POST-IRRADIATION DIARRHEA

(A study of its mechanism after pelvic irradiation)

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DIARRHEE NA BEKKENBESTRALING

(Onderzoek naar het mechanisme)

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN
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Ter nagedachtenis aan mijn moeder
Albertha Swaters

Aan Enny
Robbert
Ivo

The road goes over on and on
Down from the door where it began,
Now far ahead the road has gone
And I must follow, if I can.
Pursuing it with weary feet
Until it joins some larger way
Where many paths and errands meet
And whither then? I cannot say

De weg gaat verder, eindeloos
Vanaf de deur waar hij begon
Ik moet hem volgen rusteloos
Tot ver achter de horizon
Met rappe voeten tot hij aan
Een grote weg raakt in 't verschiet
Kruispunt van komen en van gaan
En waarheen dan? Ik weet het niet

J.R.R. Tolkien
(uit "the lord of
the rings").

CONTENTS

CHAPTER I

1.1. General Introduction.

In radiotherapy of pelvic cancers, the X-ray dose to be delivered to the tumour is limited by the tolerance of healthy surrounding tissue. In the past, with orthovoltage equipment, skin tolerance was the main limiting factor. With the introduction of megavoltage equipment, it became possible to deliver a higher radiation dose to deep-seated lesions, but inevitably also to neighbouring normal tissues. As a result, local cure rates were increased, but so was the number of complications.

In recent years we encountered a number of serious complications of irradiation of pelvic organs. It was in particular in cases of ovarian cancer where a higher dose of irradiation was applied that these distressing complications were frequent. This experience led to a more conservative irradiation protocol in these cases, resulting in a marked fall in the number of complications. In cervical and endometrial cancer the damage never was as extensive as in the ovarian cancer group. At present many patients who have to ondergo pelvic irradiation, however, will have transient or longer lasting symptoms caused by the irradiation.

Modern radiotherapy necessitates the acceptance of a calculated risk of complications in order to achieve a better cure rate. To calculate these risks, one has to know the radiation dose-effect relationship of normal tissues. In quantitative terms these risks are insufficiently known. The normal tissues most at risk when treating pelvic tumours are the bladder, the ureters, the rectum, the sigmoid colon and the small intestine.

In this study we limit ourselves to the bowel.

The literature regarding postirradiation bowel complications is very confusing. In the first place no two authors used the same criteria for what they consider to be bowel complications. Some authors only include severe complications like stenoses of the bowel and fistulas, in particular those that require surgical intervention (5, 8). Other authors include patients with diarrhea and/or malabsorption, whereas a third group will include ill defined situations that necessitate long-term hospitalization. It is clear that in this way severe and mild complications are often mixed. The result is that in different series the incidence of severe gastro-intestinal complications varies as much as from 1 to 15% (1-12). It is to be noted that in these studies damage

to the small intestine form only a minority. Another drawback of the reported studies is that all were retrospective. In addition when patients appear to have a recurrence of their tumour in parallel with radiation damage, they are often excluded from further evaluation.

In view of the rarity of the severe postirradiation bowel syndromes, a prospective study of these complications would require a very large number of patients. This type of study has never been undertaken.

This does not mean that the incidence of fistulas and stenoses in irradiation of uterine cancer is negligible (in our own institute we found 6%, unpublished data, Tj. Kuipers), but only that a prospective study is not feasible.

Newman (13) reported that in the follow-up of a group of patients, irradiated for pelvic tumours, the incidence of a change in bowel habits was substantial.

The high incidence of relatively mild bowel symptoms would make a prospective study with special attention to the incidence and course of these symptoms worthwhile.

Therefore, we studied diarrhea, either transient or lasting. It is more frequent and is possibly a reflection of the pathophysiological changes in the small intestine.

In a study of 15 patients with postradiotherapy diarrhea, Van Blankenstein (84) reported that all had frequent and loose bowel movements and feacal incontinence, despite a relatively low daily faecal weight. All had abnormal bile acid reabsorption.

On the basic of these preliminary studies, two types of intestinal radiation damage were suggested (84):

1) Patients with clinical symptoms of fistulas, stenoses, (sub)ileus, malabsorption and weight loss and rarely perforations. These are the patients with severe gastrointestinal complications of radiotherapy.
2) Patients with diarrhea, faecal incontinence but no weight loss. These are patients with relatively mild complications of radiotherapy (mild radiation enteropathy).

In the present investigation we concentrated on this second group of patients with relatively mild symptoms. We studied the incidence and course of postirradiation diarrhea in 196 patients treated for carcinoma of the uterine cervix or endometrium.

Another matter where confusion reigns in the literature is the mechanism of postirradiation diarrhea (54, 63, 64, 84).

Most authors consider insufficient reabsorption of bile acids as the cause. This is by no means certain and local factors in the rectosigmoid e.g. a decreased reservoir function should be studied as well, in particular in view of the normal faecal weight. At the time our study was started, no data were available on this subject. Recent work (82, 93) underlined the role of a damaged reservoir function.

The aims of the present study were:

1) to determine the incidence, course and prognostic signifiance of postirradiation diarrhea;

2) to assess the influence of radiotherapy factors;
3) to study the relation of bile acid metabolism to postirradiation diarrhea;
4) to investigate whether local factors (reservoir function) were primarily responsible.

In order to investigate whether factors related to the patients or the mode of treatment influenced the occurrence of side-effects a system of "risk factors" is mentioned in the literature (14, 15, 16, 18).

1.2. Risk factors for bowel damage following radiotherapy.

Factors that are assumed to influence the incidence of bowel complications can be divided into two groups:

1) Patient factors, these are characteristics of each individual patient, due either to somatotype or medical antecedents. These factors cannot be influenced.
2) Treatment factors, these are related to therapeutic measures which may be changed if necessary.

Many observations concerning these factors have been presented throughout the literature, often confusing or even contradictory. This may be due to differences in the mode of treatment, but in the majority, to differences in the way complications were defined. Most of the studies were retrospective and concentrated on those patients who actually did develop severe complications, omitting the rest of the patient population. Selection of patients cannot be avoided in this way, making comparison between different studies impossible.

1.2.1. Patient factors.

We will discuss the following "patient factors":

1) age;
2) height and weight;
3) central abdominal anterior-posterior (AP) diameter;
4) number of previous laparotomies;
5) presence of diabetes;
6) presence of hypertension or cardiovascular disease.

ad 1) For most authors (7, 9, 14, 15), *age* seemed to be of less importance. Green (16), however, suggested that the amount of small intestine in the pelvic region tended to be greater in the elderly.

ad 2) Overweight (as estimated by *height and weight)* may influence the incidence

of complications. Maruyama (7) reported no bowel complications in irradiated overweight patients, 4.5% bowel complications in the normal weight and 13.3% in the underweight group. If diabetes plus hypertension were associated with underweight, severe bowel damage was even more frequent.

ad 3) The *central abdominal anterior-posterior (AP) diameter* is strongly correlated with body weight. Potish (14) and Maruyama (7) stated that patients with a small AP diameter were more likely to develop complications. They did not explain why. Green (16) observed that these patients have more immobile small intestine in the pouch of Douglas. This pouch is also deeper in patients with a small AP diameter.

ad 4) The *number of previous laparotomies* is thought by all authors (2, 9, 10, 14, 15, 17, 18) to be of major importance. Their explanation is that under normal circumstances the mobility of the small intestine enables it to move in and out of the treatment area. In doing so, the dose of radiation absorbed by the individual gut segment is reduced. Whereas it is wellknown that previous pelvic irradiation in itself will cause intestinal adhesions, some authors (14, 18) claim that previous operations in any part of the abdomen will augment the incidence of severe postirradiation complications. A fact that they ascribe to postoperative rather than postirradiation adhesions of the small bowel. An increased incidence of rectal and rectosigmoid complications after previous abdominal surgery in these patients is also reported.

ad 5) *Diabetes* is supposed to be of poor prognostic significance (7, 14, 15, 19). Maruyama reported an increased incidence of radiation induced bowel complications in diabetics. His study concerned only a small number of patients. In the group of diabetics, radiation sequellae were found mainly in association with underweight and hypertension.

ad 6) The probability of complications is reported by Potish (14) to be significantly related with *hypertension.*

According to some authors (7, 14, 15) the common denominator of these six factors is supposed to be pre-existent vascular changes. As the underlying cause of late radiation damage is of vascular origin, pre-existent vascular changes were assumed to be unfavourable.

Many of these factors have been evaluated independently; however, they may be interrelated. Therefore, a multivariate statistical analysis of all of these factors with respect to small bowel side-effects and late complications is important in order to establish the prognostic value of each factor alone ore in combination with others.

Radiation related factors which are mentioned in the literature will be discussed

next. In addition these factors give some insight in the theoretical background of pelvic irradiation.

1.2.2. Treatment factors mentioned in the literature are:

1) total delivered radiation dose;
2) overall treatment time;
3) fraction dose;
4) treatment volume;
5) treatment position;
6) radiation quality.

Apart from these characteristics of external irradiation, other factors are important in the case of intracavitary treatment. These include:

7) dose rate;
8) methods for dose specification.

ad 1) *Total dose.* Strockbine (2) found that the number of complications increased with increasing doses of whole pelvis irradiation. The frequency of sigmoiditis, diagnosed on clinical symptoms, roentgenological and proctosigmoidal examinations, at dose levels of 40, 50, 60 and 70 Gy was 5, 10.5, 16 and 31.5%, respectively.

A problem is that the higher doses of external irradiation were given to patients with more advanced disease and these patients also received a higher dose from intracavitary treatment. It is not clear from Strockbine's results whether these external and intracavitary treatments were evaluated separately.

ad 2) The influence of *overall treatment time* on the complication rate has been studied with split course treatments (26). Such extension of treatment time failed to prevent severe intestinal complications.

ad 3) The influence of *fraction size* was investigated by Singh (27), who compared a conventional and a reduced frequency schedule.

Decreasing the number of fractions while increasing their size did not result in a change in the incidence of early reactions. However, all patients in the reduced frequency schedule developed severe late complications. The overall treatment time in both groups was about the same.

ad 4) A relation between the *treatment volume* (tissue volume irradiated) and complications is suggested by many authors (11, 15, 16, 17). It should be realized, however, that the amount of small intestine in a given treatment volume is highly variable. Therefore, the relation between treatment volume and complications will not be a simple one. It is conceivable that the complication rate

is correlated with the volume of the small bowel within the treatment volume, but this volume is very difficult to assess.

ad 5) By changing the *treatment position* of the patients Green (16) and Caspers (29) reported that the volume of small intestine within the treatment volume could be decreased. The prone instead of the supine position lifted the lower margin of the small intestinal mass 2 cm in cranial direction. It can be assumed that a change in treatment position during intracavitary irradiation will have the same effect as during external irradiation.

ad 6) With different *radiation qualities,* the dose distribution within the patient will not be the same. With increasing photon energies, the penetration of the radiation becomes deeper. In a thin patient, lower energies like ^{60}Co gamma rays and 4 MeV photons are able to give a rather homogeneous dose distribution; this will not be the case in obese patients. Higher energies are required to give a homogeneous dose distribution in these obese patients. On this point no relevant data can be found in the literature.

ad 7) *Dose rate.* In fractionated external irradiation, the overall time and the dose per fraction causes a more complicated dose-effect relation than in intracavitary irradiation, where the total dose is directly proportional to the dose rate. Gray and Kottmeier (1) observed an increased number of rectal complications when they shortened the treatment time by using higher activities in the intrauterine applicator. What they did, in fact, was to change the dose rate without changing the total dose.

ad 8) *The methods for dose specification* are very important factors in intracavitary treatment, but still controversial. Many different ways of describing the given dose are found. Fletcher (30) used the system if milligram hours, where the milligrams stand for the amount of radium in milligrams used and the hours for the treatment time. The second method, presently applied in the Rotterdamsch Radio-Therapeutisch Instituut, is the use of "point A", which is a virtual anatomical point situated 2 cm cranially of the lateral fornix and 2 cm laterally of the uterine axis (32), (see figure 4, page 40). Because of the steep dose gradient around radioactive sources, the choice of reference points for dose prescriptions greatly influences the dose in a given site. The third method is the use of a reference isodose. A reference isodose is a tridimensional contour around the source(s), in all points of which the absorbed dose is identical and where the dose applied is specified.

It is very difficult to get a clear picture from the literature of the importance of these factors separately. The range of total delivered dose and dose per fraction presently used for pelvic irradiation of gynaecological tumours is quite small (a total dose of 40-50 Gy over a 4-5 week period with a dose per fraction in the order of 2.0 Gy).

This means that no dose-effect relationship can be found; in other words, the influence of a variable X-ray dose on tissue (bowel) damage cannot be assessed, as the variation in dose of external irradiation is too small.

CHAPTER II

CHANGES IN BOWEL FUNCTIONS FOLLOWING RADIOTHERAPY.

2.1. Historical review.

Walsh (36) in 1897, two years after Röntgen's dicovery, was the first to report on the effects of irradiation on the gastrointestinal tract. Since then, there have been many reports on this subject, both from the histopathological and from the point of view of intestinal function.

2.1.1. Histopathology.

In 1942 Friedman (37) and later in 1966 Trier (38) published excellent studies on histological changes of the intestinal wall after irradiation. Both authors observed a rapid decrease in the number of mitoses, especially in the mucosa. At about two weeks after the start of the irradiation, the villi became shorter and the mucosal lining stretched out. Ulcerations eventually developed, sometimes penetrating into the serosa.
The severity of these lesions and the rapidity with which they developed were proportional to the tissue dose. Trier (38) demonstrated by electron microscopy intracellular changes in the lining cells of the villi, e.g., shortened microvilli, swelling of the mitochondria and of the endoplasmic reticulum as well as nuclear changes. According to Trier, the histology returned to normal two weeks after a course of 30 Gy.

2.1.2. Bowel function.

The most important functions of the small intestine are absorption and propulsion.

2.1.2.1. Absorption.

As early as 1924, Dodds and Webster (39) observed increased excretion of fat in the

faeces in patients undergoing abdominal pelvic irradiation. Martin (40) reported similar findings in dogs.
After the introduction of isotope investigations (mainly substances labeled with I^{131}), Reeves (41, 42) reported a transient decrease in fat absorption in patients after abdominal irradiation with orthovoltage equipment (1959) and with ^{60}Co (1963). Meanwhile, the first patient with malabsorption following pelvic abdominal radiotherapy was described by Salvesan (43). This patient had a stricture of the small intestine, combined with steatorrhea. On the basis of a review of the literature (5 patients) and six of their own patients, Duncan and Leonard (44) reported on a syndrome of diarrhea, wasting, steatorrhea, intestinal obstruction and anaemia. Steatorrhea occurred in 10 out of 11 patients, diarrhea in 9/11, intestinal obstruction in 6/11 and vitamin B12 malabsorption in 3/11.
From studies in animals, evidence was obtained that, although fat is mainly absorbed in the proximal small intestine, fat malabsorption is more pronounced after resection of the terminal ileum. This pointed to a role of bile acids in fat absorption and will be discussed in more detail later (Par. 2.3.).

2.1.2.2. Propulsion.
Both Wallace and Conard (45, 46) studied gut motility with barium meals after irradiation, the former in patients and the latter in rats. Wallace described decreased motility, whereas Conard found an initial increase followed by a slow return to normal.
However, studying intestinal motility by means of barium meals is no longer regarded as a reliable method. Results obtained with dyes and with fluid or solid markers differ considerably from each other. Cummings (47) observed more precise results by calculating mean intestinal transit time with solid radioopaque markers. More recently, specific motility studies have been performed by analysis of the migrating motor complex (48).

2.2. Diarrhea following radiotherapy.

During irradiation of the pelvic region, most patients complain about diarrhea. It should be noted that for different persons the word diarrhea has a different meaning. When diarrhea is defined as a loss of the normal consistency of the stools. The time of appearance and the severity of the diarrhea are dependent on the fractionation schedule used. With a conventional irradiation schedule of 4-5 times 2.0 Gy per week during 5 weeks, these complaints generally develop from the second week onwards. After completion of the irradiation, in most cases, the diarrhea subsides within a few weeks (86). Few data are available on the number of patients in whom the diarrhea does not subside or does even reappear.

Newman (13) reported changes in bowel habits in 12 out of 17 unselected patients, who received radiotherapy for a gynaecological malignancy. In his clinical study, Van Blankenstein (84) reported the combination of diarrhea and faecal incontinence. This observation is in agreement with the observations of Read (81), who found that diarrhea from any cause associated with faecal incontinence caused problems, whereas diarrhea without faecal incontinence was less troublesome.
Animal experiments and clinical studies suggested a relation between diarrhea following radiotherapy and bile acid metabolism.
Stryker (63, 64) reported an abnormal bile acid breath test as well as a decrease in serum bile acid concentrations at the end of an irradiation period. He found no quantitative relation between the observed change in bile acid concentrations and the severity of the diarrhea in this small, (n = 17) group of patients.
Van Blankenstein (84) found impaired bile acid reabsorption in all patients. His findings suggested that further study of bile acid metabolism in relation to clinical symptoms might be worthwhile.

2.3. Physiology of bile acids.

Bile acids are synthesized by the liver. The most important are cholic acid and chenodeoxycholic acid. These two are known as primary bile acids; the former is a trihydroxy-, the latter a dihydroxy bile acid. The bile acids are conjugated in the liver with either glycine or taurine. They are subsequently excreted with the bile and stored and concentrated in the gall bladder. Food intake stimulates gastrointestinal hormones, which in turn cause the gall bladder to empty its contents into the small intestine. Here, the detergent action of bile acids is involved in micelle formation and plays an important role in the absorption of fat and fat-soluble substances. The bile acids are reabsorbed from the terminal ileum and returned to the liver by the portal venous system. This cycle, is repeated about six times a day and is called the enterohepatic circulation (EHC) of bile acids. This cycle (Figure 1) is very efficient. In healthy persons, no more than about 2% of the bile acid pool is lost in the stools with each cycle.

A minor portion of the bile acids is deconjugated and then dehydroxylated by bacteria in the colon or terminal ileum, resulting in the formation of secondary bile acids (deoxycholic acid and lithocholic acid). Lithocholic acid is insoluble at physiological pH of the colon contents and will be almost entirely lost with the faeces. Deoxycholic acid is reabsorbed, mainly in the colon, conjugated and recycled like the primary bile acids, forming a substantial part of the bile acids secreted by the liver.
In 1936, Verzar (49) published his classic study on absorption from the intestine. He found that bile acids combine with the fatty acids (which result from lipolysis) to

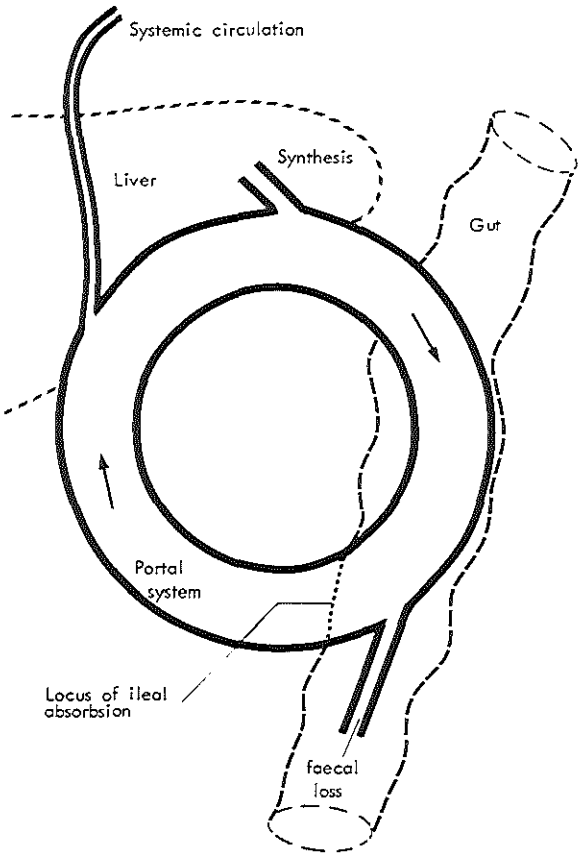


Fig. 1: Schematic representation of the enterohepatic circulation.

form soluble complexes (micelles). At that time, he still believed the bile acids and the fat to be absorbed together.

