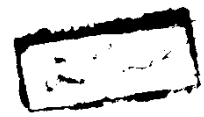
The Pathogenesis of Local Recurrence Following Resection for Colorectal Cancer

THESIS

submitted for partial fulfilment of
the M.D. degree in General Surgery



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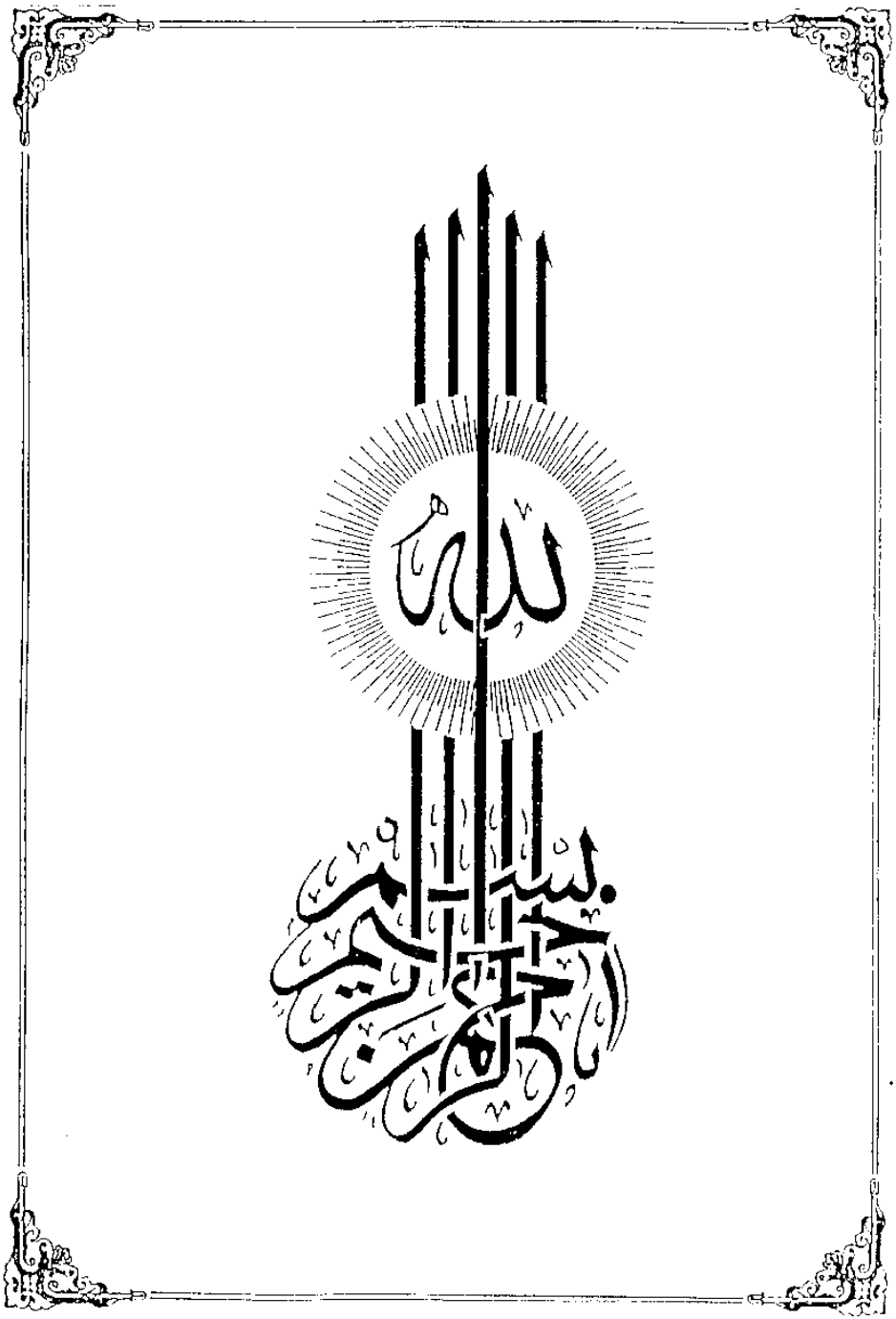

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INTRODUCTION

The morbidity of malignant tumours of the colon and rectum leads the cancer patient registries in many countries. Moreover, colorectal cancer is one of the leading causes of cancer deaths as it ranks second only to lung cancer as a cause of death from malignant disease in these same countries. In Egypt, the incidence of colorectal cancer is rising over the years and Egypt has the highest incidence of this disease among the Middle East countries. (Mehriz, 1958). Moreover, intestinal bilharziasis, a national health problem in Egypt, has been recently shown to be associated with colorectal cancer in a high proportion of patients (Hamdy et al., 1990).

