

BENEFICIAL EFFECTS OF ACUTE
CONCURRENT INFECTION, INFLAMMATION,
FEVER OR IMMUNOTHERAPY (BACTERIAL TOXINS) ON
OVARIAN AND UTERINE CANCER



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INTRODUCTION

The treatment of malignant tumors by injections of bacterial vaccines—the first form of cancer immunotherapy—is based on approximately 300 recorded cases of dramatic “spontaneous” regressions of cancer which occurred following acute bacterial infections, principally streptococcal or staphylococcal. End result studies of this method in other types of tumors have been published in recent years. (33-36; 62; 64-76)

Materials and Methods

The present study includes the microscopically proven cases of ovarian and uterine neoplasms who developed an acute concurrent infection, fever or inflammatory episode, or who received injections of bacterial vaccines—the first form of immunotherapy to be used in treating cancer. These cases were assembled from the literature and from unpublished records of physicians. Failures as well as successes have been included. All but two cases were inoperable when toxin therapy was begun. (See p. 42 and 56.) Cases receiving less than four weeks' treatment were excluded, with the exception of two who were given very large doses or intratumoral injections for a shorter time. Brief abstracts of each case precede the detailed histories in each series of cases.

Discussion

The following factors seem of importance, insofar as they influence prognosis in cases treated by bacterial toxins.

1. The stage of the disease when toxin therapy is begun.
2. Other immunosuppressive treatment given prior to toxins.
3. The type of toxin used.
4. The site, dosage, frequency and especially the duration of injections.
5. The type of reaction elicited.

Reactions were more marked, less prolonged, and better tolerated by the patients

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when injections were given in or near the tumors or intravenously in sufficient doses to produce marked reactions with chills and temperatures of 101° to 104° F. or more. The highest percentage of successful results in the inoperable cases occurred in cases that had this type of reaction. In the operable series the results varied only slightly as regards the cases receiving injections in or near the cicatrix or tumor, intramuscularly remote from the tumor, or a combination of these two routes.

Several surgeons who described the technique they used advised injections in the vicinity of the growth and gradually into the tumor itself; these include Coley, Matagne, Odier and Wyeth. The latter also used living cultures of streptococcus injected into the wound following surgical removal of sarcomas. If tumors were inaccessible, that is in the abdominal cavity or pelvis, injections were given in the gluteal region or in the abdominal wall in the immediate vicinity of the neoplasm. The importance of site of injection is described below.

The majority of the successful results had injections every 24 to 48 hours during the first part of the treatment. If frequency is decreased too soon, the disease may reactivate. See Series B, case 5, Series F, cases 1, 6, 7, and 8 for examples of reactivation of the disease when treatment was suspended too soon and final control when injections were resumed. Duration of therapy was found to be of critical importance, especially when treating inoperable cases: of the 13 inoperable cases of gynecologic cancer treated for less than two months, only 30 per cent recovered. Two of these successes received massive dosage. Of the 10 patients treated for two to six months, 50 per cent were apparent cures. Only two of the 12 cases treated for over six months died, the first during surgery in Switzerland after the toxins had controlled the disease for six years (Series G, case 3); in the second the disease reactivated, causing death 31 years after onset. (See Series B, case 5.) A number of the inoperable successes were traced 20 to 44 years. The only two operable cases received prolonged toxin therapy as an adjuvant to hysterectomy and survived free from disease for 51 and 46 years respectively (see Series C and F).

Effects of Toxin Therapy on Radiation Response of Tumors and Protection Against Deleterious Effects of Radiation

Preliminary injections of bacterial vaccines stimulate the natural resistance of patients, so that they tolerate subsequent radiation with a better response, i.e. more rapid destruction and absorption of tumor tissue with less deleterious effects on the normal tissues or organs and on the general health. Tumors that are usually resistant to radiation may respond when given priming injections of toxins first. (67, 69, 70, 71, 72, 76) Among the many experimental studies cited in these references is that of Hollcraft and Smith at the National Cancer Institute. An unpublished report by Ainsworth showed that a single prior injection of 0.05

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ml. of Coley toxins protects 100% of mice against the lethal effect of 700 r. of whole body irradiation delivered the next day. With typhoid vaccine there was 11.5% mortality, while 92.3% of the controls receiving saline died. (11) In the present study it was found that x-ray therapy was only used in two cases, Series D, case 4 (concurrent with toxins) and Series E, case 4 (prior to toxins). Both patients died.

Increased Antigenicity of Tumor Cells Conferred by Certain Infections or Their Toxins as it Relates to Site of Injection

An important point unknown during Coley's lifetime is the fact that certain strains of streptococci and a few other bacteria and their toxins can confer or increase antigenicity to substances or tissues not normally antigenic or weakly so (such as tumor cells) provided that they come into significant contact with the target tissue. (39)

Thus in treating cancer patients at the present time, it is advisable to administer some of the injections initially in or near the tumor or its metastases prior to any surgical procedure except biopsy.

This site may be combined with intracutaneous, intravenous or intramuscular injections. Only one case is known to have received intraperitoneal injections, and the result was astonishing. (See Series B, case 5.) Aerosol inhalation for pulmonary metastases may also be beneficial. The oral route has been used in recent years with BCG but to our knowledge no one has tried it with Coley toxins. For maintenance therapy it may deserve consideration.

Possible Dangers

The available evidence suggests that Coley toxins are without harmful or dangerous effects to patients or animals suffering from various types of neoplasms, provided they are administered properly as to dosage, site and the usual aseptic precautions. They should not be given to patients with severe hepatic insufficiency due to metastatic disease or other pathology nor to patients who have had severe heart conditions, nor to patients who are almost moribund, because such patients do not respond. It is not even possible to elicit the desired febrile reactions.

Effects of Toxin Therapy on Normal Tissues or Organs

A critical analysis of over 900 patients with various types of neoplasms who received toxin therapy indicates that Coley toxins produced no deleterious effects on normal tissues or on the kidneys, heart, liver or other organs. (76)

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Stimulus to Wound Healing and Regeneration of Bone

Many surgeons noted remarkably rapid wound healing in patients that were receiving toxin therapy. Others noted large areas of bone which had been destroyed by the neoplasm regenerated completely. The latter occurred in the bone sarcoma cases or in cases in which a rib was resected to gain access to a tumor in the mediastinum. (62, 70-72; 75-76)

Pain Relief

A great many surgeons noted that there was marked relief of pain occurring almost immediately after the injections were begun. In a few cases pain returned as soon as the toxins were stopped temporarily and again disappeared when they were resumed. Patients requiring large doses of narcotics were able to stop taking them. Pain relief occurred even in patients who were too far-advanced to respond markedly to toxin therapy, and who were not ultimately cured. This suggests that toxin therapy may be of value for palliation in such cases.

Cessation of Hemorrhages

A few physicians noted that patients in whom hemorrhages had occurred prior to toxins ceased hemorrhaging when the toxins were administered.

Effects on Concurrent Pregnancy and Fetus

Only three pregnant women are known to have received Coley toxins during their pregnancy. The first was given intramuscular injections during the second trimester, followed by complete regression of an inoperable sarcoma. A normal child was born at full term. A second patient with very far-advanced malignant melanoma also received the toxins intramuscularly during the latter half of her pregnancy, with marked palliation as regards pain relief, improved sleep, etc., and some evidence of temporary arrest of the extensive growths. Her child was born at about full term (labor was induced), and was entirely normal. The patient succumbed to her disease. The third case, a reticulum cell sarcoma of the humerus, was given a fairly large initial dose intravenously in the sixth month of her pregnancy. This caused a very marked reaction: the temperature reached 105.4° F. within two hours, preceded by a severe chill which began immediately after the injection. An abortion occurred a few hours later. The toxins were resumed nine days later and were given concurrently with x-ray therapy (2,000 r.), followed by complete regression of the tumor. This patient was traced well and free from disease in 1976, 32 years after onset.

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Conclusions

The number of gynecologic cancer cases benefited by concurrent infection or treated by bacterial toxin therapy is not large. However, the dramatic effects noted, even in inoperable cases, especially when such treatment was begun shortly after incomplete surgical removal, or as an adjuvant to surgery in the operable cases, suggests the need for serious consideration of such therapy now, using various immunopotentiators of microbial origin, such as the mixed toxins of *Streptococcus pyogenes* and *Serratia marcescens*, Hoffmann's Bacterial Antigen complex (BAC) Staphage Lysate (Delmont Laboratories), as well as the toxins of *Corynebacterium parvum* or *Pseudomonas aeruginosa*. These are very well tolerated and have no deleterious side effects. Instead they stimulate the hematopoietic, reticuloendothelial and lymphoid cells to greater reactivity.

Since a review of the literature on gynecologic cancers in the past few years has shown that very, very few gynecologists have even considered the importance of tumor immunology in gynecologic oncology (31b; 77a), we hope that the present study may help stimulate an interest in the potential of such therapy in these neoplasms.

OVARIAN CANCER

Ovarian cancer is the leading cause of death among patients with gynecologic malignancies. It is one of the few such cancers that seems to be increasing in frequency. It is twice as common in the nullipara with a history of inability to conceive. It occurs more commonly in Jewish women and more frequently (as do breast tumors) in women on higher fat diets. This group requires special vigilance. (39a)

Despite the advances in the treatment of other gynecologic neoplasms, little progress has been made in the treatment of ovarian cancer for the past 30 years. With the exception of the less common mucinous type, most ovarian malignant tumors when first diagnosed are stage III or IV, for which the five-year survival rate is dismally low (5 to 20%). (91) More than 10,000 of these patients die each year in the United States. The lack of symptoms until the tumor or cystic masses have enlarged, invaded the adjacent viscera or produced peritoneal seeding with ascites accounts for this. Less than 30 per cent of ovarian cancers are localized at initial diagnosis, and 70 per cent are bilateral. Only 25 per cent occur in women under age 45; 60 per cent in those 45-60.

Traditionally, radiation was thought to be the preferred post-operative treatment for ovarian cancer, but experience has shown that chemotherapy may be preferable. (91a, p. 141) If radiation is used, the liver and kidneys must be shielded so they will not receive more than 1500 rads (whole abdomen radiation). In addition, there is a possibility of small bowel injury. Patients with large, unresectable tumors are seldom benefited by radiation. (91a, p. 149)

Young believes that improved therapeutic management of ovarian carcinoma rests in a major way on the development of more effective regimens of chemotherapy (91a, p. 147). The higher frequency of advanced disease at presentation coupled with the tendency of the disease to spread to strategic sites in the peritoneal cavity that are poorly visualized at surgery and often shielded during radiotherapy, makes an effective immunotherapy combined with chemotherapy theoretically attractive.

The role of the immune response in tumor control can no longer be ignored, and the effects of our therapeutic manipulations on the patient's immunoreactivity must be carefully evaluated and correlated with prognosis (91a, p. 123).

OVARIAN CANCER

Among the few gynecologists who have considered the importance of host resistance in dealing with these neoplasms are Stone and Weingold who stated: "Survival in patients with ovarian carcinoma involves factors other than time and type of therapy. Experimental evidence suggests that the most significant factors affecting survival are the biologic activity of the tumor and the host-tumor relationship." (89a)

The prior health of such patients may affect their resistance. For example, West reported that a prior infection with mumps parotitis appears to protect women from having ovarian cancer. (102)

The following data indicate that patients with ovarian neoplasms who develop concurrent acute infections, fever or a severe burn (inflammatory reaction) may recover completely even when the disease is hopelessly inoperable.

The first form of immunotherapy, injections of the mixed toxins of *Streptococcus pyogenes* and *Serratia marcescens** has also produced some remarkable long term survivors (11 to 21 years), even in very far advanced cases.

*Formerly called *Bacillus prodigiosus*. These toxins were known as Coley's toxins or Coley's vaccine. For a description of the formulae used see ref. # 64.

