Dissemination of Cancer with Special Emphasis on Vascular Spread and Implantation *

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There are four known major mechanisms for the spread of cancer: 1) contiguity, 2) lymphatics, 3) vascular spread and 4) implantation. An enormous amount of work has been done on the spread by contiguity (local invasion) and by the lymphatics. Accordingly, the purpose of this report concerns vascular spread and implantation.

Factors Influencing Spread of Cancer

It is well known that some tumors grow rapidly whereas others grow slowly. We cannot explain this difference in growth rate except that it is related to virulence of the cancer cell and host resistance. The latter is probably more important. Coman [12] emphasized the importance of the loss of cohesiveness of cancer cells in dissemination. He explained that the benign cells are motile (as are malignant cells) but that they are attached so tightly together that they rarely break loose and circulate as do cancer cells. Coman attributed this loss of cohesiveness to a deficiency in calcium, although certain enzymes (*e.g.* hyaluronidase) may exert an influence on detachment of cells.

The mitotic time might have a role in the growth of cancer cells, but since the mitotic time of malignant cells is not shorter than that of benign cells this factor probably has significance in the uncontrolled growth of cancer cells. More important is the fact that the benign cell ceases to grow in the reparative process and no overgrowth is encountered. When a tumor develops the cells continue to multiply even though increased pressure is developed.

Several authors (Wood,[44] Zeidman,[47] and Cliffton and associates [10]) have discussed the influence of a thrombus at the site of lodgment of cancer cells on their growth and showed that heparin and other anticoagulants will discourage the growth of cancer cells.

Vascular Spread of Cancer

In 1932 Pool and Dunlop [28] reported the isolation of cancer cells from the circulating blood. Since 1955 numerous authors [13, 30] have corroborated this finding and have reported varying percentages of positive blood samples for various tumors. It is now agreed that in the early reports these cells were "overdiagnosed." Numerous blood cells including granulocytes, monocytes, histiocytes and especially megakaryocytes have been confused with cancer cells. Some of the difficulty in differentiating these various cells may stem from the possibility that the megakaryocytes in patients with cancer have a different histologic appearance from those in normal individuals, as suggested by Romsdahl and associates.[34] Lest the difficulty in positively identifying cancer cells leads one into thinking that the question of cancer cells in the blood is

* Presented before the Southern Surgical Association, Dec. 8–10, Boca Raton, Florida.

Aided by NIH Grants 3482 and 9594.

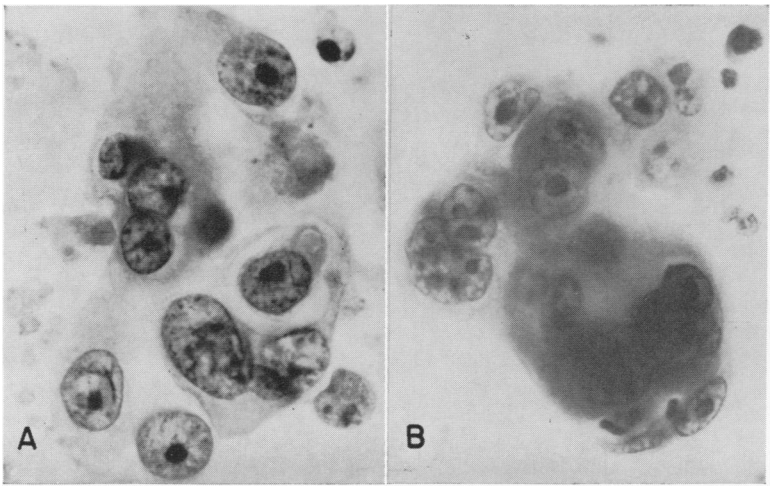

FIG. 1. Carcinoma of the kidney, Papanicolaou stain. A. Direct smear of resected tumor. B. Clumps of cancer cells isolated from blood aspirated from the renal vein during nephrectomy.

not important, we would like to emphasize that with the exception of head and neck tumors, the vascular spread of the tumor represents the most important lethal factor in progress of the disease. It is well known that metastases develop in certain organs more readily than in others. This soil hypothesis was presented by Paget in 1889. Lucke and associates [22] injected tumor cells into the intraportal and pulmonary circulations and observed the growth of tumors. They noted that larger tumors were produced in the liver than in the lungs and that the total mass of tumor in the lung was less than that in the liver. It is well known that cells and even clumps of cells will pass through capillaries (Fig. 1).

Prinzmetal and associates [29] have shown that there are vascular shunts in the lungs, kidney, liver and spleen of dogs and rabbits with a size many times the diameter of capillaries. These arteriovenous shunts will explain the transport of cells from one organ to another without going through the capillaries. They proved evidence of these shunts by injection of tiny glass spheres.

We would like to add that cancer cells may gain access to the systemic circulation through intravasation, or the passage of cells from malignant tissue into vascular channels through anatomic defects, some of which may be created by trauma.

Number of Cells Required to Produce Growth of Tumors. Years ago it was thought that the escape of a few cancer cells from the primary growth would produce metastases with consequent death to the patient in every instance. However Warren and Gates,[41] in 1936, presented evidence indicating that the mortality of embolic cancer cells was very high and evidence that this hypothesis is valid has been accumulating. In 1950 Zeidman and associates [46] reported that in a group of C57 mice injected with 104,400 Sarcoma-241 cells the average number of pulmonary metastases was only 11.5. When 5,400 cells were injected the average number of pulmonary metastases was 1.7; when 900 cells were injected the average number of pulmonary metastases was 0.31. Fisher and Fisher [14] noted that when 100 Walker-256 tumor cells were injected into the portal vein, tumors developed in only 30 per cent of the rats. If 5,000 cells were injected, 58 per cent of the animals developed tumors. Moore and associates,[26] working with the Ehrlich Ascites tumor, noted that when 100,000 cells were injected intraperitoneally, tumors developed in 28 of 37 animals; when cells were inoculated subcutaneously, tumors developed in 96 of 102 animals.

Time of Disappearance of Cells Following Intravenous Inoculation. Madden and

Malmgren [23] injected various numbers of MPC-3 tumor cells into the tail vein of BALB/c mice and counted the cells in the blood from the right chamber of the heart at varying intervals after inoculation of cells. They found that after the inoculation of 50,000 cells, none were found in the blood in the right side of the heart. After the inoculation of 1,000,000 cells, an average of three cells per 0.5 ml. of blood were encountered 3 to 5 min. following intravenous inoculation. Following the injection of 5,000,000 MPC-3 tumor cells, an average of 739 cells were found per 0.5 ml. of blood, but the count dropped sharply to an average of nine at 3 min. and an average of three at 10 min. Hengesh and associates [19] likewise noted rapid disappearance of cells from the blood stream after intravenous inoculation of 4,000,000 Ehrlich Ascites tumor cells. The cells were injected into the tail vein and blood samples obtained by direct cardiac puncture at the time of sacrifice. Although a large number of cells were found in the blood immediately after injection, at the end of 30 min. no tumor cells could be recovered.