Tappeiner's (50) data, confirmed by Baker and Searle (51), indicated that the bile acids, in contrast to other water soluble substances, are poorly reabsorbed from the jejunum but rapidly from the ileum. Lack and Weiner (52) clearly demonstrated the specific and active role of the ileum in this bile acid reabsorption.

In 1968, Dietschy (53) reviewed the mechanism of intestinal reabsorption of bile acids. In principle, bile acids can be present in the intestinal lumen as free or as conjugated bile acids; under normal conditions, all bile acids are conjugated. Above a certain concentration, which differs for each bile acid, they will form micelles. These micelles enable fat soluble substances like fatty acids and cholesterol to remain emulsified in the watery environment of the intestine. The bile acids may be seen as a constant stream of detergent running through the small bowel.

Bile acid transport across the intestinal wall can be either active or passive. As mentioned above, in the ileum it is active.
Nowhere in the small intestine, except for the terminal ileum, are bile acids absorbed against a concentration gradient. The efficiency of this transport mechanism was not the same for all bile acids; the trihydroxy bile acid cholic acid was more efficiently reabsorbed than were the dihydroxy compounds deoxycholic and chenodeoxycholic acid. Tauroconjugates more rapidly than glycoconjugates (53). In contrast to this active process, nonspecific passive absorption of bile acids can take place in the small and large intestine. This process is of some importance only for the nonionic forms of the bile acids and is therefore mainly confined to the nonconjugated forms. Passive absorption of ionized bile acids is dependent on the chemicophysical properties of the bile acid involved (e.g., number of -OH groups), but is quantitatively not very important (53).
The environmental conditions such as pH, temperature and concentration of counter-ions also have an influence. Measurements show that, in passive absorption (diffusion) of ionized bile acids, dihydroxy acids are better absorbed than the trihydroxy forms and glycoconjugates better than tauroconjugates (53).
The quantitative significance of extraileal absorption is not precisely known, but it certainly is not negligible, as can be concluded from the presence in bile of dihydroxy bile acids originating from passive absorption in the large intestine. It should be borne in mind, however, that the fact that a certain bile acid can be absorbed under experimental conditions does not necessarily prove that this will also happen in healthy persons or under pathological conditions (87).

2.4. Serum bile acids.

The normal serum level of bile acids is very low. This is due to their efficient extraction by the liver from both portal venous and arterial blood. This extraction is 70-90%, depending on the bile acid concerned. Among patients, there is a wide variation in extraction for any given single bile acid. The systemic venous serum level is the result of the input into the portal venous system and the extraction by the liver. This input is directly related to the reabsorption from the gut. According to LaRusso et al (56), the hepatic bile acid clearance in a patient remains constant and is not influenced by portal serum levels. If this assumption is correct, fasting and postprandial serum bile acid level determinations would provide a reliable estimate of bile acid reabsorption.
The ratio between the individual bile acid concentrations (cholic versus chenodeoxycholic versus deoxycholic acid) is estimated to be 40 - 40 - 20% in bile, 40 - 30 - 30% in portal venous blood and 15 - 45 - 40% in systemic venous blood (57). This indicates that each bile acid has its own specific rate of intestinal reabsorption and

hepatic clearance. As a consequence, a change in these concentration ratios in the bile, as seen after ileectomy, ileal disease or the blind loop syndrome, will result in a change in serum levels of total bile acids.
LaRusso et al (56), Schalm et al (58) and Hepner et al (59) demonstrated a distinct diurnal pattern for the serum concentrations of each of the individual bile acids, cholic, chenodeoxycholic and deoxycholic acid. Each bile acid had its own characteristics of postprandial increase and return to fasting levels. The differences in the time at which the postprandial peaks were observed were due to differences in the mechanism and site of reabsorption.
In patients with malabsorption due to ileal disease or ileectomy, postprandial serum levels were lower. Throughout the day, they remained relatively constant for chenodeoxycholic acid, while they gradually diminished for cholic acid. This is consistent with depletion of the cholyl, but not the chenyl pool (58). This different effect on both primary bile acids might be explained by the better proximal reabsorption of chenodeoxycholic acid. The cholic acid synthesized during the night, however, is almost completely lost after the first passage through the small intestine.
In conclusion, systemic serum total bile acid levels are:
1) the result of the portal input (reabsorption) and hepatic extraction;
2) related to the relative proportion of individual bile acids in the bile;
3) dependent on the time of the day, in relation to meals.

2.5. Methods for analysing the entero hepatic circulation of bile acids (a review of the literature).

The enterohepatic circulation can be investigated at several levels, as shown in the schematic representation (Figure 1, page 22);
1) the duodenal level, where the bile from the gall bladder is introduced;
2) the level of the ileum, where active reabsorption takes place;
3) in peripheral venous blood. This is a reflection of the spillover of bile acids returned to the liver by the portal venous blood.
The following methods are mentioned.

2.5.1. Isotope dilution technique.

With the isotope dillution technique as described by Lindstedt (70) and Hoffman (71), labeled bile acids, ^{14}C cholic acid and ^{14}C chenodeoxycholic acid are administered orally or intravenously. The labeled bile acids will mix with the endogenous bile acid pool. Duodenal bile samples are obtained by duodenal intubation. A steady state is assumed. The slope of the line when plotted logarithmically represents the fractional turnover rate of the administered bile acid. The isotope dilution technique,

therefore, makes possible the determination of several parameters of bile acid metabolism:

1) cholic and chenodeoxycholic acid pool size;
2) daily fractional turnover rates of the two primary bile acids;
3) daily synthesis rates of the two primary bile acids.

2.5.2. Direct measurement of the loss of bile acids.

A decreased reabsorption of bile acids at the ileal level results in spillover to the colon. There, deconjugation and dehydroxylation take place and even some passive absorption. The amount recovered from the stools nevertheless is a good approximation of this ileal spillover.

2.5.2.1. The amount of bile acids in 24-hour stools can be determined chemically. If there is a steady state, it is a reflection of the bile acid synthesis, as the amount synthesized equalise the amount lost. High faecal levels indicate bile acid malabsorption (91).

2.5.2.2. Faecal excretion of a labeled bile acid (labeled within the steroid moiety of the bile acid) can be determined. The biological half-life can be calculated by counting the daily excretion of the tracer (62).

2.5.2.3. The ^{14}C cholylglycine breath test.

The test is based on the knowledge that under biological conditions only bacteria can deconjugate bile acids and that the amino acid released is metabolised and partly exhaled as CO_2.

In the cholyl-1-^{14}C-glycine the ^{14}C label is in the carboxyl carbon atom of the glycine moiety. The amide bond is rapidly cleaved by bacterial enzymes. After the cleavage, the free ^{14}C-glycine is metabolized and $^{14}CO_2$ is released. Abnormal exposure to deconjugating bacteria can take place either in the small intestine as a result of proximal intestinal bacterial overgrowth or in the colon following bile acid malabsorption (72).

A tracer dose of ^{14}C cholylglycine is given in a testmeal. It mixes with the endogenous cholylglycine pool. In the case of excessive deconjugation, increased amounts of $^{14}CO_2$ will appear in the breath. At given time intervals after ingestion of the tracer, the patient blows expiratory air into a vial containing a measured volume of an organic base and an indicator that signals the trapping of a definite amount of CO_2. The vial is placed in a liquid scintillation counter and the $^{14}CO_2$ specific activity is determined.

2.5.3. Determining bile acid concentrations in the blood serum.

Serum concentrations of individual and total bile acids can be determined by several methods.

2.5.3.1. Gas chromatography is an accurate method for determining individual bile acids in a mixture. The sensitivity is moderate to high, depending on the method used. A disadvantage of the method is that no information concerning the conjugation with taurine or glycine is obtained. With high pressure liquid chromatography, the several conjugates can be separated. The sensitivity, however, is rather low and therefore the method is not suitable for serum (95).

2.5.3.2. Generally, a radioimmuneassay can only determine a specific bile acid or conjugate. The specificity of the antibodies is variable, but well circumscribed. The sensitivity is high (88, 89).

2.5.3.3. Enzymatic methods use oxydation of -OHgroups present in the bile acid moiety. The most frequently used method specifically determines the presence of a free 3α-OHgroup (found in 95% of all bile acids in the serum). The sensitivity is limited but sufficient (31).

2.6. The interrupted enterohepatic circulation (EHC) of bile acids.

Since 1965, several authors have reported on steatorrhea with decreased or absent recycling of bile acids after ileal resection. In 1967, Austad (54) reported two patients with this syndrome; one of them had chronic diarrhea following pelvic radiotherapy. After intravenous injection of ^{14}C labeled taurocholic acid, almost none of the radioactivity was recovered on duodenal samplings, while 70-80% was recovered in controls. This indicated decreased recycling of bile acids. Heaton (55) repeated the test with either ^{14}C labeled taurocholic acid or ^{14}C labeled glycocholic acid, labeled in the steroid moiety. He observed the same lack of recovery. Another interesting finding was that the amount (very small) of residual radioactivity in duodenal samplings obtained at 24 hours was the same, regardless whether taurocholic acid or glycocholic acid had been injected. Only 10% of the bile acids were tauroconjugates. This indicates that in the colon glycine and taurine were completely split off and at subsequent reconjugation in the liver mainly glycine compounds were formed.
The patients described by Austad et al. (54) had the following features in common; whether caused by radiotherapy or by other factors, the syndrome of the interrupted enterohepatic cycle consists of:

1) diarrhea;
2) steatorrhea, often mild;
3) malabsorption of bile acids;
4) ileal disease in most cases.

The major clincial feature is diarrhea caused by an increased overflow of bile acids into the colon. Dihydroxy bile acids are cathartics, i.e. they induce water and electrolyte secretion in the colon and stimulate motility of the colon. Steatorrhea is a common, but not essential finding, depending on whether the faecal loss of bile acids results in bile acid depletion in the small intestine to the extend that ingested fat can no longer be emulsified. As the result of the decreased reabsorption in the ileum, the amount of bile acids returning to the liver is reduced. This causes increased de novo sythesis of bile acids in the liver until a new steady state is reached, resulting in a sustained overflow of bile acids into the colon, thus maintaining diarrhea (Figure 2a, 2b pages 28, 29). The observed diarrhea has been termed "cholegenic diarrhea" and the syndrome "cholerheic enteropathy" (90). No investigations concerning the natural course of this syndrome have been done. A number of questions therefore remains, such as: will the liver go on synthesizing bile acids at a higher level and will the remaining small bowel eventually compensate for the loss of function?
Clinical experience suggests that no adaptation takes place. The symptoms remain unchanged. It should be noted that these observations concern interruption of the EHC not only from radiotherapy but from any cause.

2.7. Interrupted enterohepatic circulation (EHC) after radiotherapy.

During radiotherapy for gynaecological malignancies, a varying length of the small intestine lies within the treatment area. A large proportion of this consists of terminal ileum.
If radiation injures specific bile acid reabsorption sites in the terminal ileum, bile acid malabsorption with its concomitant diarrhea may contribute to the symptoms of radiation enteritis.
Berk (61) suggested that one of the main mechanisms of radiation enteritis was "cholerheic enteropathy". He suggested the prevention of diarrhea with cholestyramine. Several other authors have also suggested the importance of bile acids in relation to radiation damage to the intestine.
Jackson (60) reported that, in experimental animals, interruption of the enterohepatic circulation by means of a bile fistula reduced the symptoms after irradiation and resulted in smaller loss of electrolytes and in a longer survival time.
The interruption of the enterohepatic circulation was demonstrated by different

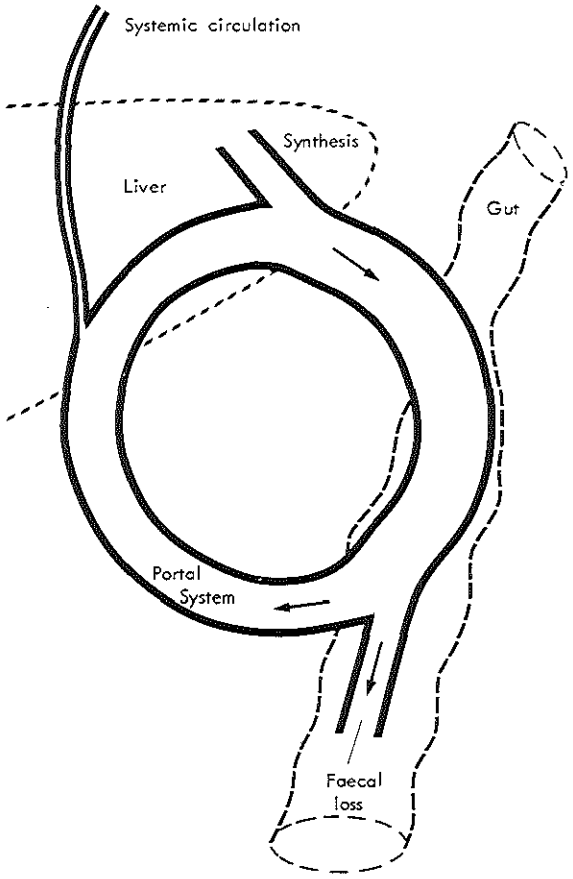


Fig. 2A: Partial interruption of the enterohepatic circulation leading to decreased bile acid reabsorption and increased faecal loss, which leads to moderate diarrhea. The amount of bile acids returning to the liver by portal venous system is decreased and as a result the synthesis by the liver increased. The bile acid concentration in the intestinal lumen is within normal ranges, thus preventing steatorrhea.

methods: Austad (54) used duodenal intubation with an isotope dilution technique; Van Blankenstein (62) measured faecal excretion of ^{14}C labeled taurocholic acid; Stryker (63) used the ^{14}C-cholylglycine breath test. More recently (64) he determined the bile acid concentrations in peripheral venous blood (Radioimmuneassay).
A decreased recovery of labeled bile acids in the bile, an accelerated faecal excretion of labeled bile acids, an increased excretion of $^{14}CO_2$ in the breath test and a decrease in postprandial concentrations of bile acids in the serum all indicated an impaired reabsorption of bile acids after irradiation.

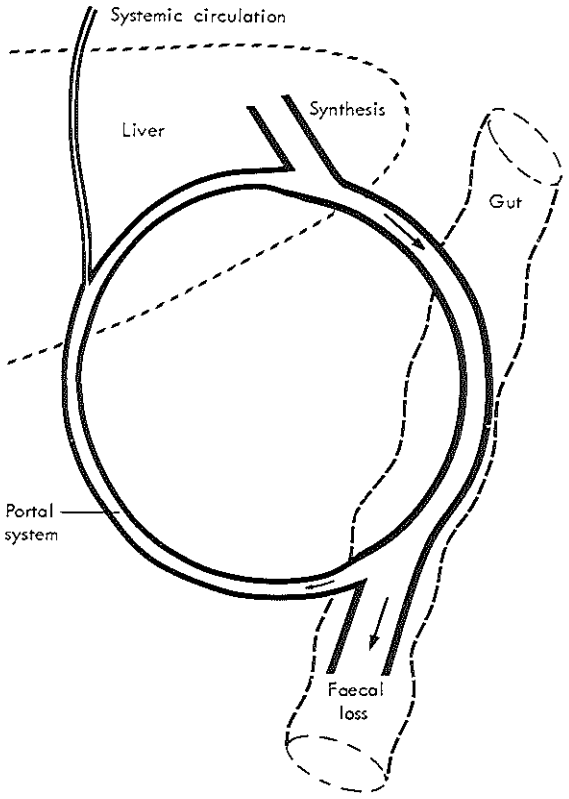


Fig. 2B: More severe interruption of the enterohepatic circulation leading to decreased bile acid reabsorption, increased faecal loss and severe diarrhea. The amount of bile acids returning to the liver by venous portal system is reduced strongly. In spite of maximally increased synthesis, the bile acid concentration in the intestinal lumen drops below the critical micellar concentration and steatorrhea develops.

2.8. Physiology of the rectum.

The ampulla recti has a reservoir function. The wall of the rectum allows volume extension. As soon as the sigmoid is maximally filled, a both intrinsic and spinal reflex sets in motion a propulsive peristaltic wave. When the faeces reaches the rectum, the pressure inside increases and the wall is stretched. This is registered by stretch receptors, which in turn decrease the tone of the internal anal sphincter while the external anal sphincter tone increases, thus closing the anal canal. The volume of the ampulla recti increases under the influence of the increased pressure, until the pressure becomes normal again. Then the internal sphincter regains its tone. If the pressure remains elevated, the patient will experience an urge to defaecate, accompanied by a

continuous relaxation of the internal anal sphincter. If the person responds to the urge to defaecate, he adopts the defaecation posture and the barriers to defaecation are removed by a straightening of the anorectal angle and relaxation of the sphincter (94).

CHAPTER III

STUDY DESIGN

3.1. Background.

Throughout the literature, the incidence of radiation damage of the intestine varies considerably. This is due to differences in definition and partly to differences in radiotherapeutic strategy. On the basis of our previous experience we have distinguished two types of radiation damage to the intestine:

1) severe complications which include fistulas, stenoses, ileus and malabsorption with weight loss and rarely perforation;
2) relatively mild complications like diarrhea and faecal incontinence without weight loss.

We have concentrated on the incidence of these relatively mild complications during irradiation. They are termed acute effects or acute radiation reactions. When these relatively mild symptoms occur after completion of the irradiation, they are termed "late" effects.

The pathophysiology of the postirradiation diarrhea is not clear. Although there are several indications that a disturbed reabsorption of bile acids plays a role, the relatively low total daily faecal weight is not in agreement with this assumption. When the study began, there was no literature available on a possible direct effect of radiation on the rectosigmoid function.

3.2. Working hypothesis.

Our working hypothesis is based on the results of a clinical study (84). In this study the combination of diarrhea, faecal incontinence, impaired bile acid reabsorption and a relatively low daily faecal weight was found.

Whereas in the literature, fistulas and stenoses form the main topic of publications on radiation bowel damage, we thought it important to concentrate on a less severe damage. Therefore, we have chosen a change in stool habits, e.g., diarrhea, as the phenomenon to be studied.

Our first assumption was that irradiation of the pelvic region leads to damage of the ileal mucosa. As a result, the enterohepatic circulation of bile acids would be interrupted and this would manifest itself as impaired reabsorption of bile acids. With appropriate tests this impaired reabsorption would result in two phenomena:

1) a lower than normal bile acid concentration in the serum at ± 2 hours after the emptying of the gall bladder, i.e., after a test meal (postprandially);
2) a shortening of the biological half-life of an orally administered dose of radioactively labeled bile acid.

Our second assumption was that the faecal incontinence was not only the direct result of the irradiation but also of a pre-existing weak anal sphincter mechanism (81), especially in multiparous women. The fact that this latent incontinence had not become manifest, should then be attributed to the firm stools that result from the average Dutch diet. However, when the stool consistency would change to watery, the incontinence would become manifest. From these two assumptions, the following hypothesis was adopted for this study: The cause of the clinical symptoms after radiotherapy to the pelvic region is a combination of impaired reabsorption of bile acids and a pre-existent, but latent, impaired faecal continence.

It seemed logical to test this hypothesis by measuring the bile acid losses as well as the anal sphincter mechanism in a population of patients irradiated for pelvic malignancy.

3.3. Patient selection.

Eligibility and entry criteria.

Patients were admitted to or excluded from the study on the basis of the following criteria.

Eligibility:

Patients referred to the Rotterdamsch Radio-Therapeutisch Instituut (RRTI) for radiotherapy of a carcinoma of the cervix or of the uterine corpus.

This could be for either exclusive radiotherapy (carcinoma of the uterine cervix) or postoperative radiotherapy (either a carcinoma of the endometrium or the uterine cervix). The treatment consisted of a course of megavoltage external irradiation with or without intracavitary treatment.

Exclusions:

1) patients unable to fulfil protocol requirements as given below; this could be due either to health problems or sociogeographical problems;
2) patients with a colostomy;
3) patients with acute or chronic overt gastrointestinal disorders.

