Cancer 54:235-246.

Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tomayo R, Brown GS, Concannon J, Rotman M, Seydel HG 1980. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat cell carcinoma of the lung. Cancer 45:2744-2753.

Perman JA, Modler S, Barr RG, Rosenthal P 1984. Fasting breath hydrogen concentration: normal values and clinical application. Gastroenterology 87:1358-1363.

Pescatori M, Anastasio G, Bottini C, Mentasti A 1992. New grading and scoring for anal incontinence: Evaluation of 335 patients. Dis Colon Rectum 35:482-487.

Pietroletti R, Blaauwgeers JLG, Taat CW, Brummelkamp WH, Becker AE 1989. Intestinal cells in radiation enteritis. Surg Gynecol Obstet 169:127-130.

Phillips TL, Marjolis L 1972. Radiation pathology and the clinical response of lung and esophagus. In: Vaeth JM Ed., Frontiers of Radiation Therapy and Oncology, University Park Press, Baltimore:254-273.

Piver MS, Barlow JT 1977. High dose irradiation to biopsy confirmed aortic node metastases from carcinoma of the uterine cervix. Cancer 39:1243-1246.

Pounder RE, Gomes MF, Lokschin F, Logan LH 1983. The L-rhamnose/lactulose permeability test: non-invasive assessment of small intestinal mucosal damage. Gastroenterology 84:1276 (abstract).

Priestman SG, Priestman TJ, Canney PA 1987. A double-blind randomised cross-over comparison of nabilone and metoclopramide in the control of radiation-induced nausea. Clin Radiol 38:543-544.

Priestman TJ, Roberts JT, Lucraft H, Collis CH, Adams M, Upadhyaya BK, Priestman S 1990. Results of a randomised, double-blind comparative study of ondansetron and metoclopramide in the prevention of nausea and vomiting following high-dose upper abdominal irradiation. Clin Radiol 2:71-75.

Priestman TJ, Roberts JT, Upadhyaya BK 1993. A prospective randomised double-blind trial comparing ondansetron versus prochlorperazine for the prevention of nausea and vomiting in patients undergoing fractionated radiotherapy. Clin Oncol 5:358-363.

Prior A, Stanley KM, Smith ARB, Read NW 1992. Relation between hysterectomy and the irritable bowel: a prospective study. Gut 33:814-817.

Proano M, Camilleri M, Phillips SF, Brown ML, Thomforde GM 1990. Transit of solids through the human colon: regional quantification in the unprepared bowel. Am J Physio 258: G856-G862.

Proano M, Camilleri M, Phillips SF, Thomforde GM, Brown ML, Tucker RL 1991. Unprepared human colon does not discriminate between solids and liquids. Am J Physio 260: G13-G16

Raunch K, Wieland H 1972. Therapy of radiogenic colitis with salicylazosulfapyridine. Strahlentherapie 143:660-663.

Read M, Read NW, Barber DC, Duthie HL 1982. Effects of loperamide on anal sphincter function in patients complaining of chronic diarrhea with fecal incontinence and urgency. Dig Dis Sci 27:807-814.

Read NW 1989. Gastrointestinal motility: Which Test. Wrightson Biomedical Publishing Ltd., Petersfield.

Read NW, Al-Janabi MN, Bates TE, Holgate AM, Cann PA, Kinsman RI, McFarlane A, Brown C 1985. Interpretation of the breath hydrogen profile obtained after ingesting a solid meal containing unabsorbable carbohydrate. Gut 26:834-842.

Read NW, Al-Janabi MN, Holgate AM, Barber DC, Edwards CA 1986. Simultaneous measurement of gastric emptying, small bowel residence and colonic filling of a solid meal by the use of the gamma camera. Gut 27:300-308.

