BENEFICIAL EFFECTS OF ACUTE BACTERIAL INFECTIONS OR BACTERIAL TOXIN THERAPY ON CANCER OF THE COLON OR RECTUM

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INTRODUCTION

Carcinoma of the colon and rectum has now reached an incidence of over 70,000 cases a year in the United States — a higher incidence than any other site. Sixty-five per cent of the women and 70 per cent of the men with these cancers die within five years. These over-all five year survival rates have remained constant for over 25 years, with few exceptions*. As Fletcher has pointed out, these statistics are a sobering reminder of the lack of progress that has been made in the treatment of this disease. (24)

The evidence presented here suggests that one may be able to improve these results by paying more serious attention to host resistance factors. Thus one must consider how present day methods of treatment may affect the course of the disease, and whether there is a place for adjuvant therapy designed to stimulate the local and systemic resistance of the patient so as to destroy incipient or inoperable metastases at the time of surgery and prevent recurrence or further spread.

In recent years fundamental studies have been made of the various factors which may stimulate natural resistance to cancer and allied diseases. Cases of so-called spontaneous regression have been analyzed in this connection. It was found that the majority of these patients had some form of infection, fever or inflammatory episode, often not considered by the reporting physician to have been of any consequence, because until recently so little was understood about the various immunological defenses which may be activated by such complications. (21, 22, 23, 25, 47, 48, 51)

The reticuloendothelial system is the site of the body's host defensive reactions and, in recent years, has been implicated as a determinate factor in resistance to cancer. (19) If, in cancer patients depression of reticuloendothelial function occurs in association with surgical stress, the delicate balance between the malignant tissue and the host is altered in favor of the tumor. The duration of the operative procedure and the decrease in systolic pressure during or immediately following surgery, as well as the elevated levels of plasma adrenocortical steroids that result from surgical stress, may be some of the mechanisms involved.

Impairment of reticuloendothelial function in surgical patients may explain the rapid progression of cancer occasionally noted following surgery. (19) On the other hand, stimulation of the reticuloendothelial system by whatever means, such as concurrent infection, inflammation, bacterial toxin therapy, fever or heat (including electro-coagulation), appears to lessen the incidence of recurrence or progression of the neoplasm. (31, 33) As Donovan suggested, it would be of interest to correlate the degree of reticuloendothelial function with survival in a large series of cancer patients, for a relationship may exist which would explain the differing clinical course of patients with pathologically similar neoplasms. (19)

The integrity and functional capacity of lymphoid tissues also appear to be of distinct importance in natural resistance to cancer. The possible role of the appendix in this connection has recently received attention. McVay studied 914 cases coming to autopsy in three institutions and concluded that the colon and, to a lesser degree, the lung, breast, cervix, stomach and pancreas may be organs on which the appendix may confer some degree of protection. (37a) Independently Bierman has confirmed these findings in a study of 1287 consecutive postmortem records and in 122 living patients with lymphomas and leukemias. These data suggest a systemic and local protective effect is produced by the appendix, and that the function of the appendix may influence the induction of leukemia, lymphoma or other neoplastic disease. (3)

*The end results of Strauss (60-65) and Turnbull (48) are far better than this and are discussed below.

A number of surgeons are beginning to question the advisability of performing radical prophylactic lymph node dissections for various malignancies such as malignant melanoma or mammary carcinoma, believing that in so doing we may be destroying one of the patient's important host defenses against the neoplasm. Future research should be directed toward increasing the functional capacity of the RES and the lymphoid tissues.

The present end result study comprises the known cases of carcinoma of the colon and rectum in whom concurrent infection, inflammation or fever occurred (24 cases), or to whom bacterial toxin therapy was administered (11 cases). The diagnosis were confirmed by competent pathologists in all but three cases: Series A, Cases 1 and 5; Series B, Case 1. These two small groups of cases are obviously not large enough to be of statistical validity in determining the value of toxin therapy or the possible benefits of concurrent infections or inflammation in cancer of the colon and rectum. However, the evidence presented here, together with other end result studies of various types of cancer so treated, or with similar infections, (21, 22, 25, 40, 41, 42, 47, 48, 50, 51) is sufficient to warrant much more serious study of this form of therapy and of the fundamental host-tumor relationship which appears to play such an important role in successful treatment, no matter what the modality.

Many investigators in recent years have shown that bacterial infections or their toxins stimulate the hematopoietic, lymphoid and reticuloendothelial tissues (4) and that small doses of bacterial toxins protect these tissues against the lethal effects of radiation (1, 2, 3, 6, 15, 32, 55, 56). Other studies indicate that preliminary toxin therapy or concurrent infections may markedly potentiate the response of neoplasms to subsequent radiation. (10, 25, 28a) This occurs without increasing the sensitivity of normal tissues. (18). A case of carcinoma of the colon in which prior infection appeared to cause an excellent response to a rather small amount of x-ray is described below, (Series A, Case 16). Another to whom radium was given following a preliminary course of toxins, followed by further toxin therapy, also did remarkably well. (Series B, Case 3).

Until recently, physicians using toxin therapy were unaware of the fact that streptococcal organisms and their toxins are able to stimulate a host response to substances or tissues which do not normally elicit such a response in an animal or patient. (57) For example, Glynn and Holborrow found that four strains of streptococci, three Group A and one Group C, and a strain of *Staphylococcus aureus,* when grown on agar media gave rise to agar antibodies in antisera prepared against them. (27) Burky found that by combining staphylococcus with lens substance, rabbits were sensitized to lens and developed high precipitin titres for lens tissue. (9) A diverse group of bacteria in addition to streptococci show this property, i.e., *Shigella shigae, Salmonella typhi, Bacillus anthracis, Hoemophillus influenzae* and *Neisseria meningitidis.*

In order to elicit this response, the organisms do not need to be alive, but they must come into significant contact with the target tissue. These findings suggest that in treating patients with bacterial toxin therapy, more effective results may be obtained if at least some of the initial injections are made in or near the tumor. If tumors are inaccessible or impermeable, or in an organ into which it would be dangerous to make such injections, one might remove sufficient tumor tissue at biopsy so that it would be mixed with the toxins and subsequently injected intradermally.

In this connection it is of interest to note that the majority of so-called spontaneous regressions of malignant tumors occurred in patients who developed streptococcal or staphylococcal infections. (23, 25, 50, 51, 59, 66)

The older surgeons here and in Europe were aware of the fact that if their patients developed postoperative wound infections or pelvic abscesses they were more apt to remain free from recurrence or metastases. For example, Grey Tur-

ner, of England, noted this in some of his publications on cancer of the colon. (28) More recently, Dunphy commented on this point in a report of four cases of cancer of the rectum and colon in which favorable results had rather unexpectedly been obtained: "The possible role of inflammation in limiting the distant spread of these tumors occasions comment – in Cases 1, 2 and 4 there were local abscesses in and around the growth and in Case 3 the tumor was of an extremely inflammatory character. . .Whether or not an inflammatory reaction sealed off the lymphatic vessels at the base of the mesentery is a problem for pure speculation and future observation." (20)

Apparently few physicians were aware of the work of Lohmann, who studied the effects of inflammatory exudates *in vitro* and found that they caused death of cancer cells within 14 hours. She cautioned that one should preserve and intensify the inflammatory capacity of the body to a maximum in cancer patients, so that every neoplastic cell may be destroyed. (37)

Ungar discussed the evidence in favor of the view that patients who tend to have acute inflammatory episodes and infectious diseases have a low incidence of cancer. He studied the histories of 68,385 cases admitted to the Basle University Clinic in Switzerland from 1927-1945. These studies showed that even when comparing the various decades of life, the number of infectious children's diseases was on the average *three times as high in the non-cancerous patients as in those who were admitted for cancer. (37)*

Histamine liberated in areas of inflammation activates the reticuloendothelial system, according to Jansco. (34) Antihistamine acts as an inhibitor. Thus a variety of evidence adds up to the fact that it is important to elicit an inflammatory reaction.

Garlock, in reporting on 25 years' experience at Mount Sinai Hospital with surgery for cancer of the colon and rectum, stated: "The ever present little understood problem of individual tumor virulence and the host response seems to have particular significance in cancer of the bowel." (26)

Since there is now considerable evidence that acute concurrent infections, fever and inflammation may cause complete or partial regressions of cancer, or lessen the chances of recurrence or metastases following surgery, one must seriously question the wisdom of continuing to give antibiotics as a routine procedure before and after cancer operations. This point is of special importance in cancers of the gastro-intestinal tract, as indicated by Zwaveling, who found that pre-operative disinfection of the intestines or colon is likely to promote the growth of spilled tumor cells. (73) He concluded from his animal experiments that tumor cells have less chance of growth in a milieu in which there was suppuration resulting from bacterial infection. He noted, however, that bacteria unaccompanied by suppuration did not inhibit tumor growth. (73)

Vink also warned that bowel disinfection (sulfasuxidine and streptomycin) favors the growth of recurrence or metastases. "Pathologists state that tumor cells will now grow in intact bowel mucosa: infection of the bowel with organisms seems to be an important preventing factor. In modern times with the routine bowel disinfection, conditions may be altered, favoring the survival chance of the tumor cell." (68)

Cohn and Atik became interested in this problem and reported on the influence of antibiotics on the spread of tumors of the colon. (12, 13) They stressed the importance of controlling the spill of tumor cells during an open operation of the gastrointestinal tract and added: "However, the possibility that control of the bacterial flora might increase the rate of metastases from a tumor within the colon has not been widely considered in spite of Vink's paper in 1953, and the suggestions throughout the years, such as those inherent in the use of Coley's toxins, that there might be some connection between bacteria and tumor growth." (12) They concluded from their experiments on rabbits in

which Brown Pearce carcinoma was implanted at a suture line of the colon, that control of bacterial flora, plus increased trauma to the colon, significantly increased the incidence of tumor growth in the anastamosis. (12)

Weilbaecher, Bornside and Cohn further reported that "bacteria exert an inhibitory effect on tumors of the colon." (70) They cited Miller and Ketcham as showing a decrease in the implantation and growth of tumor cells in experimental infected wounds in mice and reported that *an intimate contact between bacteria and tumor cells was necessary for inhibition of tumor growth,* since infection at a distant site had no effect on local tumor growth.

They also studied the growth of Brown Pearce carcinoma in the peritoneal cavity of the rabbit following simultaneous introduction of approximately 50 million cells of Escherichia coli, Streptococcus faecalis, Bacillus species and Bacteroides species. They found that with the exception of those receiving streptococcus there was little evidence of stimulation or inhibition from these inoculations. (70)

Christensen's long term studies at the State Serum Institute in Copenhagen have shown that rabbits with Brown Pearce carcinoma which were subjected to massive infection with hemolytic streptococci had fewer metastases than the controls: none of the infected animals versus 50 percent of the controls developed metastases. (11)

In a retrospective study of 1042 colon resections performed at Presbyterian Hospital and Frances Delafield Hospital in New York City, Herter and Slanetz found that general postoperative complications occurred with parallel frequency in the patients who received preoperative intestinal antibiotics and those who were prepared by mechanical measures alone. "Staphylococcal enterocolitis developed rarely, *but with greater frequency following antibiotic preparation.* . . Super-infection, in the form of unopposed fungal or pathogenic bacterial growth following sterilization, has received much attention." (31a)

In the discussion following this paper, Altemeier, of Cincinnati, Ohio, called attention to the fact that "if you use a neomycin and Sulfathalidine bowel preparation, the total number of bacteria in the intestinal tract may be expected to decrease, however, in over half the cases, the colonization of the bowel by an antibiotic-resistant, virulent Staph. aureus may be anticipated." He added: "It may be of interest that for the past 4½ years I have not used preoperative bowel preparation with antibiotics in the management of any of my private cases. It is also of interest that there have been no cases of enterocolitis or wound infections in those patients in our multiphase study who were prepared by mechanical means without preoperative antibiotic preparations. Our work. . .supports Dr. Herter and Dr. Slanetz' conclusions that preoperative bowel preparation with antibiotics is of limited or no use in decreasing postoperative complications after colon resections performed intraperitoneally. We would go further and say that it may be harmful under certain conditions. . ." (31a, p. 171)

Herter, in closing, reported that in the past four years he and a number of other surgeons at Presbyterian Hospital, had given no antibiotics at all postoperatively except in difficult low anterior resections, in which there was a fair degree of obvious contamination. (31a)

Until very recently, the emphasis of many investigators who are trying to reduce the incidence of recurrence or metastases, by adjuvant therapy, has been on the use of cytotoxic chemotherapeutic agents. Beginning about 1961, Cole and Rousselot started using intraluminal chemotherapy in the treatment of cancer of the colon and rectum. They injected nitrogen mustard or 5-Fluorouracil into the lumen of the bowel just after the tapes are applied preliminary to resection. By this procedure they endeavor to destroy viable tumor cells disseminated within the isolated area during operative manipulation, and through absorption of the agent into the veins or lymphatics, into which cancer cells

might have migrated. In the 5-FU series the drug was also given intravenously on the first or second day after surgery. In the four year follow up of the HN2 patients, survival was 69 percent, versus 48 percent in the controls, but at the end of five years there was no difference in survival between the treated and the control groups. In the two year follow up of the 5-FU patients, the survival rate was 71 percent, versus 57 percent for the controls. This improvement was sustained at four years. There was no increased morbidity from the procedure for either drug. (14, 53, 53a)

Late in 1953 Turnbull, of the Cleaveland Clinic, adopted a no touch isolation resection technic which he has used on 677 patients with cancer of the colon (by May 1967). With this technic the lymphovascular pedicles are isolated and divided as the first step of the resection; the colon is divided at the elected sites of resection as a second step, and the isolated segment is then removed in a prograde direction. The tumor is not touched or handled directly by the surgeon or his assistants before or during the operative procedure. This technic has resulted in remarkably better end-results than is being achieved by other surgical technics. The five year survival rate for 105 Class A colon cancers was 98.9%; for 212 Class B, 84.9%; for 156 Class C, 67.3%. Almost a third of the cases coming to surgery were considered incurable, i.e. 204 or 32.8%. Palliative resection, using this technic resulted in a five year survival rate of 13.1%. The overall five year survival rate for the entire series of 677 patients was 59.6%, over twice the expected rate. It is hoped that Turnbull's technic will be widely adopted in order to salvage 35% more patients than has been possible in the past with the usual surgical procedures. These results were reported by Turnbull at the American Surgical Association in May 1967. (66a)

It would seem that the most hopeful and effective combination of therapies should include an attempt to stimulate immunological competence in cancer patients, and that such therapy should start prior to any surgery except biopsy, and before any radiation or cytotoxic chemotherapy. The need for such adjuvant therapy was first considered by the late William B. Coley, M.D. (15, 47) Matagne, of Brussels, Belgium also outlined such a technic and used it successfully for many years. (40, 41, 42) Their observations and clinical experience were largely based on empirical theories. Only recently have Martin and his associates carried out significant experimental work which clearly indicates the desirability of carefully planned combination therapy. (38, 39) He suggested that alteration of the host defense mechanisms appears to be responsible for the failure of chemotherapy to effect eradication of established cancer. Reduction of tumor size by simple surgery restored the curative effect of chemotherapy in animal tumors. These studies showed that cure can never, or only rarely, be effected on large well established tumors by chemotherapy alone. However, by combining these three modalities, it was possible to produce striking cure rates of 70 to 80 percent. These results could be nullified by administering an anti-immune (anti-inflammatory) agent such as cortisone. (39) These findings emphasize the need to avoid giving cancer patients any agent which may lower his immunologic responsiveness, especially prior to surgery or radiation.

Strauss was among the first to treat large numbers of cancers of the colon and rectum conservatively. (60-65) Beginning in 1913 he has used electrocoagulation on over 400 such cases with excellent results: approximately 75 percent five year survivals free from disease, 30 percent 10 year survivals. A considerable number of patients have survived more than 10 years and some have died of other causes and at autopsy no cancer cells were found, or if present were contained and quiescent, producing no symptoms. Strauss believes that surgical diathermy produces not only destruction of most of the neoplasm, but also stimulates production of antibodies which immunize the patient against further progress of the disease. It is now apparent that local heat and inflammatory reaction produced by electrocautery stimulates the lymphatic and reticuloendothel-

ial cells. In addition, the absorption of neoplastic and normal tissue breakdown products appears to increase the immune responses of the patient to his tumor.

Strauss believes that surgeons in many large clinics in this country and abroad are now advocating more conservative surgery in these cases. "In our extensive experience with cancer of the colon, it has been our custom to do wide resections and to remove local glands. . .Our survival rate compares most favorably with that of surgeons who remove half to three-quarters of the colon with extensive lymph node resection along the aorta. Is it not better to preserve as much of the tumor-free colon as possible rather than do these mutilating, extensive removals of the colon? Also, we now believe that following a wide resection of the stomach or colon, if the remaining glands in the area are coagulated instead of removed, there is a minimum scattering of cancer cells through the abdomen. . .With our ever increasing knowledge of host resistance to cancer, I believe the trend in the next decade will be toward more conservative surgery rather than toward more extensive radical procedures." (63)

Madden first treated a case of rectal carcinoma by fulguration in 1954 because the patient steadfastly refused abdominoperineal resection. In 1960 fulguration was established as the primary definitive treatment for rectal cancer. The average survival in 24 cases treated in six years was 49.6 months. Madden noted that in the first two or three days after fulguration there is a general systemic reaction with two to four degrees elevation of temperature. This is followed by weight gain, correction of preexistent anemia and improved general appearance and a subjective sense of well being. (37b)

Another surgeon who has reported unusually good results from local electrocoagulation is Wassink. (69) Local cautery of presumably inoperable cancer of the rectum combined with radiation is used and Wassink believes that the heat potentiates the effects of the radiation.

It would seem that in treating cancer of the colon and rectum now and in the future, surgical diathermy may be combined with bacterial toxin therapy given prior to and following the electrocoagulation of the tumor when this procedure is feasible, or before and after resection in cases not amenable to surgical diathermy. Such combined therapy should minimize the spread of blood borne metastases.

Another factor which must be seriously considered is the deleterious effects of corticosteroids on the course of the disease in cancer patients. Kelly, in a review of the literature in 1959 (35), and in subsequent reports, cited some of the extensive animal experiments since 1950 which clearly indicate that corticosteroid therapy may accelerate the growth and dissemination of malignant tumors. He cited a number of cases in which the rapid spread of metastases occurred soon after corticosteroids had been administered to patients for conditions other than cancer. Zeidman concluded that cortisone increases the number of metastases and also increases the incidence of arrest of tumor cell emboli. (72) As mentioned above, Martin found that cortisone nullified the beneficial effects of a host-stimulating agent such as zymosan in combination therapy of animal tumors. (39) We know of five patients in whom cortisone therapy was followed by rapid dissemination of metastases. Two of these patients had cancer of the colon. One is included in the present report as Case 20, Series A. The family refused to release the medical record on the second case, so it is not included.

These findings suggest that one should avoid administering any immunosuppressive drug to patients who are known to have cancer, or who have had it in the past. In eliciting the prior history of cancer patients who present themselves for treatment, if it is found that they have recently received any of these drugs, one may be able to counteract their deleterious effects by prompt administration of choline, (31) bacterial toxins, zymosan or BCG prior to any surgical intervention except biopsy and prior to radiation, as well as following surgery or radiation.

Black and Speer pointed out that there is a disturbing possibility that some of the chemotherapeutic agents now being used systemically as adjuvants in the primary treatment of cancer may actually do more harm than good by their damaging effects on the lymph nodes and upon hematopoiesis. These authors further noted that any agent directed toward enhancing host resistance would be unlikely to be effective in the advanced stage of the disease, in which the lymphoreticuloendothelial system has undergone degenerative changes. Yet such advanced cases are customarily utilized for testing all potential therapeutic agents. They concluded: "It would seem reasonable to evaluate host stimulating agents as adjuvants in the primary treatment of cancer." (5)

Analysis of over 1200 cases of cancer treated by bacterial toxin therapy (principally the mixed toxins of Steptococcus pyogenes and Serratia marcescens), or who developed concurrent bacterial infections accidentally or by inoculation, indicates that patients in the terminal stage of the disease are rarely cured, although a number had complete or partial temporary regressions. One terminal carcinoma of the colon with extensive metastases, ascites and pleural effusion, made a complete and apparently lasting recovery following a course of intradermal injections of mixed bacterial toxins. (See Series B, Case 11) Possibly the periodic administration of influenza vaccine before and after his toxin therapy may have favorably influenced this patient's immunologic responsiveness, so that a brief course of toxins was sufficient to produce complete and permanent regression. This patient is in excellent health, entirely free from disease over nine years after onset.