**SERIES A: OVARIAN CARCINOMA WITH CONCURRENT
INFECTION, INFLAMMATION, FEVER OR HEAT CAUSING
REGRESSION OR APPARENT CURE
BRIEF ABSTRACTS**

Years Traced
After Onset

1. POZZI: M.B., aged 25; bilateral malignant ovarian papilloma; onset, April 1876; abdomen size full term pregnancy, tapped 6 times, 10-16 liters ascitic fluid each time; given 2 injections iodine intraperitoneally, 100 and 150 grams each, causing peritonitis; bilateral oophorectomy: left tumor size full term fetal head, right one half as large; masses involved uterus, filled pelvis; operation difficult, pelvic floor filled with tumor debris, blood; October 26, 1878: *post-operative fever, infection for 4 weeks; complete recovery, no recurrence for 20 years*; ascites then returned, with edema of legs: exploratory operation December 10, 1899: mass infiltrated pelvic floor, no attempt at removal, drainage established; *edema and ascites ceased*; fairly well a year; died May 4, 1901. (82,83,84) 25 (Died)

2. BURT: Miss D., aged 33; bilateral ovarian papillomata disseminated extensively over peritoneum; onset March 1886; ascites by September 1888; "turpentine blue pill" given; *75 hot vapor baths taken for 4 months beginning December 1889, ascites reduced, felt better*; at operation March 1889, 2 quarts fluid escaped; papillomatous cyst size of infant head found on right side, cyst half as large involved left ovary; omentum, bowels studded with innumerable papillary metastases; prognosis hopeless; bilateral oophorectomy; cavity thoroughly washed out with boiled water to get rid of tumor debris; *right thigh extensively burned by hot water bag immediately after operation*; took weeks to heal; *complete recovery, gained 20 pounds; no recurrence; in good health.* (7) 5½

3. CODMAN: Mrs. R.U., aged 32; large inoperable papillary adenocarcinoma ovary with diffuse wart-like metastases over whole peritoneum; date of onset not recorded; June 30, 1900: incision for "pelvic abscess", drainage through vagina; July 8, 1900: exploratory laparotomy, no attempt at removal; *vaginal sinus persisted for over 10 years, discharging pus and occasionally necrotic tumor tissue*; December 22, 1910 reoperated; *peritoneum entirely free from metastases*; huge pelvic papillary adenocarcinoma removed including rectum; artificial anus made; *no recurrence or further metastases*; died at 77, March 8, 1944. of "chronic myocarditis due to carcinoma of the intestines". (14) 44

4. CODMAN: Mrs. S.P., aged 55; inoperable extensive ovarian adenocarcinoma involving all pelvic organs and peritoneum; onset September 1915; tumor extended from pelvis to 5 cm. above umbilicus; explored March 13, 1916; no attempt at removal; 9 days later drainage established

SERIES A: BRIEF ABSTRACTS

Years Traced
After Onset

- with large rubber tube from vagina through partly cystic tumor into abdomen; radium applied through tube at intervals for 9 months; *severe intractable radium burns*, required excision, spring 1918; abdomen opened, *huge pelvic mass had become operable*, was removed (5 hour operation); *no trace of peritoneal metastases; post-operative abscess in abdominal fat; subacute appendicitis* March 15, 1920; appendectomy March 23, 1920; 8th radium treatment April 14, 1920 given in vagina; recurrence 1921, explored May 23, 1921; masses of cancer on omentum, ascites; death June 8, 1921. (14) 6
5. GAUDRAULT: A.S., 26; metastatic inoperable papillary cyst adenocarcinoma ovaries (bilateral), extensive peritoneal implants, entire pelvis; onset, November 1935, discomfort lower abdomen, back, legs; symptoms increased markedly fall 1938, ascites, cachexia; abdomen distended, tender; exploratory laparotomy, November 1939, 2 liters ascitic fluid evacuated, large papillary growths both ovaries, extensive peritoneal implants entire pelvis, no attempt at removal, biopsy taken; intestinal obstruction December 1939; tapped 63 times over 2½ years, 5,000-10,000 cc. each time; maintained on morphine (to 30 mg. every 3 hours); weight decreased to 80 lbs.; patient demanded 2nd operation, June 1, 1942; appearance altogether different, all metastatic papillary growths were encapsulated in large mass to left and 2 smaller ones to right, all adherent to adjacent organs, rectum, uterus, bladder; growth dissected, removed with great difficulty, except for 4 cm. portion on right fossa, some contents spilled in abdomen, removed with care; *postoperative fever (99° - 104° F) for over 3 mos., also suppuration and discharge from abdominal sinus*, 2 transfusions, no more morphine; *complete recovery; no further evidence disease*; only complaints in 1975: hypertension, osteoarthritis and functional gastrointestinal complaints; alive 1976. (11; 38) 30½
6. SEMPLE AND WEST: Aged 29; round cell scirrhous carcinoma of left ovary, metastases to liver and lymph node; date of onset unknown; February 1950 concurrent chronic miliary tuberculosis with lassitude, cough; (tuberculin reaction negative at first); streptomycin with P.A.S.; numerous calcified opacities seen in abdominal films July 1951; August 1951 amenorrhea; by December 1951 liver enlarged 5 cm. below costal margin; tuberculin reaction now positive; chest films showed generalized small pulmonary opacities, essentially unchanged for previous 22 months, except for being harder and probably calcified; multiple round calcified opacities on abdomen over a wide area anteriorly; laparotomy, January 1952: liver enlarged to below umbilicus; studded throughout with white nodules; one was removed; right ovary was cystic, left represented by a cyst and a round tumor 6 cm. in diameter; this ovary was removed; the pathologist reported this lesion, the liver metastasis and a

SERIES A: BRIEF ABSTRACTS

Years Traced
After Onset

cervical node metastasis all showed scirrhous ovarian carcinoma "*provoking intense fibrosis with granules of calcification; in many places the growth shows evidence of being strangled by fibrous tissue*"; uneventful recovery; reasonably well, x-rays showed little change. Last traced 1955. (87)

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**SERIES A: OVARIAN CARCINOMA WITH CONCURRENT
INFECTION, INFLAMMATION, FEVER OR HEAT
DETAILED HISTORIES**

CASE 1: Bilateral malignant ovarian papilloma confirmed by microscopic examination by Dr. Chambard, in the histology laboratory of the College of France in Paris.

PREVIOUS HISTORY: M.B., aged 25, of vigorous constitution. Menses began at 14, but were very irregular. She developed chloroanemia, and at the age of 19 a complete amenorrhea lasting four years, until January 1876. Thereafter the periods were regular. Onset, in April 1876 she developed abdominal pain, with distention and fever, lasting four weeks, and it was believed that she had peritonitis. After this acute episode the abdomen remained voluminous and even continued to increase in size. On August 31, 1876, she was tapped for the first time, and 10 liters of a lemon-colored ascitic fluid were obtained. She was again tapped on November 28, 1876, at which time 12 liters of fluid were obtained.

INDUCED INFLAMMATION: At this time 100 grams of tincture of iodine were injected into the abdominal cavity, followed by intense pain, fever and distention of the abdomen. These symptoms lasted 36 hours and were regarded as being due to a slight case of peritonitis.

CLINICAL COURSE: The ascitic fluid rapidly returned, but was less abundant. A third tapping was done June 17, 1877, and 13 litres of ascites were evacuated.

FURTHER INDUCED PERITONITIS: At this time 150 grams of tincture of iodine were injected into the peritoneal cavity, followed by a violent peritonitis lasting 15 days.

CLINICAL COURSE: Three weeks later the abdomen was as large as it had been prior to the third tapping. The patient then put herself in the hands of an "empiric", and was given repeated purgatives, followed by notable diminution in the ascites, which then remained stationary for eight months. On March 2, 1878, a fourth tapping was done, evacuating 16 liters of fluid. The ascites did not recur for seven weeks. A fifth tapping was done on June 22, 1878, 14 liters being withdrawn. Finally, at the end of August 1878, the patient consulted Dr. Samuel J. Pozzi, of Paris, France. At this time the patient's abdomen was the size of a full-term pregnancy. There was very superficial fluctuation uniformly present over the entire abdomen. The general condition was excellent, except for some digestive difficulty and a stubborn constipation, requiring constant use of purgatives. Walking was painful due to the weight of the abdomen. The patient could not do any work at all and she insisted upon an operation. Prior to this she was tapped a sixth time: 14 liters of ascitic fluid were evacuated and examined by Drs.

A: DETAILED HISTORIES

Mehu and Chambard who stated that the fluid contained rather numerous leukocytes, a great deal of mucin and rather numerous edematous lymphatic cells, a few red blood cells and a few bits of cholesterol. Not a single epithelial cell was found. Immediately after tapping, Pozzi examined the patient and found a very well-defined tumor in the left flank, of about the size of a full-term fetal head, of elastic consistency, apparently intimately connected with the uterus, as indicated by vaginal examination. The tumor extended beyond the median line on the right, and appeared to extend deeply into the pelvis. A few days after the final tapping, the ascites had again formed in the abdomen. The patient was seen by Dr. Terrier. He made a diagnosis of solid tumor of the left ovary with a large cyst, and symptomatic ascites. Surgical intervention was believed possible, although the involvement of the uterus indicated that there might be "great surgical difficulties".

SURGERY: Pozzi and Terrier operated on September 26, 1878, assisted by four other surgeons. They found marked vascularity of the abdominal walls, requiring the application of numerous hemostats. On opening the peritoneal cavity a large quantity of ascitic fluid was evacuated and a cauliflower mass, the size of a full-term fetal head, was found which filled the entire pelvis and extended up to the hypogastric region. It appeared to be made up of innumerable small cysts which were agglomerated into one mass. It was attached to the broad ligament and to the uterus which it encased. The original 8 cm. incision was enlarged another 4 cm. to the umbilicus. The polycystic mass was separated and removed with great difficulty, leaving two pedicles which were much too short. The pelvis was then cleaned carefully, as it had been covered with blood and much debris from the tumor, which had broken into fragments, having the aspect of hydatid cysts. It was then noted that the abdominal cavity had a very unusual appearance: the parietal peritoneum was wine-red in color, indicating an increased vascularity, as was noted in the abdominal walls. The intestines were matted together in one voluminous mass by adhesions. These two factors, increased vascularization and adhesions, were deemed a result of the two injections of tincture of iodine, followed by induced peritonitis which the patient had experienced. The large space formerly occupied by the tumor, especially the recto-vaginal cul-de-sac, was gaping extensively, and Pozzi decided to leave a drainage tube in this empty space, because he was sure it would become filled with serosanguinous fluid. The operation took 1½ hours.

POST-OPERATIVE FEVER AND INFECTION: The first two days after operation the patient had a rather high fever: 39.5° C. There was abundant serosanguinous drainage from the tube. Lavages of the vagina and the wound via the drainage tube were done with dilute alcohol and phenol. The third day the temperature was 38.2° C. The general condition seemed better and the abdomen was no longer painful on pressure. Suppuration appeared in the drain and in the vagina. The temperature spiked daily (to 39.8° C. on the 7th post-operative day). She

A: DETAILED HISTORIES

remained febrile for 16 days after operation (38.5° to 39.8° C.) By October 10, 1878, suppuration had almost ceased. The patient had to be catheterized for the first 16 days after operation. Thereafter this was unnecessary, and although she continued to have a slight fever, convalescence began. On October 18, 19, and 20 there was some retention of pus in the wound and on October 20, two large spoonfuls of pus drained from the suprapubic sinus. The sinus was probed and found to be 20 cm. in depth. On October 22, 1878, a small abscess broke open spontaneously on the lower part of the cicatrix, 2 cm. above the insertion of the drain. About two spoonfuls of pus drained out.

CLINICAL COURSE: From this time on there was steady and rapid improvement. The sinuses, where the drain and the abscess had been, closed promptly. The patient returned to her home in the country the end of November, two months after operation. A curious fact was noted: she again menstruated at the end of October and the end of November. This persistence of the menses, in spite of double oophorectomy, however, was not considered exceptional by some gynecologists. The patient made a complete recovery. She remained well 20 years, to the middle of 1898. Ascites then again appeared. The abdomen enlarged considerably, with edema of both legs, due to compression.

FURTHER SURGERY: A second operation was performed on December 10, 1899. The inoperable tumor was quite fixed to the pelvic floor, and as the patient was in very bad condition, Pozzi did not attempt to remove it, but merely drained it.

CLINICAL COURSE: The patient made a rapid though temporary recovery. The ascites and the edema of the legs disappeared, and her health was again satisfactory for about one year. Death occurred on May 4, 1901, 25 years after onset.

COMMENT: In citing this case in 1904, Pozzi stated that this case presented the longest survival of any of his ovarian cases, and added: "I am not aware of any other example of relapse after such a long recovery. If this patient had died two years sooner she could have been quoted as an example of permanent cure; in fact she was so mentioned in the second edition of my Treatise on Gynecology, 1897."

REFERENCES: 82; 83; 84.

INFLAMMATION

Thornton, an English gynecologist, in reporting his end-results in the surgical treatment of ovarian tumors, stated that following removal of malignant ovarian tumors in which extensive peritoneal implants were left, these "may disappear either with the removal of the tumor and the cessation of the irritation which

A: DETAILED HISTORIES

started its peritoneal growth, or possibly by the irritation (inflammatory action) induced by the sponging, etc., at the time of operation." (92; 97)

The following case is an example of the type cited above by Thornton. In addition, the patient had a severe burn with absorption of the toxins and inflammatory exudate this produced. For another instance in which a severe burn occurred see Lomer's case in the section on uterine cancer.

CASE 2: Bilateral ovarian papillomata disseminated extensively over the peritoneum.

PREVIOUS HISTORY: Miss D., aged 33. Menses began at 15, a regular cycle, of three or four days' duration, always associated with severe pain. Except for chronic constipation, painful menses and sick headaches, she had always considered herself well until onset, in March 1886, when she began to feel pain in the right ovarian region on reaching or stepping up. She could not lie on the right side. She experienced fullness after eating even a very small quantity. Two years after onset she began to have frequent "irritation" of the bladder. This continued and her chronic constipation became very much worse. About September 1888, the abdomen began to enlarge with ascitic fluid. In March 1889, she first consulted a physician who made a diagnosis of "gas and water" in the bowels. The treatment was "turpentine, blue pill", etc. In November 1889, Dr. Mary Carleton was consulted and a diagnosis of ovarian tumor was made. The patient was referred to Dr. Frank L. Burt of Boston, Massachusetts, whom she consulted in March 1890.