Patients thus entering the study were registered and the following pretreatment routine had to be completed:

1) medical history and physical examination;
2) routine hematology and biochemistry;
3) serum bile acids determined in the fasting patient and at 2 hours after a meal;
4) diet history taken by a dietitian;
5) a questionnaire concerning bowel motions filled out by the patient;
6) a faecal continence test according to Read (81) performed*;
7) all stools collected over a 4 day period;
8) faecal excretion of a tracer dose of isotope labeled bile acid determined** (62).

During irradiation, the patients kept daily records of their bowel movements. They visited the dietitian at least once a week and were given dietary advice mainly when they complained about diarrhea, both in the acute and in the follow-up period. The following determinations were repeated in the middle of the course of radiotherapy and at the end:

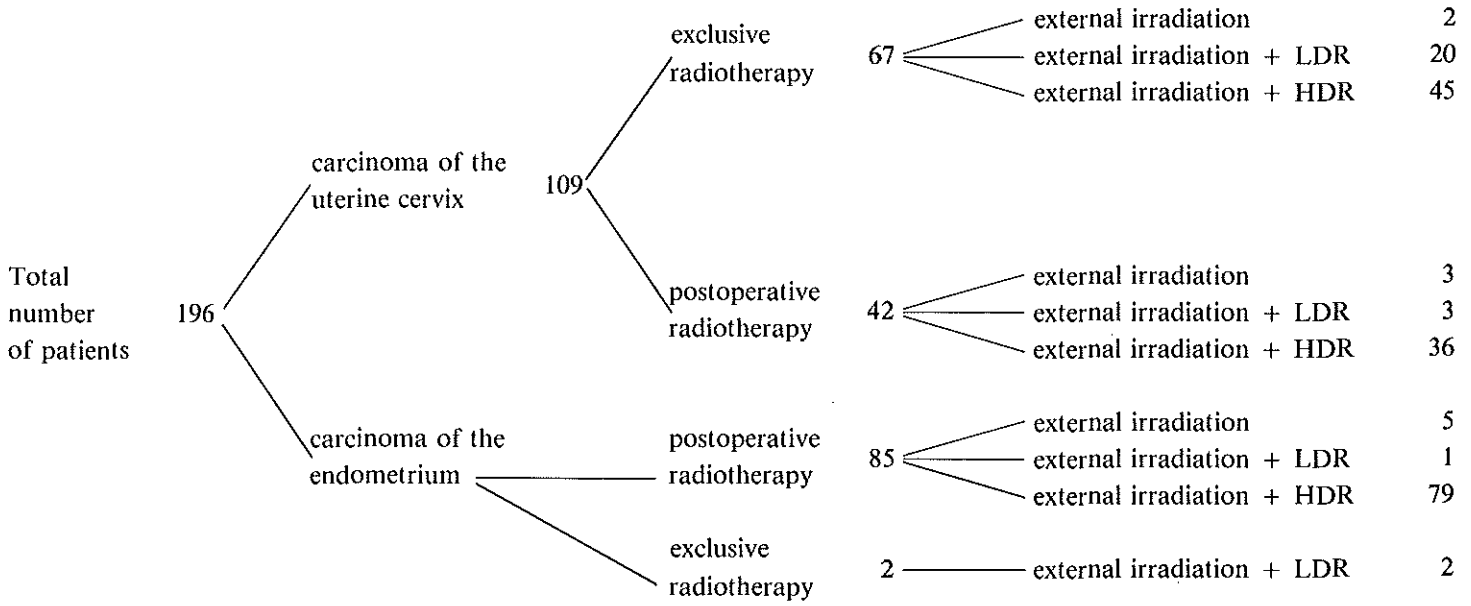
1) serum bile acids, fasting and postprandial;
2) all stools collected over a 4 day period;
3) faecal excretion of labeled bile acids.

Follow-up: The first follow-up visit was at 6 weeks after the end of the irradiation. It consisted of a visit to the dietitian and radiation oncologist. The patient was asked whether she had symptoms and a physical examination was performed. The above-mentioned determinations were repeated at 6 weeks and 6 months after the end of the treatment.
During follow-up, patients regularly visited the out-patient department. During the first year, this was bimonthly, in the second year every 3 months and in the third year every four months. During the fourth year, this took place every six months and from then on at least once a year. At these visits, the patient was seen by the referring gynaecologist or by the radiation oncologist on an alternating basis.
A total of 196 patients has been studied; 109 with carcinoma of the uterine cervix and 87 with a carcinoma of the endometrium. The mode of treatment is illustrated in Table I.

* introduced in 1981.

** only in a selected group of patients (Par. 3.5.2.)

TABLE I. The number of patients included in the study in relation to diagnosis and mode of treatment.



LDR = intracavitary irradiation at low dose rate
HDR = intracavitary irradiation at high dose rate

3.4. Methods of treatment.

3.4.1. History of the treatment protocols at the Rotterdamsch Radio-Therapeutisch Instituut.

3.4.1.1. External irradiation.

Until 1965, external irradiation was generated by 200-300 KV orthovolt machines. Then, megavolt equipment became available. At first, 60 Co (1.25 MeV) was used and later linear accelerators with increasing energies of 4 up to 32 MeV were employed.

The advantages of this megavolt irradiation were:

1) greater penetration resulting in a higher dose at the required depth;
2) lower surface dose, thus sparing the skin;
3) shorter treatment time;
4) less difference in absorbed dose in soft tissues and bone;
5) less scatter, which means sharper edges of the treatment field.

With orthovolt machines, the target volume included the parametria and the main dose-limiting factor was the skin. With the introduction of megavolt machines, the total dose could be increased from 30 - 50 Gy.

In the early years of megavolt therapy, the target volume (as used in conventional orthovolt therapy) was not increased. Later, it was enlarged to include the regional iliac lymph nodes up to the level of the aortic bifurcation.

Field sizes were determined by anatomical reference points. Three categories of field size can be distinguished:

1) standard gynaecological pelvic portals (sgp), Fig. 3A;
2) sgp and para-aortic portals (sgp + pao), Fig. 3B;
3) whole pelvic peritoneal cavity (wpp) + pao, Fig. 3C.

The standard gynaecological pelvic portals (Fig. 3A) encompass the area of the primary uterine tumour and the regional lymph nodes, including those at the aortic bifurcation. In the case of proven lymph node involvement within this area, the para-aortic nodes were included (sgp + pao, Fig. 3B). In this case the lower border of Th12 is taken as the upper limit of the field. Growth of the primary tumour penetrating the uterine wall and/or ovarian or pelvic peritioneal metastases were conditions for extending the target volume to the whole pelvic peritioneal lining (wpp + pao; Fig. 3C).

A tumour in the lower third of the vagina and/or metastases in the inguinal lymph nodes were indications for including the whole vagina and/or the inguinal areas in the target volume.

The treatment technique is dependent on the central abdominal diameter of the patient. If this does not exceed 20 cm, only anterior-posterior fields are used. When it measures more than 20 cm, a combination of anterior-posterior and lateral fields is used in order to spare the skin. The lateral portals (Fig. 3D) encompass the area of the standard pelvic portals. During 1980, the use of lateral portals was discontinued, for technical reasons.

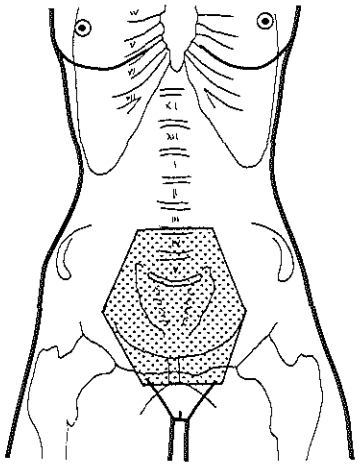


Fig. 3A: Standard gynaecological pelvic portals (s.g.p.).

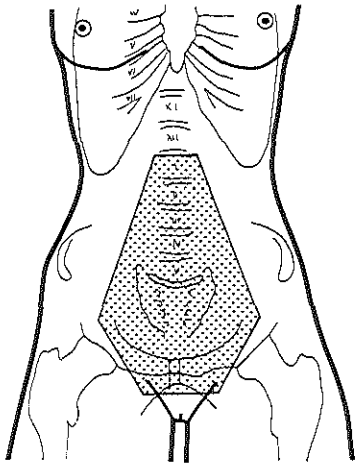


Fig. 3B: Standard gynaecological pelvic plus para-aortic portals (s.g.p. + p.a.o.).

3.4.1.2. Brachytherapy is therapy from close by. This can be performed as either interstitial therapy, which means inserting radioactive needles or wires into the tissues of the target volume, or as intracavitary therapy, which means application of radioactive sources to an existing natural cavity, e.g., the vagina or the uterine cavity. From the beginning of this century, intracavitary treatment was performed by using radioactive sources in a preloaded applicator. The disadvantage of this system was the high radiation exposure for medical personnel. To keep this exposure as low as possible, the time available for applications or dosimetry had to be short. For the patient, the long treatment times (sometimes up to 5 days) were very troublesome. With the introduction of "after-loading" techniques, the exposure of medical personnel was reduced. In this technique the applicator was inserted without radioactive sources. Dosimetry could then be performed at leisure, while the sources were

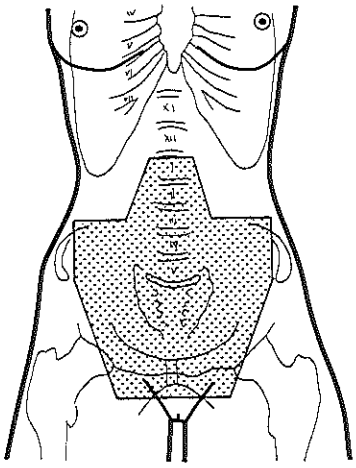


Fig. 3C: Whole pelvic peritoneal lining plus para-aortic portals (w.p.p. + p.a.o.).

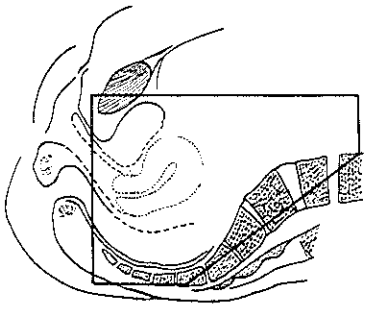


Fig. 3D: Lateral pelvic portals.

introduced afterwards. The discomfort to the patient and the radiation exposure to the nursing staff, however, remained the same.

In 1964, Henschke (33) developed the first remote-control after-loading device: from outside the treatment room, the radiation sources could be removed from the patient before the personnel entered the room; this decreased exposure of the nursing staff to minimal levels and provided better conditions for delivering nursing care to the patient.

The remaining problem thus was the long treatment time and, inherent to this, the uncertainties in the dose distribution for the healthy tissues at risk (due to possible change in position of the applicator).

There are radiobiological data (96) to suggest that a low dose rate, which implies the long treatment time, is of advantage for the treatment of some tumours and for sparing normal tissues, especially when the cells have a short cycle time. Some clinicians attempted a compromise by using intermediate dose rates that permitted the total treatment time to be reduced to about 24 hours.

In 1967, O'Connel (34) introduced the first high dose rate remote-control after-loading machine for intracavitary treatment, the Cathetron. The treatment time per session could now be reduced to 5 - 30 minutes, depending on the activity of the sources. Even treatment on an out-patient basis became possible.

For the intracavitary treatment of carcinoma of the uterine cervix, the modified Stockholm system (92) was used at our Institute until 1980. This system involved 3 applications separated by about 2 weeks. During the first application a vaginal box

with a diameter according to the size of the cervix is placed against the cervix at the top of the vagina. During the second application, an intrauterine tube is inserted into the uterine cavity. The length of this tube is adjusted to that of the intrauterine cavity. The third application is the same as the first one. The intrauterine applicator was after-loadable; most vaginal applicators were not.
For postoperative treatment of carcinoma of the uterine cervix, one or two vaginal applications with a vaginal box were performed.
For postoperative treatment of carcinoma of the endometrium, a vaginal cylindrical applicator with one linear central source and two semi circular top sources was used. The length and diameter of these cylinders were adjusted to the size of the postoperative vagina. These applicators were after-loadable.
In 1976, the treatment with the Cathetron machine was started at this Institute, at first for only the postoperative treatment of carcinoma of the endometrium. Since 1978, it has also been used for postoperative treatment in carcinoma of the cervix. In 1980, it was further extended to curative treatment of carcinoma of the cervix, exclusively by means of radiotherapy.

Along with its introduction in the curative treatment of carcinoma of the cervix, our treatment policy was changed. The former treatment policy was as follows. The target area of the intracavitary treatment was the region of the primary tumour and the main goal of the external irradiation was the treatment of the regional lymph nodes. During the external irradiation or at least part of it, the effective area of the intracavitary treatment was shielded off (treatment strategy A). If this policy had been continued with the Cathetron, at least 4-5 applications would have been necessary. This would have meant a great burden on the patient and the department. Therefore, the strategy was changed as follows. The external irradiation covered the target area of the intracavitary irradiation as well as the regional lymph nodes and, after completion of the external beam therapy, a booster irradiation with intracavitary treatment was given to the area of the primary tumour (treatment strategy B). This also gave us the opportunity to eliminate uncertainties in dose that always exist at the edge of a shielded area.

3.4.2. Total dose and fractionation.

3.4.2.1. External irradiation.

The total dose and the fractionation schedule were chosen according to the field size. When standard gynaecological pelvic portals were used, daily fractions of 2.0 Gy were applied. When the para-aortic nodes were included, the fraction size was decreased to 1.8 Gy and, if the large pelvic portals were applied, it was further reduced to 1.5 Gy.

Two treatment strategies were used consecutively during this study.

A) In the treatment of carcinoma of the uterine cervix, in 80% of the fractions of external irradiation, central shielding of the effective area of the intracavitary treatment was done. In postoperative treatment of a carcinoma of the endometrium, 30% of this area was shielded.

B) In this treatment policy, no central shielding was used and, after the external irradiation, an intracavitary booster treatment was administered to the area of the primary tumour.

Table II: The fractionation schedules used throughout this study.

Treatment strategy	Treatment area	Total dose (Gy)	Number of fractions**	Dose per fraction (Gy)
A	sgp	50.0	25	2.0
A	sgp + pao	52.2*	29	1.8
A	wpp + pao	54.0*	36	1.5
B	sgp	46.0	23	2.0
B	sgp + pao	48.6	47	1.8
B	wpp + pao	49.5	33	1.5

* The para-aortic region is shielded after 40-45 Gy.

** Daily fractionation: 5 fractions a week.

The total dose and fractionation before the introduction of the Cathetron (strategy A) is shown in Table II.

When the fraction dose was changed, the number of fractions and the total dose had to be adjusted. In order to achieve the same biological effect, this was done according to the nomogram of Shuttleworth and Fowler (35). When we changed the strategy, the total irradiation dose was decreased to 46 Gy for standard gynaecological pelvic portals and in the same degree for the other portals (strategy B; Table II).

3.4.2.2. Intracavitary irradiation.

With strategy A, the following treatment schedules were applied:

I) Carcinoma of the uterine cervix exclusively treated by irradiation. The course of external beam therapy was interrupted in order to apply intracavitary treatment after 1, 3 and 5 weeks. Thirty Gy in two fractions (first and third interruptions) were delivered at a dose rate of 0.5 Gy per hour with a vaginal box and 30 Gy in one fraction at a dose rate of 0.6 Gy per hour with the uterine applicator. These doses were specified at point A (2 cm cranially of the fornix lateralis and 2 cm laterally of the uterine axis; Figure 4).

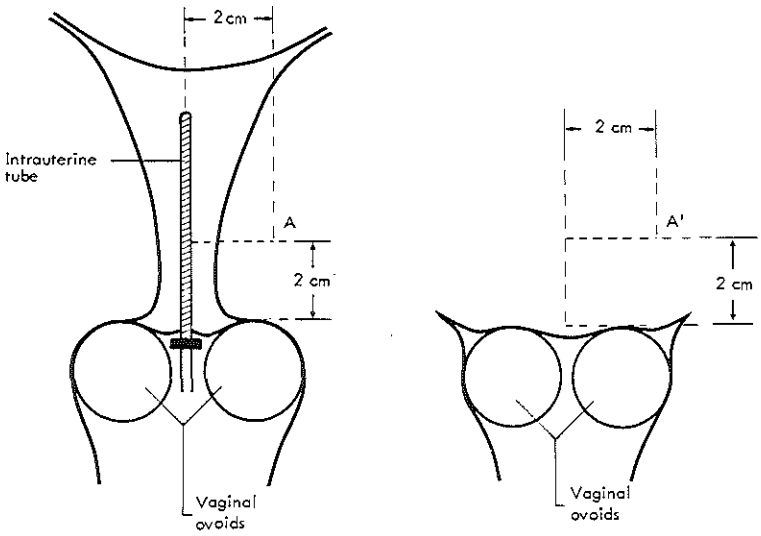


Fig. 4: Schematic representation showing "point A" (left) and "point A'" (right).
"Point A" 2 cm cranially of the fornix lateralis and 2 cm laterally of the uterine axis (after Todd and Meredith; ref. 32) and "point A'", reference point for postoperative intracavitary irradiation, 2 cm cranially of the vaginal vault and 2 cm laterally of a line between the ovoids.

II) Carcinoma of the uterine cervix treated by surgery and subsequent irradiation. The course of external therapy was interrupted in the first or second week to deliver by means of a vaginal box a dose of 15 or 30 Gy in one or two fractions at a dose rate of 0.5 Gy per hour. These doses were specified at point A' (2 cm cranially and 2 cm laterally of the vaginal vault; figure 4).

III) Carcinoma of the endometrium treated by postoperative irradiation. The course of external beam therapy was interrupted during the first or second week for two consecutive days to administer two fractions of 8.0 Gy in about 20 minutes at a depth of 0.5 cm from the vaginal epithelial lining by means of a cylindrical vaginal applicator.

In strategy B, the following treatment schedules were applied.

I) Carcinoma of the uterine cervix treated exclusively by irradiation. The course of external therapy was not interrupted, but intracavitary treatment started at two weeks after completion of this course. Then two combined (intravaginal and intrauterine) applications, separated by one week were given. With each application, a dose of 8.5 Gy was delivered to point A in 25 minutes.

II) Carcinoma of the uterine cervix treated by surgery and subsequent irradiation. The course of external beam therapy was not interrupted, but intracavitary

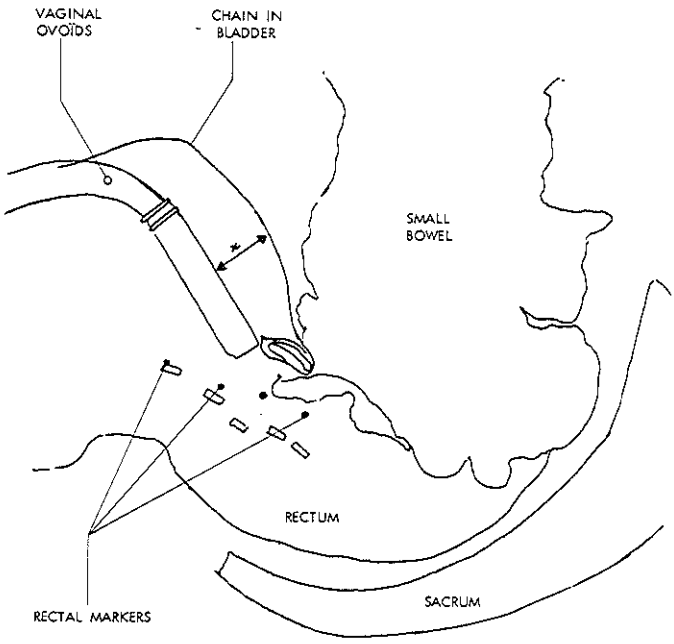


Fig. 5: Lateral representation of a radiograph taken from a patient treated postoperatively with intracavitary irradiation for a carcinoma of the uterine cervix.
Note the little chain which marks the floor of the bladder. The distance between the central axis through the vaginal ovoids and the chain in the bladder: x is used for dose specification.
Note the proximity of the small bowel and the rectum to the sources.

treatment was started at two weeks after the completion of the course. Then, two applications, separated by one week, each delivering 6.5 Gy in 35 minutes at point A', were given. More recently, instead of two applications, only one has been given, but the dose has been increased to 9.25 Gy in about 25 minutes. At the same time, the depth at which this dose was delivered was then individualized for each patient. This was done by determining the distance between the ovoids source position and the lining of the bladder mucosa on a radiograph as indicated by a small chain inserted into the bladder (Fig. 5).