Many patients who die from cancer of the large bowel have previously undergone what was hoped to have been a curative resection, only to return with lethal recurrent or metastatic disease. Some patients in whom surgical cure has been successful will later develop a second, metachronous cancer elsewhere in their large bowel.

Local recurrence is a major cause of morbidity and mortality following surgery for large bowel cancer. The reported incidence is variable but its average figure is around 14% (Phillips et al., 1984 a). Around 80% of cases present within the first 2 years of operation and for the

majority of patients no further curative surgical intervention is feasible (Stulc et al., 1986). There is strong evidence to implicate one or more of the following possible causes in the pathogenesis of local recurrence after curative resection of colorectal cancer:

1. Inadequate tumour resection either in the longitudinal plane or in the radial plane of the bowel.
2. Implantation of viable tumour cells on raw areas or serosal surfaces to regrow and cause local recurrence.
3. Inherent abnormality of the large bowel mucosa that renders it susceptible to the development of tumours. This may result in the formation of synchronous or metachronous tumours or recurrence in the suture line of large bowel anastomosis.

The results of therapy of patients with large bowel cancer did not show any noticeable improvement in the last few decades for which insufficient knowledge of the pathogenesis of the disease is partly responsible. Studies of the pathogenesis of colorectal cancer and the factors modifying it is difficult in humans because of ethical reasons. This situation calls for carrying out experimental animal studies on the pathogenesis of tumour growth. The solution to this problem would facilitate the elaboration of measures for prevention and early diagnosis of

intestinal tumours. Thus an animal model for colorectal cancer is an important part in the armamentarium of colorectal cancer researchers.

While some forms of cancer occur spontaneously in animals, it is known that neoplasms of the intestinal tract are rare, especially in rodents (Lingeman and Garner, 1972). Numerous attempts have been made to induce tumours of the large intestine in experimental animals. In recent years a number of chemical carcinogens have been discovered which provide investigators with a reasonably accurate animal model of human colorectal cancer. These compounds when administered to rodents produce benign and malignant neoplasms of the colon and rectum which are similar to their human counterpart in many respects. They provide the opportunity to study under controlled laboratory conditions the induction of colorectal cancer, and the effect of manipulations of the immune system, diet, gut bacteria and other factors on tumour production.

AIMS OF THE WORK

1. Taking into consideration the frequency of local failure as a mode of recurrence of colorectal cancer after presumed curative resection, and the different theories suggested for the pathogenesis of this type of recurrence, the first aim of this work is the exploration of some factors that might be of significance in the aetiology of local recurrence of colorectal cancer after curative resection. The factors studied are patients' age and sex, site of primary tumour, presence of intestinal obstruction, tumour mobility, Dukes' stage, tumour grade, presence of synchronous polyps, blood vessel invasion, effect of blood transfusion and postoperative sepsis.

2. Taking into consideration the usefulness of experimental animals in exploring unknown areas of cancer research, the second aim of this work is to explore the validity of the hypothesis of the presence of an area of unstable large bowel mucosa around the suture line of anastomosis that predisposes this area in particular to metachronous carcinogenesis as a result of the action of a yet unidentified carcinogen, that is possibly present in the human faeces. This metachronous cancer later appears as suture line recurrence. This experiment will be done in the DMH colorectal cancer rat model.

HISTORY OF SURGICAL TREATMENT OF CARCINOMA OF THE RECTUM AND COLON

Colorectal surgery, as a speciality, parallels the development of surgery in general. The ancient Egyptians, Greeks, Romans, Byzantines and Arabs, all treated and wrote about different conditions of the gut and anus. They were mainly concerned with anorectal disorders such as haemorrhoids (sometimes called condylomata), perianal fistulae and perianal abscesses and wounds of the intestine (Graney and Graney, 1980). In the fourteenth century John of Arderne an English surgeon who followed teachings of Arab surgeons wrote a classic description of cancer of the rectum as follows:-