HEAT THERAPY: During this intervening four-month period the patient took about 75 steam baths. These reduced the ascitic fluid somewhat, and made her feel better.

SURGERY: In March 1890, Burt diagnosed ovarian tumors and advised surgical removal. He operated on April 20, 1890. On opening the peritoneum about two quarts of fluid escaped. On the right side a cyst the size of an infant head was found, which proved to be a papilloma with partly fluid contents. A similar growth, about half the size, involved the left ovary. The omentum and bowels "were studded with thousands of papillary masses. The omentum was considerably thickened, and both omentum and bowel presented a very congested and angry appearance". These conditions were considered by the seven physicians present to indicate an absolutely hopeless prognosis. A bilateral oophorectomy was performed in the usual manner. The cavity was thoroughly washed out with boiled water to get rid of as much debris as possible. Numerous small pieces of tumor were washed away. The wound was closed over a very small rubber tube which was left in place 48 hours.

A: DETAILED HISTORIES

CONCURRENT BURN: The patient received an extensive burn on the right thigh from a hot-water bag following her return from the operating room. This took several weeks to heal and did not present a healthy appearance much of that time. Burt stated: "I cannot but feel that it was beneficial to the patient. I do not, however, under similar circumstances, recommend quite so extensive a counter-irritation if indicated at all." (7)

CLINICAL COURSE: The patient made a complete recovery. She gained 20 pounds in weight. At examination a year after operation there was no evidence of recurrence of the tumors or the ascites. She remained in perfect health when Burt reported the case in September 1891, 15 months after operation and 5½ years after onset.

REFERENCE: 7

CASE 3: Inoperable papillary cyst adenocarcinoma of the ovary with diffuse metastases scattered over the whole peritoneum, confirmed by microscopic examination at Massachusetts General Hospital in 1900 and reviewed by Dr. Robert E. Scully on April 1, 1955.

PREVIOUS HISTORY: Mrs. R.U., aged 32, of Lawrence, Mass. The family history was non-contributory. The patient had never been pregnant. Menses began in her 12th year and had always been regular. She had had some leucorrhœa of about 2½ years' duration. Prior to onset she weighed 187 pounds.

CONCURRENT INFECTION: Under diagnosis of pelvic abscess the patient was operated upon by Dr. F.B. Harrington at Massachusetts General Hospital on June 30, 1900. An incision was made in the vagina, some papillocystic material was curetted out and drainage was established.

SURGERY: Nine days later, at Harrington's suggestion, Dr. E.A. Codman opened the abdomen and found a large inoperable pelvic mass and diffuse wart-like metastases scattered over the whole peritoneum.

FURTHER INFECTION: The vaginal sinus persisted for over 10 years and discharged pus and occasionally necrotic malignant tissue. Although the tumor grew and ulcerated, the patient's general condition improved. From year to year she returned to the hospital seeking radical operation and was refused as she was considered hopeless by the various surgeons to whose services she was admitted.

FURTHER SURGERY: Finally, on December 22, 1910, 10½ years after the original operation, Codman was persuaded to attempt another. To his surprise, on opening the abdomen he found "the peritoneum perfectly free from metastases, the

A: DETAILED HISTORIES

growth being limited to the huge pelvic tumor which was adherent to the neighboring structures . . . After a sort of nightmare operation, I succeeded in removing the entire tumor with all the pelvic organs including the rectum. An artificial anus was made." (14)

CLINICAL COURSE: After a long tedious convalescence the patient recovered, and when last seen by Codman on August 14, 1916, he stated she was "fat and well", six years after the second operation and 16 years after the first. All papillary specimens showed typical papillary cyst adenoma. The large tumor was more solid than cystic. On September 12, 1936, the patient was seen in the tumor clinic by Dr. Joe V. Meigs and no evidence of malignant disease could be made out. No lymph nodes were palpable. She appeared to be "entirely free from disease". Her weight had originally been 187, then 167, and since the death of her husband it was 125 pounds. She died on March 6, 1944, at North Andover, Massachusetts, at the age of 77. The cause of death was reported as "chronic myocarditis, due to carcinoma of intestines." Death occurred 44 years after onset of papillary carcinoma of the ovary.

REFERENCES: 14

CASE 4: Inoperable adenocarcinoma of the ovary (psammona) involving all the pelvic organs and invading the peritoneum with little tubercles, confirmed by microscopic examination by Dr. Wright at Massachusetts General Hospital.

PREVIOUS HISTORY: Mrs. S.P., aged 55, of Freedom, New Hampshire. The patient's father died of Bright's disease, her mother of carcinoma of the breast and an aunt of carcinoma of the stomach. The patient had had two children, one of whom was living and well. She had peritonitis for six weeks at the age of 45. Dr. Reginald Fitz stated that it was of ovarian origin. She developed menopause rather suddenly at the age of 47. Onset, in September 1915, she first noticed an abdominal tumor "when lying on her stomach". There was no pain or discomfort and no loss of weight. When first seen by Dr. E.A. Codman on February 25, 1916, she appeared to be vigorous and well nourished. The tumor had pulled the cervix so much toward the abdomen that it was difficult to reach it. It lay anteriorly and the tumor in the posterior cul de sac felt hard rather than cystic. The tumor mass extended from the pelvis to 5 cm. above the umbilicus and appeared to be more or less fixed. The pre-operative diagnosis was fibroma of the uterus or cystoma of the ovary.

SURGERY: On March 13, 1916, Drs. E.A. Codman and A.R. Barrow operated through a large right rectus incision. The peritoneum was so thickened that it was difficult to find a place to cut into. They found an extensive malignant tumor mass

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involving all the pelvic organs and invading the peritoneum with little tubercles. A piece of peritoneum was excised and reported as adenocarcinoma. The condition was considered inoperable and the abdomen was closed. Codman decided to attempt to obtain through and through drainage, as the tumor was evidently partly cystic, and to treat it with radium from the inside through the pathway thus obtained. Drs. H.A. Kelly of Baltimore, John G. Clark of Philadelphia, Francis D. Donahue and R.B. Greenough of Boston were all consulted by the patient's family as to whether such a procedure would be justifiable. The family was advised that the attempt should be made although no precedent existed.

RADIATION: On March 22, 1916, Codman again operated, and carried a large rubber drainage tube through the mass into the abdomen and out through the vagina. Radium was introduced through this tube as follows: April 3, 1916: 43.8 mc., duration one hour in each of seven positions 2.5 cm. apart; April 10, 1916: 65.5 mc., one hour in each of six positions 2.5 cm. apart; April 19, 1916: 108.5 mc., one hour in each of four positions. On that date it was noted in the hospital records that the tumor had decreased very considerably. Codman stated: "To my great astonishment the bulk of the tumor vanished, so that at the time of her discharge on July 29, 1916, there was only a small pelvic mass left. From being almost moribund, her condition had become one of almost perfect health. On May 15, 1916, she received 60.9 mc., apparently externally. On September 22, 1916, she received 54 mc. applied to the mass in the left vault by a special applicator for two hours. At this time Greenough noted "the presence of a very definite mass in the left vault: probably the remains of the old tumor."

CONCURRENT BURN AND INFECTION: The external radium therapy was followed by a severe radium burn which appeared in July 1917 to the left of the abdominal scar and from which the patient suffered a great deal, as it remained open and ulcerated. On March 21, 1918, she was readmitted for treatment of these burns which proved so intractable that Codman decided to excise them. At this time the general condition was excellent, the only remains of the original extensive tumor was an irregular mass occupying about half the pelvis.

FURTHER SURGERY: On April 10, 1918, Codman and Dr. G.A. Daland, Jr. operated. The burns were excised and the abdomen opened. The pelvic mass seemed operable and after a five hour operation, Codman succeeded in removing it with the uterus and adnexa. He reported: "To my great surprise the peritoneum now showed no trace of disease, and the uterus and its adnexa, which previously were indistinguishable in the cancerous mass, were now plainly recognizable, though adherent. The disease seemed wholly confined to the ovaries, which measured $7\frac{1}{2} \times 6\frac{1}{2} \times 4$ cm. and $8 \times 6\frac{1}{2} \times 5$ cm., respectively. Vaginal drainage was established, and the abdominal wound was closed. The appendix which contained a concretion was not removed. A small pedunculated fibroid tumor which was present at the first operation was removed at the last operation. It showed no

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apparent change in size in spite of the energetic radium treatment. . . . Microscopic examination showed that the ovarian tumors resembled the original tumor, but the cells showed no mitoses. In the abdominal scar a few areas of disease were also found."

POST-OPERATIVE INFECTION: An abscess developed in the abdominal fat, also a very small recto-vaginal fistula.

CLINICAL COURSE: Codman reported on May 15, 1918, that the patient was well, had gained much weight, and that there was no evidence of recurrence. She was still having some trouble with the second radium burn which had developed six months after the last radium treatment.

SUB-ACUTE APPENDICITIS: On March 13, 1920, the patient developed mild symptoms of pain and tenderness in the right iliac fossa. Operation by Codman under novocaine and ether on March 23, 1920 showed a sub-acute appendix. Codman stated that there was no positive evidence of malignant disease and there were many adhesions in the pelvis. He performed an appendectomy.

FURTHER RADIUM: On April 15, 1920, the eighth and final radium treatment was given consisting of 122 mc. in a so-called Veldec applicator in the vagina, in front of the cervix, directly upward to radiate the pelvic peritoneum tilted to two positions, duration 12 hours.

FURTHER SURGERY: A year later, on April 21, 1921, the patient was readmitted, and on May 23, 1921, an exploratory operation was performed for recurrent cancer of the ovary. The abdominal cavity was full of bloody fluid; masses of cancer were present on the omentum. The incision was closed. The disease progressed causing death on June 8, 1921 of general peritoneal carcinosis and metastatic carcinoma of the liver. Death occurred almost six years after onset.

In reporting this case in 1918, Codman attributed the favorable outcome up to that time to the following factors: 1. The tumor could be treated from within outwards. 2. The calcareous deposits by the cancer cells indicated that there was a tendency toward replacement of cancer tissue with lime salts. 3. The calcareous deposits could set up secondary radiation. 4. The toxic products of destruction could be drained away. 5. The patient had already shown that she could develop a very large malignant tumor without producing general cachexia. 6. The patient herself showed indomitable courage and optimism.

COMMENT: It would seem that the inflammation produced by the unusual method of administration of radium internally in this case, in addition to the absorption of the toxic products produced by the radium burns and the abscess, may have played a significant role in increasing this patient's defenses against her neo-

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plasm. The findings, both gross and microscopic, at the second operation indicate that large primary tumors may become quiescent and metastases disappear in such cases. The patient remained free from further evidence of disease for five years before metastases finally reappeared.

In evaluating the case, Codman added: "In order to have some idea of what the usual outcome of such cases is, I determined to trace all similar cases which had been operated on at the Massachusetts General Hospital in the last 25 years. . . . I found 41, excluding all cases which died in the hospital after operation, and all cases in which the records did not give adequate proof of the existence of malignant or papillary peritonitis at the time of operation, and also my own cases. I succeeded in tracing all. All but two of these 41 cases died of the disease. These two were of the colloid type, one living at least nine years, and the other over four years. . . . Thirty per cent died in less than two months and seventy-four per cent in less than a year. These are rough figures but they are conservative. They show that as a rule the condition is rapidly fatal. . . . However, my own cases seem to show that the peritoneum had the power to kill and replace cancer cells under certain conditions."

He then asked: "How does cancer kill?" . . . , and concluded that in the vast majority of cases severe cachexia is the cause, and that if we could prevent cachexia, we could prolong many lives indefinitely. . . . We know the wonderful power the peritoneum has in dealing with sepsis and with tuberculosis. Who has not marvelled at seeing the smooth shining surface of the peritoneum, in some cases at second operation, which a few weeks earlier he saw red and turgid with an angry inflammation? And the return to normal after severe tuberculous involvement is now almost expected. I believe that you may also look for such results in a small proportion of your malignant cases." In conclusion he stated: "1. The peritoneum has a special power of resistance and repair after diffuse infection with septic organisms of tubercle bacilli, and in a minor degree after diffuse invasion with cancer cells of ovarian origin. 2. It is possible for nature unaided to cause the retrogression of peritoneal metastases and the gross limitation of a diffuse malignant condition into operable tumors. 3. Radium . . . may also aid the peritoneum in a battle which otherwise is only slightly in favor of the growth."

REFERENCES: 11; 14.

CASE 5: Metastatic papillary cyst adenocarcinoma of both ovaries, with extensive papillary peritoneal implants in the entire pelvic cavity, confirmed by microscopic examinations following both operations. (For microphotograph see 38.)

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PREVIOUS HISTORY: A.S., aged 26, housewife. The family and previous personal histories were non-contributory. The patient was married, but had never been pregnant. Her husband was well. Onset, in early November 1938, she began to have some discomfort in the lower abdomen, back and legs. During September and October 1939, this discomfort increased markedly and other distressing symptoms developed. She was admitted to Margaret Pillsbury General Hospital on November 7, 1939, a year after onset. Physical examination revealed her to be pale and cachectic. The abdomen was distended and tender, and on percussion the presence of fluid was detected. No masses were felt. Pelvic examination revealed a small uterus in normal position, not movable, and a tender diffuse mass in the pelvis. A tentative diagnosis of tuberculous peritonitis or adenocarcinoma was made. Blood examinations were within normal limits.