Read NW, McFarlane A, Kinsman RI, Bates TE, Blackhall NW, Farrar GBJ, Hall JC, Moss G, Morris AP, O'Neill B, Welch I, Lee Y, Bloom SR 1984. Effect of infusion of nutrient solutions into the ileum on gastrointestinal transit and plasma levels of neurotensin and enteroglucagon. Gastroenterology 86:274-280.

Read NW, Miles CA, Fisher D, Holgate AM, Kime ND, Mitchell MA, Reeve AM, Roche TB, Walker M 1980. Transit of a meal through the stomach, small intestine, and colon in normal subjects and its role in the pathogenesis of diarrhea. Gastroenterology 79:1276-1282.

Read NW, Sun WM 1989. Anorectal manometry, anal myography and rectal sensory testing. In: Read NW Ed., Gastrointestinal motility ; Which Test. Wrightson Biomedical Publishing Ltd, Petersfield:227-241.

Reeves RJ, Cavanaugh, PJ, Sharpe KW, Thorne WA, Winkler C, Richter JE, Blackwell JN, Wu WC, Johns DN, Cowan RJ, Castell DO 1987. Relationship of radionuclide liquid bolus transport and esophageal manometry. J Lab Clin Med 109:217-224.

Reeves RJ, Cavanaugh PJ, Sharpe KW, Thorne WA, Winkler C, Sanders AP 1965. Fat absorption studies and small bowel x-ray studies in patients undergoing Co-60 teletherapy and/or radium application. Am J Roentgenol 94:848-851.

Reeves RJ, Sanders AP, Ishley JK, Sharpe KW, Baylin GJ 1959. Fat absorption from human gastrointestinal tract in patients undergoing radiation therapy. Radiology 73:398-401.

Richter JE, Barish CF, Castell DO 1986. Abnormal sensory perception in patients with esophageal chest pain. Gastroenterology 91:845-852.

Ritchie J 1973. Pain from distention of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 14:125-132.

Robb TA, Davidson GP 1983. An inexpensive gas chromatograph for breath hydrogen analysis. Clin Chem Acta 134:235-241.

Roberts JT & Priestman TJ 1993. A review of ondansetron in the management of radiotherapy-induced emesis. Oncology 50:173-179.

Roda A, Roda E, Aldini R, Festi D, Mazzella G, Sama C, Barbara L 1977. Development, validation and application of a single tube radio-immunoassay for cholic and chenodeoxycholic acid conjugates in human serum. Clin Chem 23:2107-2113.

Rodier JF, Janser JC, Rodier D, Dauplat J, Kauffmann P, Le Bouedec G, Giraud B, Lorimier G 1991. Prevention of radiation enteritis by an absorbable polyglycolic acid mesh sling. Cancer 68: 2545-2549.

Roovers J, Evrard E, Vanderhaeghe H 1968. An improved method for measuring human blood bile acids. Clin Chem Acta 19:449-457.

Roswit B, Malsky Sj, Reid CB 1972. Radiation tolerance of the gastrointestinal tract. In: Vaeth JM Ed., Vol 6 Frontiers of Radiation Therapy and Oncology, University Park Press, Baltimore:160-181.

Rubin P, Casarett GW 1968a. Alimentary tract: esophagus and stomach. In: Clinical Radiation Pathology Volume I, Saunders, Philidelphia:153-192.

Rubin P, Casarett GW 1968b. Alimentary tract: Small and large intestines and rectum. In: Clinical Radiation Pathology Volume I, Saunders; Philidelphia:193-240.

Ruppin H, Hotze A, During A, Reichert M, Baeur J, Stoll R, Herbst M, Mahlstedt J 1987. Reversible funktionsstorungen des intestinaltraktes durch abdominelle strahlentherapie(Reversible functional disorders of the intestinal tract caused by abdominal radiotherapy). Z Gastroenterol 25:261-269.

Ruppin H, Stoll R, Hotze A, During A, Reichert M, Herbst M, Mahlstedt J 1985. Evaluation of disturbed small intestinal function following abdominal radiotherapy. Gastroenterology 88:1562(abstract).