Influence of Trauma and Manipulation of Tumor on Dissemination of Cancer. In 1913 Tyzzer inoculated Japanese waltzing mice with tumor cells subcutaneously and massaged the subsequent tumor to determine the effect on metastases in the lungs. He found that only 9 per cent of control mice (not subjected to massage) developed pulmonary metastases, whereas 66 per cent of 34 mice having massage of their tumor developed pulmonary metastases. Romsdahl [33] of our laboratory recently conducted similar experiments with the Walker-256 tumor following inoculation of Walker cells into the thigh muscles. Twelve to 21 days after inoculation, when tumors had developed, the tumors were massaged for 30 seconds. Blood was obtained from the vena cava. Before manipulation no tumor cells were noted. During manipulation a large number of tumor cells were found, but at the end of 15 min. none were demonstrable.

Robinson and Hoppe [31] of our laboratory conducted an experiment to determine what effect trauma would have on the development of metastases following inoculation of cells. Under pentobarbital anesthesia 1,000,000 cells were inoculated into the aorta and the thigh was subjected to trauma (produced by allowing a 3-pound hammer to fall repeatedly from a height of 3 in. on the thigh). In half the animals trauma was applied one minute before cell injection and in the other half one minute after the injection. The animals were sacrificed at the end of 20 days. The number of tumor nodules developing after inoculation of cells was five to eight times as high in the traumatized limb as in the control limb. Alexander and Altmeier [2] conducted some experiments determining the effect of trauma on the spleen (produced by injection of nitrogen mustard) in rabbits following the inoculation of V2 carcinoma cells. They noted that 67 per cent of the test animals developed metastases to the damaged spleen whereas metastases were found in only 8 per cent of the control animals. They also noted that "even intestinal damage from operative manipulation resulted in an increase in intestinal metastases." However these cells were also inoculated *intra-arterially,* which may not allow clinical interpretation because human tumor cells (lung cancer excepted) escape into the veins.

There is considerable doubt as to how often recurrences in a wound made for incision of a cancer develop from blood-borne cells and how often they are due to implantation by cells dislocated at the time of the operation. To test this hypothesis, Vernick and associates [39] of our laboratory made several hundred incisions through the skin and muscle in various animals one hour previous to inoculation of cancer cells. In rats the Walker-256 tumor (25,000 to 500,000 cells) and the Guerin uterine tumor

were utilized; in rabbits the V2 tumor was utilized; in mice the Sarcoma 180 was used. In none of the animals (including 520 incisions in 130 rats) did the intravenous injection of tumor cells result in the growth of a metastases in an incision. However when 1,000,000 V2 carcinoma cells were given *intra-arterially* four tumors were found in 24 incisions made in nine rabbits. Since most of the cancer cells disseminated in the vascular system of human patients travel by way of the veins, Vernick and associates concluded that lodgment of cells in their *wounds* via the vascular system rarely occurred, and that this could not be interpreted as being a common source of wound implants in the human being. Although we believe that the lodgment of circulating cancer cells in a *wound* with development of a metastases rarely takes place, we recently observed a patient (to be reported in detail elsewhere) who developed metastatic nodules in two wounds made 6 months after esophagectomy for cancer during construction of a new esophagus; at the time of both operations there was no evidence of residual cancer, but metastatic areas must have been present somewhere.

Significance of Venous Invasion by the Tumor. For decades pathologists have called attention to the invasion of veins by the tumor in histologic sections. Brown and Warren [8] were among the first to attach significance to this finding. In an autopsy series they noted that visceral metastases (all organs) were found in 70 per cent of 70 patients having vein invasion, whereas visceral metastases were found in none of 30 patients without venous invasion. Sunderland [37] noted that in patients with Dukes-C colorectal carcinoma (*i.e.* those with lymph node metastases) the 5-year survival rate was 57.7 per cent in patients without venous invasion compared to 20 per cent in patients with venous invasion. Also in a study of patients with colorectal carcinoma Grinnell [16] noted that venous invasion was found in 36 per cent of patients with rectal carcinoma and in 33 per cent of patients with colonic carcinoma. In his series the 5-year survival rate was 37 per cent in patients with venous invasion and 75 per cent in patients without venous invasion. This corresponded closely to the relationship of lymph node metastases in his series, since the 5-year survival was 83 per cent in patients without node metastases compared to 41 per cent in patients with node metastases. In perhaps the most significant report on this subject Collier and associates,[11] in a study of 225 consecutive cases of resected primary lung carcinoma, found that only 6 per cent of 65 patients with histologic evidence of vein invasion were alive at the end of 5 years, whereas 72 per cent of 28 patients without vein invasion survived 5 or more years. Those authors concluded that the presence of vascular invasion was of more prognostic value than either the lymphatic involvement or the type of surgical resection.

The Relationship of Vascular Spread to Cancer in the Lymphatic System. In most patients vascular spread of cancer does not take place until the lymph nodes are involved, but this is by no means always true. The senior author recently observed a patient with carcinoma of the sigmoid which, upon removal and examination in the surgical pathology room, revealed no involved lymph nodes. However within a few weeks the patient returned with pain in the hip and a roentgenogram revealed a large bone metastasis in the ileum 3×4 cm. in diameter.

Willis [45] made a detailed study of the site of metastases after death and reported that in 59 fatal cases of cancer of the colon 31 had metastases in the liver, but in 11 the liver was the only site of metastases.

Distant metastases occur in head and neck cancer much more commonly than considered by the average surgeon. Willis reported that in 64 autopsies in patients with head and neck cancer distant metas-

tases were found in 39 per cent of cases. Most of these were in the lung and liver, although metastases were found in 16 miscellaneous sites. Hoye and associates [21] assembled data from ten sources on the incidence of distant metastases in head and neck cancer and found a range of 5 to 50 per cent and an average of 21 per cent.

Wound Contamination and Implantation

There is a moderate amount of controversy concerning the origin of recurrent nodules in the wound following a major operation for cancer. It is obvious that some of the local recurrences are due to inadequate removal of the primary tumor. At the time of operation the surgeon usually knows whether or not he has excised the tumor adequately; if his line of excision extends close to the tumor, the probability of residual tumor is strong.

Excluding the inadequate excision of the tumor, implantation may be spontaneous or iatrogenic. Spontaneous implantation of cancer cells is well known, as exemplified by the peritoneal metastases so often found at operation for cancer of the gastrointestinal tract. These metastases are obviously spontaneous. On other occasions there may be no demonstrable metastases in the thoracic or peritoneal cavity but in a variable length of time, metastases may develop; these may have been spontaneous insofar as cells may have desquamated from the primary tumor before operation, unrelated to the operative manipulation. On other occasions it seems very probable that there may have been no cells drifting spontaneously from the primary tumor, but the surgeon may have disseminated the cells by operative manipulations.