SURGERY: On November 9, 1939 an exploratory laparotomy was performed. About two liters of straw-colored fluid was drained from the abdomen. Exploration revealed a small uterus in good position and large papillary growths of both ovaries, with extensive peritoneal implants in the entire pelvic cavity. Three other physicians in consultation considered the disease was too extensive and advanced for surgery to be of any benefit. A biopsy was taken and the abdomen was closed. The patient was discharged on November 22, 1939, still complaining of some abdominal discomfort.

CLINICAL COURSE: On December 2, 1939 she was seen at home, complaining of severe abdominal distress and distension. She had had no bowel movements for 48 hours and had expelled very little flatus. Intestinal obstruction was feared. She was therefore admitted to New Hampshire Memorial Hospital on December 3, 1939, as a hopeless case. Consultants advised thoracentesis and morphine, and believed x-ray therapy would be of no help. During the next 2½ years she was tapped 63 times and from 5,000 to 10,000 cc. of fluid was evacuated each time. She was kept comfortable with morphine, the dose being increased to 30 mg. given every three hours.

FURTHER SURGERY: The patient then insisted on a second operation, "no matter what the outcome might be." Accordingly, on June 1, 1942 Dr. Gerald L. Gaudrault operated intending only to explore and insert a mushroom catheter to relieve her of further taps. At this time her weight was about 80 pounds. Upon opening the abdomen no peritoneal implants were present. A fair amount of straw-colored fluid was found, but the appearance of the pelvis was altogether different. All the papillary growths were encapsulated in one large mass to the left and two smaller ones to the right. All were adherent to the adjacent organs, rectum, uterus and bladder. The growths were dissected and removed with great difficulty, except for a small portion about 4 cm. in diameter on the right fossa. Some of the contents were spilled in the abdominal cavity and removed with care. The uterus was not removed in order not to prolong this difficult operation. A

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mushroom drain was inserted and the abdomen closed. A culture was taken from the abdomen at the time of this operation and it proved sterile (no growth).

POSTOPERATIVE FEVER AND INFECTION: The postoperative course was rather stormy because the patient was deprived of morphine. She was given two blood transfusions. The temperature remained elevated (99° - 104° F.) from June 1 to September 2, 1942. There was discharge from June 1 to August 5, 1942. That morning it ceased, but later that day a profuse, purulent discharge was noted, lasting until August 20, 1942. The abdomen did not heal until September 12, 1942.

CLINICAL COURSE: The patient was then transferred to the Medical Service. She improved, gradually gained weight and was discharged on November 27, 1942 having been hospitalized nearly three years. Thereafter she was checked regularly at six month intervals. She had one scant menstrual period and occasional hot flashes. She continued to gain weight (to 140 pounds, a gain of 60 pounds) and she felt well, working every day. On August 22, 1963, Gaudrault reported that "other than chronic ailments such as arthritis and bursitis she is enjoying life. . . hasn't seen a doctor for about 18 months." She was last traced in July 1976, over 30 years after onset.

REFERENCES: 11; 38.

CASE 6: Round cell scirrhous ovarian carcinoma, of slow growing type, provoking intense fibrosis with granules of calcification, with metastases to the liver and a lymph node, confirmed by microscopic examination following operation.

PREVIOUS HISTORY: Aged 29, a psychiatric nurse. The family history and previous personal history were not recorded.

INFECTION: In February 1950 the patient complained of lassitude and unproductive cough of two months' duration. A chest film suggested miliary tuberculosis. She was admitted to a hospital where she remained afebrile, the sputum being negative for tuberculosis and the Mantoux reaction negative at 1 to 100 dilution. A 60-day course of streptomycin with P.A.S. was given and the patient was discharged with the possible diagnosis of chronic miliary tuberculosis or sarcoidosis. During 1951 there was a little loss of weight, together with mild attacks of diarrhea and unproductive cough. In July 1951, she was readmitted to a hospital, where in the course of barium enema studies, numerous calcified opacities were noted in the abdominal films.

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SURGERY: A cervical lymph node biopsy was reported as showing "typical epithelial tubercles of sarcoid."

CLINICAL COURSE: In December 1951, at her final hospital admission she was complaining of lassitude and a slight cough and also amenorrhea of four months' duration. Physical examination revealed a thin woman in fairly good general condition. Small firm cervical lymph nodes were palpable and the liver was enlarged 5 cm. below the costal margin. The tuberculin reaction was now positive. Chest films showed generalized small pulmonary opacities, a picture essentially unchanged for the previous 22 months, except that these opacities were now harder and probably calcified. A film of the abdomen revealed multiple rounded calcified opacities lying anteriorly over a wide area.

FURTHER SURGERY: In January 1952, a laparotomy was performed with the intention of removing these calcified masses, the diagnosis of sarcoidosis being considered untenable. The liver was found to be enlarged to below the umbilicus and was studded throughout with white nodules varying in size, some showing central umbilication. One of these was removed. The right ovary was cystic and the left was represented by a cyst together with a round tumor the size of a billiard ball. This ovary was removed. Histologic examination of this lesion and the hepatic nodule and review of the cervical node which had been excised six months before and erroneously diagnosed as a "sarcoid", showed "round cell scirrhous ovarian carcinoma provoking intense fibrosis with granules of calcification. In many places the growth shows evidence of being strangled by fibrous tissue."

CLINICAL COURSE: The patient made an uneventful recovery and was discharged from the hospital in February 1952. She was seen at intervals thereafter, remaining reasonably well, x-rays taken in 1955 of the chest and abdomen showed little change. This was over five years after onset.

REFERENCES: 41; 87.

NOTE: The possible beneficial effect of chronic appendicitis on survival is suggested by the following case.

Hutcheson reported a case with bilateral cystadenocarcinoma of both ovaries which were removed together with the uterus and the appendix. The histologic examination at that time was bilateral cystadenoma of the ovary (revised upon review to papillary serous cystadenocarcinoma), chronic appendicitis and hyperplasia of the lymph nodes. No postoperative radiation was given. The patient remained asymptomatic for 33 years. Then she developed edema of the right lower extremity, abdominal swelling and constipation. The disease progressed, causing death in six months. Autopsy revealed a broad, grayish, honeycombed

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extremely fibrotic and partially necrotic tumor 4×8 cm. in diameter involving the right hemipelvis and iliac region, invading the right ilium and extending from the anterior superior spine along the anterior border of the ilium to invade the right pubic bone and surround the femoral vessels. It infiltrated the serosal surface of the cecum. The distal third of the right ureter was surrounded and compressed by tumor with hydroureter and hydronephrosis. There was one metastasis in the liver and others to the nodes along the iliac, aortic and mesenteric vessels. (45a)

**SERIES B: INOPERABLE OVARIAN CARCINOMA TREATED BY
COLEY TOXINS: 7 CASES
BRIEF ABSTRACTS**

The following cases are the only recorded cases of inoperable ovarian carcinoma treated by Coley toxins for at least a month, with microscopic confirmation of diagnosis. Those terminal cases who received from 6 to 11 injections were excluded although the immediate effects on two were good.

- | | Years Traced
After Onset |
|--|-----------------------------|
| <p>1. MERIWETHER: Mrs. D., aged 37; date of onset not recorded; recurrent inoperable ovarian adenocarcinoma; operation September 8, 1896 for enormous cyst adenoma; severe hemorrhage, pelvis packed with gauze; next spring large sinus opened, from which soft tumor mass 8 cm. wide protruded; condition inoperable; biopsy, May 5, 1897: Coley toxins (Buxton VI) into tumor or abdominal muscles; former caused marked reactions, chills, latter caused no chills; <i>tumor decreased to half original size in 3 weeks</i>; patient left city, <i>treatment suspended for 3 weeks</i>; <i>tumor immediately increased rapidly</i>; <i>injections resumed, mass began to slough and again decreased</i>; <i>treatment given at long intervals</i>; <i>effect upon tumor mass perceptible at every injection within 24 hours</i>; <i>after treatment finally stopped mass grew rapidly</i>; death 3 weeks later. (61)</p> | Died |
| <p>2. CALKINS: G.V., aged 29, onset, about June 1914; terminal papillary adenocarcinoma, apparently primary in very large degenerated multilocular ovarian cyst; metastases to mesenteric lymph nodes, small and large intestines, peritoneum, liver; patient cachectic, had lost 50 pounds, extremities swollen; she weighed only 60 pounds; June 29, 1916; primary removed, metastases not touched; a week later toxins (Tracy XI) begun, given every 48 hours for 9 months, resumed after month's rest for another 6 months; <i>metastases disappeared completely</i>; patient gained 83 pounds; remained in excellent health until death, cerebral hemorrhage, March 21, 1936. (10; 11; 16)</p> | 20 |
| <p>3. COLEY: Mrs. K.A.W., aged 45; onset December 1906, papillary adenoma right ovary involving intestines, uterus, with numerous papillomatous nodules over peritoneum, omentum; April 25, 1907: exploratory laparotomy, incomplete removal; May 26, 1908: toxins (Parke Davis XII) given i.m. remote from growth, caused intense local soreness, no marked reactions; <i>temporary improvement, gained 20 pounds, felt fine</i>; recurrence; toxins resumed (not given aggressively), <i>again some temporary improvement</i> from 14 doses; disease progressed, death June 27, 1910. (6; 16; 60a)</p> | 3½ Died |
| <p>4. COLEY: Miss G.A., aged 59; onset, December 1914; inoperable papillary cyst adenoma primary in left ovary, removed at first operation, 1914;</p> | |

SERIES B: BRIEF ABSTRACTS

Years Traced
After Onset

recurrence; subtotal abdominal hysterectomy, bilateral salpingo-oophorectomy May 31, 1916 (by W.J. Mayo), abdomen filled with myxomatous material, large ruptured cyst adenoma right ovary; recurrence 1925, mass in umbilical region, fluid in abdomen; 3rd operation June 4, 1925 (Mayo), secondary papillary peritonitis: cysts on peritoneum, omentum and abdominal wall, also many floating myxomatous bodies; incomplete removal; clinically malignant; x-ray therapy, June 1925; disease not controlled; toxins (Parke Davis XIII) begun January 15, 1926; *marked reactions; remarkable improvement during first 6 weeks; abdomen diminished 8 cm., general condition improved, patient up and about; then developed severe colitis (15-20 stools daily), fever 104.5°F. for 7 days, prostrated; abdomen steadily and rapidly enlarged (gas, fluid, tumor); condition critical; spontaneous opening formed, drained 2-3 quarts necrotic tumor tissue and fluid first day, several pints daily for next 10 days; complete disappearance abdominal growth; regained her health; further recurrence 1927, death September 1927.* (16)

13

Died

5. SENECAL: Mrs. G.L., aged 38; onset, summer 1932; terminal bilateral papillary cyst adenocarcinoma ovaries, broad ligaments, metastases to omentum, liver; exploratory laparotomy; condition inoperable; abdomen enormously distended, to 1½ times full term pregnancy; extreme cachexia (had lost 31 pounds); general condition grave, prognosis hopeless; onset, January 1933; September 3, 1933: toxins given in large doses intra-abdominally; *abdomen flattened to normal in 4 weeks, decreased 23 cm. in circumference; patient gained weight, strength;* toxins then given less frequently (once a week); growth recurred, grew slowly; April 4, 1934 re-operated: "hysterectomy, bilateral salpingo-oophorectomy"; whole tumor finally freed; *toxins resumed for a year; no further recurrence; patient gained 61 pounds, excellent health for 16 years;* 1950 developed nodules in rectovaginal wall, considered metastatic; brief intensive course intravenous toxin therapy given in May 1951 with one very severe reaction, *gained weight, in very good health; symptom-free for 2½ years;* October 1953 vaginal bleeding; explored; large pelvic and abdominal mass almost entirely removed including large portion of fundus of bladder, portion on pelvic floor deep in pelvis left untouched; severe coronary occlusion early 1954; hospitalized several weeks; gained weight, recovered; May 1954: large residual mass to right of rectum began to break through vagina; further very radical operation; further attempt to transplant ureters May 1954; cardiac reserve very low; death May 29, 1954. (11; 16; 60a; 64, case 30)

21

Died

6. JOHNSTON: M.M., female aged 38; inoperable adenocarcinoma of ovary,

SERIES B: BRIEF ABSTRACTS

Years Traced
After Onset

- widespread pelvic metastases; onset 1959; laparotomy, biopsy by Crawley: "frozen pelvis, widespread pelvic disease"; 1960: Johnston XV toxins for 2½ years (136 i.v., 26 i.m.) *gradual progressive improvement in pelvic findings, gained 32 pounds; complete regression; in good health when last seen 1970.* (11; 48) 11
7. COLE: Mrs. A.B., 53; onset June 1963 adenocarcinoma of left ovary with metastases to peritoneum following panhysterectomy; x-ray (49) post operatively; condition worsened, 20 pound weight loss; nausea, emesis, very severe pain; Spring 1964: gastroenterostomy for duodenal ulcer, metastases not removed; June 1964, hydroxyurea (not tolerated), no response); August 1964 Refuin for 5 months with no response; April 1965: Coley toxins, 5 i.d. weekly for 2 or 3 weeks, then one weekly (0.2cc.); *pain, nausea and emesis soon ceased, gained over 20 pounds; resumed normal activities; Coley toxins continued for several years; when no longer available Hollister Stier's mixed respiratory vaccines given weekly; in excellent health for 13 years; June 1976: while in Italy sudden severe hemorrhage from duodenal ulcer, anemia required transfusions; weight decreased to 79 pounds; explored by Cole after return home: "no evidence of cancer"; convalescence uneventful, July 1976.* (11) 13

NOTE: Two other metastatic ovarian carcinomas are known to have received Coley toxins. The first was given six intravenous injections of these toxins in 1953 at Memorial Hospital for a lesion which had metastasized to the omentum and peritoneum. This case has not been included statistically because so few injections were given, however it is of interest to note that the immediate result was reported as "little short of magic": the hypostatic pneumonia cleared up overnight, color better, eyes brightened, spirits improved . . . , tumor receded." The disease progressed causing death a year later. (60a) The second, a recurrent inoperable case with metastases in the left pelvis, ankle edema and urinary symptoms, received 11 injections in 18 days, with definite marked regression evident in two weeks and clinical improvement. The mass continued to decrease in size and the patient was pain free but death occurred 4 months after toxins were given. Both these cases were also given x-ray therapy. (60a)

**SERIES B: INOPERABLE OVARIAN CARCINOMA TREATED BY
COLEY TOXINS
DETAILED HISTORIES**

CASE 1: Recurrent inoperable adenocarcinoma, confirmed by microscopic examination of a specimen removed from the recurrent growth.