Salazar PM, Rubin P, Keller B, Scarantino C 1978. Systemic (half-body) radiation therapy: response and toxicity. Int J Radiat Oncol Biol Phys 4:937-950.

Salminen E 1990. External beam radiation treatment of urinary bladder carcinoma; an analysis of results in 203 patients. Acta Oncologica 29:909-914.

Sanders AP 1959. Fat absorption from the human gatrointestinal tract in patients undergoing radiation therapy. Radiology 73:398-401.

Schemann M, Ehrlein H-J 1986. Postprandial patterns of canine jejunal motility and transit of luminal content. Gastroenterology 90:991-1000.

Schiller LR, Hogan RB, Morawski SG, Santa Ana CA, Bern MJ, Norgaard RP, Bo-Linn GW, Fordtran JS 1987. Studies of the prevalence and significance of radiolabelled bile acid malabsorption in a group of patients with idiopathic chronic diarrhoea. Gastroenterology 92:151-160.

Schoeman MN, Holloway RH 1994. Stimulation and characteristics of secondary oesophageal peristalsis in normal subjects. Gut 35:152-158.

Schofield PF, Carr ND, Holden D 1986. Pathogenesis and treatment of radiation bowel disease: discussion paper. J Roy Soc Med 79:30-32.

Schofield PF, Holden D, Carr ND 1983. Bowel disease after radiotherapy. J R Soc Med 76:463-466.

Schrock TR, Deveney CW, Dunphy JE 1973. Factors contributing to leakage of colonic anastomosis. Ann Surg 177:513-518.

Schwizer W, Maecke H, Fried M 1992. Measurement of gastric emptying by magnetic resonance imaging in humans. Gastroenterology 103:369-376.

Sciarretta G, Fagioli G, Furno A, Vicini G, Cecchetti L, Grigolo B, Verri A, Malaguti P 1987. Se-75 HCAT test in the detection of bile acid malabsorption in functional diarrhoea and its correlation with small bowel transit. Gut 28:970-975.

Seaman WB, Ackerman LV 1957. The effect of radiation on the esophagus. Radiology 68:534-540.

Sedgwick DM, Howard GCW, Ferguson A 1994. Pathogenesis of acute radiation injury to the rectum: A prospective study in patients. Int J Colorect Dis 9:23-30.

Seeman H, Gates JA, Traube M 1992. Esophageal motor dysfunction years after radiation therapy. Dig Dis Sci 37:303-306.

Seow-Choen F, Goh HS, Eu KW, Ho YH, Tay SK 1993. A simple and effective treatment for haemorrhagic radiation proctitis using formalin. Dis Colon Rectum 36:135-138.

Shanahan TG, Mehta MP, Bertelrud KL, Buchler DA, Frank LE, Gehring MA, Kubsad SS, Utrie PC, Kinsella TJ 1990. Minimization of small bowel volume within treatment fields utilizing customized "Belly Boards". Int J Radiat Oncol Biol Phys 19:469-476.

Shearman DJC, Finlayson NDC 1989. Absorption and its disorders. In: Diseases of the gastrointestinal tract and liver. Churchill Livingstone, Edinburgh:359-406.

Sheikh S 1991. Neuropeptide Y and Peptide YY: major modulators of gastrointestinal blood flow and function. Am J Physiol 261:G701-G715.

Sher ME, Bauer J 1990. Radiation-induced enteropathy. Am J Gastroenterol 85:121-128.

Sherrah-Davies E 1985. Morbidity following low dose rate Selectron therapy for cervical cancer. Clin Radiol 36:131-139.

Siegle M-L, Ehrlein H-J 1988. Digestive motor patterns and transit of luminal contents in canine ileum. Am J Physiol 254:G552-G559.

Smith AN, Varma JA, Binnie NR, Papachrysostomou 1990. Disordered colorectal motility in intractable constipation following hysterectomy. Br J Surg 77:1361-1366.