> "Bubo is an apostem breeding within the anus in the rectum with great hardness but little aching. This I say, before it ulcerates, is nothing else than a hidden cancer, that may not in the beginning of it be known by the sight of the eye, for it is all hidden within the rectum, and therefore it is called bubo, for as bubo; i.e. an owl, is always dwelling in hiding so

that this sickness lurkes within the rectum in the beginning, but after passage of time it ulcerates, and, eroding the anus, comes out. And often it erodes and wastes all of the circumference of it so that it may never be cured with man's cure. But if it pleases God, that made man out of nothing, to help with his unspeakable virtue; which, forsooth, is known thus: the leech put his finger into the anus of the patient, and if he finds within the anus a thing hard as a stone, sometimes on one side only, sometimes on both, so that it permits the patient to have egestion, it is bubo [cancer] for certain. Signs, forsooth, of ulceration are these: the patient cannot abstain from going to the privy because of aching and pricking and that twice or thrice within one hour; and he passes a stinking discharge mixed with watery blood.

Ignorant leeches will assure the patient, that he has dysentery, that is, the bloody flux, when truly it is not.

I never saw nor heard of any man that was cured of cancer of the rectum, but I have known many that died of the foresaid sickness" (Zimmerman and Veith, 1961).

Development of surgical treatment for rectal cancer

The first to propose surgery for cancer of the rectum was Morgagni (1689-1771) in the eighteenth century. He also described the crypts and columns which still bear his name (Graney and Graney, 1980). Fajet was the first to perform an operation for rectal cancer in 1739. It was a very limited extraperitoneal excision of the rectum done entirely via the perineal route and was known as posterior resection (Goligher, 1984). However the first successful posterior resection was done by Jacques Lisfranc, a surgeon of La Pitié Hospital in Paris, in 1826. Pinault, a student of Lisfranc, published a thesis in 1829 reporting 9 cases (Meade, 1968). This operation was inadequate leaving an uncontrolable sacral anus (Rankin, 1937). According to Mettler (1947) although these operations were spoken of as rectal removals, they were really only anal excisions with more or less of the lower end of the rectum taken out and were still only palliative and not curative procedures. Theodore Billroth, the father of visceral surgery, continued to perform the operation of posterior resection in the second half of the nineteenth century (Meade, 1968). Verneuil in 1873 revived interest in the resection of the rectum for carcinoma and he modified Lisfranc procedure by adding excision of the coccyx to improve exposure (Graney and Graney, 1980). Theodore Kocher, a Swiss surgeon, in

1875 and 1876 began to close the anus with a purse string suture at the beginning of the operation to prevent contamination and he used also to excise a portion of the sacrum as well as the coccyx to make the operation more radical (Graney and Graney, 1980). Paul Kraske described his operation of sacral excision of the rectum in front of the Fourteenth Congress of the Deutsche Gesellschaft für Chirurgie in 1885, and with his name it has ever since been associated (Goligher, 1984). This operation and minor modifications by Hochenegg, Badenhauer, Levy and Rydygier were popular into the twentieth century (Graney and Graney, 1980). Vincent Czerny in 1883, finding that he could not complete a resection of the rectum by the sacral route, turned the patient over and completed the operation abdominally, thus introducing for the first time, not as a premeditated plan, the abdominoperineal operation which was to be developed and perfected by W.E. Miles of London in the early part of the twentieth century (Rankin, 1937). Miles operation was introduced in 1907. It was the first proper radical operation for rectal carcinoma and is still performed nowadays. However, when it was first performed, the immediate mortality rate was 36.2%. Because of this high mortality, abdominoperineal excision was only very slowly adopted by surgeons in general, and not till late 1930's was it all widely used (Goligher, 1984). Following

the work of many investigators who showed that the lymphatic spread of rectal cancer is mainly in an upward direction, a natural trend was to think about sphincter saving resections. Many operations for excision of rectal cancer while preserving the sphincters are known, the most famous that are used now are the standard anterior resection, also known as the Mayo Clinic operation or Dixon's operation, the Hartmann's operation, the Turnbull-Cutait abdominoanal pullthrough resection, the Parks' abdominotransanal resection with endocavitary sutured coloanal anastomosis, the abdominosacral resection of Localio and the abdominotrans-sphincteric resection of Mason. Recently, there is a new trend towards local removal or destruction of primary rectal tumours. Many methods are available and they are suitable only for rectal cancer that fulfills certain known criteria (Goligher, 1984).

Development of surgical treatment for cancer of the colon:

Development of surgical treatment for carcinoma of the colon followed quite a different course. Throughout the centuries, physicians acquired considerable knowledge of colostomies from observation of the fistulae caused by trauma or disease. However, the medical profession was unquestionably preceded by our veterinary colleagues in the performance of this operation since the latter are recorded