III) Carcinoma of the endometrium irradiated exclusively as an adjuvant to surgery.

The course of external therapy was not interrupted, but intracavitary (vaginal) treatment was started at two weeks after the completion of the course. A single

application delivering 9.0 Gy at a depth of 0.5 cm in about 25 minutes was given.

A schematic representation of the schedules applied is shown in Figure 6.

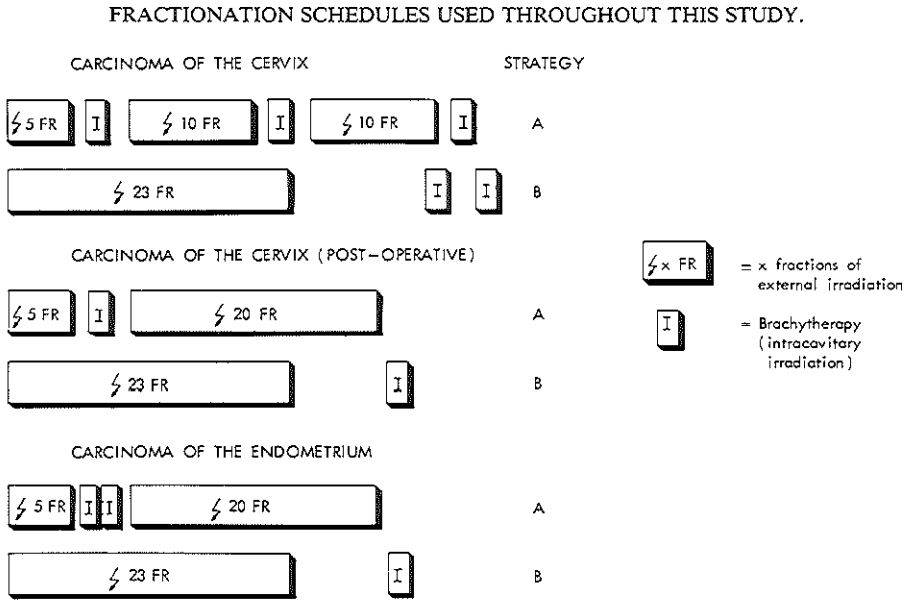


Fig. 6: Fractionation schedules of external and intracavitary irradiation according to diagnosis and treatment strategy. For treatment strategies A and B, see par. 3.4.2.2.

3.4.3. Dosimetry.

3.4.3.1. External irradiation.

The total delivered dose was specified in the midplane. We assumed that an equal dose was delivered at the dose reference points, respectively, points A en A' (Figure 4, page 40).

3.4.3.2. Intracavitary irradiation.

As mentioned above, the doses delivered in intracavitary irradiation for carcinoma of the uterine cervix were specified at points A and A' (for postoperative irradiation). For postoperative irradiation in carcinoma of the endometrium, the delivered dose was specified at a depth of 5 mm beneath the epithelial lining of the vaginal wall. These doses were converted to the dose at point A'. For the calculation of the absorbed dose in the small intestine the patient was given 200 ml of barium orally at

one hour before the application. After insertion of the applicator, anterior-posterior, lateral and stereo radiographs were taken (examples are shown on page 44 and 45). With stereo X-ray photogrammetry (66, 83), we were able to calculate the absorbed dose at several points of the intestine. It should be pointed out that these photos were not *diagnostic* radiographs; therefore, there was not always an optimal filling of the bowel.
For the calculation of the total absorbed dose (external plus intracavitary) in the small intestine, the highest detected dose was taken into account. The combination of external and intracavitary irradiation was expressed according to the TDFformula and for a subgroup, also according to the L-Qformula. For the TDF and L-Qformulas used, see Appendix I.

3.5. Tests for intestinal function.

A table giving all the tests and the times at which they are performed is shown in Appendix II.

3.5.1. Serum bile acids were measured according to the enzymatic 3 α hydroxysteroid dehydrogenase method (sterognost - 3 αRRA) (31).
This test set contains a lyophilized preparation of 3 αHSD, NAD, buffer salts and stabilizers. In a bile acid containing serum sample, the reaction as shown below will occur.

$$\begin{array}{c} \text{3 } \alpha \text{ hydroxy bile acid} \\ \text{NAD}^+ \end{array} \longrightarrow \begin{array}{c} \text{3 } \alpha \text{ keto bile acid} \\ \text{NADH} + \text{H}^+ \end{array}$$

The amount of NADH generated from the oxidation of the bile acid in the serum is then determined spectrophotometrically with an LKB Reaction Rate Analyzer (31). This enzymatic method determines the total quantity of bile acids, but does not discriminate between different bile acids. The bile acids which are sulfated or glucuronidated at the 3 α position cannot be determined. The reproducibility is satisfactory within a run as well as for day to day runs. The coefficient of the variation is about 10% for values in the range of 4 μmol/l and decreases to around 6% for values in the order of 10 μmol/l (31). Total serum bile acids were determined in the fasting state and at two hours after a standard meal which consisted of orange juice, scrambled eggs, toast and coffee. In a subgroup of patients, serum samples were taken when fasting and every 30 minutes up to two hours after ingestion of the standard meal. This was done in order to get a better impression of the postprandial changes in serum levels and to test the validity of the two hour postprandial sampling in the entire group of patients.

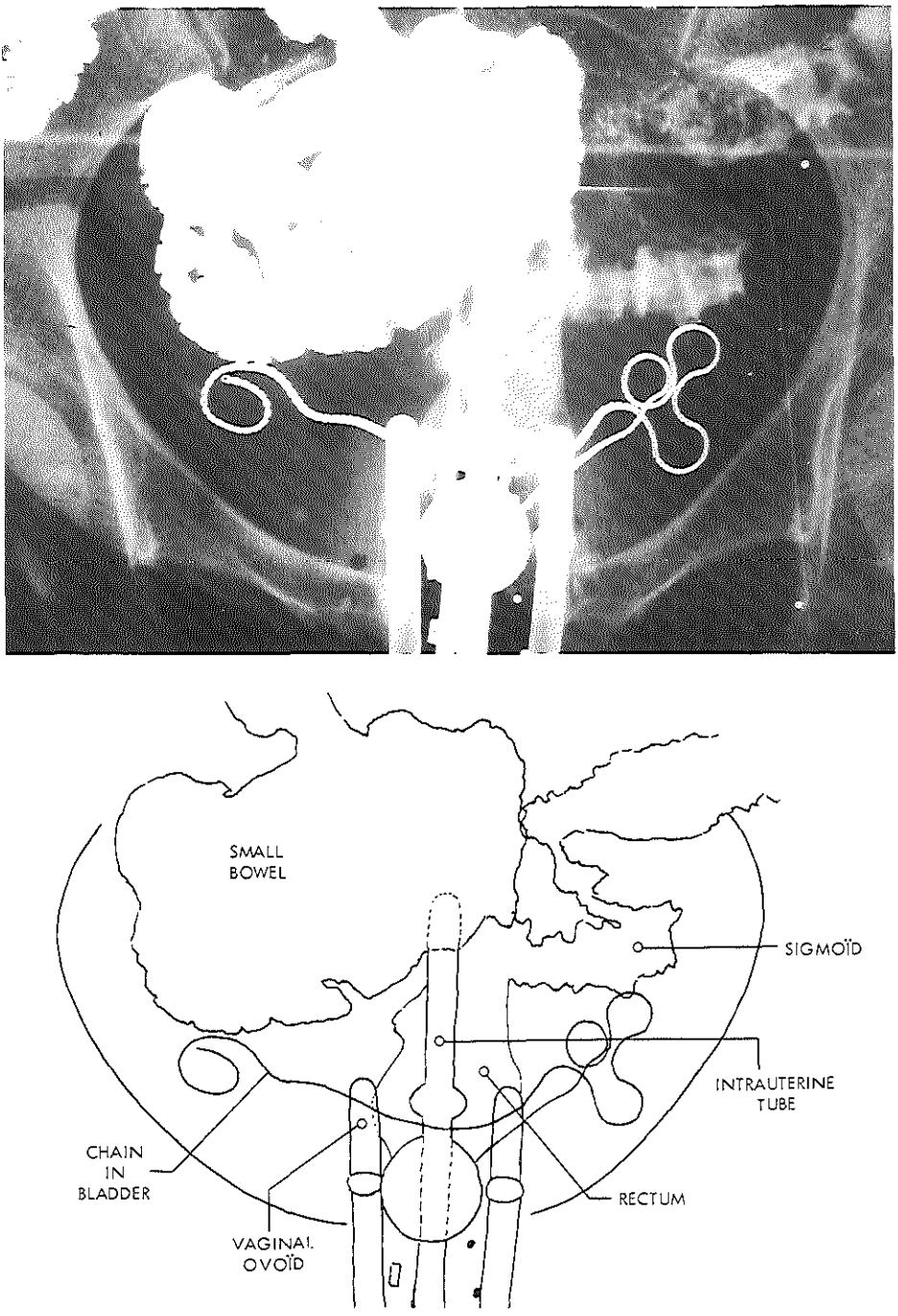
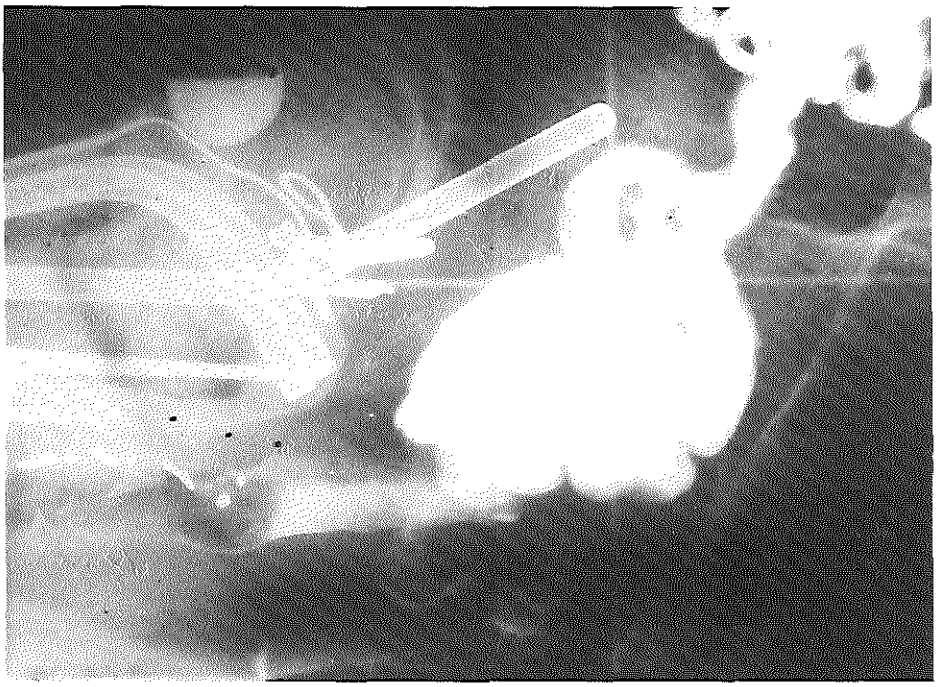
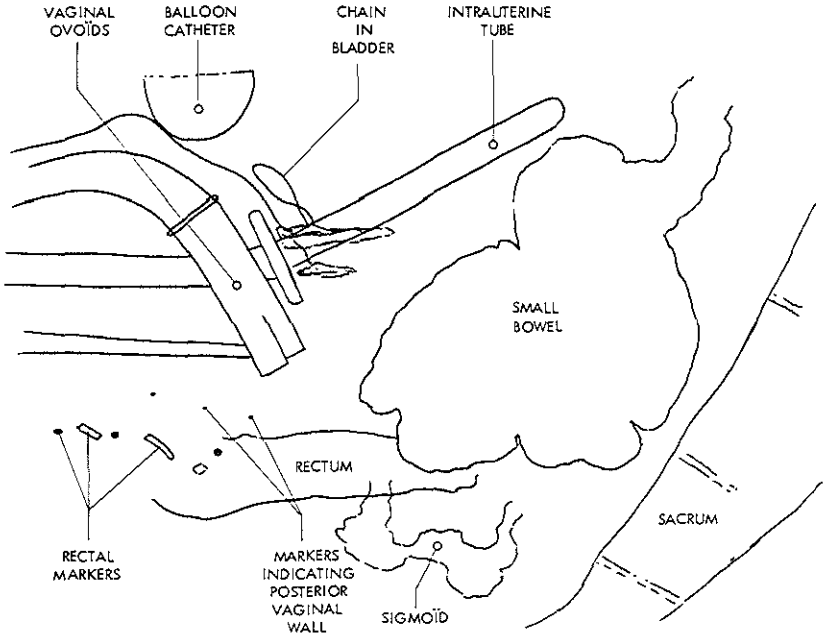


Foto Ap: Anterior-Posterior (AP) radiograph and schematic representation for dosimetric purposes. Note the proximity of the rectum and small intestinal mass to the ovoids and intra-uterine tube. The small chain in the bladder indicates the floor of the bladder, which is also closeby.





Lateral: Lateral radiograph and schematic representation for dosimetric purposes. Note the proximity of the rectum and small intestinal mass to the ovoids and intra-uterine tube. The small chain in the bladder indicates the floor of the bladder, which is also closeby.

3.5.2. Faecal excretion of bile acids.

The patients were asked their consent before this test was performed. The biological half-life of an orally administered tracer dose of radioactive labeled cholic acid was determined as follows. At time 0, a dose of 200 KBq (5 μCi) ^{14}C labeled taurocholic acid or 370 KBq (10 μCi) ^{75}Se labeled homotaurocholic acid was administered. During the following 5 days, all stools were collected in 24-hour portions. To judge the reliability of the collection, 25 radioopaque markers were also administered at time 0. At least 20 markers had to be recovered in the stools to consider a test reliable. For ^{14}C, the determination of the excreted radioactivity was done according to the method described by Van Blankenstein et al (62) and, for ^{75}Se, according to Delhez et al (65). The biological half-life (T/2) and the curve of disappearance could be calculated from the daily excretion counts.

3.5.3. Faecal weight.

For 4 consecutive days all stools were collected in 24-hour portions. The specimen collection containers were then weighed and, after subtraction of the empty weight, a mean daily faecal weight was calculated over this 4-day period.

3.5.4. Transit time.

The 25 markers were administered at time 0. Then, during 4 days, all stools were collected in 24-hour portions. The collecting containers were X-rayed and the number of markers in each collector counted.

The mean intestinal transit time in days was then calculated according to the following formula:

$$MTT = \frac{(n_1 \times 1) + (n_2 \times 2) + (n_3 \times 3) + (n_4 \times 4)}{n}$$

In this formula n_1, n_2, n_3, n_4 and n stand for the number of markers on each day and the total number of markers counted, as proposed by Cummings (47).

3.5.5. Continence test.

Patients were tested with a rectal saline infusion test as described by Read (81); 1500 ml of normal saline at body temperature was infused into the rectum at a constant speed of 60 ml per minute. The patients sat on a chair with a central ope-

ning and a collector underneath. They were asked to try to retain all of the infused saline. The two factors in this test were the volume infused at the time that the first leakage occured and the total volume leaked by the end of the test.

3.5.6. Diet history.

Prior to the irradiation all patients paid a visit to the dietitian. For one week, they kept records of everything that they ate and drank. These data were analysed and scored on composition (fat, carbohydrates, proteins, etc.). The scoring system is shown in Appendix III.

3.5.7. Stool habits.

3.5.7.1. Acute reactions.

The patients kept daily records of their stool habits during the irradiation on a form which was distributed before the start of the irradiation. They were asked to not on this form all additional complaints and medication used. Theis list was checked by the dietitian at least once a week.

3.5.7.2. "Late" effects.

A history of stool frequency, consistency of the stools and the occurrence of abdominal cramps was recorded at each follow-up visit. Changes in stool habits were arbitrarily scored.

Stool frequency:
- 0 = no change
- 1 = variably increased, 0-2 x
- 2 = 2-3 x increased
- 3 = 4-5 x increased

Stool consistency:
- 0 = no change
- 1 = variably changed
- 2 = only watery stools

Abdominal cramps:
- 0 = none
- 1 = abdominal cramps

The scores for frequency and consistency were added to express the change in stool habits (class 0-6).

3.5.8. Continence.

During follow-up, the patients were asked to fill out a questionnaire (Appendix IV) concerning their faecal continence. The anwers were arbitrarily scored as 0-4.

0 = no change
1 = faecal urge
2 = serious imperative urge
3 = incidental incontinence
4 = continuous incontinence.

3.6. Statistics.

For statistical analysis of the data, nonparametrical methods were used. The nature of the analysis was in the first place descriptive. Median values and interquartile ranges of scores and differences were calculated. To estimate the change of values in time, Wilcoxon's matched pairs signed rank test was used.
Differences between subgroups were analysed with Wilcoxon's rank sum test, a chi square test or Fischer's exact test.
Spearman's rank correlation was used to estimate the correlation between ordinal variables and scores of differences.

CHAPTER IV

RESULTS OF INTESTINAL FUNCTION STUDIES.

In our patient population it was not always possible to perform all tests at the scheduled intervals. This resulted in exclusion of varying numbers of patients for each test. The inclusion criteria employed are given with each set of results.

4.1. Serum bile acids.

For the serum bile acid study patients were regarded as evaluable if at least three test results out of the possible five were obtained. Between January 1980 and January 1982, 196 patients proved to be evaluable for a longitudinal study of bile acids. The median values (and interquartile ranges) of the fasting level and the two-hour postprandial serum level of bile acids are shown in Fig. 7. The difference between the two-hour postprandial and fasting levels, the postprandial increase is shown in Figure 7 (and Appendix V).

The median fasting level decreased during radiotherapy and gradually returned to pretreatment values. The median two-hour postprandial level decreased considerably during therapy but returned to its pretreatment level after 6 weeks. As a consequence, the median postprandial increase became less during therapy, with a tendency to recover at 6 weeks. At 6 months, however, it was again somewhat below pretreatment levels. After exclusion of the 31 patients who had undergone gastric surgery or cholecystectomy the results for the remaining 165 did not differ from that of the original 196. Patients treated for carcinoma of the endometrium had higher fasting and two-hour postprandial levels than did those treated for carcinoma of the uterine cervix before as well as after radiotherapy (Figure 8).

Any type of previous abdominal surgery followed by radiotherapy was also associated with higher fasting and postprandial levels (Figure 9).

The serum bile acid levels determined at half-hour intervals for up to two hours postprandially are shown in Figure 10.

It can be seen that, during radiotherapy, the median values were below the pretreat-

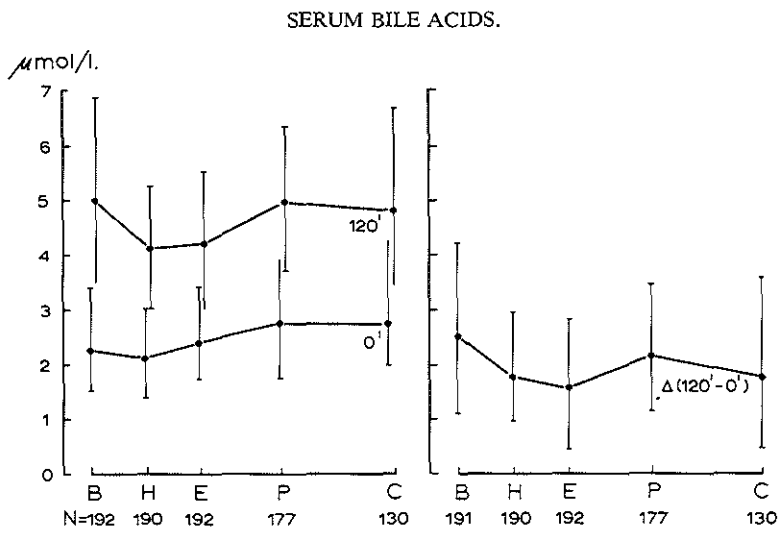


Fig. 7: Serial serum bile acid levels during and after pelvic radiotherapy. Fasting (o') and 2-hour postprandial values (120') at different times. On the right, the postprandial serum bile acid increase is plotted. There is a temporary fall in serum bile acid concentrations.
(B = before RT; H = midway RT; E = End of RT; P = 6 weeks after RT; C = 6 months after RT).