PREVIOUS HISTORY: Mrs. D., aged 37. No details were given.

SURGERY: Dr. F.T. Meriwether operated on September 8, 1896, for an enormous cyst adenoma. Hemorrhage was so severe that the pelvis had to be packed with gauze, which was removed on the third day.

CLINICAL COURSE: The wound healed but the next spring a sinus opened with a serous discharge. Examination on April 30, 1897, showed a large opening in the abdomen at the lower angle of the incision. Palpation inside the sinus revealed a rather soft, broken-down mass, from which on May 4, 1897, two ligatures were removed. At this time the external mass was 8 cm. in diameter and protruded 2.5 cm. through the sinus. Examination of this tissue showed it to be adenocarcinoma.

TOXIN THERAPY (Buxton's VI): Injections were begun by Meriwether about May 5, 1897. The dosage was increased rapidly to 2 minims given into the tumor which at times produced marked prostration with a febrile reaction of 104° F., a chill, cyanosis, and a pulse of 140 to 160. Some injections were made in the abdominal muscles at a distance from the tumor. These did not cause a chill, even in doses of 10 minims. After three weeks' treatment the tumor had decreased to half its former size.

CLINICAL COURSE: At this time the patient moved to the country and no treatment was given for three weeks. At the end of this period the tumor was 20 cm. in diameter and was raised 8 cm. above the abdomen.

FURTHER TOXIN THERAPY: Injections were resumed, and the mass again began to slough and to decrease in size. The depression following the injections was objectionable to the patient, and therefore treatment was given only at long intervals, further treatment being refused after August 12, 1897. Meriwether stated: "The effect upon the tumor mass was perceptible at every injection within 24 hours."

CLINICAL COURSE: After the injections were stopped, the mass grew rapidly and death occurred three weeks later, in early September 1897.

COMMENT: This case would indicate that treatment was suspended too soon (after

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only three weeks) and that the injections were given too infrequently, thereby diminishing the effect on the neoplasm. It would appear that during the second course of toxin therapy no injections were given into the tumor or its immediate periphery. Patients seemed to note greater depression when all the injections were given by the intramuscular route remote from the tumor, and such treatment produced much slower regression of the tumors. A few local injections combined with intravenous therapy seem to be especially effective in carcinoma or epithelioma.

REFERENCE: 61

CASE 2: Inoperable papillary adenocarcinoma of the ovary with extensive metastases to the mesenteric lymph nodes, small and large intestines, peritoneum and liver. The pathologist reported: "Sections taken from the degenerated ovarian cyst and from different portions of the peritoneal cavity were examined microscopically and pronounced papillary adenocarcinoma."

PREVIOUS HISTORY: G.V.W., female, aged 29, stenographer, of Watertown, New York. The family history was non-contributory and the patient had always been well. Onset, for two years prior to consulting Dr. F.R. Calkins, she had noticed that her abdomen was increasing in size, but because she was a Christian Scientist, she had not consulted a physician. Calkins stated that when he first saw the patient in June 1916 she weighed only 80 pounds, the girth of her abdomen was over 92 cm., and she was decidedly cachectic in appearance, pale and extremely anemic. She had lost over 50 pounds in weight and had been unable to eat for two weeks. She had consulted another leading surgeon of northern New York State who refused to operate because of her weakened condition and the advanced stage of malignancy. She had been confined to bed for over a month and the prognosis was very grave. The abdomen was greatly distended, the abdominal wall not exceeding 0.75 cm. in thickness, and large blue veins radiated over the abdomen. The extremities were swollen, but the heart and lungs showed no evidence of disease.

SURGERY: On June 29, 1916, Calkins operated under general anesthesia. A lower median incision was made and the abdomen explored. It was found that the tumor consisted of a very large multilocular ovarian cyst, which had undergone extensive malignant degeneration, involving the greater portion of the colon, the small intestines, the liver and the parietal peritoneum. The cyst was firmly adherent in many places to the intestines and to the parietal peritoneum, particularly on the posterior surface. No hope was entertained of saving the patient's life, but it was thought that if she could survive the operation, temporary relief of her

SERIES B: DETAILED HISTORIES

symptoms could be obtained by removal of the cyst. No attempt was made to remove large portions of the metastatic areas on the bowel, the liver or the parietal peritoneum. The appendix, which was as large as a banana, was removed, and a pan-hysterectomy and double oophorectomy was performed. There was so much bleeding from the adhesions in the pelvis that the whole pelvic cavity was packed with three-meter abdominal sponges and a drainage tube was inserted. The patient was returned to her room almost in a dying condition. Under heavy stimulation she rallied from the operation and soon showed marked improvement, which continued without any complications.

TOXIN THERAPY (*Tracy XI*): Injections were begun by Calkins on July 6, 1916, one week after this operation, and were given every other day. The patient was discharged from the hospital three weeks after operation, at which time she was able to be up and about and complained of no pain or discomfort. The metastases regressed completely under continued treatment. The injections were given every other day for nine months, and after a month's rest were resumed and given twice a week for another six months. Immediately after operation, the patient weighed only 60 pounds. She gained weight steadily under toxin therapy. Calkins' usual technique in administering the toxins was to use deep intramuscular injections in all his cases, usually in the gluteal region, occasionally the pectoral. He diluted with saline, or if this was not available, boiled water. The site of injection was massaged thoroughly and there was no induration at the point of injection, indicating thorough and rapid absorption. His initial dose was usually 0.3 cc., increased by 0.1 cc. each time until a profound reaction occurred, which was usually a week or two after the initial injection. There was usually a reaction within two hours, and the leukocytes would increase from 2,000 to 5,000. The appetite was usually nil on the day of the injection, so they were given every other day at first. There was usually some loss of weight (three to five pounds) in the early part of the treatment, then a rapid gain. An iron tonic was usually given. The duration of treatment was usually about six months to one year, with intervals of rest, decreasing the frequency during the last six months.

CLINICAL COURSE: Calkins reported that 10½ years after treatment the patient weighed 140 pounds, a gain of 80 pounds, and that she was in excellent general condition. She was last examined in December 1933, at which time she was perfectly well except for hypertension, which did not prevent her working steadily as an accountant. She died of a cerebral hemorrhage on March 21, 1936, 22 years after onset of the ovarian cancer. There was never any recurrence or metastases.

REFERENCES: 10; 11; 16.

CASE 3: Inoperable papillary adenoma of the ovary involving the intestines confirmed by microscopic examination at Memorial Hospital following operation.

SERIES B: DETAILED HISTORIES

PREVIOUS HISTORY: Mrs. K.A.W., widow, aged 45. The family and previous personal history were non-contributory. Menses began at 18 and the flow lasted three or four days, a 30 day cycle, and there was no leukorrhea. The patient married, had one child and one miscarriage. Menses occurred in August 1906, again in January 1907, then stopped until March 1907. Onset, in December 1906, a small umbilical hernia developed which increased in size. A physician was consulted who told the patient that she had an ovarian cyst. During the five months prior to admission, December 1906 to April 1907, the patient stated that she had no symptoms except incontinence of urine during December, January and February. At examination on admission to Memorial Hospital, on April 22, 1907, a small umbilical hernia was found which admitted the tip of the little finger. The abdomen was distended, the uterus being pushed over to the right and flattened out. A hard mass in the left broad ligament bulged into the vagina and appeared to be connected with the abdominal tumor.

SURGERY: Dr. William B. Coley performed an exploratory laparotomy on April 25, 1907, through a 10 cm. median incision. About six to eight quarts of dark brownish fluid were evacuated. Scattered over the peritoneum and omentum were numerous papillomatous nodules, one of which was removed for biopsy. A solid tumor consisting of fused coils of intestine, the uterus and the right ovary was found in the right side of the pelvis. The left ovary was the site of a papillomatous tumor. No attempt was made to remove all the growths.

TOXIN THERAPY (Parke Davis XII): Injections were begun on May 26, 1907, and 27 were given in the pectoral or gluteal muscles. These caused intense soreness. Antiphlogistine was applied to relieve this. The initial dose was 0.5 minim, which was gradually increased to a maximum of 10 minims. No marked reaction occurred during the first two weeks' treatment, but during the last ten days four or five moderate reactions occurred, 101.4° F. to 102° F., and two slight chills. The patient complained occasionally of aching in her limbs following an injection.

CLINICAL COURSE: The patient was discharged improved on July 2, 1908. She did not menstruate again after the operation in April 1908. She gained 20 pounds and stated that she felt fine. She was readmitted on May 21, 1909, because she had noted that the abdomen was getting larger. Physical examination at this time revealed that the abdomen was not as hard as it had been before, but there was a hard mass in the right pelvis, which was irregular in outline. The patient's appetite was good, but she was constipated and had frequent micturition especially at night.

FURTHER TOXIN THERAPY: Injections were resumed on May 21, 1909, and during the next 28 days 14 were given in doses of 0.5 to 8 minims, causing no marked reactions. However, on June 26, 1909, after the fourth injection the temperature

SERIES B: DETAILED HISTORIES

continued to rise to 103° F., finally subsiding to normal on June 30, 1908. No febrile reactions occurred thereafter and no chills.

CLINICAL COURSE: The patient was discharged improved, but this improvement was only temporary and death occurred on June 27, 1910, two years after onset. (Compare this case with that of Calkins in which the toxins were continued for a year.)

REFERENCES: 6; 16; 60a.

NOTE: Incomplete details were found of a case of recurrent ovarian cancer treated by Dr. Robert T. Morris in 1912: In April 1912, Morris removed a large right multilocular ovarian cyst which was adherent and filled the entire pelvis. A part of the growth was evidently undergoing malignant degeneration. Morris told the relatives but not the patient that recurrence might be anticipated. When recurrence appeared in the left inguinal lymph nodes shortly thereafter, "the patient did not choose to disclose the fact." When finally obliged to see Davis and Morris in May 1912, the case was inoperable: "The large indurated mass seemed to be diffuse, and to involve the blood vessels and nerves of Scarpa's triangle in such a way that any operation would have been necessarily incomplete at best." Morris advised Davis to at least try the Coley toxins on the ground that the family would feel that nothing was left undone. Shortly after the toxins were begun he reported a favorable change in the case, and this proceeded to such a point that the mass of lymph nodes became smaller and movable; i.e. the condition had become operable. In November 1913, Morris therefore removed the entire mass, without injury to vessels or nerves, and leaving no macroscopic evidences of the growth. The patient remained well and the scar area looked healthy when the case was reported to Coley in a personal letter from Morris on December 17, 1913. The disease was not controlled—she was readmitted again in January and June 1915, with metastases in the left inguinal lymph nodes. Although no records of her death were found in New Jersey, she is believed to have died of the disease.

REFERENCES: 16.

CASE 4: Recurrent papillary cyst adenoma of the left ovary, with secondary papillary cyst peritonitis, clinically malignant, confirmed by clinical and microscopic examinations at the Mayo Clinic.

PREVIOUS HISTORY: Miss G.A., aged 59, a retired school teacher. The patient's mother died of cancer of the throat, and one sister of heart disease at 36 years of age. The date of onset is not recorded.

SERIES B: DETAILED HISTORIES

SURGERY: In December 1914 the patient was first operated upon, and part of the left ovary was removed with a papillomatous cyst. There was myxomatous fluid in the abdomen at that time.

CLINICAL COURSE: She was first seen at the Mayo Clinic in May 1916 because of a recurrence of the abdominal tumor with free fluid and multiple small fibromyomata of the uterus with papillomatous cysts.