Operable and inoperable patients who received toxin therapy alone or as an adjuvant to complete or incomplete surgical removal or radiation, had a significantly higher than expected survival rate. Among the failures, in both the toxin treated and infection series, the period of survival was far longer than expected.

Bochus (6) pointed out the 75% of patients affected with hepatic metastases from carcinoma of the colon die within six months and 85% within a year. It is therefore significant that five patients with liver metastases recovered completely and remained free from disease when last traced from 8½ to 15 years after onset. Two of these patients had concurrent infection, the other three received toxin therapy. Of the failures with liver metastases, two with concurrent infection survived four and five years. Two toxin treated cases survived three and six years, two others succumbed in 11 and 21 months.

Many observers have noted that there is an average duration of at least eight months between onset of symptoms to the time the patient is brought in for treatment of cancers of the colon and rectum. Therefore a large percentage of these patients are first seen by their physicians when the disease is no longer operable. This is beyond the control of those who must treat them. However, they *can* control the timing of the various modalities with which they attempt to treat these neoplasms.

Conclusions:

In view of the importance of immunological factors in cancer, until recently so largely ignored, it would seem essential to plan the sequence of therapies so that whatever host stimulating agent is used (bacterial toxins, zymosan, BCG) it should be instituted prior to radiation, surgery or cytotoxic drugs, all of which are known to deplete or inactivate the lymphoreticuloendothelial system. Antibiotics should also be avoided since their use has not met with sufficient freedom from complications, and there is real danger that the incidence of metastases in these cancers will be increased when the normal intestinal flora is altered by such treatment. It is not only the stage of the disease which may affect response to treatment, but whether prior therapies or advanced age have rendered the patient immunologically incompetent to respond. Much more intensive research along these lines appears warranted.

SERIES A, BENEFICIAL EFFECTS OF ACUTE INFECTION, INFLAMMATION OR FEVER ON CANCER OF THE COLON OR RECTUM, 24 cases

The abstracts are listed chronologically. The name in parenthesis following each case number refers to the physician or hospital handling the case. At the end of each abstract references are listed. The diagnoses were confirmed by microscopic examination in all but Cases 1 and 5. More details regarding histology appear in the detailed histories which are given following these brief abstracts.

Years Traced After Onset

1. (STRANDGAARD)*:* Mr. S., aged 75; extensive inoperable intra-abdominal carcinoma apparently primary in sigmoid flexure, involving small and large intestine and omentum; adherent to prostate, bladder and bony pelvis with subcutaneous metastatic nodules in abdominal wall; ascites, emaciation; (date of onset not recorded); laparotomy, May 1912, condition hopeless, most of appendix epiploica involved; lateral colostomy; rapid growth of tumor in incision, increased to enormous size; *10 days postoperatively erysipelas over entire body; complete regression of tumor masses in abdomen and wound, normal bowel movements per rectum;* acute nephritis caused death 3 mos. after infection. (59, Case 1) less than 1 year

2. (STRANDGAARD): J. K., male, aged 62, inoperable carcinoma sigmoid flexure, adherent to spine and anterior rectum; (date of onset not recorded); exploratory laparotomy, August 25, 1913 showed large arteries involved, infiltration; palliative colostomy; *10 days later erysipelas on buttocks lasting 3 wks., very ill; improved markedly*: *extensive tumor entirely disappeared, no longer palpable by abdominal or rectal examination, intense pain ceased completely, general condition improved extraordinarily;* 3 wks. later symptoms recurred, general condition declined rapidly, death 5 mos. after regression had occurred. (59, Case 2) (died) less than 1 year

3. (GREY TURNER): Female adult, typical constricting carcinoma sigmoid flexure; admitted about 1915 with intestinal obstruction, so much distension that caecostomy required to drain large bowel; exploratory laparotomy 3 wks. later revealed growth low in sigmoid, adherent to lt. pelvic wall; *abscess opened between appendix and growth;* lt. oophorectomy-salpingectomy required due to involvement; anastamosis impossible, lt. inguinal colostomy done, caecostomy closed; *complete recovery, no recurrence or metastases;* in perfect health 9 yrs., then hemiplegia due to vascular degeneration; *n.e.d. 10 yrs after operation.* (28) 10 yrs.

Years Traced After Onset

4. (MOST): Male, aged 57; recurrent extensive inoperable carcinoma rectum; general condition poor, considerable weight loss; inoperable apple-sized mass present when first seen, April 1918; symptomatic treatment only; appeared better, May 1918, so x-ray therapy tried; general condition continued to improve, so palliative surgery attempted, June 28, 1918; tumor firmly fixed to bladder incompletely removed, base cauterized; good recovery, except for complete bladder paralysis; recurrence on perineum apparent 20 mos. later, of rapid growth, soon made sitting, standing or walking painful; bedridden; again seen summer 1920, extremely debilitated, dreadful pain; *bleeding and profuse ichorous suppuration from growth in anus;* hospitalization and further palliative surgery advised, refused; relatives then applied wet mud packs; became psychotic September 1920, condition hopeless; *further poulticing; growth gradually but completely regressed, complete recovery, resumed occupation;* 1922, fell fracturing femur, not due to metastases, complete healing; no further evidence of disease, *alive and well October 1927, almost 10 yrs. after onset.* (22, pp. 387-389; 45a) 10 yrs.

5. (SIREDEY) : Male, aged about 50; operable carcinoma rectum; (date of onset not recorded); 1924, iliac anus produced, few days later surgical removal large tumor size of hen's egg; *pelvic abscess postoperatively;* convalescence prolonged as several operations were necessary, *including incision and drainage of abscess,* anastamosis of intestine, closure of iliac anus, successful repair of sphincter; *complete recovery, excellent health, returned to active life,* resumed work, well 8 yrs.; then thoracic, costal, pleuropulmonary metastases, disease generalized, *death over 10 yrs. after infection.* (26) (died) over 10 yrs.

6. (MULLEDER) : Male, aged 65; carcinoma rectum; onset 6 mos. prior to to admission, hemorrhages, rapid weight loss; radical operation, all affected lymph nodes apparently not removed; *postoperative erysipelas spread over whole wound, lasted 2 wks., high fever, extremely ill: complete recovery, gained almost 31 pounds, no evidence recurrence or metastases 2 yrs. after onset;* end result unknown. (46) 2 yrs.

7. (DUNPHY) : Male, aged 58; adenocarcinoma cecum extending through and beyond bowel wall, invading abdominal wall in region old appendectomy scar, extensive involvement regional lymph nodes; onset, late June 1930, anorexia, diarrhea; *6 wks. later large abscess in r.l.q. in region appendectomy scar, incised, drained;* 2 wks. later rt. colectomy, entire thickness parietes generously excised; readmitted 2½ yrs. later; weight loss, large local recurrence; excision en bloc, *no nodes involved;* well, n.e.d. thereafter; last traced *well 1939, over 9 years after onset.* (20) over 9 yrs.

8. (RUBENS DUVAL) : Miss D., aged 51; inoperable carcinoma cecum, with peritoneal metastases; exploratory laparotomy, June 1932; during operation primary tumor extending to ascending colon, ruptured, resection intestine necessary; thereafter frequent episodes pain, emesis, fever; very thin, general condition poor, bedridden; *fistulae present, 1 near colostomy drained pus, other in rt. iliac fossa densely indurated;* tumor extracts given orally; *further febrile episodes,* attacks of emesis; then developed *fungus infection (thrush), fever to 104°F.;* tumor extracts

continued during infection; *appetite, strength, general health improved, returned to normal life;* end result unknown. (54)

9. (DUNPHY): Female, aged 36; adenocarcinoma sigmoid colon, extensive regional lymph node involvement; onset, May 1936, abdominal cramps, rectal bleeding; 3 mos later laparotomy, rt. transverse colostomy; *large pelvic abscess postoperatively requiring colpotomy;* 1 mo. later sigmoid resected; colostomy closed 2 wks. after resection; *well 15 mos.,* then symp- of recurrence; reoperated 18 mos. after 1st, solid tumor mass removed involving sigmoid, mesentery, retroperitoneal tissue, lt. adnexa; permanent colostomy; asymptomatic 4½ yrs.; readmitted for repair of ventral hernia; n.e.d. except for small egg-sized nodule along lt. ureter, considered probably scar tissue, not touched; 1 yr. later died peritonitis following laparotomy for acute obstruction due to recurrent cancer, *over 5½ yrs. after onset.* (20) (died) 5½ yrs.

10. (MEMORIAL HOSPITAL): Mrs. H. H., aged 64; inoperable epidermoid carcinoma rectum, grade II; (date of onset not recorded); December 1, 1938, exploratory laparotomy, sigmoid colostomy; postoperative recovery only fair (psychological reasons?); x-ray (2400 r): *severe streptococcal sore throat, January 1939, could not swallow, fed parenterally, hospitalized 10 days; also had macular, non-itching, pigmented rash over trunk, neck, extremities;* radium packs February 2 to March 8, 1939 (12,000 mch.) *complete regression by May 1939;* radiation ulcer causing severe pain by February 1940, required perineal resection of rectum 3 mos. later; *tissue showed no evidence malignancy*: August 1941, metastases lt. groin; x-ray (2150 r), some decrease in size; improved 1943; disease then slowly progressed, *death March 21, 1946, 9 yrs. after onset, 7 yrs. after streptococcal infection.* (44, 48) (died) 9 yrs.

11. (DUNPHY): Male, aged 52; large fixed rapidly growing adenocarcinoma sigmoid colon, direct extension to urinary bladder, terminal ileum, many lymph node metastases, tumor of extremely inflammatory character; onset, February 1938, rectal bleeding, weight loss; rt. transverse colostomy, sidetracking ileo-ileostomy 18 mos. after onset; *postoperative wound infection;* 3 wks. later tumor resected, including sigmoid, terminal ileum, upper third bladder; recurrence in l.l.q. 2 yrs. later; at 2nd operation large tumor mass separated with difficulty, lt. ureter resected, end-to-end anastamosis; many regional lymph nodes involved; permanent colostomy; *n.e.d. thereafter, well January 1946, almost 8 yrs. after onset.* (20) 8 yrs.

12. (SNYDER, CLARK & RUBINI): D. B., female, aged 26; inoperable annular ulcerative adenocarcinoma sigmoid colon, penetrating to small bowel, bladder and uterus, with metastases to regional lymph nodes; family history was then negative for cancer, but an only son developed adenocarcinoma of cecum and ascending colon 19 yrs. later (see below, case 21); patient had mild rheumatoid arthritis; late in 1938 constipation developed and weight loss (30 lbs.); exploratory laparotomy, January 20, 1939; obviously inoperable lesion involving 8 cm. of mid-portion of sigmoid with palpable nodes in mesosigmoid; because of bleeding and impending obstruction, palliative incomplete resection was done; *postoperative wound infection, fever to 102°F. for 10 days, leukocytosis*

(15,750 wbc); slow recovery, (no antibiotics); remains of growth completely regressed, no further evidence disease: died other causes at 78 in 1953, 14½ yrs. after onset. (56a) 14½ yrs.

13. (DUNPHY): Male, aged 68; adenocarcinoma of rectum with blood vessel invasion; onset, November 1939, rectal bleeding; 3 mos. later abdominoperineal resection, large slightly fixed tumor in lt. posterior wall of rectum removed; *postoperative cystitis, abscess in posterior wound;* 8 mos. later perineal recurrence; radical perineal resection 22 mos. after 1st operation, also prostatectomy; urinary incontinence thereafter; *asymptomatic 4 yrs.*, then further perineal recurrence; refused hospitalization; bedridden due to cancer when case was published, *over 7 yrs. after onset.* (20) (alive with disease over 7 yrs.)

14. (LEVINE AND WEINER): Mrs. G. M., aged 34; diffuse inoperable adenocarcinoma apparently primary in omentum with metastases in peritoneum, mesentery, ovary, liver; onset during 1st pregnancy, but not apparent until soon after confinement, March 1, 1940; several peritoneal implants taken for biopsy, attempts to biopsy liver metastases abandoned due to extreme friability, marked bleeding; prognosis hopeless; *immediate postoperative course very stormy, temperature persistently elevated, pulse poor, abdomen markedly distended, peritonitis; all traces of carcinoma and metastases disappeared, normal menses in 6 wks.;* again became pregnant 3 yrs. later; fearing reactivation of the disease, total hysterectomy performed with bilateral salpingo-oophorectomy; no evidence of cancer seen at operation; in excellent health thereafter; last traced 1955, *15 yrs. after onset.* (36, 48) 15 yrs.

15. (FALLIS AND BRENNAN): J. K., male, aged 41; extensive adenocarcinoma involving lt. half of transverse colon with metastases to abdominal wall at sites of fistulae; 10 lb. wt. loss in 2 wks., pain; September 1941, explored, mass considered due to ruptured diverticulum with *abscess formation, pus aspirated from abscess;* cigarette drains inserted, sulfanilamide in wound; *stormy course,* pain, nausea, vomiting; condition deteriorated, became bedridden; 2nd sinus opened, both finally discharged feces, normal bowel movements ceased per rectum indurated area about old scar and fistulae 12 x 20 cm. in diameter biopsied February 27, 1942, revealed metastatic adenocarcinoma invading subcutaneous tissues, *with massive areas of necrosis;* tumor mass superficial to skin margin about scar and sinus tract excised, base of large growth arising in colon untouched; condition became worse, lost 24 lbs. in 3 mos.; wound entirely healed by July 1, 1942; *then began to improve rapidly, gained 62 lbs. in July;* colostomy closed that fall; *extensive carcinoma regressed completely; no further evidence of disease, in excellent health;* small epigastric hernia repaired, appendectomy, September 5, 1957, no evidence of cancer present; wedge resection rt. middle lobe for indeterminate lesion which proved to be old infarct, 1963; repair of large ventral hernia, 1966; cholecystectomy, 1967; over weight but in good health thereafter (225 lbs., height 6 ft.); alive and well 1968, *26 yrs after onset.* (22, 48) 26 yrs.

16. (MAYO CLINIC): Male, aged 45; inoperable obstructing adenocarcinoma of descending colon, extending into sinus tract above crest of ilium;

September 1950, *developed abscess in lt. flank, incised and drained twice;* 40 lb. wt. loss; May 1951, acute obstruction; colonic stoma established; exploratory laparotomy 6 mos. later revealed hard, irregular mass involving descending colon, solidly fixed to bony pelvis; *sinuses above crest of lt. ilium drained pus (streptococcus)*; curettage of sinus yielded masses of malignant tissue; x-ray (3000 r in 12 days); *sinuses healed in 1 mo., inoperable growth disappeared; re-explored September 1953, lesion had completely regressed, 15 cm. segment of lower bowel absent: apparently absorbed following necrosis and regression after infection and x-ray;* side to side colostomy done; 2 mos. later colonic stoma closed, bowel function normal thereafter; entirely well 7 yrs., except for mild asthma, regained lost weight, returned to work as farmer; returned August 1960 because of marked tenderness in l.l.q. of abdomen; reoperated August 23, 1960, found to have 2nd primary carcinoma sigmoid 7 cm. below anastamosis; *marked inflammatory reaction surrounded it, more like diverticulitis than carcinoma;* (a mucus-producing adenocarcinoma showing marked round cell infiltration of all layers of bowel but none of lymph nodes were involved metastatically, 2nd lesion definitely different from 1st histologically); resection, end-to-end anastamosis; complete recovery, *no further evidence of either cancer 1965, 15 yrs. after onset of 1st, 5 yrs. after onset of 2nd.* (21, 22, 23, 48, 67) 15 yrs.

17. (PATRIZIO): F. W., female, aged 55; adenocarcinoma rectum at junction of sigmoid; onset, September 1951, recurrent episodes of diarrhea, bleeding, colic, *occasional chills, slight fever,* slight tenderness across lower abdomen; February 1952, *stool cultures for Salmonella barielly; antibiotics given (sulfasuxidine, chloromycetin); stools remained positive except for 2 mos. period;* hospitalized June 1952, barium studies, biopsy, abdominoperineal resection distal sigmoid and rectum; *complete recovery,* no further evidence of cancer or dysentery infection; alive and well 1969, *over 17 yrs. after onset.* (48, 49) 17 yrs.

18. (ELLISON): R.M., male, aged 59; adenocarcinoma rectum with metastases to peritoneum and mesentery; onset, August 1952; resection January 1953; recurrence few mos. later, peritoneal metastases present, especially along lt. pelvic brim and over sacrum, large metastatic nodes present in base of mesentery; 2nd operation July 1953 for removal of these nodules; *virus pneumonia, February 1954, febrile for 2 wks.* at routine followup examination, August 11, 1955, barium enema caused perforation of colon; emergency operation that day, *n.e.d. clinically or histologically; well next 2 yrs.,* then tired very easily; fall 1957 urinary symptoms (non-functioning lt. kidney) due to large metastatic (?) tumor involving urinary bladder; nephrostomy, palliative x-ray (5800 r); *death October 26, 1958, over 6 yrs. after onset.* (21, 48) (died) over 6 yrs.

19. (STONE): Female, aged 60, operable infiltrating adenocarcinoma sigmoid colon; onset, November 1954; at operation 3 mos. later, annular growth penetrating all layers of bowel found on lower sigmoid, no metastases seen; resection, end-to-end anastamosis; 6 implants of her tumor placed in subcutaneous fat of abdominal wall, beginning 7 days after operation, at daily intervals, under local anesthesia; (tumor tissue removed at surgery and kept frozen); none of tumor implant sites became infected or "took," but patient developed *multiple staphylococ-*

cal abscesses of buttocks and back; no recurrence or metastases; in good health until 1962, then hospitalized for heart attack, also developed a "bad back"; *alive and well 1968, 14 yrs. after onset.* (48, 58) 14 yrs.

20. (DELOR): Mrs. H. P., female, aged 45; operable adenocarcinoma colon, adherent to ovaries and uterus; (5 cases of gastric or bowel cancer in family); onset, intermittent lower abdominal cramps, constipation; stools normal, no blood or mucus, symptoms worse during menses; 3 mos. after onset, *severe sore throat, septic temperature to 103°F., marked cervical, some axillary and inguinal adenopathy;* no masses noted in abdomen; continued to have bouts of abdominal cramps intermittently; throat cultures negative; 3 sigmoidoscopies negative; explored May 1957; bowel wall firmly adherent to ovaries, uterus, 15 cm. involved; resection, side-to-side anastamosis, bilateral oophorectomy, complete hysterectomy; *regional lymph nodes negative for cancer, showed lymphoid hyperplasia; postoperative exacerbation of febrile lymphadenopathy, finally diagnosed as cat scratch fever by viral laboratory, fever lasted 4 wks; thereafter asymptomatic; no recurrence or metastases, in good health 1968, 12 yrs. after onset.* (17, 48) 12 yrs.

21. (SNYDER, CLARK & RUBINI): N. B., male, aged 60; inoperable, poorly differentiated adenocarcinoma of cecum and ascending colon, involving terminal ileum, with tremendous seeding of entire peritoneal cavity and omentum by metastatic lesions; (his mother had developed inoperable adenocarcinoma of sigmoid colon in 1939 and recovered following wound infection after incomplete surgery, see above, case 12); he had had moderate rheumatoid arthritis which had been quiescent for yrs.; onset, early 1958, constipation; barium enema suggested carcinoma; exploratory laparotomy revealed tremendous seeding of entire peritoneal cavity, regional lymph nodes grossly involved, condition obviously inoperable; biopsies of primary and several nodes; thereafter increasing anorexia, large tender mass in rt. lower quadrant present, April 1958, when Nitromin given (20 mg. orally daily for 10 days); no leukopenia, mass decreased in size; 2nd laparotomy, April 30, 1958, to avoid incipient obstruction; growth had spread to involve loops of terminal ileum, hard studded masses of tumor in mesentery of small bowel; *considerable inflammation surrounded tumor, local infection thought to be present;* palliative hemicolectomy and by-pass performed; tumor tissue remained in mesentery, peritoneal fat and along iliac crest, some were biopsied; removal incomplete; chloramphenicol given; rheumatoid arthritis, which had been dormant for many yrs., became quite severe postoperatively; triamcinalone (16 mg. daily for 2 days) caused prompt improvement; 2nd course Nitromin, May 12, 1958 (15 mg. daily orally for 10 days); again no leukopenia; *6 wks after surgery abscess on lower abdominal wall, drained, chloramphenicol again given; small fecal fistula found which later closed spontaneously; complete regression, gained 9 lbs.;* by July 23, 1958 a 3 x 3 cm. nodule palpable in *liver; this also disappeared; no further evidence disease;* 1962 developed persistent leukopenia (1,200 - 2,500 wbc), thrombocytopenia and absolute eosinophilia, frequently marked; *alive and well, August 1968, 10½ yrs. after onset.* (56a, 100) 10½ yrs.