One of the first surgeons to have called attention to the danger of dissemination of cancer by operative manipulation was Gerster (1885). Occasionally thereafter (Lack in 1896 and Ryall in 1907), this danger has been re-emphasized. For example Ryall reported 25 patients having recurrence of one type or another in the wound made during the operative procedure. These local recurrences, secondary to dissemination by the surgeon, may occur almost anywhere in the body and under all types of circumstances. Many of them have been reported in the needle track following aspiration of a tumor with a needle and syringe. Some have been in skin grafts and some in the donor site of skin grafts. Occasionally they are found in the drainage site where the abdominal cavity was drained following a resection of a carcinoma. Ackerman and Wheat [1] made a specific study of this complication and reported local recurrences in skin grafts, on the peritoneum in the abdominal cavity, and in the peritoneal wound following abdominoperineal resection. Cancer cells actually have been found on the knives used by the surgeon.

One of the most unique examples of implantation is that reported by Beahrs and associates [6] (reporting on 4 patients) in which an adenocarcinoma from a tumor of the rectum or colon had developed in the scar of a hemorrhoidectomy. These patients had had a hemorrhoidectomy during the time when they actually had a carcinoma of the large bowel from which the cells drifted downward and implanted in the hemorrhoidectomy wound.

About 10 years ago three different groups became worried about the high incidence of development of recurrences in the suture line following resection of the colon for cancer. By utilizing precautions such as prophylactic irrigation of the bowel lumen, and ligation of the bowel several inches proximal and distal to the tumor, and excision of the crushed ends of the bowel before application of sutures, these three groups reported that local recurrences had been eliminated almost completely; this represents proof, or strong evidence, that the recurrences were due to implantation and not to lodgment of circulating tumor cells or new tumors.

TABLE 1. *Local Recurrence in Breast Cancer (after Radical Mastectomy)*

Hospital and Source	No. Cases	% Recurrence	Comments
Cleveland Clinic (Robnett, Jones & Hazard[32])	203	14.2	
Presbyterian Hosp. (N.Y.) (Haagensen[17])	356	15.2	
U. of Chicago (Allen & Rigler[3])	230	12	
Mass. Gen. Hosp. (Taylor & Wallace[38])	236	11	15% if biopsied 7.5% if not biopsied
St. Luke's Hosp. (N.Y.) (Shore[35])	116	6.9	if limited to breast
	244	21.3	if ax. nodes involved
Henry Ford Hosp. (Hoopes & McGraw[20]) Plastic closure & skin graft	97	6.1	if limited to breast
	149	20.8	if ax. nodes involved
Roosevelt Hosp. (N.Y.) (White[42])	101	10.8	if limited to breast
	137	31.5	if ax. nodes involved

As stated above, many surgeons have called attention to the probability that cancer cells disseminating from the wound at the time of operation are the cause of a major portion of the local recurrences. These cells presumably might escape from the severed ends of lymph channels and small blood vessels or may have been squeezed out of the tumor through tissue planes into the wound.

Local Recurrence. It is our contention that residual tumor is too often blamed for the local recurrence. Although local recurrence may occur in any wound following excision for cancer it appears to be more common following radical mastectomy and radical neck dissection. A survey of the literature reveals a large number of reports which give the percentage local recurrence for these operations. Table 1 shows that there is a marked similarity in the various reports regarding the incidence of local recurrence in breast cancer. Taylor and Wallace [38] reported an incidence of recurrence of 7.5 per cent in patients not biopsied and 15 per cent in patients having a biopsy. They stated that of 236 patients having radical mastectomy, 116 had a biopsy with immediate histologic examination; presumably the remainder did not have a biopsy. Another significant aspect of these data is the marked increase in the incidence when the axillary nodes were involved. Likewise, there was close agreement on this incidence in the three reports providing that data.

The local recurrence rate in the neck following radical neck dissection for cancer is higher than that following radical mastectomy. Many of these recurrences are, of course, due to inadequate excision. However we believe that a major portion are due to implantation of cells which were disseminated at operation by mechanisms already mentioned. The fact that most of the primary lesions in this group were ulcerating in the mouth, and that the neck dissection was often performed in continuity (a desirable and justified procedure), offers an obvious mechanism for dissemination of cells from the primary lesion into the neck, unless the primary lesion was completely destroyed by cautery or some such procedure at the onset of the operation. In a recent study, Beahrs and Barber [7] report local recurrence in 26.5 per cent of 616 patients having radical neck dissection for cancer of the lip, mouth and larynx and state that they believed that in 46 per cent of the recurrences "seeding" was the causative mechanism. Local recurrence rates in head and neck cancer as recorded by numerous authors are listed in Table 2.

Case Reports

Case 1. A 66-year-old man was admitted to the University of Illinois Hospitals in May, 1962 with the chief complaint of a perianal mass of 9

TABLE 2. *Local Recurrence in Head and Neck Cancer (after Radical Neck Dissection)*

Hospital	Site	No. Cases	% Recurrence
Memorial Hosp. (N.Y.) (Martin *et al.*[24])	Mouth (all sites)	303	33.3
Memorial Hosp. (N.Y.) (Harrold[18])	Mouth (floor of mouth, gingiva, tongue, buc. muc.)	204	43.6
U. of Colorado (Morfit[27])	Mouth (8 diff. sites)	58	44
Nat. Cancer Inst. (Arons & Smith[4])	Mouth (11 diff. sites)	72	43
Emory Univ. (Wilkins & Vogler[43])	Gingiva	81	27.1
Westminster Hosp. (Cade & Lee[9])	Tongue	81	19.7
Memorial Hosp. (Frazell & Lucas[15])	Tongue	227	39
Mayo Clinic (Beahrs *et al.*[5])	Tongue	217	27
Mayo Clinic (Beahrs & Barber[7])	Lip, mouth, larynx	615	26.5

months duration. At the time the perianal mass was *first noted,* there were signs of local inflammation. A biopsy revealed no evidence of malignancy. There was evidence of considerable mucous secretions from the fistula which failed to heal and continued to discharge mucus. There was no prior history of an anal fistula.

Four years prior to this illness the patient had an emergency transverse colostomy followed by anterior resection for adenocarcinoma of the sigmoid colon. At the time of colostomy closure 3½ years prior to admission, a local recurrence was found in the area of the previous anastomosis. A left hemicolectomy was then done.