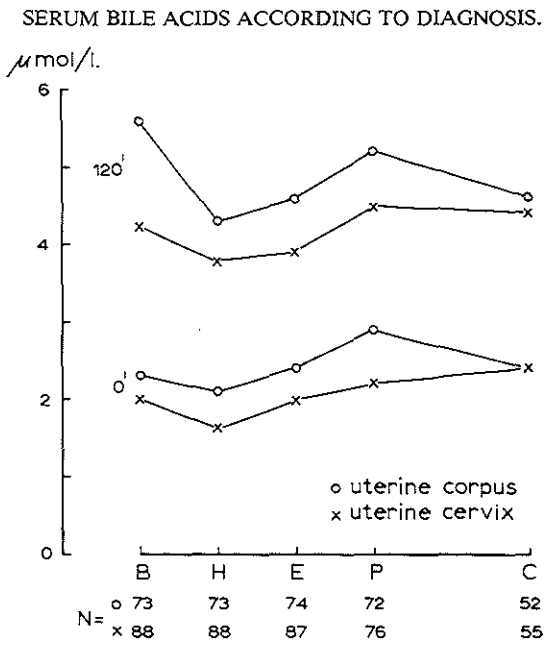


Fig. 8: Serial serum bile acid levels of patients with carcinoma of the uterine cervix (o) and those with carcinoma of the uterine corpus (x). (Median values; abbreviations see legend fig. 7).

SERUM BILE ACIDS ACCORDING TO ABDOMINAL SURGERY.

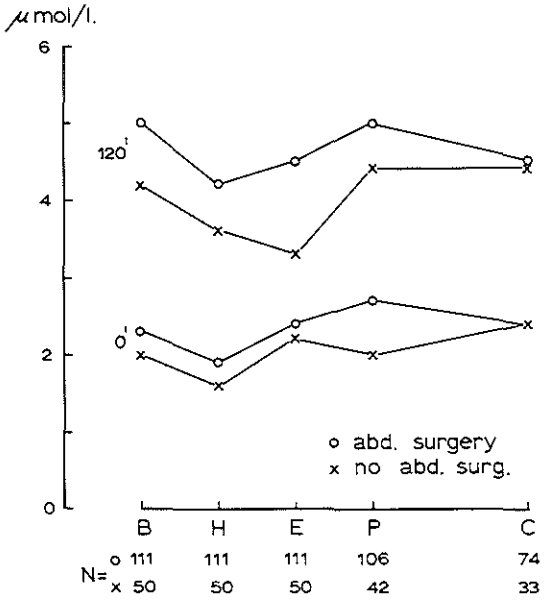


Fig. 9: Serial serum bile acid levels in patients who were subjected to any abdominal surgery (o) and those who had not undergone surgery (x). (Median values; abbreviations see legend fig. 7).

ENDOGENOUS TOLERANCE TEST.

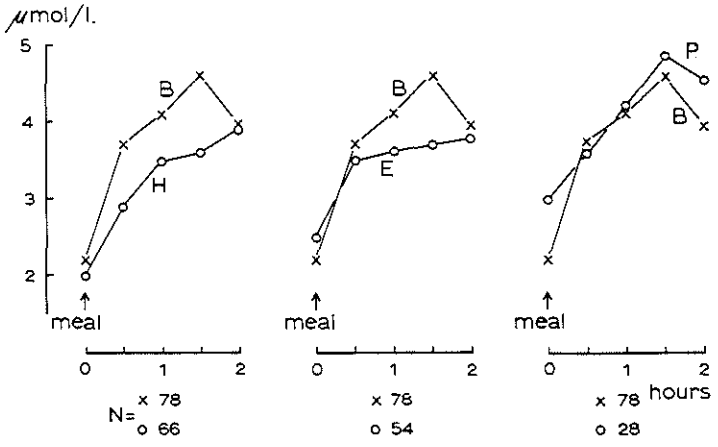


Fig. 10: Results of endogenous tolerance tests for serum bile acids (samples taken half hourly from fasting up to two hours postprandially) at different times during and after pelvic radiotherapy. During pelvic irradiation, lower serum bile acid concentrations are found after a test meal (a and b). (Abbreviations see legend fig. 7).

ment level at 30, 60 and 90 minutes. At six weeks after treatment, bile acid concentrations returned to pretreatment levels. At six months after treatment, the number of patients re-examined was too small to allow a comparison with pretreatment values.
To test the validity of the two-hour postprandial sampling in the total group of patients, the time of the peak values was noted. Before and at six weeks after irradiation, the median peak value was recorded at 90 minutes after the test meal; but, midway through the radiotherapy, it was recorded as late as two hours postprandially, although there was a considerable variation. The height of the peak, however, showed a significant decrease during therapy, followed by an increase to pretreatment levels at six weeks after treatment (Figure 11).

4.2. Faecal bile acid excretion.

The faecal loss of a radiolabeled taurocholic acid tracer dose was determined. From these losses, the biological half-life (T/2) was derived. Faecal bile acid excretion figures were available for 33 patients, although not in every phase of the study. In 7 patients, only one observation was available. These cases could not be used for statistical analysis, as only paired results for each patient were useful for this purpose. The reasons for missing or non evaluable data were sampling errors, recovery of insufficient numbers of markers in the stools, refusal to cooperate, etc.
The median values for the biological half-life of a labeled bile acid dose (T/2) are shown in Figure 12.
This plot shows that the T/2 was shortened at the end of treatment, indicating a decreased reabsorption of cholic acid. After an initial improvement at six weeks, T/2 was again below the pretreatment level at six months after radiotherapy.
As none of these patients had any bowel complaints on entry into the study, the test results at the start of radiotherapy (B) represent the "normal values" for his group of patients. A rather broad variation is evident.

4.3. Mean intestinal transit time.

The patients had to have at least two test results to be included in the analysis.
Transit times were calculated from recovered stool markers in 92 patients at different times during and after pelvic radiotherapy.
The mean distribution of marker recovery showed that the major portion of the markers was excreted during the first two days (Fig. 13). From the marker recovery, the mean transit was calculated (Fig. 14). At six weeks after treatment the mean transit time was slightly increased as compared with that at the beginning (B) and the end (E) of radiotherapy. No difference from B was observed at six months.

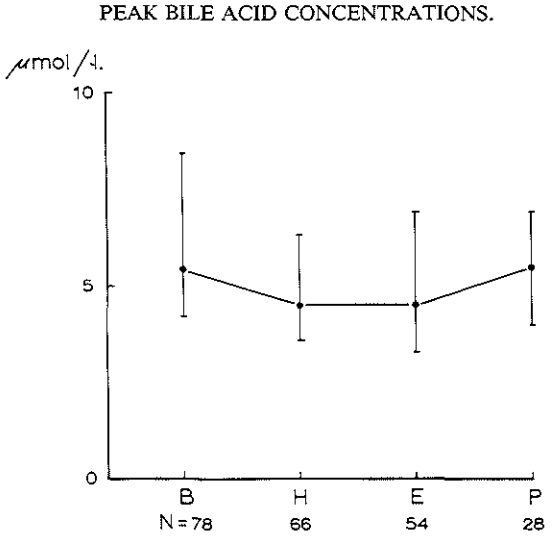


Fig. 11: The peak serum bile acid concentrations after a test meal at different times during and after pelvic radiotherapy. A temporary decrease is observed at H. (Median values and interquartile ranges; abbreviations see legend fig. 7).

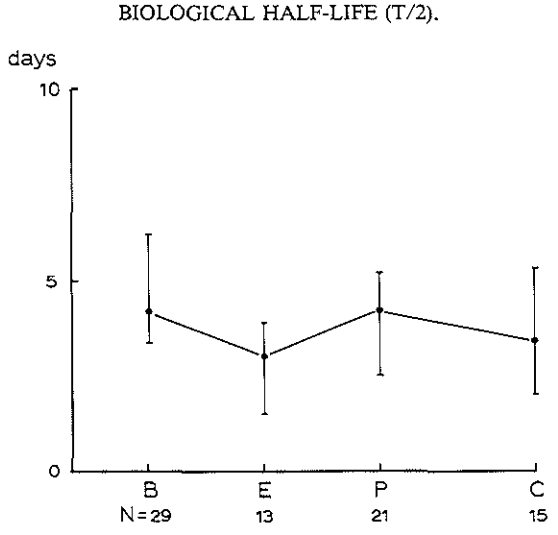


Fig. 12: Biological half-life (T/2) of an isotope labeled (^{14}C or ^{75}Se) cholic acid tracer dose during and after pelvic radiotherapy (median values and interquartile ranges; abbreviations see legend fig. 7).

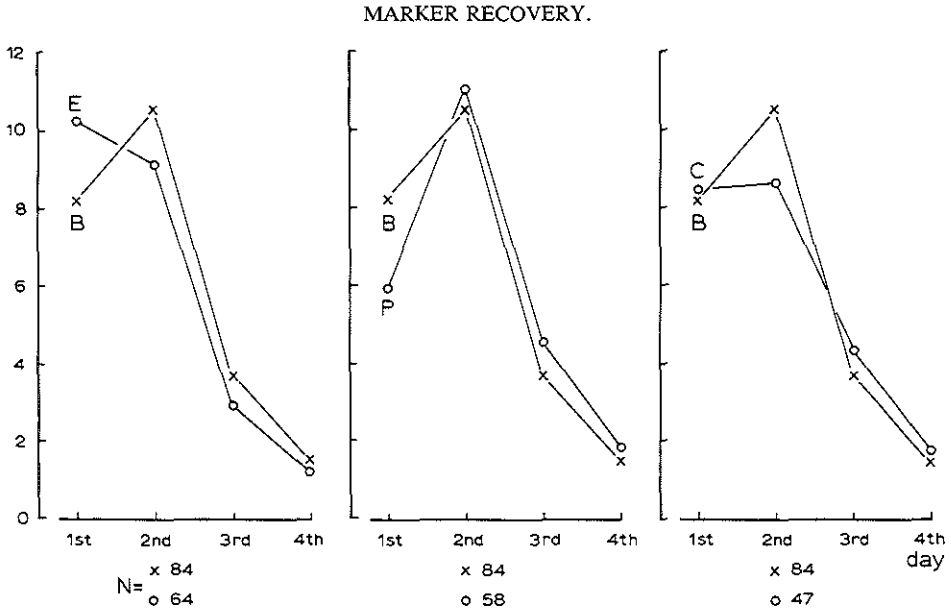


Fig. 13: Marker profiles during four days (24 hours periods) after ingestion of 25 nonresorbable radioopaque markers during and after pelvic radiotherapy.

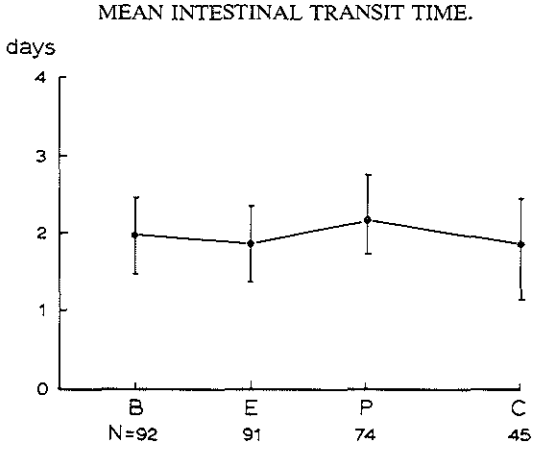


Fig. 14: Transit time at different times during and after pelvic radiotherapy (median values and interquartile ranges; abbreviations see legend fig. 7).

4.4. Total daily faecal weight.

The patients had to have at least two test results to be included in the analysis. The mean faecal weight was determined in 92 patients. A number of results had to be discarded because of insufficient marker recovery: 8 patients at the start of treatment (B), 27 at the end (E), 17 at 6 weeks after treatment (P) and 3 patients six months after treatment (C).
The median values for faecal weight at different times during and after pelvic radiotherapy are shown in Fig. 15.
It can be seen that, at the end of radiotherapy, the mean faecal weight had increased considerably, but returned to pretreatment levels at six weeks after radiotherapy.

4.5. Faecal continence test.

One-hundred and nine patients were tested for continence. The median value for the instilled volume at which the first leakage occurred was 200 ml (interquartile range, 100-300 ml).
The median value for the total leaked volume was 1100 ml (interquartile range 500-1400 ml). Twelve patients experienced no leakage at all. Twenty-two patients had leakage from the start of the test. There was a strong relation between the time of the first leakage and the total leaked volume; patients who leaked early leaked more. No relation was found between the age of the patient, parity and the test results.

4.6. Diet history.

The diet histories of 155 patients were available for analysis. The results are shown in Appendix VI. For most of the diet components, there was not much difference between individual patients, e.g. as far as proteins, fat or carbohydrates were concerned. 80% of the patients fell in the "normal" intake range for proteins and carbohydrates. A similar percentage proved to have somewhat elevated intake of fat.

4.7. Clinical symptoms.

4.7.1. Acute reactions.

During the acute phase of the radiation reactions, the most common symptom was diarrhea. At first, softening of the stool was noted; this was later combined with increased frequency. This increased frequency was especially noticeable in the morning hours or following food intake. In severe cases, it was combined with abdominal cramps and/or production of mucus and sometimes blood. During this period, patients might complain of a faecal urge or even faecal incontinence.

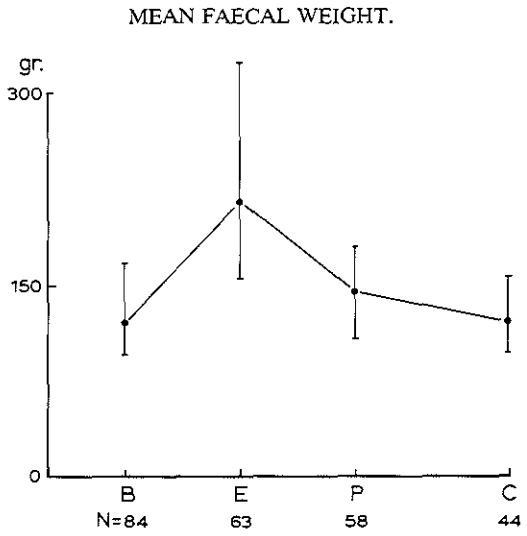


Fig. 15: Mean total daily faecal weight at different times during and after pelvic radiotherapy (median values and interquartile ranges; abbreviations see legend fig. 7). During irradiation faecal weight temporarily increased.

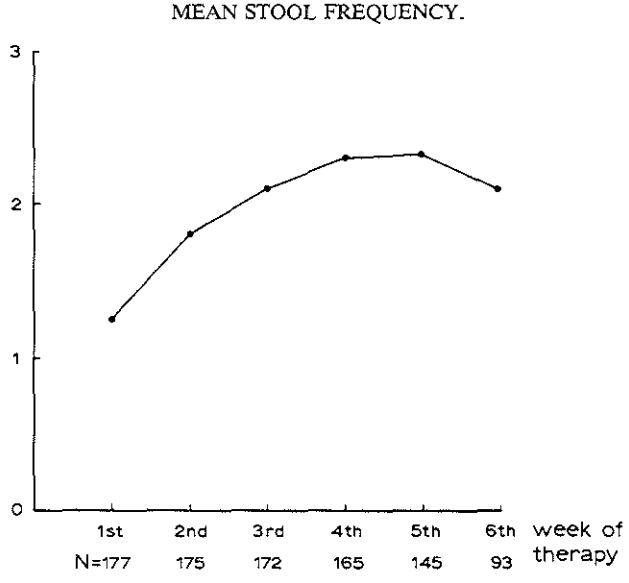


Fig. 16: Mean daily stool frequency, calculated over a one-week period during pelvic radiotherapy. Note increasing frequency up to the fourth week.

The mean stool frequency during the first week of radiation was once a day. As shown in Fig. 16, the mean daily stool frequency calculated over one week increased during the first 4 weeks and then reached a plateau. In approximately 25% of the patients, the stool frequency did not change at all, it remained within the pretreatment range.
The so-called "diarrhea factor" indicates the ratio of watery stools to the total number of stools. This factor was used to express the change in stool consistency. Stools became more fluid during the first 3-4 weeks, after which a plateau was reached (Fig. 17).

4.7.2. "Late" effects.

In most patients, the acute side-effects subsided within 2-3 weeks after the end of radiotherapy. The first follow-up visit to the out-patient department was scheduled 6 weeks after the completion of radiotherapy (P). The mean follow-up time of our patient population was 17 months, range 6 to 31. Eleven patients were lost to follow-up.
Of 185 patients, 59 experienced altered bowel motions during follow-up. 32/59 patients complaining of diarrhea during follow-up had no symptom-free period at all between irradiation and their diarrhea. Another 15 patients got diarrhea within the first 6 months (C), while in another 8 the diarrhea became manifest after the end of the first year.
The prevalence of "late" effects is shown in Fig. 18. This plot shows that, from the fifth month of follow-up onwards, the prevalence remained constant. In about 30% of the patients, the diarrhea eventually disappeared. In this subgroup the median duration of diarrhea was 6 to 7 months.
The severity of the late effects was arbitrarily classified by adding the scores for each factor (stool frequency, stool consistency and abdominal cramps; scores ranging from 0-6; Par. 3.5.7.2, 3.5.8.), with the following results:

18 patients	were in class 1;
17 patients	class 2;
15 patients	class 3;
7 patients	class 4;
2 patients	not classifiable.

4.7.3. Continence.

96/109 patients who had undergone a pretreatment continence test filled out a questionnaire. The results of this questionnaire showed no relation between the results of the continence test and the fact whether patients experienced faecal incontinence during follow-up or not (Appendix VII).

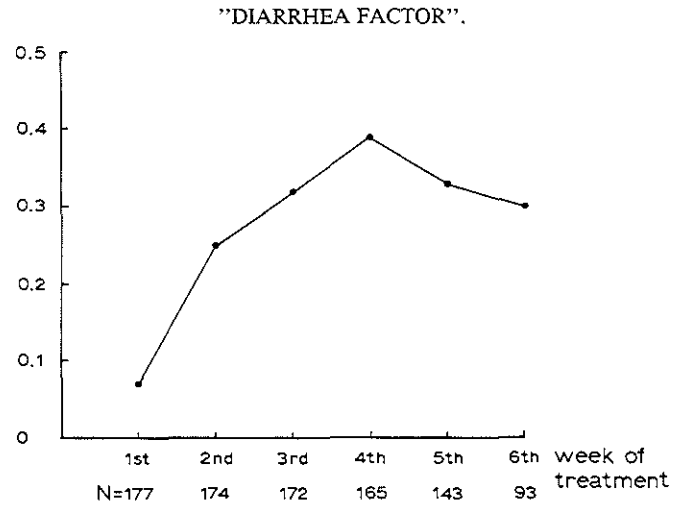


Fig. 17: "Diarrhea factor" (number of watery stools/total number of stools calculated over a one-week period) for the entire group of patients. Note an increase during the first four weeks.