22. (BRUNSCHWIG): Male, aged 55; this patient had 3 separate primary neoplasms: transitional bladder carcinoma, with numerous metastases; adenocarcinoma (Grade III or IV) of colon with localized metastases;

2nd primary bladder carcinoma in a different location; onset of 1st bladder carcinoma 1955, removal transurethrally, well 5 yrs.; 1960, filling defect lower sigmoid, interpreted elsewhere as diverticulitis; acute intestinal obstruction; laparotomy revealed numerous metastases to both lobes liver; 5 excised (metastatic bladder cancer) ; *large inflammatory mass in pelvis;* double barrelled colostomy to relieve obstruction; gained 14 lbs., returned to work; resection advised, but deferred to May 1961; *at operation liver metastases found to have regressed;* 18 cm. of colon resected containing ulcerated papillomatous lesion 3 cm. in diameter extending through bowel wall, metastatic to adjacent lymph nodes; *large lt. subdiaphragmatic abscess postoperatively, drained anteriorly in l.u.q.;* several rather severe hemorrhages through this wound; transfusions given; 3rd laparotomy, June 1961, *large subdiaphragmatic infected hematoma evacuated, fistulized* loop of lower jejunum resected, end-to-end repair of bowel; liver remained free from metastases on palpation; well next 6 mos.; admitted elsewhere, January 1961, bladder cancer cauterized, radon seeds implanted; well until March 1964, then bleeding peptic ulcer, symptoms cleared under bland treatment; late March 1964 cystectomy for recurrent bladder cancer, Grade III, ureters transplanted to rectum, *no evidence bowel cancer seen,* but bladder cancer had metastasized to kidney; downhill course thereafter; death April 25, 1964, 9 yrs. after onset 1st bladder cancer, 4 yrs. after onset carcinoma of sigmoid; *autopsy showed liver completely free of cancer, gross and microscopic, but extensive carcinoma present in pelvis.* (7, 48) (died) 9 yrs.

23. (Brunschwig) : Female, aged 68; large recurrent adenocarcinoma sigmoid colon, involving bladder and retained cervical stump (had had subtotal hysterectomy for fibroids many yrs. previously) ; 1960, bloody, feculent vaginal discharge; tumor mass 7 x 7 x 5 cm. above and to lt. of and continuous with cervix; curettage of cervical stump revealed papillary adenocarcinoma metastasis; August 1960, cobalt, not tolerated well, mass enlarged; vaginal discharge frankly fecal by October 24, 1960; laparotomy, November 21, 1960; sigmoid tumor mass 20 cm. long including retained cervix, upper vaginal vault, dome of bladder; lower descending colon anastamosed to mid-transverse colon, diverting colostomy in mid-transverse colon, bladder repaired — 3-way fistula existed; *prolonged postoperative fever, wound infection, cystitis, marked anorexia;* large recurrence appeared in hollow of sacrum by April 1961, thick grumous material evacuated, reported to be "remnants of adenocarcinoma, colon type"; patient admitted to terminal care home — prognosis regarded as hopeless; *during next 6 mos. appetite, general health improved, gained 14 lbs. in weight; large mass in hollow of sacrum disappeared;* requested closure of colostomy and fistula which was done; biopsies in field showed n.e.d., by 1965 had gained 21 lbs.; remained entirely well, until fall 1967; October 5, 1967 transthoracic esophageal gastrectomy for adenocarcinoma of stomach with metastases to celiac axis; expired November 16, 1967, *over 7 yrs. after onset of sigmoid carcinoma.* (7, 21, 44, 48) 7 yrs.

24. (White Plains Hospital) : W. A. G., male, aged 50; large poorly differentiated adenocarcinoma completely encircling ascending colon, multiple metastases to mesenteric lymph nodes, single metastasis 4-5 cm. in diameter in rt. lobe of liver; 1954, 1st divorce, psychiatric treatment;

low basal metabolism 1957, 1 or 2 gr. thyroid given thereafter daily; onset early summer 1961 during 2nd divorce proceedings, psychiatric treatment: lethargy, impaired mental function, poor concentration; 10 lb. wt. loss in mo. prior to January 10, 1962; complete physical examination including sigmoidoscopy then negative; given steroids August, September 1962 for 2 episodes low back pain; by late September 1962 vague abdominal pains, anemia, dyspnea; 5 lb. wt. loss in wk. prior to admission, October 5, 1962; barium enema revealed carcinoma ascending colon; Vitamin K, transfusion, antibiotics given prior to surgery, October 11, 1962; 6 cm. annular tumor encircled bowel below hepatic flexure, extending well into surrounding fat, metastases in adjacent nodes, mesentery; *intense inflammatory reaction in region of invasive tumor, with abscess deep to the tumor, appendix large, swollen but histologically normal; end-to-end* ileotransverse colostomy performed, omentum over rt. colon resected, local metastases in mesentery removed, liver metastasis not touched; terramycin post-op.; *slight fever 100.4°-101°F.;* October 21, 1962, small bowel obstruction proximal to ileotransverse colostomy required re-operation, ileostomy; *much reaction present around anastamosis; post-op. fever, 102.4°F.,* l.l.q. pain; discharged November 18, 1962, prognosis, 6 mos.; *gained 16 lbs., returned to work in 1 mo., "never felt better";* very active in job and outside activities; against physician's advice married in August 1963, adopted wife's 3 children; she had miscarriage November 1963; January 1964 small prepyloric ulcer, improved under bland diet; hemorrhoidectomy summer 1964; by fall 1964 fatigue again noted, also muscle pain, wasting, Dupuytren's contractures of hands, appeared chronically ill; required Dexedrine or Ritalin to function minimally; appetite decreased; January 1965 again consulted psychiatrist, "cleared as to emotional factors for these symptoms"; by March 1965 fatigue, muscle aching in back, shoulders, difficulty in concentration had all increased; then had thorough work-up at Memorial Hospital, n.e.d. clinically and biochemically, condition regarded as due to "anxiety state, gastric ulcer"; fatigue increased more markedly by June 1965, also wt. loss, dark brown urine, jaundice, confirmed by liver function tests; 3rd operation August 3, 1965, following aspiration biopsy of liver; 8-10 cm. metastasis found over dome of liver obstructing intrahepatic biliary system; gall bladder and common duct collapsed; dense adhesions freed; liver mobilized downward, n.e.d. other than this single large lesion; from which several biopsies taken; 5-FU given for about 1 mo. ending September 29, 1965, 2 more vials given in November 1965; bilirubin remained remarkably elevated on discharge. wt. had declined to 132 lbs.: 40 lb. wt. loss; prognosis regarded as about 2 wks.; returned home, able to be up and about, but not able to go to work during 9 mos. after his discharge, not bedridden until final 5 days' hospitalization; terminally had nausea, vomiting, weakness, pain and edema of lower extremities; death June 26, ing, weakness, pain and edema of lower extremities; *death June 26, 1966, about 5 yrs. after onset.* (7, 48) (died) 5 yrs.

THE DETAILED CASES OF SOME OF THE ABOVE CASES ARE GIVEN BELOW

CASE 1: Extensive inoperable intra-abdominal carcinoma of the sigmoid flexure of the colon, involving the omentum and the small intestine, adherent to the prostate, the urinary bladder and the bony pelvis, with subcutaneous nodules in the abdominal wall.

Previous History: Mr. S., merchant, aged 75, of Copenhagen, Denmark. For several years the patient had suffered from increasing obstipation, but the exact date of onset is not recorded. When admitted to Strandgaard's service in a Copenhagen hospital, a large tumor was felt in the left iliac fossa. Above the umbilicus there was a hard metastatic nodule in the abdominal wall, also two small nodules in the epigastric region which had appeared recently. Bimanual rectal examination and palpation revealed a rounded tumor mass which seemed to have infiltrated the prostate. The patient was emaciated and suffered from tenesmus which was very painful.

Surgery: A laparotomy was performed in order to perform a colostomy, since it was certain that a radical removal could not be undertaken. The operation revealed ascites and an enormous carcinoma. The sigmoid flexure and small intestine were matted together in a large hard tumor mass which was adherent to the bony pelvis and the posterior portion of the urinary bladder. At the slightest attempt to separate the adhesions hemorrhage occurred. The disease was so far advanced and widespread that there was hardly any of the appendix epiploica that was not involved. The prognosis seemed so hopeless that Strandgaard felt inclined to close the incision without performing a colostomy, but two other surgeons urged that it be done for the patient's sake. Strandgaard stated: "There could be no question of producing this in the usual way (due to the extent of the disease) . . .I had to make a lateral colostomy, and worst of all I had to pull out two portions of the diseased epiploica. I thought I could later remove these by cauterization. Surprisingly the patient stood the operation quite well, and I was going to cauterize four days later when I was extremely sorry to see that the growths had started to increase in size enormously. Although I cauterized them as well as I could, it was clear to me that through the colostomy operation I had stimulated the growth of cancer in the incision and I feared the neoplasm would close the colostomy. The temperature remained normal for 10 days and the colostomy worked well." (59)

Concurrent Infection (Erysipelas) : Fever then developed, the patient complained of backache and a few days later an erysipelas infection was apparent in the lumbar region. The patient was very ill, the temperature high, and the infection spread over the body (trunk and extremities). Twice saline infusions were necessary. The infection finally subsided and Strandgaard noted that the "colostomy wound which had formerly been the site of a tumor mass, was completely clean and granulating. The abdominal tumor could no longer be felt and the subcutaneous metastases were gone, something which the patient himself observed, and was happy to see since he had been worried about these nodules. Shortly thereafter he began to have normal bowel movements through the rectum, and his general condition flourished in every way." After five weeks he was allowed to go home. Symptoms of urinary infection (nephritis) then developed. He again had tenesmus, but this improved when he went to the country, where he went about his garden and felt quite well. During the summer holiday, while Strandgaard was away, the patient died suddenly with signs of acute nephritis. No autopsy was performed. In reporting the case Strandgaard stated that death was apparently due to urinary tract infection

brought about by absorption of a rapidly regressing malignant tumor near the bladder. (59, Case 1)

CASE 7: Adenocarcinoma of the cecum extending through and beyond the bowel wall and involving the abdominal wall in the region of an old appendectomy scar, with extensive involvement of the regional lymph nodes, confirmed by microscopic examination following resection at Peter Bent Brigham Hospital, Boston, Mass.

Previous History: E.K., male, aged 58. The family and previous personal history were not recorded except that the patient had had an appendectomy in 1895. Onset, in late June 1931 he developed anorexia and diarrhea.

Concurrent Infection: Six weeks later he developed tenderness and swelling in the appendectomy scar. He was admitted to the hospital three days later. There was a large abscess in the right lower quadrant pointing in the appendectomy scar, though its etiology was not clear. Incision and drainage of this abscess was necessary.

Clinical Course: Two weeks later barium enema revealed a large filling defect in the cecum.

Surgery: A right colectomy was performed with an end-to-end ileotransverse colostomy. The tumor had invaded the abdominal wall about the appendectomy scar. The entire thickness of the parietes was generously excised in this area.

Clinical Course: Convalescence was uneventful. The patient was readmitted 2½ years late complaining of pain in the right flank, loss of weight and a lump in the scar. Examination revealed a large, ill defined mass that appeared to involve the abdominal wall. Some observers felt that the liver was involved.

Further Surgery: At the second operation a large mass was found involving the abdominal wall and round ligament of the liver. It was excised en bloc with the tissues of the abdominal wall. The 12.5 x 10 cm. defect in the latter was closed by sliding over the left rectus and the right external rectus. Pathological examination revealed a solid mass of adenocarcinoma. No lymph nodes were identified. Histologically the tumor was observed to be invading tissue planes but was growing slowly.

Clinical Course: Convalescence was uneventful. The patient remained well, with no further evidence of disease when last traced in 1939, over nine years after onset. (20)

CASE 10: Inoperable epidermoid carcinoma of the rectum, Grade II, confirmed by microscopic examination at Memorial Hospital in 1938 by Dr. Fred Stewart, following biopsy. A node removed from the groin in 1946 was also examined by Stewart and reported to be epidermoid carcinoma.

Previous History: Mrs. H.H., aged 64, of Bernardsville, New Jersey. The family history was non-contributory. The patient was a widowed secretary. She had had one pregnancy 38 years previously, followed by infection. A repair operation and uterine suspension was performed nine years later, in 1909. She had always vomited easily. For four to six years prior to admission she had had excessive flatus. (She gave her history very reluctantly and vaguely.) In the three or four years prior to admission to Memorial Hospital she apparently had had an increasing number of stools but no diarrhea, that is three or four a day at times. Menopause occurred at the age of 51 and was uncomplicated. There were no cardiac or urinary symptoms, but she had frequent headaches

whenever she had any other disturbance. Onset, in 1936-37 she began to have occasional rectal pain apparently unrelated to stool, often in the middle of the night. She would then have a feeling of a mass in the rectum which she would try to expel on the toilet. No blood, mucus or change in size of stool was noted. Shortly before admission she felt twinges of sharp pain in the rectum, but no abdominal pain or distention. In the year prior to admission she had had increased flatus which she had been unable to control, but there was no fecal soiling. Examination on admission to Memorial Hospital, November 11, 1938, revealed a healthy looking, middle aged woman with good musculature, nourishment and color, weighing 150 pounds.

Surgery: On November 27, 1938 a specimen was removed from the rectum by Dr. Binckley and proved to be epidermoid carcinoma, Grade II. On December 1, 1938 an exploratory laparotomy and sigmoid colostomy was performed under spinal anesthesia. No evidence of metastases to the lymph nodes or liver were found. A small module was felt in the rectosigmoid, but it proved to be a diverticulum. Adhesions were present in the omentum and lateral anterior peritoneum secondary to the post partum infection and operation in 1909. The postoperative recovery was only fair, and this was believed due to psychological reasons.

Radiation: She received six high voltage x-ray treatments totalling 2400 r between December 19 and 30, 1938, two each over the left and right posterior pelvis and perineum. She was discharged on January 7, 1939.

Postoperative Infection: A few days after her return home the patient developed a severe streptococcus sore throat with a temperature of around 104°F., for which she was hospitalized locally for 11 days. It was necessary to administer parenteral fluids because she could not swallow. She returned home in a weakened condition She also developed a "macular, pigmented, non-itching rash over the trunk, neck and upper extremities", which persisted when she was readmitted to Memorial Hospital (was this erysipelas?), on February 20, 1939. The colostomy had functioned well, the patient was able to eat everything. Rectal examination at this time revealed pigmentation about the anus due to the radiation and a stenosing firm, indurated mass 4 cm. within the anus, confined chiefly to the right lateral and anterior walls. The lumen was narrowed. There were no inguinal nodes, and no masses or tenderness within the abdomen. The patient had arteriosclerotic heart disease.

Further Radiation: She was then given 12 radium pack treatments totalling 18,000 mch., between February 23, and March 8, 1939. On March 1, 1939 Binckley examined her and reported that "it was difficult to locate the tumor," although "there was a small amount of induration at the right inferolateral rectal wall — not definite." She was discharged improved on March 8, 1939.

Clinical Course: She was again seen at Memorial Hospital in May 1939 at which time it was stated that there was no evidence of disease. She was advised to keep her colostomy, which had been working much better since she had taken vitamins. She remained free from disease and got along well although she asked to have the colostomy closed. Binckley did not think this should be done.

Radiation Ulcer: In February 1940 a small radiation ulcer developed at the margin of the anus and caused quite severe pain requiring opiates to control. Two small hemorrhages occurred from this area. Examination on her third admission to Memorial Hospital, May 13, 1940, showed several areas of telangiectasia around the anus, with a small radionecrotic ulcer at the margin on the right side.

Further Surgery: On May 18, 1940 a perineal resection of the rectum was performed by Binckley. There was a moderate degree of ulceration and some thickening. He added: "One could not be sure whether this was malignant or postradiation reaction. Pain was perhaps not nearly so severe as patient claims, as she is very apprehensive and nervous. However, it was thought advisable to remove the anal canal." The tissue failed to show any evidence of malignancy. Convalescence was uneventful and she left the hospital in good condition.

Clinical Course: She remained free from disease until August 1941, when a mass was found in the left groin, which was considered as undoubtedly metastatic. The patient refused to have anything further done at Memorial Hospital. For a time there was some decrease in the size of the mass, but by April 1942 it was again its original size. At this time the patient wrote: "I haven't had a day that has been free from discomfort in my rectum, and part of the time it has nearly knocked me out." She was again seen by Binckley in February 1943, having been able to continue doing part time secretarial work during that year. She apparently improved during 1943. The disease then slowly progressed causing death from inanition on March 21, 1946. This was over nine years after onset, seven years after the first operation and the streptococcal infection and five years after the metastases developed in the inguinal nodes.

Comment: Note that in this case the streptococcal infection occurred following x-ray therapy and prior to radium treatments. Doubtless this infection helped to potentiate the response of this inoperable tumor to the radiation, causing complete regression. It is a pity that so much radiation was given leading to ulceration and painful sequelae, requiring radical resection of the rectum. (44,48)

CASE 11: Rapidly growing adenocarcinoma of the sigmoid, with direct extension to the urinary bladder and terminal ileum and many lymph node metastases, confirmed by microscopic examination following resection at Peter Bent Brigham Hospital, Boston, Mass.

Previous History: Male, aged 52. Onset, in February 1938 the patient began to have rectal bleeding, tenesmus and loss of weight which continued during the next 18 months. He was finally admitted in July 1939, with a large, fixed mass in the left lower quadrant. Barium enema showed a filling defect in the sigmoid, with direct extension to the bladder and terminal ileum.

Surgery: A right transverse colostomy and a sidetracking ileostomy were performed by Dr. J. E. Dunphy.

Concurrent Infection: The patient developed a postoperative wound infection.

Further Surgery: Three weeks later resection of the sigmoid, terminal ileum and upper third of the urinary bladder were performed. The colostomy was closed two weeks later. Dunphy noted that the tumor was "of an extremely inflammatory character."

Clinical Course: Convalescence was uneventful. The patient was readmitted two years later because of abdominal cramps and rectal bleeding. There was an ill defined mass low in the left lower quadrant just at the base of the pelvis. Barium enema revealed evidence of extrinsic pressure on the sigmoid.

Further Surgery: At operation a mass of solid tumor was found to involve the sigmoid, mesentery, bladder, left ureter and retroperitoneal tissues. It was separated with difficulty from the iliac vessels. The ureter was resected but

because of lateral displacement it was sufficiently long to permit end-to-end anastamosis. A permanent colostomy was performed. The serosa over the posterior aspect of the bladder was removed with the tumor, but the bladder wall was not involved. Pathologic examination revealed that the tumor was a mass of adenocarcinoma in fat that was involving the bowel wall. It was extremely anaplastic with many lymph node metastases.