Examination on admission revealed a well circumscribed, elevated, ulcerated mass 3 × 2.5 cm. on the perineal skin just anterior to the anus. During rectal examination mucous secretions exuded from a single fistulous opening at the margin of the tumor mass. A small polyethylene catheter could be inserted easily into the opening of the fistula and threaded upward until it entered the internal opening of the anal fistula in an anterior crypt of Morgagni (Fig. 2A). No tumor was palpable or visible within the rectum, and proctosigmoidoscopy to 22 cm. was negative. A biopsy of the perianal mass revealed this to be a mucous-producing adenocarcinoma. There were no palpable inguinal lymph nodes. Liver function tests were normal.

The patient *refused* abdominal perineal resection but consented to a local excision. Accordingly on May 18, 1962 a wide perineal excision was carried out, including a portion of the external sphincter and the internal opening of the fistula. The postoperative course was uneventful.

Dissection of the specimen revealed a circumscribed, lobulated tumor measuring 3 × 2.5 × 2.5 cm. (Fig. 2B). Upon opening the fistulous tract from the external to the internal opening, it was found to be single and lined by rough grayish

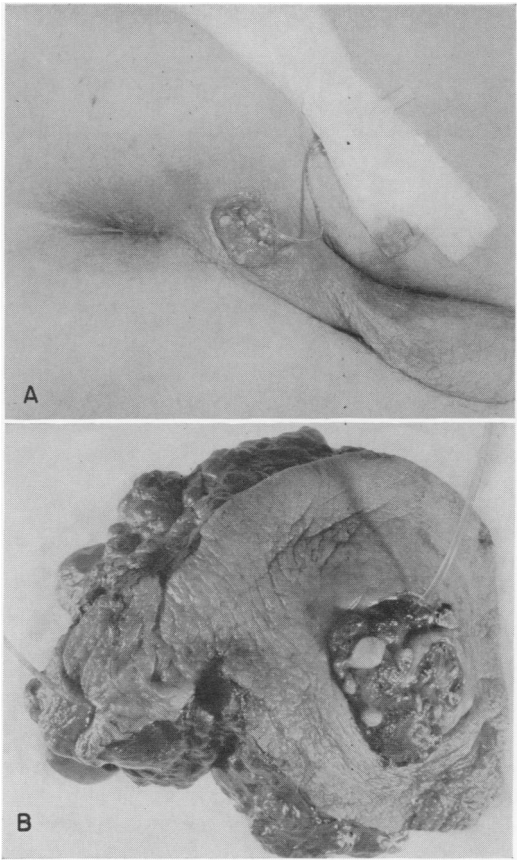

FIG. 2. Photographs of patient (Case 1) with implantation of mucinous carcinoma in a perianal fistula. A. Photograph of lesion on perineum adjacent to the base of scrotum. Note polyethylene tube which has been inserted into the single fistulous tract. B. Gross photograph of resected specimen which includes a portion of internal sphincter and mucosa. Tumor is limited to skin and subcutaneous tissue and there is no evidence of tumor in or near the rectal mucosa.

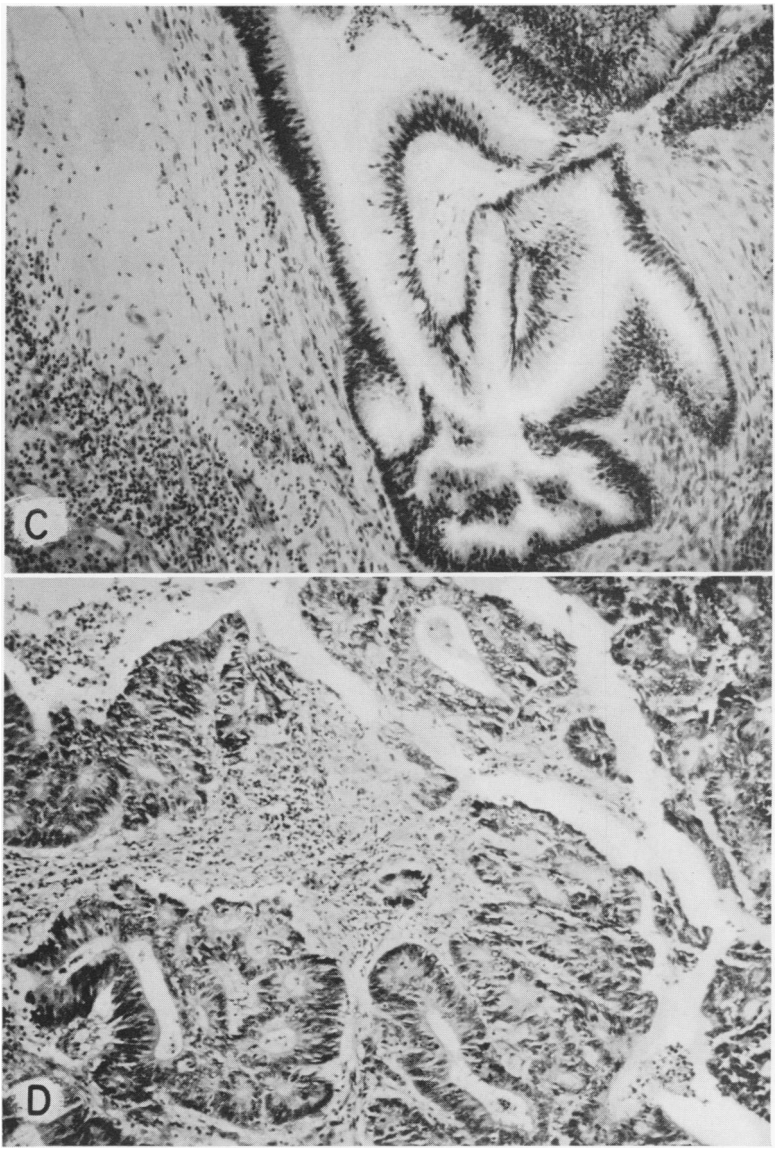

FIG. 2. C. Photomicrograph showing a mucinous adenocarcinoma of lesion shown in B. D. Photomicrograph of colon tumor resected 4 years prior to the lesion on the perineum. The pathologists report this tumor as similar to the original colon tumor removed 4 years previously.

tissue. Microscopic examination of the mass showed mucinous adenocarcinoma (Fig. 2C) and a fistulous tract lined by gradulation tissue. There was no evidence of glandular epithelium lining the fistulous tract, and there was no muscularis mucosa. The microscopic pattern of the mucinous adenocarcinoma was similar to the original colon tumor removed 4 years previously (Fig. 2D).

The patient is living and without evidence of recurrence 2½ years later.