Smith DH, DeCosse JJ 1986. Radiation damage to the small intestine. World J Surg 10:189-194.

Smith DH, Pierce VK, Lewis JL 1984. Enteric fistulas encountered on a gynecologic oncology service from 1969 through 1980. Surg Gynecol Obstet 158:71-75.

Smout AJPM, van der Schee EJ, Grashuls JL 1980. What is measured in electrogastrography? Dig Dis Sci 25:179-187.

Snape WR Jr, Battle WM, Schwartz SS, Braunstein SN, Goldstein HA, Alavi A 1982.Metoclopramide to treat gastroparesis due to diabetes mellitus. Ann Intern Med 96:444-446.

Soffer EE, Mitros F, Doornbos F, Frieidland J, Launpach J, Summers RW 1994. Morphology and pathology of radiation-induced esophagitis. Double-blind study of Naproxen vs placebo for prevention of radiation injury. Dig Dis Sci 39:655-660.

Solassol C, Joyeux H, Dubois JB 1979. Total parenteral nutrition (TPN) with complete nutritive mixtures: An artificial gut in cancer patients. Nutr Cancer 1:13-18.

Solomon AK, Chasan B, Dix JA, Lukacovic MF, Toon MR, Berkman AS 1984. The aqueous pore in the red cell membrane: Band 3 as a channel for anions, cations, nonelectrolytes and water. Ann N Y Acad Sci 414:97-124.

Stark M, Szurszewski J 1992. Role of nitric oxide in gastrointestinal and hepatic function and disease. Gastroenterology 103:1928-1949.

Stevenson GW 1988. Proctography symposium. Int J Color Dis 3:67-89.

Stivland T, Camilleri M, Vassallo M, Proano M, Rath D, Brown M, Thomforde G Pemberton J Phillips S 1991. Scintigraphic measurement of regional gut transit in idiopathic constipation. Gastroenterology 101:107-115.

Strockbine ME, Hancock JE, Fletcher GH 1970. Complications in 831 patients with squamous cell carcinoma of the intact uterine cervix treated with 3,000 rads or more whole pelvis radiation. Am J Radiol 108:293-304.

Stryker JA & Demers LM 1979. The effect of pelvic irradiation on the absorption of bile acids. Int J Radiat Oncol Biol Phys 5:935-939.

Stryker JA, Demers LM, Mortel R 1979. Prophylactic ibuprofen adminstration during pelvic irradiation. Int J Radiat Oncol Biol Phys 5:2049-2052.

Stryker JA, Hepner GW, Mortel R 1977. The effect of pelvic irradiation on ileal function. Radiology 124:213-216.

Stryker JA, Mortel R, Hepner GW 1978. The effect of pelvic irradiation on lactose absorption. Int J Radiat Oncol Biol Phys 4:859-863.

Summers RW, Glenn CE, Flatt AJ, Elahmady A 1992. Does irradiation produce irreversible changes in canine jejunal myoelectric activity? Dig Dis Sci 37:716-722.

Summers RW, Kent TH 1970. Effects of drugs, ileal obstruction, and irradiation on rat gastrointestinal propulsion. Gastroenterology 59:731-739.

Sun WM, Donnelly TC, Read NW 1989a. Anorectal function in normal subjects; effect of gender. Int J Color Dis 4:188-196.

Sun WM, Donnelly TC, Read NW 1989b. Impaired internal anal sphincter in a subgroup of patients with idiopathic faecal incontinence. Gastroenterology 97:130-135.

Sun WM, Donnelly TC, Read NW 1992a. Utility of a combined test of anorectal manometry, electromyography, and sensation in determining the mechanism of "idiopathic" faecal incontinence. Gut 33:807-813.

Sun WM, Edwards CA, Prior A, Rao SSC, Read NW 1990a. Effect of oral nicardipine on anorectal function in normal human volunteers and patients with irritable bowel syndrome. Dig Dis Sci 35:885-890.