Clinical Course: Convalescence was uneventful. Both kidneys functioned normally. The patient remained well and free from further recurrence in January 1946, almost eight years after onset, and 5½ years after the second operation. (20)

CASE 14: Diffuse inoperable adenocarcinoma, apparently primary in the transverse colon and gastrocolic omentum with metastases in the peritoneum, mesentery, ovaries and liver, confirmed by microscopic examination by Dr. Mendel Jacobs, at Beth El Hospital, Brooklyn, and by Dr. Ludvig Hektoen, of Chicago, who cut fresh sections from the original block of tissue. (36)

Previous History: Mrs. G.M., aged 34, of Brooklyn, New York. Menses began at 12½, a regular 28 day cycle, lasting eight or nine days. An appendectomy was performed in 1932. The patient married at the age of 25 and conceived easily. She was under some mental strain during the entire pregnancy as her husband had been out of work for some time and could find only part time employment. On November 22, 1939, she was delivered spontaneously after a short labor and a perfectly normal pregnancy. The immediate post partum course was uneventful, and she was discharged on the tenth day. Onset, soon after her discharge she began to have colicky pains in the upper abdomen, also weakness, fatigue, epigastric fullness, nausea, emesis, anorexia, frequency of urination and weight loss. These symptoms gradually became worse, however, repeated examinations revealed only a small pedunculated fibroid attached posteriorly to the uterus. Despite these symptoms the patient continued to nurse her baby until February 1, 1940, nine weeks after confinement. She was advised by Dr. William Levine to remain under observation and was seen again 3½ months later, still complaining of the above symptoms. At this time Levine found a large, tender, fixed mass in the mid-abdomen, not connected with the uterine fibroid. The liver was also enlarged and tender. X-ray studies of the gastrointestinal tract revealed no evidence of gastric or duodenal ulcer or new growth. A mass density in the right upper quadrant was suggested which was extracolic and extrarenal.

Surgery: The patient was readmitted four months post partum. An exploratory laparotomy, April 15, 1940, revealed free hemorrhagic fluid in the peritoneal cavity. The liver was enlarged, nodular and contained numerous metastatic nodules. There were multiple implants on the peritoneum and in the omentum. There was also a large firm mass in the gastrocolic omentum and the transverse colon. It was not possible to say whether this mass arose from the lumen of the gut. The uterus contained two pedunculated fibroids, and both ovaries were studded with peritoneal implants. Several metastatic nodules were taken for biopsy. An attempt was made to take a liver biopsy but was abandoned because of extensive friability and marked bleeding.

Concurrent Infection: The immediate postoperative course was very stormy. The abdomen was markedly distended and the patient vomited. The temperature was persistently elevated, the pulse poor, the prognosis grave. After several days the distension diminished, the temperature declined, food was tolerated and the patient was discharged on the 14th postoperative day. When seen two weeks later she complained of headaches, weakness, vomiting and exhaustion. The abdomen was distended, tender and presented evidence of

free fluid in the peritoneal cavity. The liver was palpable and multiple masses were still felt in the abdomen.

Clinical Course: A few weeks later the spasticity and tenderness in the upper abdomen still persisted but the masses were not felt and the liver enlargement had receded. The patient still complained of some pain in the upper abdomen but vomiting had ceased, the appetite had improved and she had gained four pounds. Pelvic examination revealed a fibroid in the cul de sac. On May 24, 1940, six weeks after the operation the patient menstruated for the first time in the six months since her confinement. During her period she felt nervous and had slight abdominal pain. By this time she had gained 11½ pounds. There was still slight tenderness in the upper abdomen but no masses were palpable, nor could the liver be felt. During the next year she remained under observation and continued to improve. Her weight was normal, her menses regular and she had no complaints.

Further Pregnancy: In April 1943, three years after the laparotomy, the patient was found to be pregnant. Because of her previous history she was readmitted for study and consultation. The surgical, medical, and pathologic departments were consulted. In view of her previous malignancy they all advised terminating the pregnancy by abdominal hysterectomy and sterilization.

Further Surgery: At operation the liver edge was found to be regular and smooth. There were a few adhesions between the omentum and the parietal viscera. The uterus was enlarged, bluish, soft and contained several pedunculated fibroids on its posterior wall, and a larger degenerated fibroid on the left side. There were also numerous subperitoneal elevations, a total hysterectomy with bilateral salpingo-oophorectomy was performed. Microscopic examination of the uterus, tubes, ovaries and sections of the omentum revealed no evidence of carcinoma. The postoperative course was uneventful.

Clinical Course: She was seen periodically and except for slight menopausal symptoms, she had no complaints. The case was reported by Levine and Weiner in 1945 at which time there was no evidence of recurrence or further metastases. In October 1951 she consulted Levine because of hemorrhoids and shortly thereafter a hemorrhoidectomy was performed. For several months prior to October 1953 she was under the care of an otolaryngologist for "repeated discomfort" in her throat. A biopsy of lymphoid tissue in the throat was negative for malignant changes. Levine again examined the patient on October 20, 1953, at which time she was hospitalized with a high fever. Physical examination revealed many palpable lymph nodes in the cervical region and a congested throat. After a few days of antibiotic therapy and ordinary general care the temperature returned to normal, the nodes receded and she was much improved. All laboratory studies pointed to infectious mononucleosis. An additional finding was that she had a rapid Cephalin flocculation and high thymol turbidity, indicating impaired liver function. Subsequent tests showed that these were returning to normal. She was discharged on October 28, 1953. She was last traced in good health in May 1955, over 15 years after her recovery following concurrent infection and fever. She then moved and attempts to trace her subsequently have failed.

Comment: In reporting this case the authors cited various references relating to the influence of pregnancy on the growth rate of malignant tumors, including DeLee and Greenhill who state that the termination of a pregnancy by birth or abortion significantly increases neoplastic growth and that during pregnancy progesterone checks the carcinogenic action of estrin. This they believed explained the extensive rapid growth of the neoplasm in their case soon after delivery. (36, 48)

CASE 15: Extensive adenocarcinoma of the transverse colon with metastases to the abdominal wall, confirmed by microscopic examination following biopsy of the metastases at Henry Ford Hospital, Detroit, Michigan. (22)

Previous History: J.K., male, aged 42. The family and early personal history were not recorded.

Concurrent Infection: The patient was admitted to Henry Ford Hospital in September 1941, because of abdominal pains of two weeks duration. He had lost 10 pounds in weight in these two weeks. Physical examination on admission revealed very marked tenderness to light palpation in the left lower quadrant and to a lesser degree in the left upper abdominal quadrant. The impression at this time was that he had an intra-abdominal inflammatory process, probably a ruptured diverticulum.

Surgery: Because the condition did not improve with conservative management, an operation was performed by Dr. Lawrence Fallis on September 18, 1941. On opening the peritoneal cavity a mass was found occupying the left half of the transverse colon. Numerous loops of small intestine, which were adherent to this mass, were dissected away and an abscess cavity was entered. Pus was aspirated and cigarette drains were placed. Sulfanilamide powder was placed in the wound. The surgical diagnosis was ruptured diverticulum with abscess formation. The postoperative course was stormy, but the patient gradually improved and was discharged on October 15, 1941.

Clinical Course: He continued to have recurrent attacks of pain, nausea with vomiting and was finally readmitted on December 26, 1941 stating that about December 11, 1941 he had begun to feel generally bad, had had some abdominal pain and had become progressively weaker. Five days later he stopped work and went to bed. At this time he noted that the drainage at the site of the former operation began to contain feces. A barium enema revealed a narrowing of the distal transverse colon which was interpreted as an organic stenosing lesion. The patient was afebrile and was discharged on December 29, 1941. He was readmitted on February 1, 1942 with a new sinus next to the old one at the left lateral aspect of the wound. He had gone progressively downhill in the previous month. Bowel movements through the anus had ceased, and all fecal material appeared to be passing through the fistulae.

Further Surgery: A transverse colostomy was performed uneventfully on February 4, 1942 in order to divert the fecal stream.

Clinical Course: The region about the old scar and fistulae gradually showed further induration and elevation, and by February 24, 1942 this indurated area was 12 x 20 cm. in diameter. The fistulous tract was noted to be partly occluded by friable white material.

Further Surgery: A biopsy was taken from the involved skin of the abdominal wall on February 27, 1942. Microscopic examination showed metastatic adenocarcinoma invading the subcutaneous tissues. Poorly differentiated tubular glands were present and massive necrosis was noted to affect large areas of the tumor. The tumor mass superficial to the skin margin and about the old fistulous tract was excised. No effort was made to destroy the base of the tumor or the portion which arose in the colon itself.

Clinical Course: By March 25, 1942 the patient was up and about and was discharged home on April 1, 1942, weighing 135 pounds. On his way home he had one of Dr. Koch's "cancer cure injections." He continued to lose weight and to go downhill until about June 20, 1942 remaining in bed. During this time he became a devotee of Christian Science. On July 1, 1942 he

weighed about 113 pounds, having lost 22 pounds in the previous three months. From that time on he began feeling stronger and gained weight. By mid-July the wound near the fistulous tract had healed completely. His appetite was enormous and by the end of July he had gained 62 pounds (in a month). He returned to Henry Ford Hospital on August 28, 1942, appearing in excellent health. The fungating lesion previously present at the site of the fistulae and involving the abdominal wall had completely disappeared.

Further Surgery: A crushing clamp was applied to the colostomy spur. The patient was discharged from the hospital on September 2, 1942. He was readmitted on November 19, 1942 for closure of the colostomy, which was performed by Fallis. The abdomen was not opened at this time.

Clinical Course: The patient remained in excellent health thereafter.

Further Surgery: On September 6, 1957 he underwent repair of a small epigastric hernia and an appendectomy was performed by Dr. Raymond D. Benson, of Billings, Montana. A limited exploration of the abdomen through the small hernia incision revealed no evidence of carcinoma. An exploration of the right lower quadrant through a McBurney incision also failed to reveal any remains of the extensive carcinoma. In 1963 he had a wedge resection of the middle lobe of the right lung for an indeterminate lesion which proved to be an old infarct. Also in 1963 he had an operation for small bowel obstruction due to adhesions. In 1966 an operation was performed for repair of a large ventral hernia. Barium enema that year showed no lesions. Chest films showed a slightly enlarged heart, but no other lesions. In February 1967 a cholecystectomy was performed in Mesa, Arizona.

Clinical Course: The patient remained in good health thereafter, though overweight (225 pounds), his height being six feet. He was last traced on February 9, 1968, 26½ years after onset.

References: 22, p. 396-399; 48.

CASE 16: Inoperable, perforated, obstructing adenocarcinoma of the descending colon extending into the sinus tract above the crest of the ilium, confirmed by microscopic examination at the Mayo Clinic.

Previous History: Male, aged 45, farmer. The patient had been in good health prior to onset.

Infection: In September 1950 he first developed pain in the left flank, accompanied by fever and loss of weight. A small, tender, fluctuant mass slowly appeared in this region. After some weeks this was incised and drained by a local physician. Foul smelling pus continued to drain from the abscess for about two months. The abscess then recurred and was again incised in March 1951. Thereafter the sinus and purulent drainage persisted. During this interval the patient's weight declined from 170 to 130 pounds, but he had no symptoms referable to the bowel.

Surgery: In April 1951 the colon became acutely obstructed necessitating the establishment of a colonic stoma. On abdominal exploration at this time, a hard nodular irregular mass was found involving the lower portion of the descending colon. The mass was so solidly fixed to the bony pelvis that the lesion was considered inoperable. The postoperative course was uneventful. The patient gained a few pounds in weight.

Further Infection: However, he continued to have aching pain in the left lower abdomen and subsequently several sinus tracts appeared above the left ilium from which there was purulent drainage. The patient was first seen at

the Mayo Clinic in October 1951. He appeared chronically ill and weighed 135 pounds. There was a colonic stoma in the right upper quadrant of the abdomen. Immediately above the crest of the left ilium there were two small sinuses from which pus was draining. A tender, hard, ill defined mass was present in the abdomen just medial to the left anterior superior spine. Except for moderate leukocytosis and mild hyperchromic anemia, routine laboratory studies revealed no abnormalities. Proctoscopic examination was negative. X-ray examination of the colon after barium injection both into the colonic stoma and through the rectum, demonstrated a filling defect of the midportion of the descending colon. Culture of the pus from the sinuses revealed only anaerobic streptococci.

Further Surgery: On curettage of the sinus, masses of malignant tissue were recovered which proved to be adenocarcinoma, Grade I, of intestinal origin. (23, Fig. 2; 67, Fig. 1) It was concluded that the patient had a perforated obstructing carcinoma of the lower part of the descending colon. The lesion was hopelessly inoperable because of its extent and fixation. In view of the fact that the colonic stoma had been established for some six months, there seemed little reason to hope that the lesion might become operable with the lapse of more time.

Radiation: X-ray therapy was administered through anterior, posterior and lateral fields (2500 r in 14 days), by means of an orthovoltage irradiation source. The patient was discharged early in November 1951.

Clinical Course: Drainage from the sinuses stopped and the sinuses healed completely one month after his return home. The mass in the lower abdomen disappeared. The patient regained his lost weight (35 pounds) and was in robust health. He returned to the Mayo Clinic in September 1953, nearly two years later, requesting closure of the colonic stoma. At this time proctoscopic examination was negative. X-ray studies of the colon with barium revealed that the proximal loop of the colon was normal. Distally from the colonic stoma, the barium passed through the descending colon as far as the left iliac crest. Barium injected from below advanced upward as far as the mid-portion of the iliac fossa. Between the points of obstruction from above and below there was an unfilled segment approximately 6 cm. long. In view of the patient's complete recovery, together with the disappearance of the mass and the healing of the sinuses, re-exploration of the abdomen was advised.

Further Surgery: At operation, 22 months after his previous dismissal, there was no evidence whatsoever of the previously proved lesion. A segment of the lower part of the descending colon approximately 6 cm. in diameter was absent. The proximal and distal segments were closed and were not even connected by an adhesion band. A wedge-shaped segment of the mesocolon had disappeared as well. Careful examination failed to reveal metastases in the liver, peritoneal implants or other residual tumor. The two blind ends of the colon were mobilized and excised for examination for the presence of carcinoma. No tumor tissue was found on either gross or microscopic examination. The ends were then closed and a side-by-side colocolostomy was carried out. The postoperative course was uneventful. The colonic stoma was closed in November 1953. The patient was discharged shortly thereafter, at which time his bowel was functioning normally.

Concurrent Inflammation: He remained well except for mild asthma for the next seven years.

Clinical Course: In August 1960, symptoms of obstruction of the large bowel developed rather suddenly, including colic bloating, vomiting and obstipation. All symptoms yielded to conservative treatment in approximately 10

days. The patient was then referred to the Mayo Clinic for further therapy. A firm, irregular tender mass was found in the left lower abdominal quadrant. Proctoscopic examination disclosed an extraluminal mass 16 cm. above the dentate line, which impinged on the lumen of the bowel. The bowel was fixed so that visualization higher up was impossible. X-ray examination was unsatisfactory essentially because of tenderness and inability of the patient to retain barium.

Further Surgery and Inflammation: Abdominal surgical exploration showed that the mass involved the upper part of the sigmoid flexure. *The bowel was fixed by an intense inflammatory reaction more suggestive of diverticulitis than of carcinoma. The bowel seemed to be involved by an almost purulent inflammatory reaction,* although there was no gross evidence of perforation. Otherwise, the findings were negative; there was no evidence of recurrence of the original lesion, and the previously established anastamosis, several centimeters above the newly involved region of the bowel was not affected. The remaining portion of the descending colon was mobilized and resected. Colonic continuity was re-established by end-to-end anastamosis between the side of the transverse colon and the lower part of the sigmoid. Pathologic examination revealed that the lesion was a mucus-producing adenocarcinoma situated 7 cm. below the site of the former anastamosis. (66, Fig. 2) The lesion had not extended beyond the wall of the bowel, and most careful study did not reveal perforation. There was marked round cell infiltration of all layers of the bowel wall but none of the lymph nodes were involved metastatically. The lesion seemed definitely different histologically from the first carcinoma which had not produced any mucus and which had been Grade I. The conclusion reached after comparison of the two lesions was that they were two independent primary neoplasms.

Clinical Course: The patient made a complete recovery. He remained free from recurrence or metastases in 1965, 15 years after onset of the first neoplasm and five years after onset of the second carcinoma of the colon.

Comment: In reporting this case in 1954, Fergesen and Black stated: "It is not difficult to conceive of the spontaneous cure, by necrosis and sloughing of the invaginated segment of the bowel, of an intersuscepting carcinoma of the colon. However, . . .it must be most unusual for a carcinoma which has infiltrated through and beyond the limits of the colonic wall to disappear spontaneously. . . .It seems unlikely that it resulted solely from roentgen therapy. The less anaplastic adenocarcinomas of the colon are relatively radioresistant. The treatment given was not particularly intensive as judged by the complete lack of cutaneous changes. Certainly the amount of treatment was not sufficient to destroy a portion of the colon and mesocolon. The complete disappearance of the colonic segment and its mesocolon can be explained more probably by assuming that they became infected and were ultimately absorbed. The proximal colonic stoma evidently protected the peritoneal cavity from fecal contamination and peritonitis. . ." (23)

It is now apparent that preliminary infection or injections of bacterial toxins can protect patients or animals against the deleterious effects of subsequent radiation, while at the same time the radiosensitivity of the tumor is increased. Note that in this case no skin changes were observed and complete regression of an inoperable tumor occurred following a rather small dose of x-ray. In reporting this case in 1961 Thomford and Black stated: "Everson and Cole, in a comprehensive review of spontaneous regression of cancer, did not find any other instances of total disappearance of locally inoperable carcinoma of the colon. . .It is obviously of considerable interest that both lesions were associated with a violent localized inflammatory reaction. The inflamma-

tory process associated with the second lesion at least had not resulted from free perforation so far as could be determined by careful gross and microscopic examinations. The speculation that malignant tissue was the inciting factor is provocative." (66)

In this case local infection first developed 19 months prior to the development of acute intestinal obstruction due to the carcinoma, whose date of onset is unknown. During those 19 months, infection recurred and suppuration continued after the colostomy was performed. Although this infection did appear to stimulate an intense local inflammatory reaction to the tumor, regression of this extensive inoperable tumor did not occur until x-ray therapy, considered inadequate for cure (2500 r) had been given. During the next seven years the patient remained in excellent health except for mild asthma, which is not often seen in cancer patients. As to why this man's tissue reaction was so different from the usual cancer patient, it is believed that the preliminary prolonged local infectious process in 1950-51, from which streptococcus was isolated, increased the patient's ability to elicit a marked immune response. (27, 57) Ainsworth (1), Cole, et al (15), Hollcraft and Smith (32, 55, 56) have reported on the protective effects of bacterial endotoxins on animals receiving radiation. More recently, Chandler, et al (10) have observed that preliminary injections of bacterial toxins can render radioresistant tumors responsive to subsequent radiation. Thus in the above case it is probable that the preliminary and concurrent infection potentiated the effects of the small amount of x-ray therapy given, while protecting the normal tissues.

CASE 22: This patient had three different primary malignant tumors: a) transitional carcinoma of the bladder with numerous hepatic metastases; b) carcinoma of the colon with localized metastases; a second primary carcinoma of the bladder in a different location. All were confirmed by microscopic examinations at Memorial Hospital, New York.

Previous History: Male, aged 55. The family and previous personal history were not recorded, except that at the age of 33 the patient presumably had a coronary occlusion (later questioned). Onset, in 1955 he developed a cancer of the bladder.

Surgery: This was removed transurethrally in June 1955, and was reported to be a transitional cell carcinoma with frank invasion of the bladder wall.

Clinical Course: The patient remained well five years. Barium enema on September 22, 1960 showed a 1.5 cm. filling defect in the lower sigmoid having the appearance of a polyp and also a segment of bowel which had a rather irregular mucosal pattern that never fully dilated. This was interpreted as diverticulitis.

Further Surgery: Two polyps were removed at 5 and 10 cm. through the proctoscope. The bowel appeared normal up to 15 cm. An acute bend in the sigmoid prevented further inspection. The patient was discharged, returned home and did fairly well for a brief period. He then suddenly became acutely ill with intestinal obstruction and was again hospitalized. Laparotomy was performed and both lobes of the liver were found to be studded with numerous metastatic nodules. Two other metastatic nodules were excised from the right lobe of the liver and two from the left for biopsy. These showed masses of close packed, small malignant cells, metastatic cancer of the bladder. Numerous other metastases were left in place. There was also a large inflammatory mass in the pelvis causing the obstruction. It was assumed that this resulted from the diverticulitis. To relieve the obstruction a double barrelled colostomy was performed from the transverse colon.