Comment. Mucous-producing adenocarcinoma complicating an anal fistula is exceedingly rare. We believe this patient provides a clear example of implantation in the fistula-in-ano from the previous colon tumor. However the possibility of colloid carcinoma arising in a congenital fistula-in-ano must be excluded. The fistulous tract in this patient was lined by granulation tissue and not rectal mucosa, thus excluding a colloid carcinoma arising in a congenital tract. In addition, mucoid carcinoma developing on a long-standing *high* fistula-in-ano must

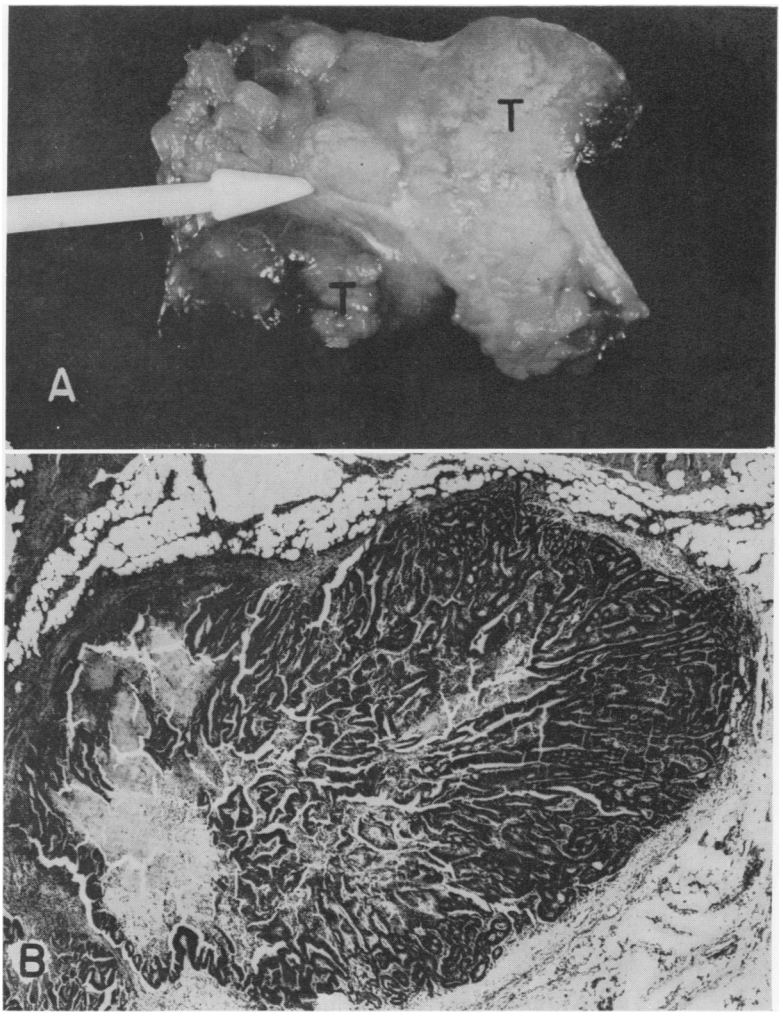

FIG. 3. A. Cross section of nodule (Case 2) appearing just beneath skin at site of needle biopsy of liver metastasis performed 8 weeks previously. Excised specimen includes skin, subcutaneous tissue and muscle. Implant is designated by "T." Note subfascial portion of tumor deep to the fascia (arrow). B. Low-power photomicrograph demonstrates tumor to be adenocarcinoma. Primary tumor was an adenocarcinoma of colon excised 3 years previously.

be excluded. It will be recalled that the upper half of the anal canal (that part above the anal valves) is lined by the same type of mucosa as the rectum; the lower half is lined by *transitional* and *squamous epithelium.* It is clear that this case represents the more common, low level fistula with the internal opening at or below the valves, thus excluding the possibility that the colloid carcinoma arose at the internal opening which is surrounded by squamous epithelium. For these reasons we believe that the tumor in the fistula was an implant from the adenocarcinoma of the sigmoid removed 4 years previously.

Case 2. A 43-year-old white woman had an anterior resection for adenocarcinoma of the sigmoid in 1960. One year earlier she had a polyp of the transverse colon excised. In August, 1963 a cutaneous liver biopsy with a needle was done because she had developed severe right shoulder pain and an enlargement of the liver. The biopsy was reported as metastatic adenocarcinoma of the liver. One month later the patient was explored to determine the resectability of the liver metastasis. There was a large solitary metastasis in the right lobe of the liver extending nearly into the left lobe, and hepatic arterial infusion with 5-fluorouracil was done instead. Approximately 2 weeks after discharge and 8 weeks after the needle biopsy had been performed, an erythematous papular lesion 3 mm. in diameter was noted in the subcutaneous tissue just beneath the skin at the

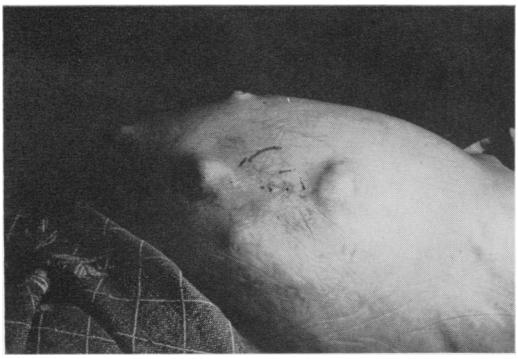

FIG. 4. Multiple subcutaneous tumors implanted by paracenteses, each lying beneath a healed paracentesis wound (Case 3). Abdomen is distended with ascitic fluid.

site of the needle biopsy in the ninth interspace. For the next 6 weeks this enlarged steadily to 1.5 cm. in diameter on the surface with a large subcutaneous component. Because the mass appeared to be a wound implant from the needle biopsy and now causing increasing discomfort, it was excised on December 4, 1963, 6 weeks after it had been noted initially. A cross section of the mass is shown in Fig. 3A and a photomicrograph in Fig. 3B. Unfortunately a course of intrahepatic arterial infusion of 5-FU in September, and repeated infusions on an outpatient basis, failed to have any beneficial effect on this lesion. The patient expired at home on March 1, 1964. There was no postmortem examination.

Comment. The patient described in Case 2 is an example of an implant in the needle tract in the skin following a needle biopsy of the metastatic mass in the liver. Apparently the needle was contaminated by the biopsy of the hepatic metastasis, and cells were dislodged subcutaneously just beneath the skin as the needle was withdrawn. The growth was remarkably rapid, insofar as a small mass (3 mm. in diameter) was noted at the site of the needle puncture 8 weeks after biopsy. The rapid growth of the implant was consistent with the growth of the tumor elsewhere, because the patient died 8 weeks after the skin implant was excised.