Sun WM, Peck RJ, Shorthouse AJ, Read NW 1992b. Haemorrhoids are associated not with hypertrophy of the internal anal sphincter, but with hypertension of the anal cushions. Br J Surg 79:592-594.

Sun WM, Read NW 1990. Occult spinal lesions: a common undetected cause of faecal incontinence. Lancet i:166.

Sun WM, Read NW, Miner PB 1990c. The relationship between rectal sensation and anal function in normal subjects and patients with faecal incontinence. Gut 31:1056-1061.

Sun WM, Read NW, Miner PB, Kerrigan DD, Donnelly TC 1990d. The role of transient internal anal sphincter relaxation in faecal incontinence? Int J Color Dis 5:31-36.

Sun WM, Read NW, Prior A, Daly JA, Cheah SV, Grundy D 1990b. Sensory and motor responses to rectal distention vary according to rate and pattern of balloon inflation. Gastroenterology 99:1008-1015.

Sun WM, Smout A, Malbert C, Edelbroek MAL, Jones K, Dent J, Horowitz M 1995. Relationship between surface electrogastrography and antropyloric pressures. Am J Physiol 268:G424-G430.

Tanghoj H, Stenstam M, Tobiasson P 1985. Effects of sucralfate and cholestyramine on bile acid absorption. Gastroenterology 88:1699 (Abstract)

Thaysen EH, Orholm M, Arnfred T, Carl J, Rodbro P 1982. Assessment of ileal function by abdominal counting of the retention of a gamma emitting bile acid analogue. Gut 23:862-865.

Thompson DG, Binfield P, De Belder A, O'Brein J, Warren S, Wilson M 1985. Extra-intestinal influences on exhaled breath hydrogen measurements during the investigation of gastrointestinal disease. Gut 26:1349-1352.

Thompson DG, O"Brein JD, Hardie JM 1986. Influence of the oropharyngeal microflora on the measurement of exhaled breath hydrogen. Gastroenterology 91:853-860.

Tippett MD, Holloway RH, Horowitz M, Maddox A, Russo A, Moten J 1994. Esophageal motor function responsible for abnormal esophageal transit in insulin-dependent diabetes mellitus. Gastroenterolgy 106:A70 (abstract).

Tochner Z, Barnes M, Mitchell JB, Orr K, Glatstein E, Russo A 1990. Protection by Indomethacin against acute radiation esophagitis. Digestion 47:81-87.

Trier JS, Browning TH 1966. Morphological response of the human small intestine to x-ray exposure. J Clin Invest 45:194-204.

Vanagunas A, Jacob, Olinger E 1990. Radiation-induced esophageal injury: A spectrum from esophagitis to cancer. Am J Gastroenterol 85:808-812.

Van Blankenstein M, Hoyset T, Horchner P, Wilson JHP 1977. Faecal bile radioactivity, a sensitive and relatively simple test for ileal dysfunction. Neth J Med 20:248-252.

Van de Kamer JH, Bokkel Huinink T, Weyers HA 1949. Rapid method for determination of fat in faeces J Biol Chem 177:347-355.

Van de Velde V, Legrand M, Van Rooy P, Van Peer A, Woestenborghs R, Heykants J, Verlinden M 1988. Dose-proportionality of the pharmocokinetics of loperamide oxide and loperamide after oral dosing of 2 to 16 mg of loperamide-oxide to healthy volunteers. Janssen Clinical Research Report 6:N59 830.

Van de Velde V, Legrand M, Woestenborghs R, Van Peer A, Heykants J, Verlinden M 1987. Oral bioavailability of loperamide-N-oxide after single intake of a 4 mg capsule in healthy subjects. Janssen Clinical Research Report 3:N56 635.