FURTHER SURGERY: Dr. William J. Mayo operated on May 31, 1916 and did a subtotal abdominal hysterectomy with removal of both ovaries and tubes. The abdomen at that time was filled with myxomatous material. The pathological report showed multiple small fibromyomata of the uterus, bilateral salpingitis, a large ruptured ovarian cystadenoma of the right ovary, and left chronic oophoritis covered with colloid material.

CLINICAL COURSE: Nine years later, the patient returned to the Clinic with a mass in the umbilical region. Fluid had accumulated in the abdomen.

FURTHER SURGERY: Mayo again operated on June 4, 1925. He found secondary papillary peritonitis. He stated: "There were cysts in every direction on the peritoneum, omentum and abdominal wall and many floating myxomatous bodies. The fluid and myxomatous material were removed and as many of the cysts were removed as possible. The pathologist reported pseudo-mucinous material containing remnants of papillomata from a papillary cystadenoma. The condition was clinically malignant." The patient made a satisfactory post-operative recovery.

RADIATION: X-ray therapy was given between June 16 and 27, 1925 (700 r. per field, 200 K.V. to the upper left, upper right, lower left and lower right quadrant of the abdomen, then to the upper and lower lumbar regions posteriorly.) The patient was then referred to Dr. William B. Coley for toxins because the disease had not been controlled.

TOXIN THERAPY (Parke Davis XIII): Injections were begun about January 15, 1926, and for the first six or eight weeks two injections a week were given at Coley's office producing rather marked febrile reactions (103° - 104° F.). He stated that very remarkable improvement took place during the first four or six weeks' treatment. The swelling of the abdomen diminished 10 cm., the general condition showed marked improvement and the patient was able to be up and about.

CONCURRENT COLITIS: "About March 15, 1926, following an ordinary dose of toxins, her temperature rose that evening to 104.5° F. and it failed to go down; this was accompanied by severe colitis (as many as 15 or 20 stools a day) and a good deal of prostration. This condition continued in spite of symptomatic treat-

SERIES B: DETAILED HISTORIES

ment for about a week. The abdomen steadily and rapidly increased in size. While the swelling of the abdomen was partly caused by gas, there was a great deal of fluid or tumor present. . . . In view of her great prostration and frequent operations, and the possibility of adhesions, I did not dare to make any attempt to aspirate or to open the abdomen. She had developed a few rales, and I thought the condition might be associated with the grippe; but her temperature slowly subsided at the end of two weeks, getting down to 100° to 102° F., and she was able to take a fair amount of nourishment. I did not think she could last more than a few days when suddenly a small grayish spot developed in the middle of one of the old cicatrices in the mid-abdomen; in two days this softened down, leaving a clean-cut opening about $\frac{1}{4}$ of an inch in size, permitting the discharge of a very large amount of fluid and broken-down tumor material. This happened in the night, and the nurse thinks that about two or three quarts were evacuated. . . . She continued to discharge several pints of this material a day for ten days. Yesterday I examined her for the first time in ten days, having been laid up with an attack of grippe and unable to see any of my patients. I found her abdomen perfectly flat and normal in appearance; the clean-cut opening had nearly healed, her appetite is fine; temperature normal, respiration 24. The explanation is that the toxins broke down the large tumor mass, that the patient began to develop septic absorption, and that finally, Nature, in order to get rid of this material, produced an opening in the abdomen, more effective and safer than the surgeon could have done. If she does recover, it will be almost as marvelous as the case of Dr. Calkins, which led us to suggest the treatment in the case of Miss A." (see Case 2, above). It is not known how much longer the toxins were continued, nor is the site of injection stated in Coley's records, but at this period he was treating most of his patients by intramuscular injections in the gluteal region.

CLINICAL COURSE: The patient regained her health and on October 30, 1926, Mayo wrote Coley: "It is gratifying to know that Miss A. has been so extraordinarily benefited by the toxins. The results in her case augur well for the future. . . ." The patient remained in good health in December 1926. However, recurrence developed again in 1927. No further toxins were administered, the disease progressed and death occurred in September 1927, 13 years after onset.

COMMENT: Compare this case with that of Calkins (Case 2), or with that of Senecal (Case 5), in which following persistent sustained toxin therapy the patients were traced 20 years.

REFERENCE: 11.

CASE 5: Very extensive bilateral papillary cyst adenocarcinoma of the ovaries, with metastases in the omentum and both broad ligaments, apparently involving the liver, confirmed by microscopic examinations at

SERIES B: DETAILED HISTORIES

St. Luke's Hospital, New Bedford, St. Ann's Hospital, Fall River, and Drs. John E. McWhorter and D.A. De Santo, pathologists at the Hospital for Special Surgery, New York, who reported on the specimen removed at the second operation:

"Gross: Specimen is a pelvic mass measuring $8 \times 4 \times 3$ inches. In the center of the mass is a uterus. This has been sectioned sagittally. The cervix shows healed scars. The uterine wall appears natural and the organ is normal in size and shape. In the right broad ligament is an irregularly shaped mass $4 \times 3 \times 3$ inches, which has been sectioned in several places. The mass consists of a multilocular cyst, some of the sub-divisions of which contain gelatinous material and others papillary tumors having a racemose appearance. In the left broad ligament the mass is larger and measures $5 \times 4 \times 2$ inches. It is similar in structure to the tumor of the right, but is more solid, with several areas of central softening.

"Microscopic: Sections from the right and left ovaries show a fibrous cyst wall lined by tall columnar epithelium, thrown into complicated papillary folds. The papillae are supported by delicate stalks of connective tissue. The cyst wall is infiltrated by daughter cysts, which in turn are lined by papillary ingrowths of epithelium. Many areas of the tumor show a mucinous degeneration. Sections from the cervix and uterus show sclerosis of the vessels, and are otherwise natural.

"Diagnosis: Bilateral papillary cyst adenocarcinoma of the ovary. Fibrosis uteri."

In February, 1949 Dr. Sophie Spitz of Memorial Hospital reviewed the sections on this case and concurred in the diagnosis.

PREVIOUS HISTORY: Mrs. G.L., aged 38, of Pawtucket, Rhode Island. The family history was negative for cancer, tuberculosis or insanity. The patient's father died at 72 of uremia. The mother was living and well. The patient had had nine brothers, three of whom died of unknown causes, and seven sisters, six of whom

SERIES B: DETAILED HISTORIES

had died. She had had whooping cough, measles and mumps as a child. The menses began at 11 and had been irregular before marriage, sometimes skipping three or four months. After marriage in 1920, at the age of 25, there had been a regular 28-day cycle. There had been no dysmenorrhea but some leukorrhea since marriage. In 1921 a son was born weighing 11 pounds, a normal delivery. Two years later she had a miscarriage. There were no other pregnancies. Onset, the patient was first seen by Dr. Raymond E. Senecal in January 1933. She had lost 15 pounds in weight in the previous six months, felt easily tired, and had noticed a fullness in the lower abdomen, although the periods remained regular.

SURGERY: On February 27, 1933 an exploratory laparotomy was performed at St. Luke's Hospital, New Bedford. The uterus, adnexa and gastro-intestinal tract appeared not unlike those found in advanced cases of tuberculous peritonitis. The organs were atrophied and so changed that they could scarcely be identified. The appendix was removed, and also a node from the omentum. The pathological diagnosis at this time was "omental implantations of cyst adenoma and chronic periappendicitis."

CLINICAL COURSE: The patient was discharged from the hospital in an ambulance on March 9, 1933, after a stormy convalescence, following which she did not improve. Her abdomen became greatly distended and she presented a picture of general anasarca. She was sent to the country, where she took daily sun baths. Her condition progressed unfavorably. At this time the patient was in an extremely bad condition. Her weight had decreased to 69 pounds, a loss of 31 pounds, and rectal feeding was considered necessary. A roentgenologist was consulted but he regarded the prognosis as hopeless.

TOXIN THERAPY (Parke Davis XIII): Injections were begun by Senecal on September 3, 1933. The patient was given eight alternating doses of 8 and 16 minims each (0.5 and 1 cc.) intra-abdominally, on September 3, 4, 5, 6, 8, 10, 12, 17, 1933. The reactions at times were very marked, the temperature ranging between 101° and 104.8° F. In describing the results of the treatment, Senecal wrote: "From the beginning the progress of the case was miraculous. Her abdomen, which at first was distended to one and one-half times a full-term pregnancy, rapidly flattened down to normal; it decreased from 34½ inches to 25¾ inches in the first four weeks. Her appetite became voracious and she gained weight and strength."

No toxins were given between September 17 and October 12. Another series of seven injections was given as follows: October 12, 27, 29, November 1, 6, 11, 1933. Each injection produced a marked reaction, usually with a chill lasting half an hour. The dose for this second course was maintained at 0.5 cc. (about 8 minims).

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The patient was discharged from the hospital on November 13, 1933, having received a total of 15 injections, the total dosage being about 144 minims (9.5cc.). (It should be emphasized that this was much higher than that usually advised by Coley. Under the dosage prescribed in the Parke, Davis & Co. package, this patient would probably have received about 20 minims during the first eight injections, whereas Senecal administered 96 minims in those first eight doses.)

During November only two injections a week were given, and early in November a mass appeared in the pelvis which was hard, nodular and easily palpable externally. Injections were made directly into this mass, but only one a week was given during December, January and February. The mass increased slowly in size. The total number of injections given in the six-month period between September 1933 and March 1934 was 36.

FURTHER SURGERY: In March 1934 it was decided that the patient return to the hospital for further exploration. At this time the abdomen was flat and soft, but a mass was palpable in the lower quadrant which seemed somewhat fixed. There was no pain. The patient was given two blood transfusions, on March 28 and April 2, 1934, each time receiving 500 cc. of whole blood and 1000 cc. of saline. The operation was performed on April 4, 1934 at St. Ann's Hospital, Fall River, under spinal anesthesia, and "consisted of hysterectomy, bilateral salpingo-oophorectomy with removal of all growths around the tumorous condition. At first the mass appeared inoperable and only a semblance of the fundus uteri was recognized. However, the whole tumor was finally freed." The specimen was examined by several pathologists, as stated above, the diagnosis being adenocarcinoma of all the adnexa. The patient left the operating room in poor condition but made a good operative recovery.

FURTHER TOXIN THERAPY (Parke Davis XIII): Injections were resumed about June 1, 1934 and were continued for about a year following this operation. At first they were given by Senecal, twice a week, but during the latter part of the treatment the patient administered them herself, the site being the thighs. She began to gain weight shortly after the toxins were resumed and this continued steadily, so that by December 1934 she had gained 40 pounds. Senecal wrote to Coley in regard to this case in February 1935 and stated: "There is no doubt in my mind that this patient owes her life to Coley's fluid." (16)

CLINICAL COURSE: There was no further recurrence or metastases. The patient reported in July 1945 that she had had no illness of any kind in the 12 years since toxin therapy was begun, and that she weighed 130 pounds, a gain of 61 pounds since September 1933. In June 1950 she consulted Dr. Robert V. Lewis, of Providence, who reported: "Mrs. L. came to me because she was having a sense of discomfort in her rectum when she sat down. On examination the rectovaginal wall and the surrounding tissues were full of nodules about the size of grapes.

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They were freely movable, firm and non-tender in themselves." (11) She weighed 114 pounds in July and 119 pounds in August. Laboratory studies were essentially negative. Dr. Emery Porter, a surgeon, and Dr. Russell Bray, a gastro-enterologist, were seen in consultation. Bray found nothing in the rectum on proctoscopy and sigmoidoscopy. During the next four months Porter and Lewis followed her condition and there was absolutely no change. On October 28, 1950 Lewis reported: "It is our impression that these nodules are entirely inactive." She was again seen in mid-November, at which time she was in good physical condition and had no complaints. Lewis reported on April 3, 1951 that the nodules in the rectovaginal wall had enlarged during the previous three months, and that the vaginal mucosa at one point had been slightly eroded by one of the lesions. She had lost 10 pounds in weight, but the clinical findings were otherwise negative. There was no anemia. The patient was again seen by Porter, the surgeon who was following her, and he stated that the only feasible operation in her case would be an abdominoperineal resection and removal of the rectovaginal wall. He stated that these lesions are not amenable to less radical surgery. At this time Lewis suggested further toxin therapy. The patient was admitted to Memorial Hospital on May 14, 1951.

FURTHER TOXIN THERAPY (*Sloan Kettering XIV*): A series of 12 intravenous injections were given daily between May 14 and 25, 1951, under the direction of Dr. Alexander Brunschwig. Much larger dosage was used than is usually given for the intravenous route: 1, 1½, 2, 4, 6, 8, 9, 12, 16, 20, 22, and 24 minims. However, no very marked febrile reactions occurred until the final dose. The febrile reactions for the first 10 doses were: 100.6°, 100.2°, 101.2°, 102.2°, 101.3°, 102.8°, 103.8°, 102.2°, 101.4°, 103.4° F. There was also some nausea and emesis after the first two injections, and severe backache after the first. Chills lasting 10 to 45 minutes followed all but the eighth and ninth doses. The house surgeon noted on May 24: "This patient has apparently developed an immunity to Coley's toxins; despite rapid rise in dose, reaction has been mild." On May 25 the final dose of 24 minims was given at 9:20 a.m. At 10.30 the patient had a severe chill lasting 45 minutes. Her temperature then rose rapidly to 114° F., rectal. (This was checked on three thermometers as no patient in over 900 who have received Coley toxins ever had over 108° F., the maximum usually being 104° to 105° F.) The patient was given a cold sponge bath and ice packs and her temperature soon went down to 104° F. Four hours later her condition appeared to have returned to normal, with no ill-effects. It was stated on May 26, 1951 that the nodules in the vaginal vault appeared distinctly softer, but not appreciably smaller.