Clinical Course: The patient was informed that he had diffuse liver metastases and that life expectancy was brief. Clinically he did well. He gained 14 pounds in weight and returned to work. He took little interest in learning colostomy regulations and was content to let the feces discharge into a bag. He was first seen by Dr. Alexander Brunschwig on March 1, 1961 and was admitted to Memorial Hospital. Barium enema at this time showed a constricting lesion in the lower sigmoid colon. He was advised to have the lesion repaired as a palliative measure (since liver metastases were present). The patient elected not to have these procedures, but to return home and "await death." After a period at home in which his general condition improved, he was readmitted to Memorial Hospital, having decided to have the surgery recommended in March.

Further Surgery: On May 4, 1961, an anterior resection of the recto-sigmoid was performed, with end-to-end anastamosis of the colon. The liver was palpated and found to be free of metastases. There were no peritoneal metastases visable or palpable. The resected segment of colon was 18 cm. in length and contained an ulcerated papillomatous lesion 3 cm. in diameter. The mesenteric lymph nodes were grossly unremarkable. The microscopic findings were: adenocarcinoma Grade III to IV of the colon. The tumor extended through the full thickness of the bowel wall and was metastatic to the lymph nodes at level II only.

Postoperative Infection: Convalescence was complicated by a large left subdiaphragmatic abscess which was drained anteriorly in the left upper quadrant on May 24, 1961. Several rather severe hemorrhages occurred through this wound requiring transfusions on several occasions, between June 1 and 8, 1961. On the latter date small bowel contents appeared in the left upper quadrant of the wound and became increasingly copious.

Further Surgery: On June 21, 1961, a third laparotomy was performed to evacuate a large subdiaphragmatic infected hematoma and to resect a fistulized loop of lower jejunum with end-to-end repair of the bowel. On this occasion the entire liver was again inspected and palpated, and was again found to be free of the diffuse metastases, appearing normal except for a stellate scar near the anterior edge of the right lobe; other scattered cicatricial foci were also noted and were apparently the sites of the five biopsies in 1960. The one in the anterior right lobe was excised beyond the limits of the scar. Microscopic examination of the liver tissue was unremarkable. Sections of the bowel tissue showed inflammation and serosal adhesions.

Clinical Course: Convalescence proceeded without further complications, and normal evacuation of feces was resumed. The patient was discharged on July 8, 1961. Papanicolaou smears of the urine and cystoscopic examination were negative.

Further Surgery: On January 9, 1962 the patient was admitted to another hospital. The bladder was opened through a short suprapubic incision and multiple papillomas were cauterized and radon seeds were implanted into one area which grossly appeared to be carcinoma.

Clinical Course: The patient remained well until March 1964, when he developed a bleeding peptic ulcer. The symptoms cleared under bland treatment.

Further Surgery: In late March 1964 a cystectomy was performed in Elmira, New York for recurrent bladder cancer, Grade III, and the ureters were transplanted into the rectum. At this time there was no further evidence of bowel cancer, but the bladder cancer had metastasized to the kidney.

Clinical Course: Thereafter the course was steadily downhill. His terminal admission was for sudden onset of respiratory difficulty.

Terminal Infection: A tracheotomy was performed and a large amount of purulent material was suctioned from the lungs. He expired on the day of admission, April 25, 1964, nine years after onset of the first bladder cancer and four years after onset of the carcinoma of the sigmoid colon. Autopsy revealed carcinoma of the urinary bladder extending throughout the pelvis and metastatic to the left kidney; extensive bronchopneumonia, severe bronchiectasis, bilateral pleural effusion, chronic adhesive peritonitis, coronary sclerosis, abscess of the left kidney, bilateral hydroureters. The pathologist, Dr. Charles A. Kuonen reported at autopsy: "Although there was extensive carcinoma in the pelvis (masses 14 cm. in diameter) the liver was completely free of cancer on both gross and microscopic examination." He added: "I cannot account for this unusual situation. The patient did receive an oncolytic agent (Cytoxan), but he also had several bouts of infection and it is not impossible that this, in some way, altered his disease and prolonged his life." (7, 44, 48)

Comment: In this case an episode of pelvic peritonitis, presumably of mixed bacterial etiology, led to an emergency operation, at which time the hepatic metastases from the bladder cancer resected five years previously were discovered. The patient's history over a period of several months indicates that the peritoneal infectious process was somewhat active during this period. Whereas the hepatic metastases were observed to regress, the patient nevertheless developed a carcinoma of the colon which persisted and this apparently occurred during the period when peritonitis was present. Brunschwig concluded: "This is a unique situation among patients who show regression of cancer in that one form present (cancer of the bladder, metastases in liver) regressed, whereas another form (cancer of the colon) developed, metastasized locally, and did not regress but was resected. A year later another carcinoma developed in the bladder at a different location from the first . . ." (7) Note that following removal of the colon cancer there was a large subdiaphragmatic abscess. This tumor never recurred or caused metastases.

CASE 23: Large recurrent adenocarcinoma of the colon, confirmed by microscopic examination following resection of the primary and biopsy of the recurrence, at Memorial Hospital, New York.

Previous History: Female, aged 68. The family and previous personal history were not recorded, except that the patient had had a subtotal hysterectomy many years before, presumably for fibroids. She was seen in consultation by a gynecologist on August 1, 1960 because of bloody, feculent discharge from the vagina. Examination showed a mass 7 x 7 x 5 cm. in diameter above and to the left of the retained cervix and contiguous with it. Barium enema showed extrinsic pressure on the lower mid-sigmoid.

Surgery: Curettage of the cervical stump produced necrotic tissue which was reported to be "papillary adenocarcinoma – primary most likely in large bowel."

Radiation: Radiation therapy by cobalt beam was instituted. By October 13, 1960 the mass was found to be enlarging and the patient was not tolerating treatment very well.

Clinical Course: She was first seen by Dr. Alexander Brunschwig on October 24, 1960. She then weighed 90 pounds and had been advised to discontinue cobalt therapy. Physical findings were as described above except that the vaginal discharge was now frankly fecal.

Further Surgery: She was admitted to Memorial Hospital on November 13, 1960. A week later laparotomy was carried out in order to perform en masse excision of the sigmoid, measuring 20 cm. in length, the cervix, the upper vault of the vagina and the dome of the urinary bladder. The vaginal vault was left open and the bladder was repaired by transverse closure with an indwelling suprapubic catheter as well as a Foley catheter. The lower descending colon was anastamosed to the lower pelvic colon and a diverting colostomy was made in the mid-transverse colon. Gross study of the specimen showed a friable tumor mass above the cervical stump, segment of bowel wall and some of the urinary bladder. A sinus communicating through the tumor was present between the bladder, cervical canal and colon (threeway communication). Microscopic examination showed adenocarcinoma, partly colloid, and consistent with colon origin. The lymph nodes were normal. The bladder showed chronic cystitis and radiation changes.

Concurrent Fever and Infection: Convalescence was complicated by a period of sustained fever, wound infection, cystitis and marked loss of appetite.

Clinical Course: The patient was discharged on January 6, 1961, with a Foley urethral catheter, because a large vesicovaginal fistula had again developed due to postoperative breakdown of the bladder repair. By January 21, 1961 she weighed 88 pounds and the fistula was still large. By February 10, 1961 it had become smaller. On February 27, 1961 irrigation of the bladder seemed to indicate it had contracted considerably. On March 31, 1961 her weight was still 88 pounds. Rectal examination revealed a recurrent mass the size of a fist in the hollow of the sacrum, not previously palpated. It gave the impression of thick fluid under pressure. A #13 needle was introduced through the anus with a finger guiding it into the anal canal, directed upward into the mass and thick, semi-solid, hemorrhagic material was easily aspirated. Pressure on the mass aided evacuation of this material. Following removal of the large needle additional material escaped from the puncture wound. Palpation posteriorly with the examining needle showed that the mass was not appreciably reduced in size. The aspirated fleshy substance resembled the friable material obtained from curettage of the uterus. It was collected and sent to the laboratory and reported as "fragments of adenocarcinoma, colon type."

Clinical Course: Because of this, arrangements were made for the patient's terminal care. She was finally admitted to a nursing home on May 17, 1961. Late that spring the Foley catheter was removed and urine passed voluntarily via the urethra as well as per vagina by irregular leakage. Colostomy care by regular irrigation was satisfactory. During the summer and fall of 1961 her appetite improved and general well being ensued. In the seven months between April 1 and November 1, 1961 she gained approximately 14 pounds. By early September 1961 she felt that her general condition was such that the colostomy should be closed. She was again seen by Brunschwig on November 6, 1961 who described her general condition as follows: "The patient looks so well she doesn't seem to have ever had advanced pelvic cancer." Vaginal examination showed a vesicovaginal fistula about 2 cm. in diameter high in the vaginal vault. On rectal examination the site of the colostomy was found patent and surrounded with minimal induration. The large mass, which had been present in the hollow of the sacrum the previous March, had completely disappeared. No radiation or chemotherapy had been administered since November 1960.

Further Surgery: The patient was readmitted to Memorial Hospital and after preparation (chest films were negative) laparotomy was again performed. Inspection and palpation of the abdominal cavity was negative for evidence

of cancer. There was moderate old inflammatory reaction about the large vesicovaginal fistula. The posterior aspect of the bladder was freed and the 2 cm. fistulous opening well delineated, its edges freshened and closed with three layers of sutures. Palpation in the hollow of the sacrum and about the lower anastamosed colon showed no evidence of cancer. Biopsies were taken of the sacrum in the area occupied by the large recurrence. Microscopic study of these tissues was reported as showing scar tissue only, and no evidence of neoplastic cells.

Clinical Course: In January 1963 the patient remained well. She was seen by Brunschwig at intervals and remained in good health with no further evidence of disease. By 1965 she had gained 21 pounds. She remained well until September 1967. She was readmitted on October 1, 1967. Four days later Brunschwig performed a transthoracic esophageal gastrectomy for adenocarcinoma of the stomach with metastases to the celiac axis. Death occurred on November 16, 1967, over seven years after onset. (7, 22, pp. 399-401; 44, 48)

CASE 24: Large poorly differentiated adenocarcinoma completely encircling and partially obstructing the ascending colon, with multiple metastases in the adjacent fat and mesenteric lymph nodes and with a solitary metastasis 4 to 5 cm. in diameter in the right lobe of the liver, confirmed by microscopic examination following resection of the primary lesion and the localized metastases at White Plains Hospital, New York. (Path #62366)) The liver metastasis was inoperable.

Previous History: W.A.G., aged 50, electrical engineer, of Hartsdale, New York. A paternal aunt had died of cancer of the pancreas involving the liver. The patient's father had apparently died of a cerebral hemorrhage. His sister had a hysterectomy at the age of 17 years. His mother was domineering, his father a weak character. The patient had had the usual diseases of childhood, also pneumonia twice as a child. He served as a captain in the air force in World War II. He was married in 1943, and two children were born of this marriage in 1944 and 1946. He was divorced in 1954, at which time he first consulted a psychiatrist. His second marriage was also unsuccessful and he again sought psychiatric help in 1960-61. His psychiatrist told him that his problems stemmed from being dominated by his mother and his wives. In 1957 he was found to have a low basal metabolism rate. In 1958 his P.B.I. was 3.9 and he complained of lethargy. He was then given thyroid extract (1 or 2 grains daily). He was a heavy smoker and by 1961 was smoking two packs of cigarettes daily. During his adult life his bowels had moved only at five or six day intervals and he had hemorrhoids. Onset, in the early summer of 1961, during psychiatric treatment and prior to his second divorce which became final in October 1961, very insidiously the patient noted increased fatiguability. He was seen by the family physician, Dr. Leo Cardillo on January 10, 1962. In the previous month he had lost 10 pounds in weight and had noted loss of ambition, impaired mental function, poor concentration and a tight feeling in the chest. There was left lower quadrant discomfort with a "crampy, gassy feeling". However, complete physical examination as well as sigmoidoscopy and blood chemistries were all normal. On August 5, 1962 the patient awoke with low back pain after "slumping across an ottoman the previous night." He was given ACTH, and prednisone with dramatic relief of the bloating. Successive courses of Spartase, Vitamin B-12 and Parnate were of no real benefit. On September 18, 1962 he had another episode of acute low back pain. ACTH and prednisone were again given with symptomatic relief as regards the back. On September 28, 1962 he had nocturia (five times) and stated that the previous weekend he had had sharp abdominal pains which seemed worse after

meals. (Could this episode have been due to the abscess found at surgery two weeks later?) At this time another complete blood count was made and revealed a microcytic anemia with hematocrit 30%; hemoglobin, 8.6; wbc, 8,500. He was admitted to White Plains Hospital on October 5, 1962 with vague abdominal discomfort, bloating, flatulence but no pain. For the previous three or four weeks he had been quite dyspneic on exertion and had had substernal oppression on exertion, relieved by resting. No abdominal masses were palpable. The patient was quite pale with associated tachycardia. During the week prior to admission he had lost five pounds in weight. Barium enema on October 8, 1962 revealed a carcinoma of the ascending colon. He was given Vitamin K, and four units of blood prior to operation. The bowel was sterilized. Sulfasuxidine was given preoperatively and for a week after operation.

Concurrent Abscess Revealed at Surgery: Intense Inflammatory Reaction in Region of Primary Tumor: On October 11, 1962 Dr. W. Van S. Widgeley operated. A 6 cm. large tumor mass was found in the right colon below the hepatic flexure. There were enlarged mesenteric lymph nodes palpable down to the root of the mesentery. There was a solitary metastasis 4 to 5 cm. in diam-in the right lobe of the liver directly over the hepatic veins. There was no evidence of intestinal obstruction. The entire right colon was removed including about 20 cm. of ilium and extending to the mid-transverse colon. The omentum over the right side of the colon was included in the specimen. An end-to-end ileotransverse colostomy was then performed. The hepatic metastasis was not biopsied. The pathologist reported that the annular tumor completely encircled the lumen in a band about 5 cm. wide with raised scalloped margins. Sections showed that the tumor tissue had extended well into the surrounding fat forming a band several mm. thick. Tumor was evident also in nodes in the fat immediately adjacent to the bowel wall. Just proximal to the scalloped margins of the tumor were two or three satellite nodules of firm tissue. The ascending colon proximal to the lesion at about the hepatic flexure was dilated, the muscular wall slightly thicker than usual. The appendix was large and swollen, but the serosa was smooth and glistening, the wall somewhat edematous. A cluster of enlarged nodes obviously involved by tumor were found in the ileocecal angle and a similar even larger node was found several cm. away at a point estimated to be the apex of mesenteric dissection. Microscopic examination revealed a rather poorly differentiated adenocarcinoma which had extended through all muscular coats. *"An intense inflammatory reaction accompanied the invading tumor in several areas with the formation of an abscess deep to the tumor at one point."* Tumor had largely replaced many lymph nodes including one of the largest which was found at the apex of the accompanying wedge of mesentery. The appendix was histologically normal. Terramycin was given postoperatively until October 17, 1962. The postoperative course was uneventful except for slight fever (100.4°-101°F.), until October 21, 1962 when small bowel obstruction developed proximal to the ileotransverse colostomy. On that day the patient was reoperated for relief of the obstruction and ileostomy was performed. The small bowel approximately three feet proximal to the anastamosis had knuckled up and become adherent in the vicinity of the anastamosis and surrounded by colic omentum. The bowel was acutely obstructed at this point, being markedly dilated proximally and collapsed distally. At operation the small bowel was tediously freed from the area of the anastamosis and the dense omental adhesions. Because there was so much reaction around the area of the anastamosis secondary to the bowel obstruction, it could not be determined with certainty whether the anastamosis was patent, and it was therefore decided to do a decompressive ileostomy proximal to the anastamosis. This started to function on October 24, 1962. The postoperative course was satisfactory. Chloromycetin was given for about two weeks, also Abbocillin, and narcotics for pain. On October 29, 1962

there was left lower quadrant pain and tenderness and a temperature of 102.4°F. but there appeared to be no signs of pelvic abscess. The next day the temperature was normal and the patient was much improved by November 1, 1962. Ileostomy drainage ceased by November 13, 1962. Four days later, while bending over in the bathroom, the patient fell forward fracturing his nose. This did not require treatment. He was discharged on November 18, 1962 and was told that the prognosis was regarded as six months.

Clinical Course: He convalesced for three weeks in Maine under his sister's care, gaining 16 pounds and walking a good deal each day. He returned to work about December 15th and stated that he never felt better in his life. He was promoted to head of his division in a large electric company and also became very active in a group called "Parents Without Partners", working many evenings until one or two a.m. on this activity. Dr. Cardillo reported on June 18, 1963 that the patient was doing fairly well on a full schedule. Against his physician's advice the patient was married on August 3, 1963 and he adopted his wife's three children. A month later she became pregnant but had a miscarriage in November 1963. In January 1964 he was seen by Dr. James M. Jones of Bronxville, New York. A gastro-intestinal series at Lawrence Hospital revealed a small superficial prepyloric ulcer for which he was given a bland diet with much relief. At this time fatigue again became noticeable and continued to be a serious problem. About April 1964 he noticed aching in the muscles of his shoulders and low back, directly associated with his fatigue.

Further Surgery: In the summer of 1964 a hemorrhoidectomy was performed. Thereafter the patient had two bowel movements daily.

Clinical Course: He again consulted his physician on October 9, 1964 because of pain in his shoulders and stiffness in his hands (Dupuytren's contracture). He appeared chronically ill at this time with diffuse muscle wasting and limited abduction of both shoulders (to 90°), also thickening of the skin of the fingers and limited motion of the joints. This was regarded as due to carcinomatosis with "reflex" muscular dystrophy and skin and joint changes. He then began taking Ritalin and Dexedrine (5 mg. three or four times a day) in order to function minimally. In January 1965 he again consulted his psychiatrist and was cleared as regards emotional factors. However, the knowledge regarding his prognosis and his remarriage to a much younger wife may have precipitated his gastric ulcer six months after remarriage. Early in February 1965 there was marked increase in fatigue and on March 9, 1965 the patient was admitted to Memorial Hospital in New York City for a thorough workup to try to determine the cause of his symptoms: Marked fatiguability, loss of 10 pounds in weight in 10 months, difficulty in concentrating, muscular dystrophy. He was seen by Drs. John T. Goodner, John Finkbeiner, and Gerald Klingon, a neurologist. Liver function studies, radioactive iodine and scintigram studies were normal. The question of collagen disease arose, as well as the possibility of myasthenia gravis, but these were ruled out. The patient had had a low grade leukocytosis and an unexpectedly abnormal EKG. Klingon considered the possibility of electrolyte disturbance, but potassium and magnesium studies were normal. After this extensive workup, during which time a definite diagnosis was not made, the patient became upset and signed himself out on the 13th hospital day. Goodner believed his behaviour, as well as the negative evaluation, clinically and biochemically, indicated a deep psychological factor as the possible cause of the fatigue. The medical diagnosis on discharge was "anxiety state, gastric ulcer". Soon thereafter the family physician found that he had an elevated alkaline phosphatase, and there was an impression of hepatomegaly. The patient had begged his physicians to take "a second look," believing that further surgery might be helpful during the

winter and spring of 1965, but they did not believe this was indicated. By early June 1965 there was increased fatigue, stiffness of the neck, weight loss, dark brown urine and jaundice, confirmed by liver function studies. Following this he noted occasional vomiting, only in the middle of the night, and fullness of the abdomen with some mid-abdominal pain. A G.I. series about August 1, 1965 revealed no obstruction and was essentially negative. The patient appeared to be emaciated and jaundiced on readmission to White Plains Hospital. Liver function studies revealed a markedly elevated bilirubin and other tests were compatible with obstructive jaundice.