Case 3. A 63-year-old white woman was admitted in July, 1963 with a 3-month history of weakness, dyspnea, coughing and weight loss. Pleural effusion was noted and treated by thoracentesis. Cell block were negative for malignancy, but a needle biopsy of the pleura was reported as adenocarcinoma. She was rehospitalized in October for thoracentesis and intracavitary instillation of nitrogen mustard. Ascites was noted on this hospitalization and cytologic study of paracentesis fluid showed clusters of neoplastic cells. Ascitic fluid obtained in January, 1964 was reported as negative for neoplastic cells. In February, 1964, during hospitalization for a course of inpatient intraperitoneal thioTEPA, multiple tender intra-abdominal masses were noted, and the clinical diagnosis of carcinoma of the ovary was made. Several paracenteses and a thoracentesis were necessary to relieve her symptoms. Five months after the first paracentesis in March, 1964 a small, firm, nontender, subcutaneous mass was noted at the paracentesis site. She was rehospitalized with marked weight loss, pleural effusion, marked ascites, larger intra-abdominal masses and palpable, nontender, subcutaneous masses at three of the previous paracentesis sites (Fig. 4). In April, 1964 the patient was placed in a nursing home and until her death 5 months later 12 paracentesis were performed yielding an average of 5 liters of yellow serous fluid. The intra-abdominal masses became much larger and more tender and the patient continued to lose weight. Subcutaneous nodules became palpable in many of the paracentesis sites, and these increased in size until her death on September 4, 1964. These implants varied from 1.0 to 3.0 cm. in diameter and were firm and irregular. Biopsy of one of the subcutaneous masses confirmed the clinical impression of implanted adenocarcinoma. There was no postmortem examination.

Comment. This case was rather remarkable insofar as metastatic implants appeared to grow at the site of practically every paracentesis, requiring 3 to 4 months for the development of a palpable nodule. This tumor was an adenocarcinoma of the ovary, many of which grow viciously and are rapidly fatal.

Case 4. A 62-year-old white woman was admitted to the University of Illinois Hospitals on September 3, 1964 complaining of intermittent, cramping, lower abdominal pain—relieved by bowel movements—of 3 months duration. For one month she had noted black tarry stools of narrow caliber. The only significant physical finding was tenderness in the left lower quadrant. Barium enema revealed a constricting lesion in the splenic flexure. On May 13, 1964 an ascending transverse

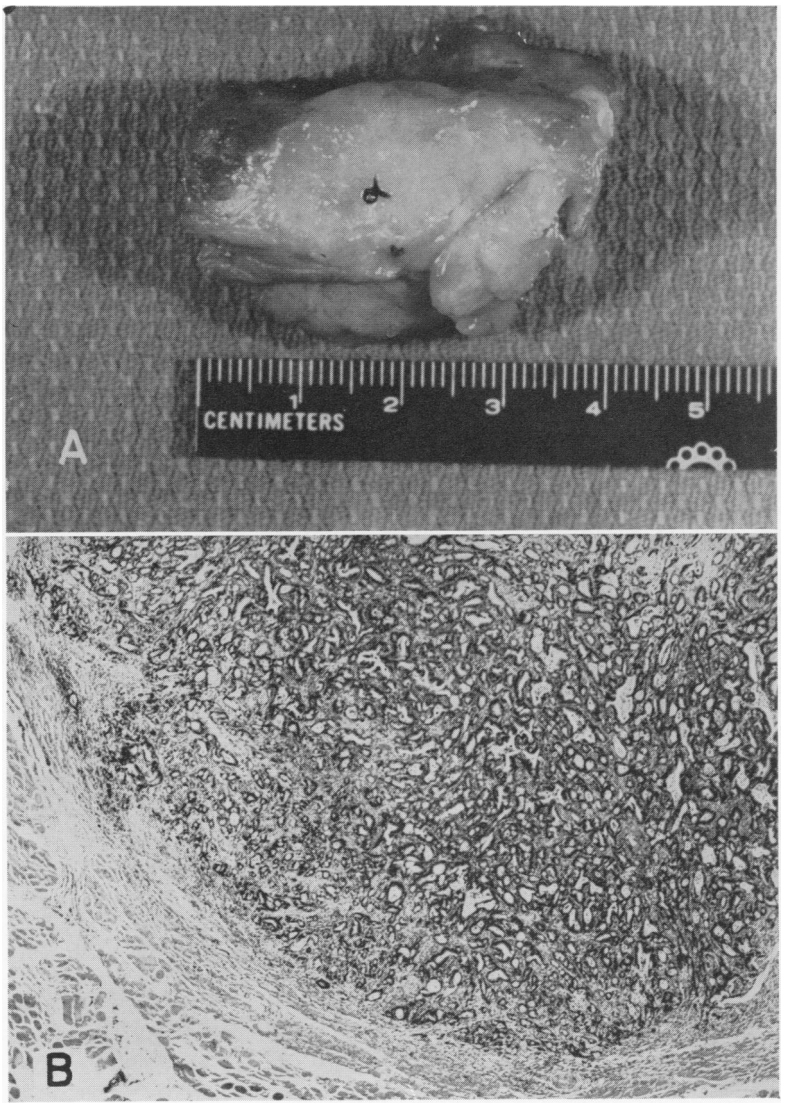

FIG. 5. A. Cross section of tumor implant (Case 4) in scar of wound noted 4 months after resection of colon. Note silk suture in central portion of tumor mass and fragments of rectus muscle attached to the tumor. B. Low-power photomicrograph shows adenocarcinoma with skeletal muscle in the left lower corner.

and upper descending colectomy was done and an end-to-end anastomosis performed. The postoperative course was uneventful but 4 months later she was readmitted with cramping abdominal pain and vomiting of several days duration. After the patient failed to respond to conservative management for small bowel obstruction, celiotomy was performed on September 14, 1964. As the incision was made a mass was encountered in the rectus muscle and completely excised. On section it appeared grossly to be neoplastic tissue in which was embedded a single silk suture (Fig. 5A). Microscopic examination reported adenocarcinoma (Fig. 5B). Numerous adhesions were found but the primary site of obstruction was an implant on the greater curvature of the stomach to which a loop of small bowel was adherent. A bypass enteroenterostomy was done because liver metastases were present. The postoperative course was prolonged but the patient eventually recovered.

Comment. This patient developed an implant in the abdominal wound 4 months after a resection of the splenic flexure for cancer. As shown in Fig. 5A a silk suture was found in the center of the mass which was about 2 cm. in diameter. Since silk sutures are often found in the recurrent tumors occasionally seen at the suture line

following resection of the colon for carcinoma, it appears that the silk suture may have a causative influence in the development of the recurrence. If it does, it might be assumed that a great majority of cells displaced into the wound during the operation die, but that if they are displaced into the tract made by the suture the circumstances for survival of the cells are much more favorable. This improved probability of survival may be related to better nutritional surroundings than would exist if the cells are lying on the surface of the wound.