CLINICAL COURSE: The patient was discharged on May 29, 1951. She gained weight and strength. She apparently had no further trouble with these nodules for about two years. On October 26, 1953, she was seen at the Rhode Island Hospital because of vaginal bleeding which had developed a week previously.

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Two vaginal biopsies were obtained, the diagnosis being recurrent papillary carcinoma of ovarian origin.

FURTHER SURGERY: On October 26, 1953 an operation was performed by Dr. George W. Waterman for a large pelvic and abdominal mass, through a mid-line incision extending from the pubes to above the umbilicus. A hard nodular mass was found involving the anterior pelvis. This was attached to the bladder anteriorly and extended out to and involved the fatty tissue over the iliac vessels in the operative region. A large mass of this carcinomatous tissue extended posteriorly and was adherent to the intestines. The omentum contained a few small, firm nodules one of which was taken for biopsy. The gallbladder contained two hard stones, but was freely movable. The surface was clean, and no other tumors were in the upper abdomen. Posteriorly there was a soft cystic mass lying beside the rectum on the right side. Attached to this were numerous hard nodes which appeared to be lymph nodes. In order to mobilize the tumor it was necessary to open the bladder and take off a large portion of the fundus. The tumor was then fairly easily circumscribed, mobilized from the large vessels on the left side and from the sigmoid posteriorly. It was possible to remove almost this entire mass. Further inspection of the tumor in the right wall of the pelvis convinced the operator that removal of this portion would be fraught with too much danger because of the size of this tumor on the pelvic floor, to warrant attempting to remove it. . . . " A large portion was deep in the pelvis and attached to the rectum. The specimens were reported as showing papillary carcinoma, consistent with ovarian origin, with invasion of urinary bladder. The patient made an uneventful recovery and seemed to be doing well. Further surgery was considered but the patient had a very severe heart attack, probably coronary occlusion and was hospitalized for several weeks under the care of Lewis.

CLINICAL COURSE: By March 1954, the cardiac condition was satisfactory and the patient had gained some weight. Cystoscopy showed the bladder wall healed without any sign of breaking through. The ureters seemed to be functioning normally. However, there was still a large residual mass to the right of the rectum. The patient was anxious to have something done about this, as the tumor was beginning to break through into the vagina.

FURTHER SURGERY: A further very radical operation was done, in which the tumor was comparatively completely removed. This operation was quite difficult and complicated, being an anesthesia problem, but was finally concluded. The ureters were necessarily divided on each side and the proximal portions anastomosed. The patient had a somewhat stormy convalescence and there was leakage from the ureters. A further attempt to transplant the ureters into the bowel was made by Drs. Landsteiner and McDuff in late May 1954. The patient had great difficulty with circulation. The cardiac reserve was very low, and she expired May 29, 1954,

SERIES B: DETAILED HISTORIES

22 years after onset of the ovarian carcinoma, having remained completely free from disease from 1934 to 1951, following toxin therapy.

COMMENT: This case seems to indicate the danger of decreasing the frequency of injections too soon, even if marked or apparently complete regression occurs during the first weeks of treatment. It is apparently the only case in which such large doses were injected intra-abdominally, and the results suggest that this route may be most effective when dealing with intra-abdominal or intrathoracic neoplasms. It is possible that if toxin therapy had been administered for a year after recurrence developed in 1951, that the patient might have remained free from further evidence of disease or if they had been given aggressively prior to surgery in 1953 that the tumor mass might have been rendered operable, as was the case in 1933, and by resuming toxins after operation, a permanent result might have been obtained.

REFERENCES: 11; 16; 60a, 64 (Case 30, pp. 89-92).

SERIES C: OPERABLE OVARIAN CARCINOMA TREATED BY COLEY TOXINS AFTER SURGICAL REMOVAL: ONE CASE

Only one case of operable ovarian cancer was found in which toxins were given in order to prevent recurrence. The complete history of this case is given. Calkins consistently used Coley's toxins as a prophylactic after operation in all other types of malignant disease, as well as in his inoperable cases, following incomplete removal. He stated that this combination yielded an 80% five-year survival rate. For his inoperable cases, see above, Case 2 of the inoperable ovarian carcinoma series, and below, Case 8 of the inoperable ovarian sarcoma series.

DIAGNOSIS: Papillary adenocarcinoma of the ovary, involving the broad ligaments, confirmed by microscopic examination by Dr. A.A. Thibardeau, pathologist of the State Institute for the Study of Malignant Disease, Buffalo, New York.

PREVIOUS HISTORY: Mrs. V.E., female, aged 26, of Watertown, New York. The family history was non-contributory. The patient had pertussis at three, chicken pox at four, measles at six, mumps at eight, and a severe attack of pneumonia and influenza at the age of 15, which left her in a very nervous condition. She suffered from tonsillitis two or three times a year for five years until her tonsils were removed at the age of 11, after which she had no further throat trouble. She had suffered from dysmenorrhea for eight or nine years prior to 1925 and this gradually became worse. She was married in 1922, at the age of 24, but did not become pregnant. Onset, the patient began to feel badly about January 1925, seven months prior to consulting Dr. F.R. Calkins of Watertown, New York. She complained of a feeling of general lassitude and indisposition, had little appetite and gradually lost weight. A diagnosis of pregnancy had been made by two physicians, although the patient had menstruated at irregular intervals. Two weeks before consulting Calkins she noticed an enlargement of the abdomen. Physical examination in July 1925 showed a well-developed healthy-looking woman, except that there was a distinct pallor of the face. The abdomen was definitely distended, such as would be noted in a seven-months pregnancy. The abdomen was flat on percussion and not sensitive to palpation. Bimanual examination revealed a normal-feeling cervix, but most of the pelvis was filled with an unyielding tumor. A preliminary diagnosis of ovarian cyst was made.

SURGERY: On July 20, 1925, under general anesthesia, Calkins operated, finding a large cyst occupying the whole lower portion of the abdomen. It was freely movable and had no adhesions. It was tapped, but the fluid was so thick and there were so many sub-divisions of the tumor itself that it prevented complete emptying of the sac. The attachment of the tumor to the broad ligament was about 8 cm. thick, evidently undergoing malignant degeneration. There was evidence of chronic appendicitis. Sections taken from the cyst and from the stump of the

SERIES C: DETAILED HISTORY

broad ligament were examined by Thibardeau, as stated above. The patient made an excellent recovery from the operation, which included a right salpingo-oophorectomy and appendectomy.

TOXIN THERAPY (*Parke Davis XIII*): One week later the injections were begun by Calkins and were made daily for the first six months, and then, after an interval of three weeks, semi-weekly with occasional intervals of rest for about four months, a total duration of ten months. The patient stated that very good reactions occurred.

CLINICAL COURSE: There was no recurrence. Her previous painful menstruation increased greatly during the year following, and on August 2, 1926, Calkins performed a dilatation and curettage, inserting a spring pessary in the cervix. About two years later the patient became pregnant and at full term gave birth to a healthy daughter, May 13, 1928. The patient remained in excellent health and never had any recurrence. Her weight in 1951 was 195 pounds, her height 5 feet 7 inches. (She had been quite overweight in 1948, weighing 217 pounds.) In November 1952 she had an attack of pyelonephritis from which she recovered completely. In September 1957 she had Asian flu. Her only problems thereafter were a psychosis for which she was hospitalized in 1967, and in 1975 congestive heart failure. She was last traced on March 24, 1976, 51 years after onset. (11).

COMMENT: This case is an example of those in which DeWitt felt that the toxins could be of the greatest benefit. As regards the types of tumors and stages of the disease in which he felt that toxin therapy should be used, he stated: "In very advanced, inoperable cases, especially of cancer, it would appear to be useless. In cases of sarcoma not so far-advanced, but still inoperable, there should be a fair prospect of success. Even in some inoperable cases of carcinoma a trial should be made. It is, however, in cases of malignant disease in which the growth has been almost, though not entirely removed by the surgeon, with the object of eradicating the remainder, and of preventing recurrence, that we should look for the greatest benefit. It is my belief that should every patient from whom a malignant tumor has been removed be treated with the toxins . . . , recurrence would be much less frequent." (31) These conclusions appear to have proven correct, judging by an analysis of over 900 cases treated by toxin therapy made since DeWitt made these statements. In view of these findings, it is a pity that this method was very rarely used in operable cancer before operation, nor was it used, except by a few physicians such as Calkins and Dr. William B. Coley as a routine procedure following surgical removal.

REFERENCES: 10; 11; 16.

**SERIES D: INOPERABLE OVARIAN SARCOMA TREATED BY COLEY
TOXINS: 8 CASES
BRIEF ABSTRACTS**

The following eight cases are the only recorded cases of inoperable ovarian sarcoma to receive Coley toxins in which the diagnosis was confirmed microscopically. The first four cases received the Buxton preparation, Type VI, the last four Tracy's, Type X and XI.

- | | Years Traced
After Onset |
|--|-----------------------------|
| <p>1. ROBERTS: Aged 18, endothelial sarcoma of left ovary with many secondary nodes upon or beneath the peritoneum of adjacent viscera with ascites; date of onset not recorded; exploratory laparotomy; toxins begun May 4, 1896 soon after surgery, given in abdominal wall steadily for several weeks; <i>all growths completely disappeared</i>; no recurrence; patient later married; alive and well 1908. (16, 18, 19, 20, 78)</p> | 12 |
| <p>2. HARRIS: Aged 31, extensive recurrent large round cell sarcoma; onset, June 1897; uterus and appendages including large solid tumor of right ovary were removed; recurrent mass caused intestinal obstruction, intense tympanites; colostomy considered but deemed dangerous due to extreme distension; <i>immediate improvement</i> followed toxin injections, October 14, 1897; bowels moved, gas expelled; all injections given subcutaneously, very little reaction though dose increased to 40 minims; <i>tumor became black, necrotic</i>, fecal matter drained through laparotomy incision which reopened; toxemia developed from immense slough; patient weakened, died November 15, 1897. (18)</p> | 5 mos. (Died) |
| <p>3. PORTER: Aged 40; date of onset not given; recurrent round cell sarcoma left ovary; recurrence in pelvis followed surgical removal; toxins given 2 months (1902), <i>complete disappearance of growth</i>; in good health four years; another recurrence in same region; not controlled by further toxins; end-result unknown, probably death (24; 81)</p> | 5 |
| <p>4. COE & COLEY: Mrs. E., aged 26; inoperable perithelial hemangiosarcoma left ovary; onset November 1904; exploratory laparotomy, very cellular infiltrating nodular tumor of rapid growth and extreme vascularity; specimen removed, condition inoperable; general health deteriorating, losing weight; February 24, 1905; toxins: 47 in 3 months, also 22 x-ray treatments of 10 minutes each; general condition so poor that aggressive toxin therapy deemed inadvisable; June 12, 1905: <i>very slow decrease in size, marked increase in mobility</i>; second attempt at removal, right salpingo-oophorectomy; tumor size of child's head easily and rapidly removed (see complete history: microscopic examination showed marked degeneration); gained 28 pounds in 6 weeks; in perfect health; <i>no recurrence</i>; became pregnant</p> | |

SERIES D: BRIEF ABSTRACTS

Years Traced
After Onset

- 6 months later; normal child born; died suddenly pneumonia January 1907; no evidence further recurrence; possibility of pulmonary metastases rather than typical pneumonia? (15; 21; 24; 60a) over 2 (Died)
5. MUDD: Mrs. C.N.J., aged 30; inoperable recurrent sarcoma left ovary; onset 1906; primary growth 18 cm. in diameter removed surgically; rapid recurrence in abdominal wall, inoperable; toxins August 1, 1907; *complete disappearance, no further recurrence*, alive and well 1919 (11; 25; 99) 12
6. TOSIER: Aged 22; inoperable spindle cell sarcoma left ovary; onset November 1907; exploratory laparotomy December 1908: condition inoperable, prognosis regarded as hopeless; toxins December 1908 for about 6 months; *immediate improvement, complete disappearance*; had normal child autumn 1910; no recurrence or metastases; last traced in good health, 1912. (11; 23; 24; 42; 98) 5
7. COLEY: M.C., aged 16; large recurrent fibrosarcoma left ovary; onset 1909; primary growth weighing 6½ pounds removed at first operation December 1909; recurrence in 5 months; February 1911 exploratory laparotomy revealed large retroperitoneal recurrent mass filling entire pelvis, abdomen; patient cachectic; March 7, 1911: toxins for 5 weeks; *immediate regression, entire disappearance in 2 months*; toxemia from absorption necrotic tumor tissue; developed symptoms diffuse pain all over body, especially in joints, right shoulder, elbows, and left leg, also very constipated; very weak, 36 pound weight loss; 9 more injections given (small doses, no reactions); *some temporary improvement*; death September 28, 1911. (24; 60a) 2 (Died)
8. CALKINS: Mrs. M.M., aged 26; large degenerated mixed cell sarcoma right ovary, double hydrosalpinx; degenerated dermoid cyst left ovary; large cauliflower masses between tumor, cecum, sigmoid flexure and rectum; appendix size of large cucumber; onset September 1919; bilateral salpingo-oophorectomy, panhysterectomy, appendectomy January 29, 1920; complete removal of growths involving intestines impossible; 1 week later toxins begun, given steadily for a year; *complete disappearance remains of growths*; no recurrence or metastases; alive and in excellent health 1927, eight years after onset, not traced thereafter. (10; 11) 8

**SERIES D: INOPERABLE OVARIAN SARCOMA TREATED BY COLEY
TOXINS: 8 CASES
DETAILED HISTORIES**

CASE 1: Inoperable endothelial sarcoma of the ovary, with many secondary nodes in the adjacent viscera, confirmed by microscopic examination following exploratory laparotomy by Dr. Horace Packard of Boston.