Further Surgery: On August 8, 1965 a liver biopsy was performed and was well tolerated but did not yield a diagnosis pathologically. After consultation with Finkbeiner it was decided to do an incisional biopsy with biliary tract exploration. This was performed on August 16, 1965. Dense adhesions were present in the right upper quadrant following the previous surgery. The liver was slightly enlarged. There was an 8 to 10 cm. metastasis over the central portion of the dome of the liver beneath the diaphragm, presumably obsturcting the intrahepatic biliary system. The gall bladder was collapsed and the common duct was collapsed as it emerged from the hilus. The dense adhesions were freed by sharp dissection and the intrahepatic space thoroughly explored, but because of the dense adhesions complete exploration of the abdominal cavity could not be made. Manual exploration revealed no evidence of peritoneal metastases. No evidence of extrahepatic obstruction was found. Dense adhesions were freed above the liver beneath the diaphragm and the liver was partially mobilized downward and the large metastasis noted. Several incisional biopsies were taken from this lesion. The postoperative course was satisfactory. Microscopic examination revealed fibrous tissue and an enlarged lake of mucin in which malignant epithelial cells were often found forming irregular acinar structures. In one of the larger fragments some residual hepatic tissue was identified but it was almost totally obscured by heavy infiltration of malignant epithelial cells. Bile stasis was prominent in the portion of recognizable hepatic tissue. On August 21, 1965 there was low grade fever, but no localizing symptoms or signs. On the night of August 27, 1965 there was severe right lower posterior chest pain requiring Demorol. This did not recur.

Chemotherapy: On August 31, 1965 5-Fluoracil was begun and was given daily by slow intravenous drip. This was well tolerated except that 11 days later the patient developed superficial phlebitis of both arms involving only some of the veins. The bilirubin fell, but was still extremely elevated at the time of his discharge, September 29, 1965. The prognosis at this time was regarded as about two weeks. Two more vials of 5-FU were given in Noverber 1965.

Clinical Course: Thereafter the patient was unable to return to work but was able to be up and around the house doing odd jobs. His weight had declined to 132 pounds and he never regained any of his lost weight. In the spring of 1966 he developed edema of the lower extremities but never became bedridden until his final hospitalization, five days before he expired. He was admitted on June 21, 1966 because of increasing nausea, vomiting, weakness and pain. His condition was very poor and he slowly ebbed away; death occurred on June 26, 1966 approximately five years after onset.

Autopsy: Postmortem examination revealed a massive metastatic focus in the liver with marked fibrosis and compression of this area resulting in occlusion of the common duct and splenic vessels. The vascular stasis was reflected in the large congested spleen which weighed 900 grams. Despite this massive metastasis there was no residual carcinoma in the large bowel and no other metastatic growths were found. The liver weighed 3850 grams and was large and indurated. On section the entire right lobe was virtually replaced by firm yellow

tumor with small satellite tumor nodules fanning out into the periphery. The left lobe of the liver was fairly well preserved though discolored by the generalized jaundice. The gall bladder was not identified due to marked fibrous adhesions from the under surface of the liver. At the periphery irregular acinar structures were observed, formed by malignant columnar epithelial cells. The adjacent hepatic tissue was somewhat distorted and compressed, and marked bile stasis was observed. Lymph nodes from the tumor area revealed hyperplasia but were free from metastatic foci. Sections from the bone revealed hyperplastic bone marrow. Sections from all the other organs and the brain revealed no evidence of metastic spread.

Comment: In this case onset occurred during the patient's second divorce proceedings and phychiatric treatment. The primary tumor was extensive and multiple satellite metastases were present as well as a large single metastasis in the liver. This widespread disease found at the first operation in October 1962 may very well have been due to the steroids administered in August and September 1962, as has been reported by several investigators and reviewed by Kelly. (35) Possibly the two episodes for which steroids were given may have been due to the abscess and acute inflammation in the region of the primary tumor. Although prognosis at surgery was regarded as about six months and the patient was told this (psychic trauma), he did remarkably well, remarried, assumed a more responsible job in his company and remained clinically and biochemically free from further evidence of disease for nearly two years. Muscular aching and further fatiguability then developed, apparently due to the systemic effects of his solitary liver metastasis which had reactivated following his hemorrhoidectomy and gastric ulcer. If this man had received no steroids in 1962 prior to surgery, it is likely that the disease would have remained localized to the colon and surgery alone might have produced a permanent result, especially since the abcess and acute inflammatory reaction was present and had increased the resistance of this area to metastatic spread. Another possibility is that if this man had received injections of bacterial toxins following his incomplete operation in 1962, his liver metastasis might have regressed completely and never recurred as was the case in the patient treated by Fowler (see Case 5, Series B). The fact that the above patient's liver metastasis remained quiescent for so long was probably due to the inflammatory reaction, abscess, lymphoid and bone marrow hyperplasia all of which are indicative of a more active host resistance than is usually found in cancer patients. This man survived approximately five years after onset and over 3½ years after initial incomplete surgery. The case is also of interest as a clearcut example of the widespread systemic changes which may occur in advanced cancer, i.e, arthropathy, muscular dystrophy, fatigue, lack of concentration, etc. Despite these, the man was able to be up and about until five days before death occurred.

Reference: 48

SERIES B, CANCER OF THE COLON AND RECTUM TREATED BY TOXIN THERAPY

11 Cases

The diagnosis was confirmed by microscopic examination in each case. The name in parenthesis following the case number refers to the physician or hospital handling the case. The abstracts are listed chronologically, and at the end of each abstract bibliography reference numbers are given. Detailed histories of these cases follow the brief abstracts. Case 1 was operable. The other ten were inoperable when toxin therapy was begun. This small series appears to include all but one case* of microscopically proven neoplasms of the colon or rectum in which toxins were administered (at least 8 intradermal injections or 15 intramuscular).

Years Traced After Onset

1. (REILY): H. G. H., male, aged 34; operable small round cell sarcoma of colon; slight anemia, occult blood in stools, palpable mass in r.l.q.; exploratory laparotomy in 1915; neoplasm found at head of colon, also mass of "inflammatory" lymph nodes; 45 cm. of ileum and cecum resected, no metastases found; toxins: Streptococcus pyogenes and Serratia marcescens (Tracy XI preparation) given every 48 hours postoperatively to prevent recurrence; *no further evidence disease*, resumed active law practice; in good health next 32 years, then developed chronic ulcerative colitis; died coronary occlusion and ulcerative colitis, April 1, 1950, at age of 70, over 35 yrs. after onset. (16, 48) — 35 yrs.

2. (W. B. COLEY): H. P., male, aged 28, inoperable carcinoma of appendix; prognosis grave; toxins begun at Memorial Hospital twice a wk. i.m., then continued at home by family physician once weekly; *pain relief, cessation of growth for some mos.;* disease then progressed causing death from starvation, October 27, 1920, over 1 yr. after toxins were begun. (16, 48) — 1 yr.

3. (W. B. COLEY): A. F. B., male, aged 45; inoperable carcinoma of cecum; onset November 1918; herniotomy, July 1919, in bed 8-10 wks. postoperatively with "suppuration"; never felt well thereafter, lost 60 lbs. in 6 mos.; explored, October 1919, tumor found involving ascending colon; November 1919, admitted to Mayo Clinic with inoperable retroperitoneal mass filling rt. iliac fossa, extending 5 cm. above umbilicus; toxins advised, referred to Coley; *after 6 doses by Coley, tumor less firm-*

*The family refused to allow a detailed history of this case to be included. Toxins were administered briefly in November 1952 for extensive metastatic carcinoma of the colon developing very rapidly after administration of cortisone. There was dramatic and prompt regression of the large mass and cessation of pain. Toxins were stopped. Cortisone was again given for arthritic symptoms followed by rather rapid progression of the disease and death in 1953, approximately 3½ years after onset. (48)

ly fixed, much smaller; 1 radium pack then given (11,920 mch.) toxins continued at home for over 4 mos., marked febrile *reactions with chills; general condition improved, gained 20 lbs., complete regression of extensive tumor;* June 1920, 2nd radium pack; in very good health 10 yrs., then hypertension, also kidney condition, not confined to bed until August 1933, 1 wk. prior to death; at this time mass apparent in stomach, doubled in size in last wk.: (type of tumor unknown); also had 2 hemiplegias, causing death August 16, 1933 over 14 yrs. after onset. (16, 44, 48) 14 yrs.

4. (Fowler): Mrs.. H. M., aged 52; inoperable carcinoma of rectosigmoid, with direct extension to small intestine and metastasis to liver; onset, early December 1952, constipation; emergency laparotomy, December 20, 1952, for *generalized peritonitis due to perforation of inflamed tumor mass in rectosigmoid area;* transverse loop colostomy; 2nd laparotomy, 16 days later condition found inoperable, mass densely adherent to small bowel, uterus, lt. ovary and lt. lateral pelvic wall; also 5 cm. metastasis in liver; January 12, 1953, proctoscopy revealed fungating easily bleeding annular tumor 18 cm. from anal verge; toxins begun (Sloan Kettering XIV preparation), 5 courses in 7½ mos., 12 to 17 injections each, first four courses i.v., last i.m.; febrile reactions averaged 103°-105°F.; *while toxins were given patient surprisingly good condition, gained weight, felt well and strong, did all her own work;* however, by June 23, 1953 tumor seemed to be growing slowly; steady downhill course after toxins were stopped; narcotics never required until final hospitalization; death November 15, 1953, 11 mos. after peritonitis. Autopsy revealed carcinoma of lt. ovary as well as carcinoma of rectosigmoid, also numerous large liver metastases with necrotic centers. (48) (died) 11 mos.

5. (Fowler): W. D., male, aged 70; adenocarcinoma sigmoid colon, involving mesentery with numerous hepatic metastases; sudden onset crampy lower abdominal pains, December 3, 1953; complete obstruction, requiring transverse loop colostomy, December 7, 1953; 14 days later primary tumor resected, axile anastamosis performed; dense fibrous stroma reaction, necrosis in tumor, growth invaded blood vessels, chronic mesentery lymphadenitis; toxins post-operatively, 10 i.v. in 13 days, febrile reactions 104°-106°F.; 3 days later loop colostomy closed; 3rd course toxins begun: 1 dose, but as patient had *gross pyuria* and leukopenia, no more were given. *Complete recovery, hepatic metastases disappeared, remained in excellent health thereafter until 1962,* then arteriosclerotic heart disease; hospitalized January 1963, death pneumonia, chronic passive congestion of heart, February 1, 1963, at 80, over 8½ yrs. after onset; autopsy negative for cancer. (48) 8½ yrs.

6. (Ehrlich): Mrs. R. P., aged 44, inoperable hepatic metastases from adenocarcinoma of rectosigmoid; onset, January 1952, constipation, rectal bleeding; treated for hemorrhoids; August 20, 1952, resection of large annular tumor, including lt. tube and ovary and preaortic lymph nodes; well about 14 mos., then pain, indigestion, hepatomegaly; March 3, 1954: exploratory laparotomy, cholescystectomy; 1 of 2 large inoperable metastases in liver biopsied; increasing discomfort, pain r.u.q., liver mass enlarged tremendously, filling rt. abdomen to pelvis; August

8-16, 1954: palliative x-ray (1300 r); no decrease in size; August 25, 1954: toxins, 21 i.v. in 30 days, febrile reactions to 104°F. *abdominal mass smaller within 24 hrs. after beginning toxins, less discomfort, blood count improved, patent felt better during toxin therapy;* when injections were stopped increasing discomfort, sense of pressure; toxins resumed briefly, October 19, 1954, 7 i.v.; *again less discomfort;* after final injection condition deteriorated rapidly, extreme weakness, weight loss; death January 9, 1955, 3 yrs. after onset. (48) (died) 3 yrs.

7. (WEHRLY): Female, aged 38; terminal squamous cell carcinoma anus, extension to rectum, bilateral inguinal nodes and hepatic metastases; onset, June 1953, rectal bleeding regarded as due to hemorrhoids; January 4, 1954, x-ray therapy; April 13, 1954, colostomy, radium needles implanted, also further x-ray therapy; liver metastases then evident; September 27, 1954, toxins, 20 in 56 days, 1st dose i.m., 19 i.v., average reactions 102°-103°F.; *no apparent benefit;* death March 8, 1955, 21 mos. after onset. (48) (died) 21 mos.

8. (FOWLER) : R. D. C., male, aged 62; extensive ulcerated adenocarcinoma sigmoid colon, filling entire pelvis, invading periocolonic fat, adherent to posterior urinary bladder, lateral pelvic walls, metastases to mesenteric lymph nodes; onset, about April 1958, influenza, vague symptoms, 20 lb. weight loss; *leukocytosis prior to surgery (15,500)* ; laparotomy, November 10, 1958, resection difficult, considered incomplete, sigmoidoproctostomy; 1000 cc blood given during surgery; *some fever postoperatively (to 101°F. on 5th day); infected hematoma in abdominal incision superficially incised, drained;* toxins November 30, 1958: 37 i.v. in 2½ mos., moderate chills, profuse diaphoresis, febrile reactions averaged 100.4° to 101.4°F., (minimum 99.8°., maximum 102.8°F.) ; complete recovery, n.e.d.; 1969, in very good health, 11 yrs. after onset. (48) 11 yrs.

9. (JANSEN): B. F., male, aged 75; infiltrating, ulcerated adenocarcinoma rectosigmoid, 6 x 6.5 cm., metastases to adjacent lymph node, lumbar spine, lt. upper femur, skin of axilla, scapular regions; onset, June 1956; operated 4 mos. loter, November 16, 1956, permanent colostomy abdominoperineal resection; well 2 yrs., then fell, compressed fracture L 5 vertebra (pathological); L 2 and C 12 also appeared involved; orthophosphate given; December 9, 1958: toxins, 25 i.v. in a little over 5 mos.; maximum febrile reaction 103°F., occurred 3 times; usually had chills; *metastatic lesions in skin, bone all regressed, patient gained weight, in good health;* 1961, *furunculosis;* last seen by Ehrlich, December 1961, in excellent health, good appetitite; died July 18, at 81 yrs., over 6 yrs. after onset, death reported as due to "'pneumonia, metastatic carcinoma." (48) (died) 6 yrs.

10. (ROSSMAN): Male, aged 45; recurrent carcinoma sigmoid colon, metastases to many intra-abdominal lymph nodes; onset, December 1958, crampy abdominal pains; resection; recurrence of symptoms several mos. later; metastatic masses palpable; toxins May 25, 1959, daily i.v. for 21 days, febrile reactions to 103°F., chills; 1 dose HN_2, June 6, 1959,

Years Traced
After Onset

then 5 FU; *no apparent benefit,* disease progressed; death July 2, 1959, 7 mos. after onset. (48) (died) 7 mos.

11. (Ricks): B. M. S., male, aged 69; recurrent adenocarcinoma colon, metastases seeding viscera and peritoneum, liver, pleura, lungs; ascites, pleural effusion present when toxins begun; onset, summer 1958; explored October 1958, lesion resected with 50 cm. of colon; postoperative x-ray; then lost 28 lb.; signs of obstruction proceeding to complete ileus, re-explored October 1959; adhesions released: abdomen found studded with metastases in all directions; 10 mg. HN_2 instilled i.p.; postoperative x-ray; disease progressed, ascites, pleural effusion, dyspnea, nausea, vomiting, hepatomegaly; abdomen tapped daily (4 to 6 qts. bloody fluid); every 2-3 days 1 qt. bloody pleural fluid containing malignant cells (Grade III) evacuated; prognosis less than 1 wk.; February 22, 1961, toxins given intradermally daily for 8 days, local inflammatory reaction at injection sites, generalized aching, chills, febrile reactions (maximum 103°F.); *pleural effusion diminished at once, after 1st injection, no further ascites after 3rd injection; weight and strength increased, complete regression, no further evidence disease;* only medication thereafter, flu vaccine injections spring and fall; alive and well February 1969 10½ yrs. after onset. (48) 10½ yrs.

SERIES B: DETAILED HISTORIES OF ALL BUT ONE OF THE KNOWN CASES OF CARCINOMA OF THE COLON OR RECTUM WHO HAVE RECEIVED TOXIN THERAPY*

Note: These histories suggest that even in some advanced cases of cancer of the colon or rectum toxins may be of very real value as regards palliation, relief of pain and other symptoms, but that to be curative (except in rare instances such as Case 11) they should be started before and after surgery, and in inoperable cases combined with incomplete surgery.

CASE 1: Small cell sarcoma of the head of the colon, confirmed by microscopic examination following surgical removal, by pathologists at the Oklahoma City University Hospital and at Washington University, St. Louis, Missouri.

Previous History: H. G. S., male aged 34, a lawyer, of Oklahoma City. The family history was non-contributory except that asthma prevailed in all the siblings. The patient was born with a right inguinal hernia and wore a truss. He had an appendectomy in 1910 following appendicitis. In 1915 he developed slight anemia, occult blood in the stools and a palpable mass in the right lower quadrant, but no special digestive changes.

Surgery: An exploratory operation revealed a sarcoma involving the head of the colon with a mass of "inflammatory" lymph nodes. About 45 cm. of the ileum and cecum were removed. No metastases were found.

Toxin Therapy (Tracy XI): After surgical convalescence, Dr. Lee A. Reily gave the patient injections of the mixed toxins of Streptococcus pyogenes and Serratia marcescens, then known as Coley toxins, as a prophylactic to prevent recurrence. They were given intramuscularly every other day in doses of 0.5 to 20 minims. The duration is not recorded but at this time the average duration for prophylactic therapy was over three months.

Clinical Course: The patient remained free from recurrence of metastases, his only symptom being looseness of the bowels. His health was uneventful and he continued his active law practice. About 1943 or 1944 he developed asthma which subsided after he gave up coffee, cigarettes, wheat flour, etc. He then gained weight. During World War II the patient had a personality change and developed an obsession about the "New Deal." During the summer of 1947 he had an acute gastrointestinal upset while visiting Connecticut, with much pain in the abdomen. X-ray examination revealed haustrations and gunbarrel type of colon. He had not worn his truss for several years and the right inguinal hernia had increased in size. During the second week of October 1947 he again obtained a truss and he then noticed that the left leg and thigh began to swell. (He had been wearing an elastic stocking for varicosities on his right leg.) Tenderness and swelling of the skin became apparent on the inner aspect of

*Family refused data on the missing case.

the left leg below the knee. The condition was regarded as thrombophlebitis. The patient was put to bed, an ace bandage was applied and he was started on Dicumarol which was given for about 10 days (1200 mgm.). He remained free from recurrence of his cancer of the colon. He died of coronary embolism and chronic ulcerative colitis on April 1, 1950 at the age of 70, 35 years after operation and postoperative toxin therapy. (16, 48)

CASE 2: Inoperable carcinoma of the appendix, confirmed by clinical and pathologic examinations.

Previous History: H. P., male, aged 28, of Trenton, New Jersey. The previous history was not recorded. The patient first consulted Dr. William B. Coley in October 1919 at which time the prognosis was hopeless, "a matter of a few weeks or months." He was admitted to Memorial Hospital, New York.

Toxin Therapy and Concurrent Infection: Injections were apparently begun by Coley at Memorial Hospital but no details were given as to type of toxin used (either Parke Davis XIII or Tracy XI), site or dosage. They were apparently given once a week intramuscularly. After he returned home the injections were continued by the family physician at infrequent intervals. The effects were as follows, as reported to Coley by a relative: "He has been about the same for a long time now, does not appear to get worse as would be expected with cancer, but has held his own for the past few months, in fact does not suffer as much pain as formerly, and always feels so much better for a few days after he has had a toxin injection, and seems to feel that Dr. H. does not take the interest he should, and thinks if he could get the treatment about twice a week it would be very beneficial, but as it is the doctor rarely comes unless they phone and ask him and it is rather discouraging to have to do that . . . We feel he does not have the faith in the method that we have . . . nor does he appear to take an interest – he never asks to see his side. The cancer appears to be at a standstill for some time now, the ulcer is not getting any larger and the small sinus in his back from the last abscess has not closed and still discharges pus, but it does not grow larger as the sore in front did so we feel that the toxin has taken hold and is benefiting him to a certain extent. He really does not suffer as much pain and does not take any more morphine than he took months ago. He has no spells of vomiting, can eat very well, and while fecal matter still comes from his side, he is also able to have bowel movements from the rectum without any physic or enema, quite frequently . . . whereas months previously this was impossible." No further details were found regarding treatment or effects.

Clinical Course: The disease finally progressed causing death from starvation on October 27, 1920. (16, 48)

Comment: This case indicates the danger of giving the injections too infrequently, in small doses intramuscularly, especially in far advanced cases. While significant palliation occurred for several months, a permanent result was not obtained. The complete lack of interest in this patient or faith in toxin therapy shown by the family physician was not conducive to success with any method of treatment as was emphasized by Rubens Duval in 1932. (54).