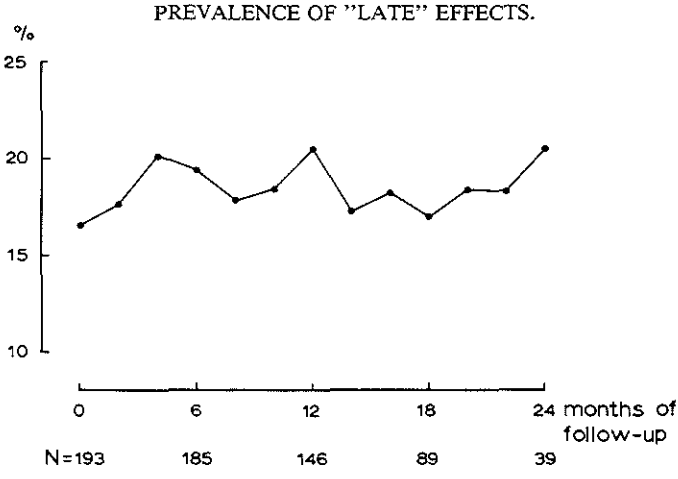


Fig. 18: Prevalence of "late" effects (number of patients with "late" effects, in relation to the total number of patients with the same duration of follow-up.

4.8. Patient risk factors.

The incidence of several patient factors is shown in table III.

Table III.

	present	absent
Abdominal surgery	n = 137	n = 59
Diabetes mellitus	n = 18	n = 178
Cardiovascular disease	n = 38	n = 158

This table indicates the number of patients in which the risk factors for bowel damage mentioned in the literature are present or absent. The large number of patients with "previous abdominal surgery" is caused mainly by the patients who were operated because of carcinoma of the endometrium.

Table IV shows the mean values and the standard deviation for the age and body build related factors:

Table IV.

Age	60 ± 11.9 years old
Height	162 ± 6.3 cm
Weight	69 ± 11.8 kg
AP diameter	22.4 ± 6.2 cm

4.9. Radiotherapy factors.

The mean values for the radiotherapy factors which were assumed to be risk factors for bowel damage, are shown in the following table (V).

Table V. Mean values and ranges of radiotherapy factors

Total dose	48.5 Gy	range	45.0 - 56.0
Total treatment time	49.5 days	range	34 - 117
Dose per fraction	1.95 Gy	range	1.5 - 2.0
Time-Dose-fractionation			
at point A	91.9	range	18 - 178
at intestine	86.0	range	23 - 155
treatment volume			
standard gynaecological			
pelvic portal (sgp)	5.770 cm^3	range	3.200 - 9.500
sgp + paraaortal	7.760 cm^3	range	4.800 - 12.900

4.10. Relation between the different test results.

Prior to the irradiation, the expected relation was found between the stool frequency (once a day or less as compared with more than once a day) and the transit time. In the group of patients with a stool frequency equal to or less than once a day, the median value of the transit time was longer (see table VI).

Table VI. The relation between the stool frequency (> 1 or < 1) and the intestinal transit time at different times during after irradiation

	Mean Transit time (days)		
Stool frequency	Before RT	End RT	6 weeks after RT
< 1	2.0*	1.9	2.2
> 1	1.6*	1.8	2.0

(median values: * = significant difference $p < 0.05$).

However, an overlap of the two groups was observed. Before as well as after irradiation, the expected relation between the transit time and the faecal weight was found: a longer transit was associated with a lower faecal weight. These correlations were highly significant ($p < 0.001$).

The relation between the biological half-life (T/2) of a labeled bile acid, the transit time and the faecal weight was studied in the group of patients with a reliable test result (minimally 20 markers recovered).

Table VII. Spearman Rank correlations between T/2 and faecal weight (R1) and rank correlations between T/2 and transit time (R2) at different times.

		T/2 vs	Faecal weight	T/2 vs	Transit Time
	n =	R1	p-value	R2	p-value
Before RT (B)	25	- 0.56	< 0.01	0.14	n.s.
End RT (E)	10	- 0.77	< 0.05	0.42	n.s.
6 Weeks (P)	12	- 0.73	< 0.01	0.81	< 0.01
6 Months (C)	10	- 0.67	< 0.05	0.50	n.s.

A clear correlation was found between the T/2 and the faecal weight both before and ater the irradiation. A shorter T/2 was associated with a higher faecal weight. Remarkebly, no relation could be found between the T/2 and the transit time, with the exception of the measurement at six weeks after the irradiation (see table VII).

4.11 Relation between acute reactions and other factors and tests.

4.11.1. Relation between acute reactions and patient risk factors.

The relation between the increase in stool frequency and in "diarrhea factor" and the presence or absence of patient risk factors is shown in table VIII below.

Table VIII. Relation between acute radiation reactions and patient risk factors. (△ = increase).

	n =	△ Stool frequency		△ "Diarrhea factor"	
Abdominal surgery:					
Absent	48	0.85	n.s.	0.27	n.s.
Present	128	0.88		0.25	
Diabetis mellitus:					
Absent	162	0.88	n.s.	0,26	n.s.
Present	14	0.72		0.20	
Cardiovascular disease:					
Absent	144	0.92	n.s.	0.28	($p < 0.01$)
Present	32	0.65		0.15	

Table IX shows the correlation of the age and body build related factors with the increase in stool frequency and in "diarrhea factor".

Table IX. Relation between acute radiation reactions and patient risk factors (△ = increase).

	△ Stool frequency	△ "Diarrhea factor"		n =
Age	- 0.02	- 0.05	n.s.	176
Height	- 0.03	- 0.05	n.s.	168
Weight	- 0.12	- 0.18	($p < 0.05$)	172
AP diameter	- 0.12	- 0.17	($p < 0.05$)	175

Altough on visual inspection of the scatter plots a broad variation was observed, on analysis in obese patients a marginally significant tendency ($p < 0.05$) was noted towards a smaller increase in stool frequency and "diarrhea factor" on irradiation. Except for patients with cardiovascular disease, where the increase in "diarrhea factor" was smaller than for patients without cardiovascular disease ($p < 0.01$), no relation between the presence or absence of the patient risk factors and the acute radiation reactions was observed.

4.11.2. Relation between acute reactions and radiotherapy risk factors.

Table X shows the increase of stool frequency and of "diarrhea factor" for the main radiotherapy risk factors.

Table X. Relation between acute radiation reactions and radiotherapy risk factor.

	n =	Stool frequency mean ± s.d.		"Diarrhea factor" mean ± s.d.	
Total delivered dose:					
< 50 Gy	79	1.07 (1.06)	($p < 0.05$)	0.33 (0.27)	($p < 0.01$)
= 50 Gy	71	0.74 (0.86)		0.21 (0.24)	
> 50 Gy	26	0.63 (0.73)		0.18 (0.21)	
Dose per fraction:					
1.8 Gy	27	0.76 (0.80)	n.s.	0.25 (0.23)	n.s.
2.0 Gy	143	0.89 (0.97)		0.27 (0.26)	
Total treatment time:					
< 43 days	64	0.67 (0.80)	n.s.	0.24 (0.24)	n.s.
44-54 days	62	1.04 (0.93)		0.24 (0.26)	
> 55 days	50	0.91 (1.12)		0.30 (0.28)	
Dose rate:					
high	151	0.90 (0.98)	n.s.	0.27 (0.25)	n.s.
low	17	0.82 (0.75)		0.14 (0.28)	

A correlation was observed between the increase in stool frequency ($p < 0.05$) and the increase in "diarrhea factor" ($p < 0.01$) on the one side and the total delivered dose on the other hand. Increasing the doses of radiation resulted in a smaller increase of stool frequency and of "diarrhea factor". No other correlations were found between the acute radiation reactions and the radiotherapy risk factors.

4.11.3. Relation between acute reactions and test results.

The correlations between the increase of stool frequency and of "diarrhea factor"

with the changes in serum bile acids (fasting and 2 hour postprandial concentrations, postprandial increase and the absolute values at the beginning (B), midway (H) and at the end (E) of irradiation), varied between - 0.17 and 0.06.
Thus these values did not indicate any correlation between the acute radiation reactions and the results of our tests.

4.12. Relation between "late" effects and other factors and tests.

4.12.1. Relation between "late" effects and patient risk factors.

Table XI shows the mean value for the age and body build related factors in patients with or without late effects.

Table XI. Relation between "late" effects and patient risk factors.

	Late effects		No late effects	
	n =	mean	n =	mean
Age	59	61 yrs	134	59 yrs
Height	57	162 cm	128	162,3 cm
Weight	58	69.2 kg	131	69.0 kg
AP diameter	58	21.9 cm	134	22.0 cm

No significant differences were observed between patient characteristics in the groups with or without late effects.

Table XII shows the incidence of patient risk factors in the absence or presence of late effects.

Table XII. Relation between "late" effects and patient risk factors.

	Late effects		No late effects	
	n =	%	n =	%
Abdominal surgery	59	71	134	72
Diabetes mellitus	59	11.9	134	7.5
Cardiovascular disease	59	22	134	17

No significant differences were observed.

In conclusion: no relation between the absence or presence of late effects and the patient risk factors could be observed.

4.12.2. Relation between "late" effects and diet history.

The development of the "late" radiation effects showed no relation with the diet history as analysed from the food intake (relative composition, proteins, carbohydrates, fat, etc.).

4.12.3. Relation "late" effects and radiotherapy risk factors.

The development of "late" effects showed no relation with the radiotherapy factors investigated. Variations in the total delivered dose of external irradiation, the total treatment time, the dose per fraction, the treatment volume, the radiation technique and the kind of intracavitary irradiation and the dose rate of the intracavitary irradiation had no measurable influence on the development of "late" effects.
The following table shows the mean values (± standard deviation) for the calculated TDF and L-Q values for patients with and without "late" effects.

Table XIII Radiation dose (expressed as TDF or L-Q) in relation to the presence or absence of "late" effects.

	Late effects		No late effects		Difference
		n =		n =	
TDF point A	94.9 ± 22.1	29	92.5 ± 22.2	58	n.s.
TDF gut	81.0 ± 11.8	24	79.2 ± 8.7	47	n.s.
L-Q point A early	100.3 ± 20.9	29	96.6 ± 17.3	62	n.s.
L-Q point A late	110.3 ± 32.3	29	104 ± 28.3	62	n.s.
L-Q gut early	86.7 ± 10.6	27	84.3 ± 8.7	49	n.s.
L-Q gut late	88.6 ± 17	27	85.5 ± 12.7	49	n.s.

TDF = Time-Dose-Fractionation
L-Q = Linear-Quadratic

No relation could be demonstrated between the radiation dose and the development of "late" effects, regardless of the mode in which the dose was expressed (TDF or L-Q).

4.12.4. Relation between "late" effects (changes in bowel habits) and test results.

4.12.4.1. Serum bile acid concentrations: the median fasting concentrations at the beginning of (B) and at six weeks after (P) the radiotherapy were higher ($p = 0.05$) for the patients developing "late" effects. The median postprandial bile acid concentrations at six weeks (P) and 6 months (C) after radiotherapy were higher ($p = 0.05$) for the patients developing "late" effects (diarrhea) (Fig. 19).

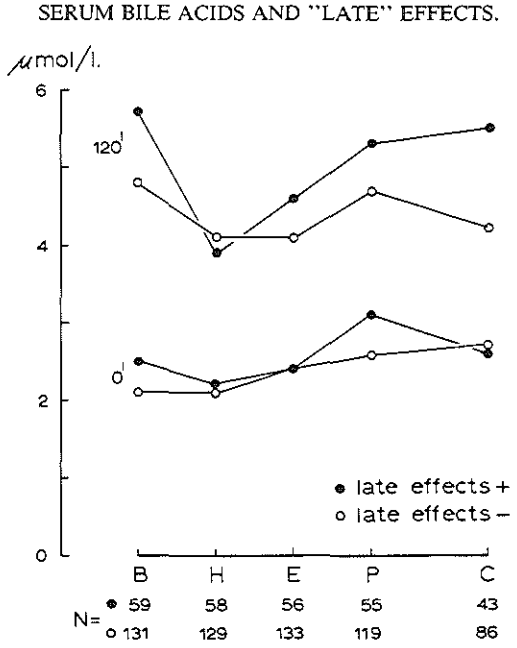


Fig. 19: Serial serum bile acid levels during and after pelvic radiotherapy. Fasting (o') and 2 hour postprandial (120') values at different times according to the occurence of "late" effects (+ or –) (median values and interquartile ranges; abbreviations see legend fig. 7).

4.12.4.2. Faecal bile acid excretion: the number of patients with a reliable test result was too small to assess a possible relation between the bile acid loss and the later development of diarrhea.

4.12.4.3. Faecal weight: no relation was observed between the development of "late" effects and the mean of faecal weight at any sampling time.

4.12.4.4. Transit time: prior to the irradiation, patients, who will develop "late" effects, have a shorter mean transit time (1.8 versus 2.2, $p = 0.02$). However, at the end of the irradiation and later, no difference in transit time was observed between patients with and without "late" effects.

4.12.4.5. Continence test: the continence test performed prior to the irradiation appeared to have no predictive value for the development of "late" effects. The entire range of total leaked volume (from no leakage to leakage of all infused saline) was found in patients who developed symptoms as well as in those who did not.

4.13. Relation between changes in stool habits and in faecal continence and testresults.

Based on the follow-up data, the entire group of patients was divided into four subgroups:

1) unchanged or hardly changed stool habit with unchanged or hardly changed continence;
b) unchanged or hardly changed stool habit with clearly changed continence;
c) clearly changed stool habit with unchanged or hardly changed continence;
d) clearly changed stool habit with clearly changed continence.

(the scoring system for changes in stool habits and changes in faecal continence is given in paragraphs 3.5.7.2. and 3.5.8.).

Table XIV shows the number of patients in the different subgroups.

Table XIV : patient population divided into the 4 subgroups (a-d) according to changes in stool habits and in faecal continence. These patients had a continence test prior to irradiation.

		Faecal continence	
		Unchanged	Changed
Stool habits	Unchanged	a 38	18 b
	Changed	10 c	32 d

This table shows that there is only a weak correlation between unchanged stool habits and unchanged continence and between changed stool habits and changed continence. The differences were not significant.

The test results for the 4 subgroups were then analysed separately.

4.13.1. Serum bile acid concentrations. No clear difference was observed between the 4 subgroups concerning serum bile acid concentrations either before or after the irradiation.

4.13.2. Faecal bile acid excretion. The number of patients was too small to divide into 4 subgroups.

4.13.3. Faecal weight. As shown in the following tables, no differences were ob-

served in faecal weight between the 4 subgroups either before or after the irradiation. Also, there was no increase in faecal weight for any subgroup after the irradiation.

Table XV: Faecal weight (in grams) before and at 6 months after the irradiation for the four subgroups a-d (median values and interquartile ranges).

Stool weight (grams)

Before irradiation				6 months after irradiation			
a	n = 15	n = 14	b	a	n = 12	n = 12	b
	110 g	140 g			100 g	140 g	
	(70-130)	(90-210)			(80-140)	(90-190)	
	110 g	130 g			90 g	120 g	
	(100-140)	(100-160)			(70-100)	(80-150)	
c	n = 8	n = 23	d	c	n = 7	n = 17	d

4.13.4. Transit time. As shown in the following tables, only slight differences in the median value of the transit time were observed before as well as after the irradiation. No clear change and specifically no decreases in transit time were found for the four subgroups after the irradiation.

Table XVI: Transit time in days before and at 6 months after irradiation for the four subgroups a-d (median values and interquartile ranges).

Transit Time (days)

Before irradiation				6 months after irradiation			
a	n = 14	n = 14	b	a	n = 9	n = 12	b
	1.9	1.5			2.0	1.6	
	(1.5-2.5)	(1.4-2.8)			(1.5-2.4)	(1.2-1.8)	
	1.8	1.6			2.6	1.9	
	(1.5-2.1)	(1.2-2.1)			(1.8-2.8)	(1.8-2.4)	
c	n = 7	n = 22	d	c	n = 4	n = 13	d

4.13.5. Continence test. The median value for the total leaked volume for the four subgroups, a-d are shown in the following table. Apart from a slightly lower median value for group c (n.s.), no differences were observed between the subgroups.

Table XVII: Total leaked volume for the four subgroups a-d (median values and interquartile ranges).

		Faecal continence	
		Unchanged	Changed
Stool habits	Unchanged	a 1110 (660-1275	b 1200 (1095-1380
	Changed	525 (210-1245) c	1005 (360-1305) d

4.14. Relation between acute and "late" effects.

We observed a difference in the acute effects, mean stool frequency and consistency among patients who subsequently experienced "late" effects and those who did not. Fig. 20 shows the change in mean stool frequency during therapy for both groups. Furthermore, 25% of the patients who dit not develop "late" effects dit not notice any change in stool frequency, while in those developing late effects al had an increased stool frequency outside the normal range during the irradiation period. Fig. 21 shows the change in "diarrhea factor" for the two groups. During the first 3 weeks of radiotherapy, a difference in "diarrhea factor" was observed between patients who subsequently experienced "late" effects and those who dit not.

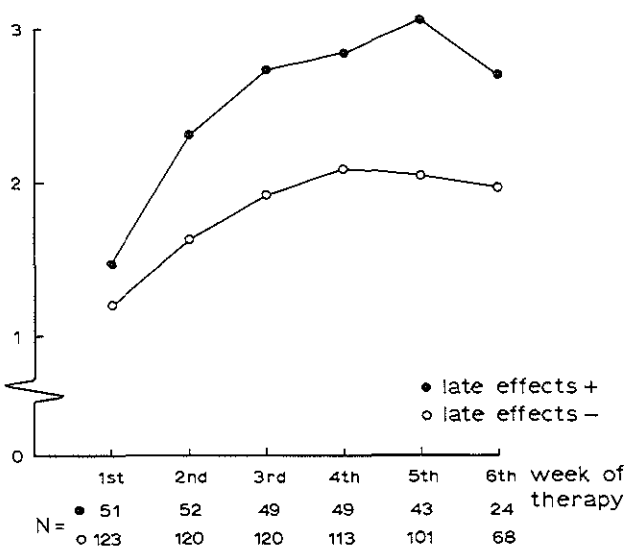


Fig. 20: Changes in stool frequency during radiotherapy, according to the occurrence of "late" effects (+ or –).

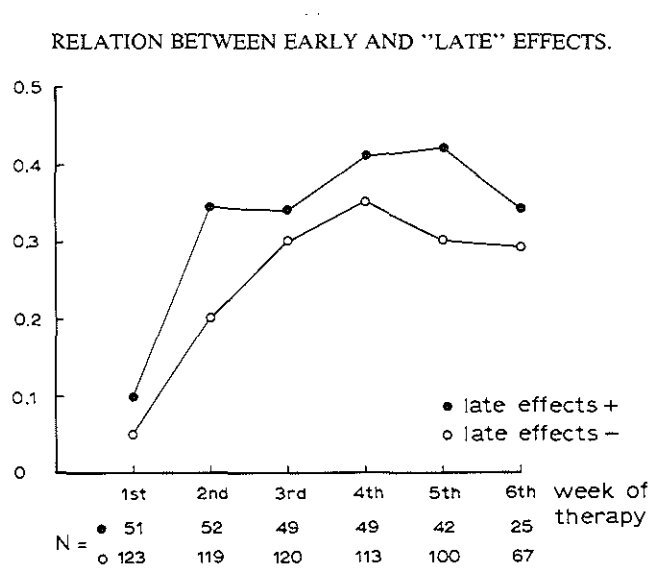


Fig. 21: Changes in "diarrhea factor" during radiotherapy according to the occurrence of "late" effects (+ or –).

CHAPTER V

DISCUSSION

5.1. Introduction.

Radiotherapy of the pelvic region is a generally accepted treatment for malignant tumours of the uterus.
This treatment, however, is not without side-effects. The most important complaints involve the gastrointestinal tract. They include diarrhea, rectal blood loss an faecal incontinence. In a small number of patients, severe complications, mainly fistulas and stenoses will develop.
Apart from these side-effects, urinary tract symptoms arise. However, consideration of these side-effects is beyond the scope of this study.
In the present study one-hundred and ninety-six patients, irradiated for a gynaecological malignancy in the Rotterdamsch Radio-Therapeutisch Instituut were prospectively followed-up in order to elucidate the incidence and pathophysiology of changes in stool habits in relation to the radiotherapy applied.
Such clinical symptoms are usually divided into acute radiation reactions and late effects.
In the literature, late effects are often defined as fistulas and/or stenoses. They sometimes develop after a long latent period, ranging up to several years.
A direct relation between acute and late effects is often denied on a priori grounds in the literature, on the assumption that the mechanism of development of both types of effects is different. Acute effects are thought to be the result of epithelial damage, while late effects would be caused by damage to blood vessels and connective tissue.
In our study, with a limited follow-up time, only four patients with severe late effects (intestinal fistulas, stenoses) were observed. These patients were not analysed separately.
As our study was directed towards the milder syndrome of diarrhea and faecal incontinence, the "late" effects as defined in our study differ fundamentally from the above-mentioned severe complications.