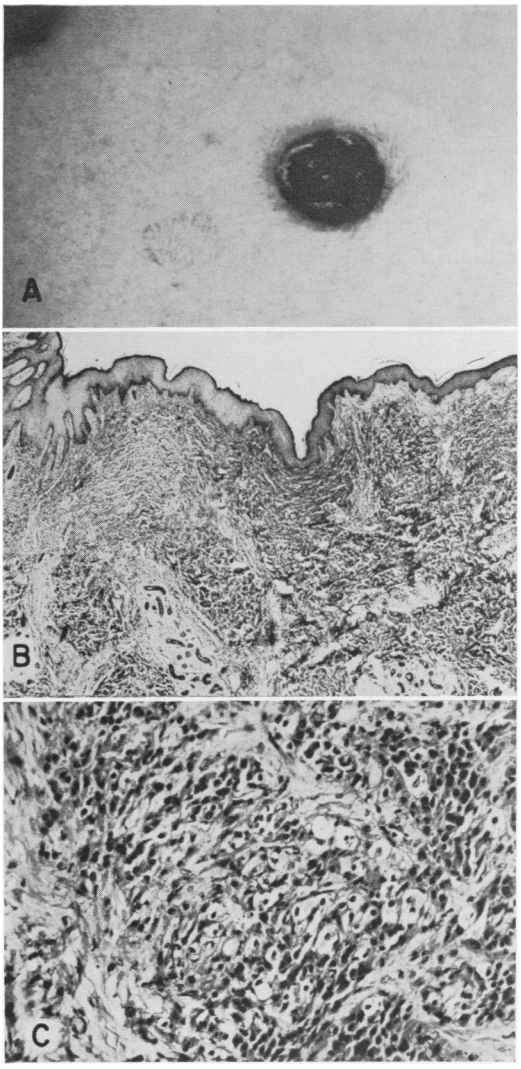

FIG. 6. A. Sarcoma implant in donor skin graft site of abdominal wall (Case 5). Nodule appeared 10 months after skin graft. B. Low-power photomicrograph shows undifferentiated sarcoma in subcutaneous tissue. Note distortion of rete pegs and variable thickness of epidermis representing donor graft site. C. High-power photomicrograph showing cellular pattern of sarcoma.

Case 5. A 24-year-old white man was well until August, 1960 when he developed pain and swelling of his left middle finger. Initial treatment with steroids failed to alleviate his symptoms and in April, 1961 the finger was biopsied and a Ray resection of the middle finger was performed on May 19, 1961 for synovioma. At the same time an axillary node biopsy revealed metastatic disease. His arm began to swell markedly prior to his first admission to the Research and Education Hospitals on July 24, 1961. The forearm was biopsied and reported as undifferentiated sarcoma. Arterial perfusion of the arm with A-8103 was performed and followed by a moderate reduction in size of the left arm. However the postoperative course was complicated by two episodes of hemorrhage in the axillary wound requiring ligation of the axillary artery. Later it was necessary to open the axillary wound because of a hematoma. This resulted in an open area which subsequently required grafting.

On September 21, 1961 a split-thickness skin graft was obtained with a Padgett dermatome from the left lower quadrant of the abdomen. The skin was applied in postage stamp fashion to the axillary wound and to a granulating area on the left elbow. These areas healed satisfactorily and the patient was discharged 10 days later.

He was readmitted in March, 1962 for treatment of a left pneumothorax. In June, 1962 the patient consented to a left interscapulothoracic amputation because extensive disease had made that extremity completely useless. At that time the abdomen was noted to be normal. On July 10, 2½ weeks after discharge, he was readmitted for skin grafting to the left shoulder area where the skin flaps had separated. At this time he was first noted to have a round cauliflower-like lesion 2 cm. in diameter in the healed donor graft site of the abdomen (Fig. 6A). This was excised and reported as a poorly differentiated sarcoma (Fig. 6B, C)—possibly angiosarcoma.

The patient's final admission for terminal care followed a few weeks later. He expired on August 31, 1962 with widespread metastases.

Comment. Local recurrences of the implantation type have been reported in the donor site, although recurrences in the graft site are perhaps more common. In this case the recurrence was not apparent

until nearly 10 months after the graft; the patient was seen and examined 9 months after the skin graft at which time there was no evidence of a recurrence. Since there was visible tumor in one or two areas in the axillary region when the skin graft was performed there was obviously ample opportunity for sarcoma cells to contaminate the surgeons gloves and be implanted into the donor site. There is, of course, the possibility that sarcoma cells were circulating in the blood stream and that some of them lodged in the traumatized area at the donor site. However, as stated previously, some experiments performed in our own laboratory by Vernix and Garside [39] showed that when the cells were injected *intravenously,* not a single implant was found later in the scar of the incisions, although when 1,000,000 V2 cells were injected into the *aorta* of nine rabbits at the time the incisions were made, a metastasis was found in four of the 24 incisions.

Irrigation of Wounds with Chemical Agents

Cancer Cells in the Wounds of Patients Having Operation for Cancer. Smith and associates [36] were among the first to report the discovery of cancer cells in an operative wound. They found cancer cells in 26 per cent of 120 wounds and suspicious cells in an additional 14 per cent. The local recurrence rate for the patients having cells in the wound washings was 40 per cent compared to the recurrence rate of 26 per cent in patients having negative washings. However when these authors studied these cases later, they found no relationship of survival of the patients to the presence or absence of cells in the wound washings.

In a recent study, Smith *et al.*,[36] concluded that irrigation with 0.5 per cent formaldehyde was effective. For example, 21 of 54 patients irrigated with saline developed a recurrence, whereas only 4 of 26 patients having their wounds irrigated with formaldehyde developed a recurrence. The group having their wounds irrigated with formaldehyde also showed a small but consistently greater survival rate.

Laboratory Experiments on the Effect of Various Anticancer Agents in Wounds. Numerous authors have attempted to find chemicals which would destroy cancer cells when used to irrigate wounds made for the excision of cancer. Our own group has tested an enormous number of compounds. Some of those which we thought might be effective turned out to be ineffective. The ineffective group included phenol, oxytetracycline, cholroazodin (Azochloramide) and benzalkonium (Zephiran chloride). Iodine itself is fairly effective. Clorpactin XCB was not effective when used in 0.5 per cent solution, which represents a concentration considered safe by us for human beings. We found 0.4 per cent formaldehyde to be reasonably effective but that sodium hypochlorite and nitrogen mustard were more effective. A chlorine compound known as ACL 60 (sodium dichloroisocyanurate) is also effective. It has considerable advantage over sodium hypochlorite because it is quite stable; sodium hypochlorite is relatively unstable and must be buffered with sodium bicarbonate to a pH of 9.0. In some additional experiments we noted that quinacrine (Atabrine), proflavine hemisulfate, chloramine-T, and iodoform were likewise effective.