CASE 3: Inoperable carcinoma of the cecum, confirmed by microscopic examination following exploratory operation in Evansville, Illinois.

Previous History: A. F. B., male, aged 45, of Princeton, Indiana. The patient's mother died of pneumonia, his father of senility. One sister developed cancer a year prior to the patient's illness and was successfully operated. The

patient had never been ill. Onset, in November 1918 he first noticed a slight swelling in the right lower quadrant, with occasional pain, particularly with constipated movements.

Surgery: The swelling increased and in July 1919 a herniotomy was performed at St. Mary's Hospital, Evansville, Illinois.

Postoperative Infection: The patient was in bed eight weeks after this operation, and there was suppuration of the wound. He never felt well thereafter. He returned home for two weeks during which he was in bed most of the time. He lost 60 pounds in weight in six months.

Further Surgery: He was then readmitted and a second incision was made by Dr. Long. A carcinoma was found involving the ascending colon. The prognosis was regarded as two months.

Clinical Course: In November 1919 the patient went to the Mayo Clinic and was seen by Dr. Charles H. Mayo, who found a retroperitoneal tumor in the right side of the abdomen which was inoperable. He referred the patient to Dr. William B. Coley for toxin therapy. Mussey of the Mayo Clinic wrote to Coley on November 25, 1919: "The general examination failed to reveal any further trouble. The Wassermann was negative . . . an x-ray of the colon revealed a filling defect which we believe to be an enteric mass." Physical examination on admission to Memorial Hospital, December 9, 1919, showed a vertical scar 12½ cm. long in the right iliac region over the right rectus. There was occasional soreness and pain about the wound and some drainage from a fistulous opening. The right iliac fossa was filled with a mass extending over the median line and upwards 5 cm. above the umbilicus, and as far as the crest of the ilium. The tumor was firm in consistency and rather hard, the overlying skin was not adherent.

Toxin Therapy (Tracy XI): Injections were begun by Coley at Memorial Hospital about December 10, 1919, 13 months after onset. It was noted that after the first six doses the tumor was less firmly fixed and much smaller.

Radiation: One radium pack treatment was administered at this time (11, 920 mch.).

Further Toxin Therapy: The patient then returned home where the toxins were continued regularly by the family physician, Dr. R. A. Cushman, of Princeton, Indiana, as an outpatient, in his office. The patient "had to rush home immediately because approximately 10 minutes later a severe chill would occur." This indicated rapid absorption of the toxins and it is believed that the injections were made in the abdominal wall in the region of the growth. On March 9, 1920 Cushman reported to Coley that the patient had gained 20 pounds in the three months on toxin therapy and that his general condition was fine. He added: "The growth seems to have all disappeared except a small nodule just below the anterior superior spine, about the size of a small plum." The dose being given at this time was 10 minims which caused little appreciable reaction. The exact duration of treatment is not recorded.

Further Radiation Therapy: On June 2, 1920 the patient returned to New York. Coley found no clinical evidence of disease, but as a precaution he administered a second radium pack treatment (12,094 mch. at 6 cm. distance).

Clinical Course: The patient remained in very good health during the next ten years. About 1930 he developed hypertension and a kidney condition. He was not confined to bed until early August 1933, about a week before he died. At this time his daughter stated that a "growth appeared at the mouth of the stomach which doubled in size within a week." The patient then developed

two hemiplegias causing death on August 16, 1933, over 14 years after onset of the carcinoma of the cecum. The growth in the esophagus which appeared shortly before death was undiagnosed, as no autopsy was performed. (16, 44, 48)

CASE 4: Inoperable carcinoma of the rectosigmoid with direct extension to the small intestine and metastases in the right lateral lobe of the liver, also carcinoma of the right ovary, either primary or metastatic from the colon, confirmed by microscopic examination following autopsy.

Previous History: Mrs. H. M., aged 52. The family history was not recorded. The patient had always been well and had never needed a doctor. Onset, early in December 1952 she developed constipation. She was admitted to Sharon Hospital, Sharon, Connecticut on December 20, 1952 with a history of a little anorexia of two days' duration, and 3½ hours prior to admission she was awakened with severe lower abdominal pain, steady in character, associated with nausea but no vomiting, no urinary tract symptoms, but some pain in the lower abdomen on voiding. Physical examination on admission revealed an acutely ill and uncomfortable woman lying quietly in bed with a temperature of 102°F.

Surgery For Concurrent Peritonitis: An emergency laparotomy was performed by Dr. George A. Fowler through a right lower pararectus incision. He found a generalized peritonitis due to perforation of an inflamed tumor mass in the rectosigmoid area. A small incision was made in the right upper rectus and a transverse loop colostomy was performed. Postoperatively the patient ran a reasonably uncomplicated course. On the 16th day a second laparotomy was performed to determine the operability of the tumor. It was found to be inoperable, being densely adherent to the small bowl loops, to the posterior surface of the left ovary and to the left lateral pelvic wall. There was also a large, hard, somewhat irregular nodule in the lower aspect of the right lateral lobe of the liver measuring approximately 5 cm. in diameter.

Toxin Therapy (Sloan Kettering Institute XIV): On January 23, 1953, 34 days after the first operation, Fowler began administering toxins. A total of 13 intravenous injections were given in 16 days with febrile reactions of 103°-105.8°F. Proctoscopy at this time revealed a fungating, easily bleeding flap of ulcerated annular tumor about 7 cm. from the anal verge. The patient was discharged on February 2, 1953. She was readmitted 14 days later for a second course of toxin injections and received 12 in 15 days intravenously, with febrile reactions of 103.8° to 105.4°F. At this time the transverse colostomy was functioning and no abdominal masses were palpable. Rectal examination was negative. The heart and lungs were normal. The patient looked fairly well and was alert and vigorous. Proctoscopy prior to this course of injections revealed the tumor was essentially unchanged, it was friable and bled easily. Several biopsies were taken. The patient was readmitted on March 13, 1953 for a third course of injections. At this time she looked well. Physically she appeared unchanged and proctoscopy revealed that the tumor was also apparently unchanged. She then received 17 more intravenous injections in 21 days, with febrile reactions of 103°-104.6°F. She was readmitted on April 27, 1953 for her fourth course of toxins. At this time she looked and felt very well, her appetite and digestion were excellent. The colostomy was functioning well and she had gained four pounds in the preceding four weeks. Examination of the abdomen revealed a non-tender, ill defined mass in the left lower quadrant. She then received 17 intravenous injections in 20 days with febrile reactions of 103°-104.8°F. She was readmitted on May 19, 1953 for a barium enema. This revealed complete obstruction to retrograde flow of barium at the rectosigmoid

junction. At this time three more intravenous injections were given causing febrile reactions of 103.8° - 105°F. The patient was readmitted on June 23, 1953 for a final course of toxins. On admission she felt well and strong and her appetite and digestion were good, the bowels were moving per colostomy and she was doing all her own housework. Examination at this time revealed a moderately obese, healthy looking woman in no distress except at the thought of being hospitalized. Examination of the abdomen revealed a suprapubic mass suggesting a two or three months' pregnancy, slightly tender on deep palpation. Fowler believed that the tumor was growing slowly in spite of therapy but he stated that the patient was being maintained in remarkably good general condition. During this final course 16 intramuscular injections were given. Following the final injection the patient had a severe chill and her temperature rose rapidly to 106.2°F. An immediate alcohol sponge, ice bags and wet sheet with fan controlled the pyrexia. The next day the patient was weak, nauseated, had some lower abdominal pain, considerable tenderness over the tumor mass and lower abdomen. She declined further injections and was discharged. (Summary: She received five courses of toxin injections in 7½ months, during which time she remained in good health, and able to lead a normal life except for the brief periods of hospitalization for toxin therapy.)

Clinical Course: For the next two weeks there was lower abdominal pain and tenderness in the region of the tumor with soreness of the lower abdominal muscles so that she could not arise from a chair without help. Gradually the worst of these symptoms subsided, but the great weakness persisted. About this time the abdomen became definitely larger with progressive increase in size. On August 1, 1953 she was seen at home, at which time a large, rounded, tender mass was palpable in the right lower quadrant and a much smaller mass that was difficult to palpate was present in the left lower quadrant. There was no evidence of ascites. The patient appeared pale and unhappy. Her appetite had been fair but she felt nauseated after eating. Physical examination on her final admission to Sharon Hospital, August 17, 1953 revealed a well developed somewhat chronically ill woman who appeared tired and somewhat pale. There was fluid in the right chest. A definite, round, moderately fixed, firm and somewhat tender mass was visible and palpable in the right lower quadrant suprapubically. Rectal examination revealed brown, foul smelling stool in moderate amount, some tenderness in the cul de sac, fullness on the right side. Three thoracenteses were performed and large amounts of pinkish, straw colored fluid were removed on each occasion and then did not accumulate further. However, her course was progressively downhill with gradual enlargement of the abdominal tumor. On August 25, 1953 two attempts were made to aspirate the tumor mass which was felt to be full of fluid, but none was obtained. The disease progressed with pronounced cachexia and tremendous weight loss. Death occurred on November 15, 1953, 11 months after she developed peritonitis as a result of perforation of the carcinoma of the rectosigmoid. Autopsy revealed a large cystic mass filling the entire lower abdomen encroaching on the left lower and right upper abdomen. This was 30 by 10 by 20½ cm. and contained areas of obvious tumor in an otherwise thin cystic wall. It was filled with dark brown, thin, watery fluid and the tumor tissue appeared to be semi-necrotic and soft in many areas. This thin cystic mass was seen to arise apparently in the region of the right ovary and was firmly attached by tumor growth to the right lower abdominal wall just above the anterior superior iliac spine. After aspirating the fluid from the cyst, the pelvic organs could be explored and the original carcinoma of the rectosigmoid was palpable behind the uterus. It was rather freely movable, but two separate loops of small intestine were densely adherent to it. Through one of these loops an ileosigmoid fistula had been established by canalization of the tumor. This fistula was approximately 1.3 cm. in diameter.

The liver contained numerous very large metastases with necrotic centers. These measured from 2 to 15 cm. in diameter, the largest being in the center of the right lobe near its upper surface. There were numerous hard, fixed pre-aortic nodes. The various biopsies of the rectal tumor and the autopsy specimens were examined by Dr. Virginia Kneeland Franz, of the Department of Pathology, College of Physicians and Surgeons, New York.

In summarizing this history Fowler stated that except during her final hospitalization, this patient never required any narcotics for control of pain and was able to lead a normal life for many months despite extensive inoperable cancer. (48)

Comment: At the time this patient was treated the only available preparation of mixed bacterial toxins was a rather weak product. In this case the toxins were not begun until 32 days after the first emergency laparotomy following perforation of the ulcerated carcinoma of the rectosigmoid. In recent years it has now been recognized that patients need not be hospitalized except for the first course of toxin therapy, and that in treating most inoperable cases more prolonged therapy is usually required. Possibly in the above case if a third laparotomy had been performed prior to her final course of toxins, much of the tumor could have been removed, and this might have made it possible to destroy the remainder by prolonged toxins. The need for such partial surgical removal has been clearly indicated by the recent studies of Martin, et al. (38, 39)

CASE 5: Adenocarcinoma of the sigmoid colon with extension to the mesentery and with numerous small metastases to the liver. The pathological report from the College of Physicians and Surgeons, New York, stated that it was a well differentiated adenocarcinoma with dense stroma reaction. Neoplastic cords were in general filled with necrotic material. The growth invaded nerve fibers and also one of the blood vessels.

Previous History: W. D., male, aged 75, of Amenia, New York. The family history was not recorded. The patient had previously been completely healthy. There was no history of change in bowel habits or any known weight loss. Onset, on December 3, 1952, he suddenly developed crampy lower abdominal pains of varying intensity. These continued and on December 10, 1952, he was admitted to Sharon Hospital, Sharon, Connecticut. Examination by Dr. George A. Fowler revealed a moderately acutely and chronically ill white male who was alert and cooperative. The abdomen was symmetrically distended and tympanic with audible peristalsis. Palpation revealed dilated loops, no herniae. Rectal examination revealed a tight sphincter, no masses and no blood. X-ray examination revealed dilated loops of small and large intestine and it was felt that an attempt at decompression might be made with the Miller-Abbott tube. This was attempted, and the small bowel was completely decompressed, but the large bowel remained dilated and filled with gas. Barium enema on the fourth hospital day revealed complete obstruction to retrograde flow of barium at the rectosigmoid junction, where there was an annular filling defect with undermined edges.

Surgery: On December 4, 1952 a transverse loop colostomy was performed. On January 7, 1953 a second laparotomy revealed a resectable tumor of the sigmoid about 15 cm. above the peritoneal reflection. Palpation of the liver revealed numerous small metastatic nodules in the substance of the liver, particularly in the left lobe, measuring 1 to 2 cm. in diameter. These were characteristically hard in relation to the surrounding liver substance. Resection of the sigmoid with axile anastamosis was carried out. The patient made an uncomplicated recovery. Twelve days later a spur crushing clamp was placed on

the transverse colostomy and 16 days post-resection the bowels were moving well by rectum.

Toxin Therapy (Sloan Kettering Institute XIV): Injections were begun by Fowler on February 4, 1953, four weeks after resection. During the first course he received 10 intravenous injections in 13 days with good chills and febrile reactions of 104° to 105°F. The patient felt well and had an excellent appetite after his discharge. He was readmitted on March 8, 1953 for a second course of toxins, receiving eight intravenously in eight days with excellent chills and febrile reaction of 104° to 106°F.

Further Surgery: Three days after the last of these injections, operative closure of the transverse loop colostomy was performed. The patient made a rapid and excellent recovery and was discharged on the ninth postoperative day.

Injection: On April 4, 1953 he was readmitted for a third series of injections, but was found to have a profound leukopenia (2,900 wbc, with 90% polys), also gross pyuria. For this reason only one injection was given at this time. (This patient therefore received a total of 19 injections in eight weeks.)

Clinical Course: He made a complete recovery, enjoyed uninterrupted good health, was able to do all his own work, re-roofed his house, grew a large garden that summer. He was examined periodically by Fowler, who reported that there was no further evidence of disease, the liver metastases having apparently regressed. The patient continued to enjoy excellent health until the summer of 1962. From September 1962 until January 1963 he was hospitalized at the Harlem Valley State Hospital for arteriosclerotic heart disease. He did well until late January 1963 when he noted swelling of the feet and shortness of breath. He was readmitted to Sharon Hospital on February 11, 1963 and expired three hours later. Death was due to bilateral pneumonia and chronic passive congestion of the heart. Autopsy revealed generalized arteriosclerosis, hypertrophy and dilation of the heart (weight 700 gms.), fibrous scar of the liver (former metastasis), bilateral pneumonia. There was no evidence of the liver metastases present ten years previously. The patient was 85 years old when he died. (48)

CASE 6: Inoperable metastatic adenocarcinoma, primary in the rectosigmoid, confirmed by microscopic examination following the primary resection as well as after biopsy of one of the two large liver metastases.

Previous History: Mrs. R. P., female, aged 44, of White Plains, New York. Onset, about January 1952 the patient began to have constipation with rectal bleeding. She put off active treatment until July 1952. She was first seen by a local physician who found she had hemorrhoids. He gave her appropriate treatment but advised her to have a barium enema and sigmoidoscopy. She deferred this for six weeks until August 12, 1952, when sigmoidoscopy at the White Plains Hospital revealed an annular lesion of the rectosigmoid which was quite large and obviously well advanced.

Surgery: On August 20, 1952 anterior resection of the lower sigmoid was done, to include the lesion. The left tube and ovary were removed as well as the pre-aortic nodes. The liver was negative to palpation at this time, but Dr. J. W. Ehrlich stated that "it was my very definite impression that the lesion had extended beyond our surgical attack."

Clinical Course: The patient was discharged from the hospital on August 21, 1952. Her condition remained satisfactory for about 14 months and she returned to work without complaint. On November 4, 1953 she was readmitted to the hospital. Barium enema and sigmoidoscopy revealed no evidence of recurrence or abnormality. However, she was complaining of some indigestion and of pain in the right upper quadrant and under the costal margin. During

the next few months there was increasing discomfort in this region and some intolerance of fatty food. Gall bladder x-rays revealed some delay in emptying. The liver was obviously enlarged but cholecystitis was not altogether ruled out.

Further Surgery: An exploratory laparotomy was done on March 3, 1954, and cholecystectomy was performed. Two large metastatic masses were found in the liver. One of these was biopsied and reported as identical with the primary lesion in the rectosigmoid.

Clinical Course: The patient was discharged on March 20, 1954, and returned to work by June, although she complained of increasing discomfort and pain in the right upper quadrant, and the liver was enlarging rapidly. There was also moderate weight loss. During June and July the mass involving the liver enlarged tremendously and became very hard, filling the right side of the abdomen down to the pelvis, and extending across the midline. The patient was unable to lie on the right side. She did not know her condition was malignant, having been told it was cirrhosis.

Palliative X-Ray Therapy: Between August 9 and 16, 1954, she received deep x-ray therapy, hoping for palliation (1300 r). The mass did not reduce in size but it did appear to be slightly smoother on palpation.

Clinical Course: She was readmitted to the White Plains Hospital on August 25, 1954. At this time she was markedly anemic. Alkaline phosphatase was 6.2 Bodansky units.

Toxin Therapy (Sloan Kettering Institute XIV): Injections were begun by Ehrlich on August 25, 1954 and 21 were given intravenously in the next month. The initial dose of 1/50 minim caused a febrile reaction of 104°F., 2½ hours after injection, and a chill lasting 35 minutes. The dose was then reduced to 1/80 minim for the next four days. These caused chills lasting 30 to 35 minutes and febrile reactions of 102.2° - 104.6°F. and headache or slight headache. It was noted on the second day of treatment that the abdominal mass was notably smaller, the pain gone and the patient stated that she felt "exhilarated." That day she was given a transfusion of whole blood (500 cc.). On the fourth day she felt less abdominal discomfort. On the fifth day she felt well and stated she was "encouraged." On September 1, 1954 a blood count showed improvement (3,700,000 rbc, hemoglobin 10.4 grams (65%.) The white count was not remarkable. By the eleventh day the abdominal mass (liver) was "definitely smaller," the appetite and morale good. Chest films showed no significant difference in appearance of the lung field since examination the previous March. The right half of the diaphragm was slightly elevated. There was no evidence of lung metastases or other significant lung pathology. Nine days later the patient complained that her side felt very heavy and ached. The last nine injections were given as an ambulatory case, the final one being on September 23, 1954.

Clinical Course: After her return home she was given injections of Vitamin B-12 (50 mcg. thrice weekly). During the next few weeks after the toxins were discontinued the patient complained of increasing abdominal discomfort and a sense of pressure in the chest. However, the abdominal mass, if anything reduced further in size. She was placed on small doses of thorazine.

Further Toxin Therapy: Injections were resumed on October 19, 1954 after a rest period of about four weeks. Seven were given intravenously in 10 days in doses of 1/80, 1/50 (four times), and 1/20 minim (twice). These caused febrile reactions averaging 103° to 104°F., with chills lasting 30 to 40 minutes. After the first of these injections the patient felt less discomfort in her side. The third dose infiltrated into the skin and caused no reaction at all. There was emesis after the first, second and sixth doses.

Clinical Course: After the toxins were stopped the patient's condition deteriorated appreciably. She became extremely weak, with marked weight loss, she was troubled with bleeding hemorrhoids and she became intensely jaundiced. After November 2, 1954 she was confined to her house, and thereafter she developed dependent edema from the groins. During the last five weeks she required sedatives and narcotics. Death occurred on January 9, 1955, three years after onset. (48)

CASE 7: Terminal squamous cell carcinoma of the anus, with extension to the rectum and bilateral lymph node and hepatic metastases, confirmed by microscopic examination at autopsy.

Previous History: A. B., female, aged 38, of Garden Grove, California. Onset, in June 1953 the patient developed "hemorrhoids and bleeding from the rectum." She was admitted to the Orange County General Hospital on January 4, 1954. Examination revealed large masses about the anus and bilateral inguinal lymphadenopathy.