We defined "late" effects as a change in bowel habits. This could be an increase in stool frequency and/or a change in stool consistency as well as faecal incontinence developing or continuing during the follow-up period.

5.2. Radiotherapy factors.

To begin with, we studied the influence of radiotherapy factors on the incidence of acute and "late" effects.
Acoording to the literature, there are several radiotherapy factors that might play a role in the development of these symptoms (Chapter I). A number of these factors was investigated by us:

1) the total delivered dose of external irradiation;
2) the total treatment time;
3) the dose per fraction;
4) the dose rate of the intracavitary irradiation;
5) the combined doses of external and intracavitary irradiation (expressed as Time-Dose-Fractionation (TDF) or Linear-Quadratic (L-Q) number).

The clinical symptoms showed no relation with any of the above-mentioned radiotherapy factors, with the exception of the total delivered dose of external irradiation. When this dose increased, the increase in stool frequency and in "diarrhea factor" was less pronounced. This is contracdictory to what was expected. The explanation might be that the higher doses were given with a different fractionation schedule (smaller dose per fraction, longer total treatment time). However, no significant differences were observed for these other factors. No relation was observed between the total dose and the "late" effects. A possible explanation is that the radiotherapy schedules applied differ only very little, thus great differences in side-effects were not to be expected. Moreover, in the case of *external* irradiation, the differences in total dose, total treatment time and dose per fraction are not independent from each other but interrelated. The reason for this interrelation is that the treatment schedules aim at an equal biological effect. However, the difference in the dose of *intracavitary* irradiation was not dependent on other radiotherapy factors, but only on the diagnosis: patients treated for a carcinoma of the uterine cervix (exclusive radiotherapy) receive a higher dose of intracavitary irradiation than do patients treated postoperatively for a carcinoma of the uterine cervix or of the endometrium. These differences in intracavitary irradiation were not reflected in clinical symptoms in our study. One should bear in mind that, with intracavitary irradiation, the dose gradient (the decrease in radiation dose at increasing distance from the source) is steep. This implies that high doses of radiation are merely limited to small volumes of tissue.

5.3. Patient factors.

If the (small) differences in the radiotherapy applied have no influence on the development of damage, are there perhaps patient-related factors (risk factors) which do have an impact?
According to the literature, there are several risk factors for the development of bowel damage (Chapter I).
These can be divided into two groups, of which the following factors were investigated by us:

A) age;
   height and weight;
   diabetes mellitus;
   possible cardiovascular disease;
B) previous abdominal surgery, especially gynaecological operations, cholecystectomy and gastrointestinal surgery.

The incidence of the clinical symptoms showed no correlation with these factors with the exception of cardiovascular disease where in the precense of this history the increase in "diarrhea factor" was smaller. No relation with the increase in stool frequency was observed. Also obese patients tended to have less acute reactions. No relation between these patient factors and the "late" effects was observed. In the literature, a pre-existent vascular change is assumed to be the underlying cause of these so-called risk factors (A) (7, 14, 15). The syndrome studied by us (acute as well as "late") did not show a correlation with any of these "risk factors", suggesting a pre-existent vascular change did not play a role.
Previous abdominal surgery (B), especially of the pelvic region, would lead to fixed loops of intestine and therefore result in higher doses of radiation to the individual intestinal segments. Postoperative fixations might thus play a role in the development of fistulas and stenoses. In our opinion, the assumption that in patients with previous abdominal surgery the loops of small intestine fixed by postsurgical adhesions would be unable to withdraw themselves from radiation damage, has to be questioned. On X-ray examination of the intestine after administration of a barium meal, a constant position of the intestine with regard to the source was observed during several intracavitary irradiations in patients with and without previous surgery. It is quite possible that radiotherapy itself causes adhesions at an early stage.

The clinical symptoms also showed no relation with the diet history of the patients before the irradiation. In theory the advice given by the dietitian to symptomatic patients could have influenced clinical symptoms. However this advice was only given after the symptoms had been recorded so that this advice is unlikely to have influenced these symptoms.
The test results after the irradiation period may have been influenced by advised or

self prescribed changes in diet. However, this was not studied. In summary, the individual sensitivity of the patients to radiation is a more important factor for the eventual development of radiation damage than the combined doses of external and intracavitary irradiation.
This individual sensitivity, however, was not reflected in the risk factors which we studied.

5.4. Clinical symptoms.

During and after radiotherapy for a gynaecological malignancy, patients often developed diarrhea and faecal incontinence.
To explain these phenomena the following hypothesis was formed:

> Irradiation of the bowel leads to damage of the intestinal mucosa. In the ileum, this will result in impaired bile acid reabsorption, which in turn results in an increased spillover of bile acids into the colon, leading to "cholerheic" diarrhea. This diarrhea, in combination with a pre-existent insufficient continence mechanism, will give rise to the clinical syndrome.

In order to test this hypothesis the following items were investigated before, during and after the irradiation:

1) stool habits (anamnestic);
2) the bile acid concentrations in the serum, fasting and 2 hours after a test meal;
3) the biological half-life of a tracer dose of labeled cholic acid;
4) mean daily faecal weight (collecting period, 4 days);
5) mean intestinal transit time;
6) the ability to retain a rectal infusion of normal saline (continence test according to Read (81), only before the irradiation).

What were the results of these tests and how did they correlate with the clinical symptoms?

5.4.1. Acute reactions.

During the irradiation, about 75% of the patients experienced diarrhea, i.e., watery stools and an increase in stool frequency. This was associated with an increase in mean faecal weight. It is important, however, that the transit time, that is mainly the time of the passage through the colon, remained unchanged. The bile acid concentrations in the serum showed a significant decrease during irradiation. This is in agreement with the shortening of the biological half-life (T/2) of an administered

tracer dose of bile acids (in a subgroup of patients), indicating an increased loss of bile acids due to impaired reabsorption.
A relation was shown to exist between the T/2 and the faecal weight at all sampling times (B, E, P and C), a shorter T/2 being associated with a higher faecal weight.
On first sight, the test results for the entire group of patients seem to be in agreement with our hypothesis that the diarrhea was caused by increased faecal loss of bile acids.
For the group as a whole the median serum bile acid concentrations fell significantly, while the faecal weight and the stool frequency rose.
There was, however, in the individual patient no relation between the magnitude of the fall in bile acid concentration and the increase in faecal weight as well as the most important complaint of the patients, the increase in stool frequency.
This suggested that another factor, probably a local one in the rectosigmoid, caused the changes in stool frequency.
The absence of a clear relation between the loss of bile acids and the stool frequency in the individual patient is in agreement with the results of Stryker (64), who observed an increase in stool frequency without a direct relation with the decrease in cholic acid concentrations in the serum.

5.4.2. "Late" effects.

In the months following irradiation, a substantial number of patients developed or continued to have complaints of diarrhea and of some faecal incontinence. According to their histories, 59/185 patients (30%) experienced these symptoms. Newman (1973) reported a considerably higher percentage of changes in stool habits, 70%, in 17 patients. But, in his relatively small study, several irradiation techniques were used and therefore the study cannot be compared with ours.
No other prospective studies into the incidence of postirradiation diarrhea have been published. Our findings indicate that the evidence of this distressing side-effect is far more frequent than in generally assumed. In our study, we found a distinct relation between the "late" effects and previously experienced acute reactions. All patients who developed "late" effects showed an increased stool frequency during the irradiation. In addition, the mean stool frequency of patients who developed "late" effects was significantly higher than for those whithout "late" effects.

5.5. Intestinal function tests.

Are these symptoms related to changes which we observed in the intestinal function tests?

In the period after the irradiation, the bile acid concentrations in the serum* and the mean faecal weight returned to normal. The transit time remained unchanged, also during the follow-up period, as it did during the acute phase (5.4.1.).
Before going further into the possible relation between the complaints on the one hand and the observed changes in bile acid metabolism on the other, we will first pay attention to the question: How can one explain the recovery of the bile acid concentration in the serum after completion of the irradiation?

Two possible explanations are suggested:

1) The damage to the ileal mucosa is completely repaired. The reabsorption of bile acids is again normal. Subsequently the amount of bile acids presented to the liver also has become normal again and the spillover of bile acids into the colon is reduced to its normal low level. In agreement with this would be the return of the faecal weight to its preirradiation level. Observations to refute this view have not been made by us apart from the shortened biological half-life of cholic acid found 6 months after the irradiation.

2) The damage to the mucous membranes of the ileum is not repaired or incompletely so. In favour of this suggestion is the fact that the biological half-life is still shortened at 6 months after the irradiation, indicating significant bile acid loss. The fact that the bile acid concentration in the serum becomes normal again in spite of this incomplete repair would then have to be explained by an increased bile acid secretion, implicating increased de novo synthesis in the liver. As a result, in spite of a lower rate of reabsorption in the ileum, the ultimate supply by portal venous blood remains the same. Evidently, there will also be increased faecal loss of bile acids. This last phenomenon was not investigated by us, but it was one of the findings in the study of Van Blankenstein (84). The observations that the fasting concentration of bile acids had recovered during the second half of the irradiation period and that the 2-hour postprandial bile acid concentration did not further decrease, plead in favour of an adaptation of bile acid secretion by the liver, by de novo synthesis.

Therefore, the bile acid concentration in the serum after irradiation may reflect a new steady state of the enterohepatic circulation (EHC) on a higher level of secretion by the liver.
The return of the faecal weight to its pretreatment level, however, indicates that the additional loss of bile acids cannot be very great**; for severe loss of bile acids would result in a marked increase in faecal weight.

* An unexplained observation, which we report for the sake of completeness, is that the bile acid concentrations in the serum of patients who developed "late" effects appeared to be (marginally) higher than in patients without "late" effects.

** Possibly, the change in stool consistency can be attributed to a slight increase in faecal bile acids.

In what other way can we determine changes in bile acid metabolism?
A number of investigators used the bile acid breath test for this purpose. With this test, the bacterial degradation of bile acids in the large intestine (sometimes the small intestine) is estimated by means of the exhaled CO_2 labeled with a tracer dose of ^{14}C (par. 2.5.2.3.).
Newman (13) found an abnormal breath test in 16 out of 17 patients after pelvic irradiation, but he did not perform the test before the irradiation. Stryker (63) found that, by the end of the irradiation, one-third of the patients showed an abnormal breath test, which nevertheless recovered in most cases. He did not find a correlation between an abnormal breath test and the stool frequency. A relation between an abnormal breath test and diarrhea during the follow-up period was not reported by him. We did not use the bile acid breath test in our study.
Van Blankenstein (84) studied patients who experienced diarrhea during postirradiation follow-up and found an abnormal bile acid breath test as well as a shortened biological half-life, without, however, the expected marked increase in faecal weight. In our study, we could confirm the shortening of the biological half-life of a tracer dose of cholic acid after irradiation, this shortening only partly recovered. Based on the findings that 1) the bile acid concentrations in the serum recovered in spite of the development of "late" effects and 2) that the faecal weight did not increase, the hypothesis that impaired reabsorption of bile acids is responsible for the "late" effects had to be rejected.

The second part of our hypothesis was that a continence mechanism that was already weak before irradiation, can be demonstrated by the rectal normal saline retention test according to Read (81), would predict the probability of developing faecal incontinence after irradiation. One should bear in mind that Read investigated the mechanism of incontinence in a totally different group of patients. None of these patients had been irradiated previously. Based on our results with Read's test, it appeared to have no predictive value for the development of incontinence in our irradiated patients. Even in patients who experienced watery stool during the follow-up period (regardless whether they were able to retain a saline enema or not). Read's test does not predict whether faecal incontinence will occur after irradiation. The second part of the hypothesis, that a weak sphincter mechanism predicts postirradiation incontinence, also had to be rejected.

On the basis of the observed "late" effects, of a changed or unchanged stool habit and of a changed or unchanged faecal incontinence, the following four subgroups were distinguished:

1) no diarrhea, continent;
2) no diarrhea, incontinent;
3) diarrhea, continent;
4) diarrhea, incontinent.

Contrary to our expectations, no differences between the four subgroups could be demonstrated in either serum bile acid levels, intestinal transit time or continence tests.
This holds for the tests performed at the beginning of the irradiatio as well as at 6 months afterwards. (The continence test was not repeated). Although no difference in bile acid metabolism among the four subgroups could be found, either before or 6 months after the irradiation, the possibility had to be excluded that the test results of the entire group had changed in the course of 6 months. This also did not appear to be the case. In other words, as a number of patients developed diarrhea and incontinence, these complaints arose in spite of unchanged transit time, faecal weight and bile acid concentrations in the serum.
The fact that a number of patients developed diarrhea in spite of a transit time that did not change, seems surprising at first sight. As the small intestinal transit time is short and relatively constant, the transit time is mainly determined by the transit from the coecum to the anus. During transport in the colon two periods can be distinguished. The coecum to sigmoid time and the time that the faeces is stored in the rectosigmoid reservoir. (When the mean stool frequency is once a day, the sigmoid to anus time is maximally 24 hours).
The unchanged transit time can be based on an unchanged coecum-sigmoid time. Although the sigmoid-anus time would also be shortened as a result of an increased stool frequency, this cannot be detected with the collection of the stools in 24-hour portions as applied.
When neither an increased faecal weight (e.g., on account of an increased loss of bile acids) nor a pre-existent insufficient continence mechanism nor a shortened transit time can explain the observed diarrhea and incontinence, what then can be the cause?
Based on the above-mentioned considerations, we think that the cause has to be found in local damage to the rectosigmoid reservoir (Par. 2.8.), by which the capacity to store the faeces for a longer period is lost. This can be accompanied by an imperative urge and faecal incontinence, the latter not being predicted by a continence test. Besides, it is likely that the relaxation of the internal sphincter, which originates by a local and spinal reflex activity when the pressure inside the rectum increases, already occurs at a lower faecal volume, as the compliance of the rectal wall is diminished. This assumption is in agreement with the results of Touchais (82) who showed that the distensibility of the irradiated rectum was decreased.

5.6. Conclusions.

The late effects after pelvic irradiation (diarrhea and incontinence) which we studied,

have to be attributed to an impaired reservoir function of the rectosigmoid due to direct radiation damage.
A relation with the bile acid metabolism and continence test according to Read as studied by us could not be demonstrated.
The "late" effects which we studied were especially seen in the group of patients which showed severe acute rections. The severe late effects (stenoses and fistulas) are exceptional with the radiotherapy schedules applied and cannot be predicted on the basis of the relatively mild, acute and "late" effects that we observed.

SUMMARY

Radiotherapy can be applied in two ways:
1) by external beam irradiation;
2) by intracavitary or interstitial irradiation.
For the irradiation of a gynaecological tumour the combination of the two is used. With external irradiation by orthovoltage machines, the dose which can be given is limited by damage to the skin. When orthovoltage therapy was replaced by megavoltage therapy, skin damage was no longer a limiting factor. It thus became possible to deliver an adequate dose to deep-seated tumours. At the same time, it was possible to irradiate larger volumes. Formerly, only the parametria were irradiated; now, it became possible to include the regional lymph nodes. This led to the possibility that damage to other organs, e.g., the intestine became the dose limiting factor. Intracavitary irradiation with radioactive sources has also played an important role, especially in the irradiation of malignant tumours of the uterus. Of importance is the steep dose gradient, which means the rapidly decreasing radiation density at increasing distance from the sources, around these intracavitary sources. This results in an inhomogeneous dose distribution within the target volume and may lead to locally high doses of absorbed radiation in normal tissues situated within this target volume. The serious complications such as stenoses and fistulas as described in the literature are mainly the results of these local high doses. The incidence of these serious complications is relatively low, 5-10%, with modern radiotherapy. A prospective study of these serious complications will therefore only be possible with a large number of patients. Yet, to get an impression of the undesirable side-effects, we performed a prospective study into other signs of intestinal damage, namely, a change in stool habits, as this is more frequently observed after "gynaecological" irradiation.

In Chapter I, following a general introduction, the risk factors mentioned in the literature are reviewed. A distinction can be made between patient factors and therapy factors. Patient factors are assumed to be based on pre-existent vascular changes and fixed intestinal loops after previous abdominal surgery. Therapy factors are the

characteristics of the irradiation, such as fractionation schedule, irradiation technique and radiation dose.

In Chapter II, the changes in bowel function after irradiation are reviewed. First, a historic review is given; then, the changes in histopathology and function, followed by a discussion of the symptoms of this intestinal damage. The main symptoms are diarrhea and faecal incontinence. Several investigators have pointed out the role that the bile acid metabolism could play in the occurrence of this irradiation diarrhea.
In the second part of Chapter II, this bile acid metabolism is further explained: The enterohepatic circulation (EHC) of bile acids is very efficient under physiological circumstances. Only a small part of the bile acids is lost by the faecal route. The liver clears almost all bile acids presented to it by portal venous blood; only a very small fraction will pass and is detectable in the peripheral blood serum. The different methods for studying the EHC of bile acids are described. The pathophysiology of an interrupted EHC of bile acids is then reviewed. If bile acids are not reabsorbed by the terminal ileum, they reach the colon where they can cause diarrhea. An interruption of the EHC as a result of radaition damage might play a role in the symptoms.

The study design is discussed in Chapter III.
The working hypothesis consisted of two parts:
1) Irradiation on the pelvic region leads to damage of the ileal mucosa which results in an interruption of the EHC of bile acids. The following increased spillover of bile acids into the colon induces water and NaCl secretion by the colonic mucosa. This is expressed as diarrhea.
2) There existed a pre-existent insufficient continence mechanism, which could be demonstrated by means of a rectal retention test with saline according to Read.

The combination of these two phenomena was assumed to be the cause of the clinical symptoms of diarrhea and faecal incontinence after pelvic irradiation. This hypothesis was tested in a group of patients who were irradiated for a malignant tumour of the uterus. The irradiation was given as the only treatment modality or as a supplement following surgery.
Before, during and after the irradiation, several tests were performed, viz., bile acid concentrations in the serum, biological half-life of a radioactively labeled tracer dose of cholic acid, mean faecal weight, intestinal transit time and a continence test (the continence test only before the irradiation). In addition, the nature and frequency of the bowel motions were recorded: daily during the irradiation and at every visit during the follow-up period.

In the second part of Chapter III, the methods of irradiation and the performance of the tests are discussed.

The results of the study are discussed in Chapter IV. During the irradiation, a decrease in bile acid concentrations in the blood serum occured. The biological half-life was also shortened. Both phenomena suggest the loss of bile acids. At the same time, the mean faecal weight increased. The intestinal transit time, however, appeared not to change. The stool frequency increased and the stools became watery. This seems in agreement with our working hypothesis that spillover of bile acids is responsible for the diarrhea. After the irradiation, the bile acid concentrations in the serum and the mean faecal weight recovered. The biological half-life of bile acids, however, remains shortened after an initial recovery. The transit time remained unchanged, also during the follow-up period. The diarrhea during the irradiation subsided in most of the patients. Still, in about 30% of the patients, a changed stool habit persisted or developed during the follow-up period.
If a smaller group of patients was investigated by means of a questionnaire, even 50% appeared to be less capable of retaining their faeces than before.

Discussion and Conclusions are given in Chapter V. The fact that no dose-effect relationship was found between the dose of radiation applied and the incidence and the severity of the observed clinical symptoms can be explained by the small spread in external radiation dose applied. The difference in intracavitary irradiation also did not influence the development of the clinical symptoms. Probably, the individual sensitivity to radiation is more important than the small differences in radiation doses. The "risk factors" mentioned in the literature also appeared to have no influence on the development of the clinical symptoms.
Although within the narrow margins of modern radiotherapy, neither the differences in external, nor in intracavitary doses of radiation appeared to have influence on the development of the symptoms and although the symptoms did not correlate with any of the so-called patient factors, the fact remains that a considerable number of patients did complain about changes in stool habits and/or incontinence after the irradiation. In view of the demonstrated changes in bile acid metabolism after irradiation, we investigated whether these changes might be the cause of the diarrhea or at least demonstrate a statistical correlation therewith.