These experiments were performed with subcutaneous wounds, irrigating the wounds one hour after the cancer cells had been implanted. Knowing that the effect of the chemical agents might be different in the peritoneal cavity because of a difference in the invasive quality and other possible factors, we conducted some experiments inoculating cancer cells in the peritoneal cavity and irrigating the cavity one hour later with various chemicals. We were surprised to find that the use of the chlorine compounds (ACL 60 and sodium hypochlorite) in the peritoneal cavity actually increased the percentage take of the tumor

cells.[25] However thioTEPA and A-8103 used in the peritoneal cavity were quite effective in sharply reducing the take of tumor cells. Vernick and associates,[40] working in our laboratory, noted that when 3 ml. of irrigant fluid were instilled in the peritoneal cavity one hour after inoculation of cells the number of animals developing tumors was 81.1 per cent in the untreated and 82.4 in those receiving physiologic saline. In contrast the number of animals developing tumors following instillation of A-8103 was 2.7, and following thioTEPA it was 3.1 per cent. These authors also noted that the instillation of chemicals into the peritoneal cavity was more effective than irrigation. For example in the animals having their peritoneal cavity *irrigated* for 2 min. with thioTEPA the per cent take was 43.4; in animals having irrigation for 4 min. it was 43.4; in animals irrigated for 8 min. it was 63.3. On the contrary, when an equal amount of thioTEPA was *injected* into the peritoneal cavity the per cent take was reduced to 8.0.

Results of these experiments—revealing a higher per cent "take" in animals inoculated with cancer cells in the peritoneal cavity, followed by irrigation or instillation of anticancer compounds, than in control animals—have been very disturbing. Since these findings were unexpected, the experiments were repeated several times and under different circumstances. However with one or two exceptions, the experiment always resulted in the same ratio of tumor development, namely about twice as many in the treated animals as in the controls. Accordingly, if we can draw a conclusion for human patients from animal data, certain systemically acting drugs like thioTEPA or A-8103, rather than locally acting drugs such as ACL 60 or sodium hypochlorite, should be used for irrigating the peritoneal cavity to destroy cancer cells.

Summary

Of the four major mechanisms for the spread of cancer we have been concerned with vascular spread and implantation. Regardless of the frequency with which cancer cells may be found in the blood stream the fact remains that in most cancers, particularly those involving the gastrointestinal tract, the vascular spread of the tumor is the mechanism which kills the patient.

Implantation of cells is a common mechanism for the spread of tumor. It may be spontaneous or iatrogenic. We can do little to prevent the former, except to minimize delay prior to operating. Iatrogenic spread can and should be prevented, but prevention requires more than the usual routine precautions. Although all possible precautions have been utilized, we still encounter instances of iatrogenic implantation, several of which are reported.

Numerous workers in our department have conducted animal experiments to find satisfactory anticancer compounds which could be utilized as irrigants to destroy implanted cancer cells. We found that sodium hypochlorite (Dakins solution) and nitrogen mustard were quite effective in experiments with rats. In studies of additional agents and their effects, we noted that halogenated compounds such as sodium hypochlorite, sodium dichloro-isocyanurate (ACL 60) and certain iodophor compounds actually increase (rather than decrease) the survival and growth of cancer cells in the peritoneal cavity, whereas they were effective in destroying cancer cells implanted in subcutaneous wounds. ThioTEPA and a piperazine compound (A-8103) were effective in destroying cancer cells in the peritoneal cavity as well as subcutaneous tissue. It appears that these compounds might be acceptable for use in the peritoneal cavity when contamination with cancer cells is significant. We have used sodium hypochlorite as an irrigant in wounds following radical neck dissection

and radical mastectomy for the past 2 to 3 years. Inadequate time has elapsed to arrive at any conclusion, but preliminary data from our series has been disappointing.

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Discussion

Dr. Benjamin F. Byrd, Jr. (Nashville): Dr. Cole let me see his complete manuscript on this fascinating continuation of his work on iatrogenic carcinoma. I think the clinical application of this continued interest of his is something for which we are all indebted to Dr. Cole. Certainly the use of irrigating agents for the topical effect of the drug has been beautifully demonstrated in this work which he has shown us here this morning. Of course, it is especially interesting that everything that kills cancer cells in the test tube does not necessarily kill it in the abdominal cavity, this fact being shown with the diminished effectiveness, the actual deleterious effects of the halogenated agents as an irrigating solution as over against the systematically effective Thiotepa.

I cannot help but believe that the work which Dr. Cole is doing will eventually bring us to a really fruitful solution to the management of metastatic cancer. We are right now beginning to see follow-up periods on our basic experimental work which carries for us individually something that we can use in the management of our cancer patients. We all stand to gain from experimental study whenever we are having local recurrences in cancer of the breast which may be affected favorably by the use of systemic cancerocidal drugs, and whenever we are having 25 to 30% local recurrences in cancers of the head and neck after radical neck dissections, which we can alter favorably by the use of one of these drugs.

I would like to speak again for one moment concerning Dr. Ochsner's paper. He mentioned in his presentation one of the possible uses of mammography. I certainly did not get up here to tell a bunch of surgeons that mammograms are satisfactory substitutes for microscopic examination, but I do want to show two instances in which preoperative mammograms might have favorably altered the patients' course.

(Slide) This is a mammogram and here is a tumor lying deep within the breast. This patient was very generously equipped with breast tissue and had in her axilla a mass which was removed. There was no palpable breast mass. The axillary mass was removed, proved to be adenocarcinoma, and then mammograms were done and the tumor found lying deep within the breast tissue. The breast was removed with radical mastectomy in a second procedure.

(Slide) This patient was an older woman in her sixties, who had an axillary mass, again with no palpable breast abnormality. This section, on microscopic examination, was diagnosed as malignant melanoma by the pathologist and by surgical pathologist as possibly carcinoma but probably a melanotic metastasis. We got a mammogram the following day (slide) which showed this tumor right here, which was not palpable. We took her back to the operating room, did a radical mastectomy. She had a carcinoma of the breast, and this, I think, really demonstrates one of the principal uses of mammography, in the evaluation of axillary masses where there is no palpable abnormality in the breast itself.

We can get something from this and probably the wealth of material which is being built up by the radiologists serves to increase their diagnostic acumen.

Dr. Walter J. Burdette (Salt Lake City): I would like to discuss Dr. Ochsner's paper. We have been interested in the possible usefulness of mammography at the University of Utah for several years as well; and Drs. William Christiansen and Carlisle Smith of the Department of Radiology have become very expert at reading mammograms. A few illustrations from the 90 cases having mammography and excision of the lesion with histologic study may be of interest to the group.

(Slide) This is an example of normal breast, this (slide) of a breast during lactation, and this (slide) is an example of gynecomastia, a lesion which is puzzling at times. This roentgen study (slide) shows chronic cystic disease in this area,