Radiation: X-ray therapy was given to the involved areas. (Dosage not recorded). On April 13, 1954 a colostomy was performed. Radium needles were then implanted about the lesion in the anus. The colostomy was then closed.

Clinical Course: On June 1, 1954, there was increasing backache, increasing swelling of the right labia but no further radiation was considered advisable.

Toxin Therapy (loan Kettering Institute XIV): Dr. Mildred F. Wehrly administered toxins between September 28 and November 22, 1954 (20 in 56 days). All but the first (which was intramuscular) were given intravenously in doses of 1/50, 1/20, 1/10, 1/3, ½, 1, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13 and 14 minims. They caused chills on all but two occasions (the intramuscular and 3rd intravenous). These averaged 30 to 40 minutes (minimum 25, maximum 65 minutes). Febrile reactions averaged 102° to 103°F. (minimum 99° F., maximum 104°F.).

Clinical Course: By November 23, the day after the toxins were stopped, there was edema of the lower extremities to the umbilicus. The anus showed gross tumor, there was an enlarged node in the supraclavicular region. By February 14, 1955 there was marked jaundice, the liver was enlarged, the condition poor. The tumor over the right vulva was increasing in size and had extended into the right inguinal region. Death occurred on March 8, 1955, 21 months after onset. Postmortem examination revealed "carcinoma of the anus, extension to the rectum, metastases to iliac and pre-aortic nodes, liver, omentum and porta hepatis; occlusion common bile duct. Obstructive jaundice. Metastases to gall bladder, cardiac dilation; acute cystitis and urethritis; ascites; pleural effusion, hemorrhage into lung parenchyma." (48)

Comment: In this case toxins were not begun until radiation had been given and the disease was terminal with widespread metastases. Only 20 injections were given in less than two months. No apparent benefit was noted.

CASE 8: Ulcerated, well differentiated adenocarcinoma of the sigmoid colon, with invasion of pericolonic fat and five metastases in the lymph nodes of the mesentery (the latter were completely replaced with tumor tissue) confirmed by microscopic examination following surgery. The pathologist noted that there was a marked inflammatory reaction in the large hard tumor which filled the pelvis and was adherent to the posterior urinary bladder and the lateral pelvic wall.

Previous History: R. D. C., male, aged 62, of Dover Plains, New York. The patient gave a vague history of influenza and of not feeling just right for about eight months prior to admission, and a recent weight loss of 20 pounds. Two barium enemas revealed an obstructing lesion in the lower sigmoid. Physical examination on admission to Sharon Hospital, Sharon, Connecticut, November 3, 1958, revealed a large, healthy looking, elderly male in no acute distress but showing evidence of weight loss. Rectal examination revealed a sense of a mass in the cul de sac. Barium enema revealed a polypoid carcinoma of the sigmoid.

Concurrent Leukocytosis: Laboratory studies revealed 10 mgm. of albumin in the urine but no other abnormalities. Blood count revealed leukocytosis (15,500 wbc.), with 77% polys.

Surgery: After several days' administration of sulfathaladine, a laparotomy was performed by Dr. George A. Fowler, on November 10, 1958. No free fluid was present in the peritoneal cavity and palpation revealed no evidence of metastases to the liver and other organs. Examination of the lower abdomen revealed a marked inflammatory reaction in the large hard tumor which filled the entire pelvis and which was adherent to the posterior wall of the urinary bladder and the lateral pelvic walls and with a very short thickened mesentery posteriorly. The upper sigmoid was displaced markedly to the right side around a diffusely oval mass lying in the left upper lateral pelvis which appeared to be a pelvic kidney since no palpable kidney was present in the left lumbar gutter. The right kidney was normal in size and position. Resection of the sigmoid colon was performed with sigmoidoproctostomy. Due to technical difficulties it was felt that not all of the cancer had been resected. The patient received 1,000 cc. of blood during the surgery. The tumor had penetrated all coats of the colon wall and extended into the pericolonic fat and had metastasized to adjacent lymph nodes. The central portion of the annular tumor was ulcerated and large areas of tumor necrosis were seen beneath the ulcer bed. The polypoid intraluminal projection at the periphery had branching finger-like configuration suggesting that the tumor might have arisen in a papillary adenoma but no histologically benign areas remained. The depth of penetration in the pericolonic fat and the presence of metastases (extensive invasion of lymphatics) placed this case in the poor prognosis group.

Postoperative Infection: The temperature rose to 100.2°F. the day after operation, gradually falling to normal on the fourth day only to rise to 101°F. on the fifth day and it then remained somewhat elevated. The patient developed an infected hematoma in his abdominal incision superficially which cultured diphtheroids, E. intermedium, nonhemolytic Staphylococcus albus and Streptococcus durans. This subsided after drainage. The patient became ambulatory and recovered well.

Toxin Therapy (Johnston XV): Because of the extent of the local tumor, it was felt that prophylactic toxins should be given. Beginning November 30, 1958, Fowler gave him eight intravenous injections while he was still in the hospital. These caused good chills and febrile reactions of 101° to 102.8°F. His only complaint was the shaking chill, the fever did not bother him at all. He was discharged improved on December 6, 1958 with the operative wound healing well. He returned to work on December 19, 1958. Injections were continued on an ambulatory basis and a total of 35 were given intravenously ending February 13, 1959, a duration of 2¼ months. The dosage ranged from 0.05 cc. of a 1 to 20 dilution to 0.8 cc. undiluted. The febrile reactions averaged 100.4° to 101.4°F. (minimum 99.8°, maximum 101.6°F.) with moderate chills and profuse diaphoresis.

Clinical Course: The patient made a complete recovery and there was no further evidence of disease. He remained in very good health in February 1969 11 years after onset. (48)

CASE 9: Infiltrating adenocarcinoma of the rectosigmoid with metastases to the adjacent lymph nodes, the lumbar spine, the skin of the axillae and scapular regions, confirmed by microscopic examinations following biopsy and surgical removal of the primary tumor and of a metastatic lesion.

Previous History: B. F., male, aged 75, of Evergreen Park, Illinois. Onset occurred in June 1956. The patient was first seen by Dr. Edward L. Jansen in October 1956 at which time there was widespread metastases, including the liver.

Surgery: A biopsy of the rectal lesion was performed.

Clinical Course: X-ray examination on November 13, 1956 revealed a marked hypertrophic change involving the lumbar vertebrae. There was also marked osteoarthritic change involving the fifth lumbar vertebra with changes suggesting some destruction and slight compression. There appeared to be slight changes in the first and second lumbar vetebrae which might well be osteoporosis. There were slight changes in the proximal femur suggestive of some destructive change. There was considerable osteoporosis in all the bony structures visualized. In addition there appeared to be destruction of the right sacroiliac joint with rather advanced changes in this region, apparently osteoporotic. The radiologist reported: "The changes involving the fifth lumbar vertebra as well as the upper femur may well be on the basis of metastases."

Further Surgery: On November 16, 1956 Jansen operated through a left rectus incision. A permanent colostomy was performed, followed by abdominoperineal resection of the tumor. About 3½ to 5 cm. from the rectal verge a carcinoma was found on the superior aspect of the rectum. The mass was circular, grey, and the center was ulcerated. It appeared malignant and had been proven to be malignant on prior biopsy. The lesion was 6 cm. long and 6.5 cm. in circumference. It did not involve the entire circumference of the intestine. Two areas of ulceration were found, and the edges of the growth were rolled and friable. The neoplasm extended to the submucosa. A lymph node 9 cm. in diameter was excised 3 cm. above the primary tumor in the adjacent fatty tissue. Sections were reported to be infiltrating adenocarcinoma with metastases in the node. (#4993)

Clinical Course: The postoperative course was satisfactory. The patient remained well for approximately two years. On October 9, 1958 he fell and was readmitted with a compressed fracture of the fifth lumbar vertebra. X-ray examination on October 21, 1958 showed a compression fracture of the second lumbar vertebra. There appeared to be marked irregularity and elongation of the body of this vertebra suggesting that the fracture might be pathological. There was definite destruction of the corticopattern of the fifth lumbar vertebra and twelfth cervical vertebra which also appeared to be metastatic. There were several calcifications in the right upper quadrant having the appearance of biliary calculi. Metastatic skin lesions were present in the axillae, the right scapular region and the abdomen. One of these was biopsied and reported to be histologically the same as the primary tumor. The patient was given orthophosphate. X-ray examination on November 18, 1958 showed slightly more recalcification in the fifth lumbar vertebra. A slight increase in sclerosis indicating callous formation was seen in the third lumbar vertebra. Changes seen in the other lumbar vertebra and in the pelvis were compatible with Paget's disease. The numerous biliary calculi were again seen.

Toxin Therapy (Johnston XV): Injections were begun by Jansen on December 9, 1958 and 16 were given at home intravenously in a little over five months: three in December, four in January, three in February, one in March, three in April and two in May, the final injection being on May 19, 1959. Febrile reactions averaged 101.5° to 102°F. (minimum 98°. maximum 103°F.,

on three occasions). Chills occurred after most of the injections, lasting 20 to 45 minutes and usually there was backache during the reaction. Occasionally the right hip ached and twice there was emesis and diarrhea. After the first week of treatment the metastases in the axillae became black. By February 6, 1959 the 4 cm. lesion in the right scapular region appeared to be healing. By March 1959 the patient's appetite was good and he felt fine.

Clinical Course: The metastatic lesions apparently all regressed and the patient gained weight and remained in good health.

Infections: In 1961 he had a bout of skin furuncles which cleared up.

Clinical Course: Jansen reported on December 21, 1961 that the patient had an excellent appetite, no weight loss and his color was good. There was no subjective or objective evidence of spinal or soft tissue metastases. "The patient expired on July 19, 1962 of pneumonia and metastatic carcinoma," at the age of 81, a little over six years after onset. Death occurred four years after toxins were begun and over four years after skin metastases had developed. It is of interest to note that the duration of life from the appearance of cutaneous metastases from internal cancers averages three months. (48, 52)

CASE 10: Recurrent carcinoma of the sigmoid colon with intra-abdominal metastases.

Previous History: P. Z., male teacher, aged 45. The family and previous personal history were non-contributory. The patient had been in good health prior to onset in December 1958, when he began to have abdominal pains due to carcinoma of the colon.

Surgery: The lesion was resected and it was found that many lymph nodes were involved.

Clinical Course: Several months later the symptoms recurred and examination revealed palpable masses in the abdomen.

Toxin Therapy (Johnston XV): Injections were begun by Dr. Isadore Rossman on May 25, 1959 and were given daily intravenously at Montefiore Hospital, New York, N.Y. They caused chills and febrile reaction averaging 102°F. (maximum 103°F.). No apparent change in size was noted in the abdominal metastases.

Chemotherapy: A single intravenous injection of nitrogen mustard (HN2) was given on June 6, 1959.

Further Toxin Therapy: Injections were continued until June 15, 1959, a total duration of 21 days.

Further Chemotherapy: The patient was given 5 Fluorouracil (5-FU).

Clinical Course: None of these agents appeared to have any effect. The disease progressed, causing death on July 2, 1959, seven months after onset of symptoms. (48)

CASE 11: Recurrent adenocarcinoma of the colon with extensive metastases seeding the viscera and peritoneum, the liver, pleura and lungs, confirmed by microscopic examination following the first and second operations. Pleural and ascitic fluid contained carcinoma cells. (Grade III).

Previous History: B. M. S., male aged 69. The family history was negative for cancer, tuberculosis, diabetes or allergies. The patient had been married

50 years. He was a retired contractor. He had had malaria in 1911. He had been followed closely by Dr. James R. Ricks between 1954 and 1958 for various minor complaints such as respiratory illnesses, back strain, an occasional bout of gaseous indigestion and hemorrhoids. He was given influenza vaccine injections spring and fall in this period. He was a strong, well nourished, alert and cooperative man whose normal weight was around 190 pounds. Onset, in the summer of 1958 he became ill and was found to have a carcinoma of the colon.

Surgery: In October 1958 the lesion was resected with about 50 cm. of colon at Wesley Hospital, Oklahoma City, Oklahoma.

Radiation: He was given a full course of x-ray therapy postoperatively.

Clinical Course: He began to lose strength and weight (28 pounds). He developed signs of obstruction in August 1959 which proceeded to complete ileus. He was admitted to Baptist Memorial Hospital, Oklahoma City on October 19, 1959.

Further Surgery: At exploratory laparotomy on October 26, 1959 a number of adhesion bands were released. The abdomen was studded with metastatic carcinoma seeding the peritoneum, the bowels and liver in all directions. The anastamosis was intact.

Chemotherapy: Nitrogen mustard (HN2) was instilled into the peritoneal cavity (10 mgm.). The patient was discharged somewhat improved, i.e., he was able to eat and defecate.

Further Radiation: He was then given 31 x-ray treatments.

Clinical Course: During 1960 there was evidence of further progression of the disease. His condition became worse, with ascites, pleural effusion, dyspnea, nausea and emesis. On February 11, 1961 he was readmitted to Baptist Memorial with ascites and massive pleural effusion. Examination at this time revealed that the liver was enlarged two finger breadths below the costal margin. There were numerous rales and fluid in both bases. The spleen was not palpable. The colon was tender, but no masses were palpable in the abdomen. The clinical impression was that the man had metastases to the abdomen, pleural effusion from his metastases, an enlarged liver and ascites. The family physician, Dr. William R. Pascall, had been tapping the abdomen daily, obtaining four to eight quarts of bloody fluid, which contained numerous malignant cells. Bloody pleural fluid, was aspirated every two or three days, about a quart each time, which also contained malignant cells. Following admission, February 14, 1961, 2900 cc. was aspirated from the left pleural cavity. Dr. Hunter the pathologist, reported 95% lymphocytes and 5% mesothelial cells which fluoresced as cancer cells, Grade II malignancy. The abdomen was tapped for ascitic fluid. The prognosis at this time was regarded as less than a week, possibly only 24 to 48 hours.

Toxin Therapy (Johnson XV): On February 22, 1961 Ricks began intradermal injections of the toxins which were given daily for eight days. The initial dose was 0.5 cc. of a 1 to 2 dilution, which was gradually increased to 1 cc. undiluted. Locally at the sites of injections there was an extensive inflammatory reaction and pain. There was also general aching and shaking chills to which the patient objected. The febrile reactions averaged 101°-103°F., and occurred three or four hours after each dose. The pleural effusion diminished within 24 hours after the first injection. The patient felt better, was able to eat and digest his food without nausea or vomiting. By the third day after toxins were begun there were no further ascites, the bowels moved normally and urine passed more freely. The patient's strength and weight increased.

Clinical Course: By March 10, 1961 the patient was home. There was no further edema, ascites or pleural effusion. Complete regression of all metastases apparently occurred. The patient regained his lost weight (30 pounds). He was seen at frequent intervals by Ricks. The only medication given in the next few years was injections of influenza virus A and B and Asian strain and adenovirus #3 and #7 (0.05 cc. each) given intradermally every month for two or three months, spring and fall. These caused some local redness and skin reaction, but no noticeable rise in temperature. The patient remained hale and hearty in February 1969, 10½ years after onset. (48)

DISCUSSION AND CONCLUSION

The apparently beneficial effects of concurrent bacterial infections or of bacterial toxin therapy on cancer of the colon and rectum have been reviewed.

The use of broad spectrum antibiotics as a routine prior to surgery for such cancers is considered inadvisable, since a sterile gut offers a much more favorable soil for tumor cell growth than normal bowel mucosa. (12, 13, 31a, 69, 71, 74)

In addition, patients with colo-rectal cancers who accidentally develop bacterial infections concurrently, should be treated without antibiotics whenever possible.

Since small doses of bacterial toxins protect the reticuloendothelial system against the deleterious effects of radiation (1, 2, 3, 8, 15, 32, 55, 56) and appear to potentiate the tumor destructive effects of subsequent radiation (10), the timing of such combination therapy is of great importance.

Because it is difficult to secure a satisfactory result, except in rare instances, in terminal cases, or in patients with very extensive lesions, palliative or incomplete resections of such lesions in the colon or rectum may offer more hope of permanent control than if toxin therapy and/or radiation are administered without such surgery.

In analyzing these 35 cases of colorectal cancer, it is apparent that even the operable cases were extensive, many had regional lymph node involvement, many had liver metastases. One was terminal with ascites and pleural effusion, and one had distant metastases to soft tissues.

According to Modlin and Walker (45) the average survival of patients with inoperable cancer of the colon, with or without palliative resection, is only 21½ months from onset of symptoms. It is therefore of interest that among the determinate inoperable infection cases in the present study the average survival rate was over six years.

In Series A, the 24 infection cases, 12 patients were alive and free from further evidence of disease when last traced eight to 17 years after onset: Case 12, 14, 16, 17, 19 (14-17 years); Case 3, 4, 20 (10-12 years); Case 7 (over 9 years); Case 11 (8 years). One patient (Case 16) developed a second primary carcinoma of the colon, histologically distinct, 10 years after onset of the first and remained well, with no evidence of either lesion five years later. Case 23 developed a carcinoma of the stomach which proved fatal over seven years after onset of her sigmoid carcinoma.

Five patients in the infection group died of their colorectal cancers five to ten years after onset: Case 5, 9, 10, 18, 24. One of these may have had a second primary rather than reactivation of the first, for he remained entirely well for over nine years: Case 5. Two were traced less than five years. One of these was entirely well at two years, Case 6: one was improving under treatment by tumor extracts, following infections, Case 8. One was bedridden with recurrent cancer seven years after onset, Case 13; one developed another type of carcinoma (bladder) which caused death four years after onset of the colon cancer, and the latter was not found at autopsy, Case 21. Two extensive inoperable carcinomas of the colon regressed dramatically following erysipelas infections, Cases 1 and 2. One of these recurred causing death 11 months after

onset and five months after infection, the other died of nephritis five months after regression had occurred.

The average survival for the 11 toxin treated cases was eight years. Four patients survived only seven to 21 months. Of these, Cases 2 and 4 had inoperable carcinomas for which no surgery other than biopsy or colostomy was attempted due to extensive disease. Both survived approximately a year with notable palliation from toxin therapy. These are examples of the need to reduce the extent of the tumor in order to make it easier to control the remains of the disease by toxin therapy, radiation or chemotherapy as recently suggested by the work of Martin and his colleagues. (38, 39)

Cases 7 and 10 survived 21 and 7 months respectively. In the former, considerable radiation was given prior to toxins. In the latter, toxins were not begun until extensive metastases were present. These patients received only 20 and 21 intravenous injections of the toxins. No apparent benefit was noted in either case.

One case survived three years (Case 6). This patient had received radiation and had enormous liver metastases when toxins were begun. Notable palliation occurred while toxins were being administered.

The other six toxin treated cases survived six to 35 years. One died of pneumonia and chronic congestive heart disease at the age of 80, nine years after onset. One died of coronary occlusion and ulcerative colitis, 35 years after onset. One died of hemiplegia, 14 years after onset, a week after he developed evidence of a second primary in the lower esophagus. One died of pneumonia and possible residual cancer at the age of 81, six years after onset. The other two patients (Cases 8 and 11) are alive and in excellent health with no further evidence of disease, over ten years after onset.

CONCLUSIONS:

The evidence presented here suggests that patients with colorectal cancer — both operable and inoperable — may have a significantly better prognosis if they develop fever, or concurrent bacterial infections, such as abscess or erysipelas before or after surgery, or if they have a local inflammatory reaction or leukocytosis of unknown etidogy. Such "complications" are more apt to be beneficial if the patient has received little or no preliminary irradiation, chemotherapy or antibiotics. When the infection occurs first, spectacular regression may occur following rather minimal doses of x-ray (Series A, Case 16). Infections may mask the presence of the carcinoma and delay the diagnosis. (Series A, Cases 16, 20 and 24).

If the disease is very extensive, or the patient elderly or in poor general condition, such infections may produce only temporary regression (Series A, Cases 1 and 2).

A patient's ability to elicit an acute inflammatory reaction in the tumor area, including lymphadenitis and leukocytosis, may be of distinct value and appears to affect prognosis favorably (Series A, Cases 11, 12, 16, 21, and 24; Series B, Cases 1, 5 and 8).

The evidence presented herein suggests that extensive research is now warranted to determine how to ultilize microbial products in the most effective ways for treatment of colorectal cancer, as well as in other types of malignancy.

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