Between the groups who did or did not develop these complaints, no differences in bile acid concentrations in the serum, mean faecal weight or transit time could be demonstrated either before or at 6 months after the irradiation. Also, there was no significant change in the test results at 6 months after the irradiation.
The incapacity to retain a considerable amount of 0.9% NaCl in the rectum during

the continence test according to Read, did not appear to be predictive for the development of faecal incontinence during the follow-up period.
Consequently, the hypothesis that diarrhea and incontinence after irradiation are the results of a combination of impaired reabsorption of bile acids in the small intestine and a weak "sphincter mechanism" had to be rejected. The observed changes in bile acid metabolism as a result of the irradiation (decreased bile acid concentrations in the serum and a shortened biological half-life) have to be explained by damage to the ileal mucosa during the irradiation, followed by a partial recovery. Adaptation of the bile acid secretion by the liver, especially as a result of increased de novo synthesis, explains the recovery of the bile acid concentrations in the serum in spite of accelerated loss by the intestine. The unchanged transit time seems surprising at first sight. However, the transit time is determined *mainly* by the coecum-anus time. With a coecum-sigmoid time which remained the same, an eventual shortening of the sigmoid-anus time could be easily unnoticed in our study, as the collection of the stools (and the administered markers) took place in 24-hour portions. Based on our study, we have to conclude that the bowel complaints of patients after "gynaecological" pelvic irradiation are caused by an impaired capacity for retention of faeces of the "rectosigmoid reservoir" as a direct result of the irradiation. Therefore, an in itself not increased amount of faeces is excreted in several portions. This is accompanied by imperative urge, leading to faecal incontinence.

SAMENVATTING

Radiotherapie kan op 2 wijzen toegediend worden:
a) door uitwendige bestraling of
b) door inwendige bestraling.
Voor de bestraling van gynaecologische tumoren wordt de combinatie van beide gebruikt.
Bij uitwendige bestraling met orthovoltapparatuur wordt de dosis die kan worden toegediend beperkt door beschadiging van de huid. Bij overgang van ortho- naar megavolttherapie was schade van de huid geen beperkende faktor meer. Het werd dus mogelijk op dieper gelegen tumoren een adequate bestralingsdosis toe te dienen. Tevens werd het mogelijk, grotere volumina te bestralen. Werden voorheen alleen de parametria bestraald, nu konden ook de regionale lymfklierstations meebestraald worden. Dit leidde ertoe, dat mogelijke schade aan andere organen o.a. de darm de dosislimiterende faktor werd.
Inwendige bestraling met radioaktieve bronnen heeft eveneens een belangrijke plaats, met name bij bestraling van kwaadaardige gezwellen van de baarmoeder. Van belang hierbij is de steile dosisgradiënt rondom deze inwendige bronnen, d.w.z. dat de stralendichtheid snel afneemt bij toenemende afstand van de bronnen. Dit leidt tot inhomogene dosisverdeling binnen het "doelvolume" en kan aanleiding zijn tot plaatselijke absorptie van hoge doses straling in "normale" weefsels, indien deze binnen het "doelvolume" gelegen zijn.
De in de literatuur beschreven ernstige complicaties zoals stenosen en fistels, zijn voornamelijk het gevolg van deze lokale hoge doses. Het vóórkomen van deze ernstige complicaties is met moderne radiotherapie betrekkelijk zeldzaam, 5-10%. Een prospectieve studie van deze ernstige complicaties is dan ook slechts mogelijk met grote aantallen patiënten. Om toch een indruk te krijgen van ongewenste bijwerkingen, verrichtten wij een prospectief onderzoek naar andere tekenen van beschadiging van de darm, namelijk een verandering in het defaecatiepatroon, daar dit na "gynaecologische" bestralingen frequent is.

In Hoofdstuk I worden na een algemene inleiding de in de literatuur genoemde risico-

faktoren voor het ontstaan van ernstige darmschade besproken. Een onderscheid kan gemaakt worden tussen patiëntenfaktoren en therapiefaktoren. Patiëntenfaktoren worden verondersteld te berusten op pré-existente vaatafwijkingen en op gefixeerde darmlissen na voorafgaande buikoperaties.
Therapiefaktoren zijn de kenmerken van de bestraling, zoals fractioneringsschema, bestralingstechniek en bestralingsdosis.

In Hoofdstuk II worden de veranderingen in darmfunktie na bestraling besproken. Allereerst wordt een historisch overzicht gegeven, vervolgens worden de histopathologische en funktionele veranderingen beschreven, gevolgd door een bespreking van de symptomen van deze darmbeschadiging. De voornaamste symptomen zijn diarrhee en incontinentie voor ontlasting. Verschillende onderzoekers hebben gewezen op de rol die het galzuurmetabolisme bij het ontstaan van deze bestralingsdiarrhee zou kunnen spelen.
In het tweede gedeelte van hoofdstuk II wordt dit galzuurmetabolisme nader uiteengezet: De enterohepatische cyclus (EHC) van galzuren is onder fysiologische omstandigheden zeer efficiënt. Slechts een klein gedeelte van de galzuren gaat langs faecale weg verloren. De lever neemt vrijwel alle galzuren uit het aangeboden poortaderbloed op; slechts een zeer kleine fractie wordt "doorgelaten" en is dan aantoonbaar in het perifere bloedserum. De verschillende methoden om de EHC van galzuren te bestuderen worden aangegeven.
Vervolgens wordt de pathofysiologie van een onderbroken EHC van galzuren besproken. Als galzuren door het terminale ileum niet worden gereabsorbeerd, komen ze in het colon waar ze diarrhee kunnen veroorzaken. Een onderbreking van de EHC ten gevolge van stralenschade van het ileum zou een rol bij de symptomen kunnen spelen.

In Hoofdstuk III wordt de opzet van ons onderzoek besproken.
De werkhypothese bestond uit twee gedeelten en luidde:
a) bestraling van het bekkengebied leidt tot beschadiging van het ileumslijmvlies met als gevolg een onderbreking van de EHC van galzuren. De hieruit volgende vergrote galzuuroverloop naar het colon wekt water en NaCl secretie van het colonslijmvlies op. Dit uit zich als diarrhee.

De tweede component van onze hypothese was:
b) het bestaan van een pré-existent onvoldoende "continentiemechanisme", dat d.m.v. een rectale retentietest met fysiologische zoutoplossing volgens Read aangetoond zou kunnen worden.

De combinatie van deze twee componenten werd verondersteld na bekkenbestraling het klinische syndroom van diarrhee en incontinentie voor ontlasting te veroorzaken. Deze hypothese werd getoetst op een groep patiënten die bestraald werden

i.v.m. een kwaadaardig gezwel van de baarmoeder. Deze bestraling werd deels als enige behandelingsmodaliteit of bij andere patiënten als aanvulling na operatie toegediend.
Voorafgaande aan, tijdens en na de bestraling werden verschillende tests uitgevoerd, te weten serum galzuurconcentraties, biologische halfwaardetijd van een radioactief gelabelde tracerdosis galzuur, gemiddeld ontlastinggewicht en passagetijd door de darm, alsmede een continentietest (deze laatste alleen vóór de bestraling).
Verder werden aard en frequentie van de defaecatie genoteerd; tijdens de bestraling dagelijks, gedurende de follow-up periode bij ieder controlebezoek. In het tweede gedeelte van hoofdstuk III worden de methoden van de bestraling en de uitvoering van de tests besproken.

In Hoofdstuk IV worden de resultaten van het onderzoek besproken.
Tijdens de bestraling treedt een daling van de galzuurconcentraties in het bloedserum op. Bovendien blijkt dat de biologische halfwaardetijd van de galzuren is verkort. Beide verschijnselen wijzen op verlies van galzuren. Tevens is er een toename van het gemiddelde ontlastinggewicht. De passagetijd door de darm blijkt echter niet te veranderen. De defaecatiefrequentie neemt toe en de ontlasting wordt dunner. Dit lijkt in overeenstemming met onze werkhypothese dat galzuuroverloop voor de diarrhee verantwoordelijk is. Na de bestraling herstellen de serum galzuurconcentraties en het gemiddelde ontlastinggewicht zich. De biologische halfwaardetijd van galzuren blijft echter na een initieel herstel verkort. De passagetijd daarentegen blijft ongewijzigd, ook in de follow-up periode.
De diarrhee tijdens de bestraling verdwijnt bij het merendeel van de patiënten. Toch houdt of ontwikkelt van de gehele groep patiënten circa 30% gedurende de follow-up een veranderd ontlastingpatroon.
Indien men echter een kleinere groep via een gerichte enquête ondervraagt, blijkt dat zelfs 50% de ontlasting minder goed op kan houden dan voorheen.

Discussie en conclusies worden weergegeven in Hoofdstuk V.
Het feit dat geen dosis-effekt relatie tussen de toegediende dosis röntgenstraling en de incidentie zowel als de ernst van de gevonden klinische verschijnselen bestond, kan verklaard worden door de geringe spreiding in de dosis stralen die uitwendig werd toegepast. Ook het verschil in inwendige bestraling bleek niet van invloed op het al dan niet ontstaan van de klinische verschijnselen. Blijkbaar is de individuele stralingsgevoeligheid belangrijker dan de geringe verschillen in bestralingsdosering. De in de literatuur vermelde "risicofaktoren" bleken evenmin van invloed op het ontstaan van de klinische verschijnselen.

Hoewel binnen de nauwe marges van de moderne radiotherapie verschillen in uit-

noch inwendige stralendoses van invloed bleken op het al dan niet ontstaan van symptomen en hoewel de symptomen met geen der zogenaamde "patiëntenfaktoren" correleerden, doet zich toch het feit voor dat een aanzienlijk aantal patiënten na de bestraling klachten krijgt en wel verandering van het ontlastingpatroon en/of incontinentie. Gezien de aangetoonde veranderingen in de galzuurstofwisseling na bestraling hebben wij onderzocht of deze veranderingen wellicht de oorzaak van de diarrhee zouden kunnen zijn, althans daarmee een statistische correlatie zouden vertonen.

Tussen de groepen die wel of niet deze klachten ontwikkelden kon een verschil in serum galzuurconcentraties, gemiddeld ontlastinggewicht of passagetijd niet worden aangetoond, noch voorafgaand aan de bestraling, noch op het tijdstip 6 maanden na de bestraling.

Evenmin bleek er 6 maanden na de bestraling een significante verandering in de resultaten van deze tests te zijn opgetreden.

Een onvermogen om tijdens de continentietest volgens Read een flinke hoeveelheid, 0.9% NaCl, in het rectum vast te houden bleek niet voorspellend voor het al of niet ontstaan van incontinentie voor ontlasting in de follow-up periode. Derhalve diende de hypothese dat diarrhee en incontinentie na bestraling een gevolg zijn van de combinatie van verminderde reabsorptie van galzuren in de dunne darm met een zwak "sfinctermechanisme" verworpen te worden. De aangetoonde veranderingen in het galzuurmetabolisme als gevolg van de bestraling (verlaagde serum galzuurconcentraties en verkorte biologische halfwaardetijd), moeten verklaard worden door beschadiging van het ileumslijmvlies tijdens de bestraling, gevolgd door een partieel herstel.

Aanpassing van de galzuur secretie door de lever, met name als gevolg van verhoogde de novo synthese, verklaart dan het herstel van de galzuurconcentratie in het serum, ondanks versneld verlies via de darm. De onveranderde passagetijd lijkt op het eerste gezich verrassend. De passagetijd wordt echter voornamelijk bepaald door de coecum-anus tijd. Bij een gelijk blijvende coecum-sigmoïd tijd kon in ons onderzoek een eventuele verkorting in sigmoïd-anus tijd echter gemakkelijk onopgemerkt blijven, aangezien de verzameling van de ontlasting (en van de toegediende "markers") in porties van 24 uur plaatsvond. Op basis van ons onderzoek moet worden geconcludeerd dat de darmklachten van patiënten na "gynaecologische" bekkenbestraling veroorzaakt worden door een verminderde opslagcapaciteit voor faeces van het "rectosigmoïd reservoir" als direkt gevolg van de bestraling.

Hierdoor moet een op zichzelf niet toegenomen hoeveelheid ontlasting, over meerdere porties verdeeld, uitgescheiden worden. Dit gaat gepaard met imperatieve drang, leidend tot incontinentie voor ontlasting.

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APPENDIX I

TDF formulas (according to Turesson and Notter, 67).
For a course of frationated external irradiation:

$$TDF = T^{-0.169} \times (d.100)^{1.538} \times N.10^{-3}$$

For intracavitary irradiation at low dose rate:

$$TDF = 2.02. (r \times 100)^{1.35} T.10^{-3}$$

In these formulas, the symbols used stand for:

T = total treatment time of a course of external or intracavitary irradiation (in days).
N = the number of fractions
d = the dose per fraction (in Gy)
r = the dose rate (in Gy/24 hr.).

The acute doses at high dose rate were converted according to the monogram of Shuttleworth and Fowler (35) into a number of fractions of 2.0 Gy and then a TDFvalue for these fractions was calculated.

L-Q formulas.

For the calculation of the L-Q value two factors are of importance: the tolerance dose and the choice of the α_1 / α_2 value. As tolerance dose, we have arbitrarily chosen 35 x 2.0 Gy for fractionated external irradiation and 65 Gy in 7 days for low dose rate continuous irradiation.
The α_1 / α_2 ratio was based on the results of Barendsen (68) and Kal (69), namely, 10 for early and 2.5 for late effects. The following formulas were used for the calculation of the L-Q percentage:

$$D\ (tol) = \frac{ETD}{RE} \text{ and } RE = 1 + \frac{d}{\alpha_1 / \alpha_2} \quad \text{for fractionated external irradiation}$$

$$\text{resp. } RE = 1 + \frac{2 \times r}{\alpha_1 / \alpha_2} \quad \text{for low dose rate intracavitary irradiation}$$

D = the dose per fraction (Gy)
r = the dose rate (Gy/hr)

APPENDIX II

	Beginning of the radiotherapy course	Midway	End	6 weeks after completion of the radiotherapy	6 months after
Serum bile acids	x	x	x	x	x
Faecal excr. of labeled bile acids	x	—	x	x	x
Total daily faecal weight	x	—	x	x	x
Transit time	x	—	x	x	x
Continence test	x	—	—	—	—
Diet history	x	—	—	—	—

Time schedule for the different tests for intestinal function.

APPENDIX III

Scoring system for the diet history.

Protein	1 = 1 g/kg body weight ± 10%
	2 = < 10%
	3 = > 50%
Fat	1 = 30% - 35%
	2 = < 30%
	3 = > 35%
Carbohydrates	1 = > 150 g - < 60 cal.%
	2 = < 150 g
	3 = > 60 cal. %
Vitamins	1 = normal
	2 = < 15%
Minerals	
Fe	1 = normal
	2 = < 10 mg
Ca	1 = normal
	2 = < 800 mg
Free sugar	1 = 20 - 25 g
	3 = > 25 g
Fibres	1 = 3 slices of brown bread + 1 portion of vegetables + 1 portion of fruit
	2 = < 1
	3 = > 1

Milk 1 = ¼ - ½ l
2 = < ¼ l
3 = ½ l or >

1 = norm
2 = lower
3 = higher

APPENDIX IV

QUESTIONS CONCERNING THE DEFEACATION PATTERN

1. How often do you have a bowel movement?
   a) not every day
   b) once each day
   c) twice each day
   d) more times per day

2. Is it normal for you to have 5 or more bowel movements per day?
   a) yes
   b) no

3. Is this
   a) less often
   b) as often
   c) more often
   than before you were irradiated?

4. Are you sometimes troubled by abdominal cramps?
   a) yes
   b) no

5. If you have answered "yes" to the above, how often do you have trouble and are there perhaps circumstances which cause the abdominal cramps?

6. Did you have troubles with abdominal cramps before you were irradiated?
   a) yes
   b) no

7. What is the nature of the stool?
   a) hard/marble-like
   b) normal/thick/well-formed
   c) pulpy
   d) liquid/waterthin

8. As compared with your stools before the irradiation, is your bowel movement now:
   a) harder
   b) not changed
   c) pulpy, but varying
   d) continuous diarrhea

9. Can you postpone your bowel movements?
   a) yes, under all circumstances
   b) yes, with difficulty
   c) I must always rush to the toilet
   d) I am unable to postpone it

10. Has your capacity to postpone defecation
    a) improved
    b) worsened
    after the irradiation?

APPENDIX V

	MEDIAN VALUES AND INTERQUARTILE RANGES		
	Fasting	Postprandial	p.p.i.
B	2.25	4.99	2.5
	1.5-3.4	3.5-6.9	1.1-4.2
H	2.11	4.10	1.7
	1.4-3.0	3.0-5.2	0.9-2.9
E	2.35	4.19	1.5
	1.7-3.4	3.0-5.5	0.4-2.8
P	2.71	4.93	2.1
	1.7-3.9	3.7-6.3	1.1-3.4
C	2.65	4.75	1.6
	1.9-4.2	3.4-6.6	0.3-3.5

Serial serum bile acid levels during pelvic radiotherapy. Fasting, 2-hour postprandial and postprandial increase (p.p.i.) at different times during and after irradiation.
(B = before RT; H = midway RT; E = end RT; P = 6 weeks after RT; C = 6 months after RT).

APPENDIX VI

	DIET HISTORY (n = 155)		
Score	Norm	Lower	Higher
Protein	123	32	—
Fat	26	3	126
Carbohydrates	127	28	—
Vitamins	59	96	—
Minerals	62	93	—
Free sugars	40	—	115
Fibres	41	72	—
Milk	41	113	1

Results of the food analysis as obtained by scoring of the diet history prior to the start of radiotherapy. The number of patients in each scoring group for all food components are given.
(For scoring system, see Appendix III).

APPENDIX VII

Total leaked volume (ml)	FAECAL CONTINENCE SCORES (0 = no problems, 4 = incontinence)				
	0	1	2	3	4
0 - 300	6	5	4	3	1
300 - 600	1	1	1	2	
600 - 900	2	1	1	2	1
900 - 1200	10	1	6	4	2
1200 - 1500	12	2	5	4	7

The relation between the faecal continence score as reported in the questionnaire (appendix IV) in patients compared to the total leaked volume during the rectal retention test according to Read (81) performed before irradiation. A small leaked volume indicates good continence. The number of patients for each combination of test result and continence score is given. No relation between the test results and the reported faecal continence during follow-up was found.

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Still round the corner there may wait
A new road or a secret gate;
And though I oft have passed them by
A day will come at last when I
Shall take the hidden paths that run
West of the Moon, East of the Sun.

Maar om de hoek wacht ons misschien
Een weg, een poort nog nooit gezien
Hoewel 'k er vaak langs ben gegaan
Komt eens de dag dat ik zal gaan
Verborgen paden, ondoorgrond
Die lopen tussen Maan en Zon.

J.R.R. Tolkien
(uit "the lord of
the rings").

CURRICULUM VITAE

Jacobus Henricus Meerwaldt werd op 11 januari 1946 geboren te Rotterdam. In 1963 behaalde hij zijn HBS-B diploma en begon met de studie van de geneeskunde aan de Rijksuniversiteit te Utrecht.
Na het artsexamen in 1970 was hij gedurende acht jaar werkzaam als huisarts te Rotterdam (Pernis).
In 1978 begon hij zijn opleiding tot radiotherapeut aan het Rotterdamsch Radio-Therapeutisch Instituut onder leiding van Prof. Dr. B.H.P. van der Werf-Messing.
Na voltooing van de opleiding is hij sinds 1 november 1982 ingeschreven in het specialistenregister als radiotherapeut en werkzaam in het Rotterdamsch Radio-Therapeutisch Instituut/Dr. Daniël den Hoed Kliniek.