Van den Eynden B, Spaepen W 1995. The Belgian General Practice Loperamide Oxide Trialists. New approaches to the treatment of acute non-specific diarrhoea: comparison of the effects of loperamide and loperamide oxide. Curr Ther Res Clin Exp (in press).

Vanek AW, Diamant NE 1987. Responses of the human esophagus to paired swallows. Gastroenterology 92:643-650.

Van Nagell JR, Maruyama Y, Parker JC, Dalton WL 1974. Small bowel injury following radiation therapy for cervical cancer. Am J Obstet Gynecol 118:163-167.

Van Nagell JR, Parker Jr JC, Maruyama Y, Utley J, Hager WD, Donaldson ES, Wood EG 1977. The effect of pelvic inflammatory disease on enteric complications following radiation therapy for cervical cancer. Am J Obstet Gynecol 128:767-771.

Varley H 1967. Determination of fat content of faeces. In: Practical Clinical Biochemistry, 4th edition. Heinemann, London:419-421.

Varma JS, Smith AN, Busuttil A 1985. Correlation of clinical and manometric abnormalities of rectal function following chronic radiation injury. Br J Surg 72:875-878.

Varma JS, Smith AN, Busuttil A 1986. Function of the anal sphincters after chronic radiation injury. Gut 27:528-533.

Watier A, Devroede G, Duranceau A, Abdel-Rahman M, Duguay C, Forand MD, Tetreault L, Arhan P, Lamarche J, Elhilali M 1983. Constipation with colonic inertia. A manifestation of systemic disease? Dig Dis Sci 28: 1025-1033.

Weems W, Seidel E, Johnson L 1985. Induction of a specific pattern of jejunal propulsive behaviour by cholecystokinin. Am J Physiol 248:G470-G478.

Weisbrodt N 1987. Motility of the small intestine. In: Physiology of the gastrointestinal tract. (Ed) LR Johnson. Raven Press, New York:631-663.

Wellwood JM, Jackson BT 1973. The intestinal complications of radiotherapy. Brit J Surg 60:814-818.

Westbrook C, Glaholm J, Barrett A 1987. Vomiting associated with whole body irradiation. Clin Radiol 38:263-266.

Wharton JT, Jones HW, Day TG, Rutledge FN, Fletcher GH 1977. Preirradiation celiotomy and extended field irradiation for invasive carcinoma of the cervix. Obstet Gynecol 49:333-338.

Whitehead WE, Engle BJ, Schuster MM 1980. Irritable bowel syndrome. Physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. Dig Dis Sci 35:404-413.

Withers HR, Rounsdahl MM 1977. Post-operative radiotherapy for adenocarcinoma of the rectum and sigmoid colon. Int J Radiat Oncol Biol Phys 2:1069-1074.

Wobbes T, Verschuren RC, Lubbers EC, Jansen W, Paping RHL 1984. Surgical aspects of radiation enteritis of the small bowel. Dis Colon Rectum 27:89-92.

Yeoh EK, Horowitz M 1987. Radiation enteritis. Surg Gynecol Obstet 165:373-376.

Yeoh EK, Lui D, Lee NY 1984. The mechanism of diarrhoea resulting from pelvic and abdominal radiotherapy; a prospective study using Selenium-75 labelled conjugated bile acid and Cobalt-58 labelled Cyanocobalamin. Br J Radiol 57:1131-1136.

Yeoh EK, Razali M, O'Brien P 1993. Radiation therapy for early stage seminoma of the testis. Analysis of survival and gastrointestinal toxicity in patients treated with modern megavoltage techniques over 10 years. Aust Radiol 37:367-369.

Yeoh EK, Spittle MF 1986. The treatment of carcinoma of the cervix and poor risk endometrial carcinoma using the Cathetron at the Middlesex Hospital: Experience since 1979. Clin Radiol 37:165-168.

Zentler-Munro PL & Bessell EM 1987. Medical management of radiation enteritis - an algorithmic guide. Clin Radiol 38:291-294.