PREVIOUS HISTORY: The patient, aged 18, unmarried, was referred to Packard by Dr. O.W. Roberts of Springfield, Massachusetts, for treatment of an abdominal tumor. Vaginal examination revealed an indistinct irregular mass palpable in the left side. The abdominal enlargement was apparently caused by accumulation of ascitic fluid.

SURGERY: Abdominal section disclosed a small nodular tumor, apparently originating in the left ovary, with many secondary nodes scattered upon or beneath the peritoneum of the adjacent viscera.

TOXIN THERAPY (Buxton VI): The patient was sent home immediately after recovering from the effects of the laparotomy and Roberts began the toxin injections, giving them into the abdominal wall. The first effect was a reaction in the wound, which had healed by first intention. It assumed a livid color, which subsided, however, when injections were suspended (Shwartzman phenomenon). After a few days the toxins were resumed and continued faithfully for several weeks, with ultimate full recovery. The growths regressed completely.

CLINICAL COURSE: The patient resumed her school work, completed her training, and married. There was no recurrence when she was last traced in 1908, 12 years after toxin therapy was begun.

REFERENCES: 16, 18, 19, 20, 78.

CASE 2: Inoperable recurrent large round cell sarcoma of the ovary, confirmed by microscopic examination.

PREVIOUS HISTORY: Aged 31, unmarried. The family history was noncontributory. Onset, in June 1897, the patient first noticed discomfort and slight pain in the front of the lower abdomen. Four weeks later the family physician discovered a tumor in the lower part of the abdomen. It grew rapidly and caused disturbance of the bowel. Examination on September 18, 1897, showed the general condition was fair, the heart and lungs normal. There was an abdominal tumor arising from the pelvis extending midway from the symphysis pubis to the umbilicus, lying

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somewhat more to the right side. The growth was movable, but not freely so.

SURGERY: A median celiotomy was performed on September 22, 1897. A large solid tumor was found originating from the right ovary, adherent to the uterus, rectum and pelvic wall. The uterus and appendages were removed with the tumor. Gauze packing was necessary to arrest hemorrhage.

CLINICAL COURSE: The patient recovered from the operation, but by October 11, 1897, she had difficulty in moving her bowels. Rectal examination showed a recurrent mass in the posterior part of the pelvis, pressing down upon and involving the anterior wall of the rectum. On October 13, 1897 tympanites became intense. The rectum higher up was virtually occluded by pressure of the rapidly growing mass. Colostomy was considered but deemed dangerous, due to extreme distension. No gas was passed per rectum. It was decided to try the Coley toxins.

TOXIN THERAPY (Buxton VI): The first injection was made subcutaneously into the arm by Dr. Harris at 4:30 p.m. on October 14, 1897. There was no apparent reaction, but early the following morning the patient expelled some gas with some fecal matter. At 10:30 a.m. that day, 2 minims were injected into the arm, with no reaction. The same afternoon, 5 minims were given, causing a mild febrile reaction. The bowels moved and considerable gas was expelled. The patient rested comfortably. On October 16, 1897 at 11:00 p.m., 10 minims were administered, producing a febrile reaction of 100° F. The bowels moved several times and gas was freely expelled. Tympanites practically disappeared. On October 18, 1897 the lower angle of the abdominal wound reopened so that the tumor could be seen. It was found to be the size of an average coconut. Injections were continued daily, increasing the dose to 40 minims. They were all given subcutaneously, in the arm or the sides of the body, remote from the tumor. Very little reaction followed the injections, except on one occasion, on October 26, 1897 when after a dose of 24 minims there was a chill and a temperature of 103° F. By October 31, the bowels moved freely, almost naturally, and the patient was able to sit up in bed, eating fairly well.

CLINICAL COURSE: On November 6, 1897 it was noticed that the tumor had become black and was sloughing, fecal matter coming through the wound. Two days later there was a bloody, watery discharge. The patient began to show signs of septic absorption from the immense slough, which involved the entire mass and opened into the rectum. She grew weaker and died on November 15, 1897.

COMMENT: It is important to note that this is one of the few cases in whom only subcutaneous injections were used, remote from the tumor. These caused no marked febrile reactions, even though massive doses were given. A comparison with other cases of large abdominal tumors indicates that if some injections are

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given into the growth or its immediate periphery, combined with intravenous injections, in doses sufficient to produce febrile reactions of 103° to 105° F. and chills, much more rapid regression occurs. Spontaneous discharge of necrotic tumor tissue often develops through the site of intratumoral injection. It may be necessary to establish surgical drainage in some cases to avoid absorption of large quantities of necrotic tumor tissue which may cause toxemia.

REFERENCES: 18

CASE 3: Inoperable round cell sarcoma of the left ovary, recurrent in the pelvis, confirmed by microscopic examination.

PREVIOUS HISTORY: Aged 40. The previous history was not recorded.

TOXIN THERAPY: Injections were begun when the condition was entirely inoperable. They were continued for two months, with the result that the growth entirely disappeared.

CLINICAL COURSE: The patient remained in good health for four years when another recurrence developed in the same region which could no longer be controlled by the toxins. (The preparation and technique used during this second course of toxin therapy are not known.)

COMMENT: Porter used an unknown preparation of erysipelas and *Bacillus prodigiosus* toxins on a group of far-advanced cases of cancer (not ovarian) in 1897, without producing any apparent cures. However, he stated that at that time, in spite of these preliminary failures, he "felt constrained to advise the method in all cases of inoperable malignant tumors and after complete removal." He noted that it may be commenced immediately after (operation) . . . "

REFERENCES: 24; 81.

CASE 4: Inoperable perithelial hemangiosarcoma of the ovary, confirmed by microscopic examination by the pathologist of the Government laboratory in Manila, Philippine Islands, in November 1904, who reported: "an apparently rapidly growing and infiltrating, very cellular growth of probably perithelial origin." Following toxin therapy for 3½ months, the remains of the growth were excised and Drs. Martha Tracy and James Ewing examined it and reported: "The tumor is very much degenerated, the contents being of almost puriform consistence. Therefore, it

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was difficult to fix and stain. Dr. Ewing is unwilling to say whether it is a sarcoma, an endothelioma or carcinoma, though of its malignancy there is no doubt." The report of a less degenerated portion of the tumor by Dr. William Clark, pathologist at Memorial Hospital, was "round cell sarcoma of the ovary."

PREVIOUS HISTORY: Mrs. E., aged 26, American born, living in Manila. Onset, early in November 1904, the patient consulted Dr. Bailey of the U.S. Army Medical Corps in Manila. He treated her for a supposed inflammation of the left ovary. When a tumor became apparent he referred her to Dr. Stafford for operation. The latter reported: "Examination revealed a large immovable mass filling the pelvis. The uterus was crowded down almost to the external genitals. There was considerable tenderness of the lower abdomen, which did not permit of much palpation, and the abdominal muscles were rigid.

SURGERY: Upon becoming anesthetized for operation, the abdominal muscles relaxed, and the tumor was seen to have grown up to and a little above the umbilicus on the right side. Upon opening the abdomen, the mesentery was found to be adherent to the outer surface of the tumor. This was dissected free and a portion incised; the tumor was seen to be nodular in character, of a dark bluish white color, and upon passing the hand down its anterior surface to the pelvis, the greater portion was found adherent. Upon pulling the tumor forward enormous blood vessels were seen, covering the back of it and springing from and above the posterior brim of the pelvis. "From the general appearance, its rapid growth, and extreme vascularity, we decided it was a malignant growth, probably sarcomatous. On endeavoring to free the tumor from the blood vessels, we found it was not adherent, but it was growing apparently from the whole of the pelvic wall, and it bled so profusely that we deemed it wiser to abandon further interference, particularly as her husband desired her to reach home to see her parents before dying. . . . A portion of the tumor was tied off and excised and sent to the government laboratory." The patient was sent back to the United States and entered Memorial Hospital on February 30, 1905. Her general health was steadily deteriorating and she was losing weight. As the tumor was firmly fixed and clearly inoperable Dr. H.C. Coe referred the case to Dr. William B. Coley for toxins.

TOXIN THERAPY (Buxton VI) COMBINED WITH RADIATION: The first injection of 0.5 minim was made on February 24, 1905, into the abdominal wall by Coley. Injections were continued three or four times a week, in gradually increasing doses to the point of producing a moderate reaction, a temperature of 101° to 102° F. The patient's general condition was so poor that Coley could not administer large doses, and often a temperature of 102° F. was followed by a good deal of depression. The highest dose reached was seven minims, the highest temperature 104.8° F., which occurred on March 30, 1905 after a dose of six minims. Most of

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the reactions were much less severe, the temperature usually not rising beyond 101° F. She received 47 injections in 14 weeks. She was also given 22 x-ray treatments of an average duration of 10 minutes each. There was a very slow diminution in the size of the tumor during this combined treatment, and marked increase in its mobility. Her general condition showed no improvement; in fact it seemed there was slight deterioration, due apparently to toxemia from absorption of necrotic tumor tissue. Coley believed her condition would not permit giving large enough doses to produce complete absorption of the tumor, and in view of the marked increase in mobility, it was decided, after careful examination, that there was a possibility of removing the tumor by operation.

FURTHER SURGERY: On June 12, 1905, a right salpingo-oophorectomy was performed by Coe, assisted by Coley. A tumor the size of a child's head was found, originating in the right ovary, markedly pedunculated and almost entirely free from adhesions. No metastases were found in other organs. The pedicle was tied off and the tumor was easily and rapidly removed, the entire operation taking not more than 15 minutes. Coley stated that the effects of the toxins upon the tumor were most remarkable as shown by the pathological reports of Ewing and Tracy.

CLINICAL COURSE: The patient made an uninterrupted recovery from the operation, gained 28 pounds in weight during the next six weeks, and returned to her home in perfect health. Within the next six months she became pregnant, and gave birth to a healthy child in the summer of 1906. She remained well up to the latter part of January 1907, when she contracted what was believed to be pneumonia and died within a few days. Her family physician, Dr. D.L. Moore, wrote Coley in December 1907 that there was no recurrence of the sarcoma to be found on examination at this time. However, a later communication indicated that there seemed a possibility that there might have been metastasis in the lung, instead of a typical pneumonia.

Coley stated that the case was interesting from several standpoints: "First because sarcoma of the ovary is an extremely malignant neoplasm. We have never yet seen a case cured by operation. Second, because the tumor, though clearly absolutely inoperable at the start, became operable by the preliminary treatment with the toxins, possibly assisted by the x-rays, although we have never had an abdominal sarcoma show much improvement from the x-rays alone . . ." (15)

COMMENT: This case may be compared with those cases of sarcoma of the ovary in which the toxins alone, without radiation or subsequent operation, produced permanent results. The microscopic and macroscopic changes produced in the tumor are of interest and may indicate the need of establishing surgical drainage to evacuate some of the degenerated tumor tissue in such cases, in order to hasten the ultimate recovery and prevent the development of toxemia and cachexia due to the absorption of large amounts of such tissue. That absorption of necrotic

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tumor tissue and regeneration of the normal tissues are inhibited by radiation may account for the apparently greater toxemia noted in cases in which both toxins and radiation are used.

REFERENCES: 15; 21; 24; 60.

CASE 5: Recurrent sarcoma of the left ovary, confirmed by microscopic examination by Dr. Malvern B. Clopton, pathologist.

PREVIOUS HISTORY: The patient, aged 30, had suffered for years with profuse menstrual periods which were irregular and too frequent.

SURGERY: A curettage was performed on November 13, 1906, with thorough examination under anesthesia. The uterus was found in good position and was not especially large. Behind the uterus in the hollow of the sacrum there was a mass as large as a lemon which felt rather hard, somewhat nodular, but was freely movable. This mass could be pushed up out of the cul-de-sac, and would fall in front of the uterus, pressing on the bladder. The patient was informed there was a solid tumor in the ovary, which should be removed by operation. Consent was not given until July 18, 1907, eight months later. The operation was performed by Dr. Harvey J. Mudd of St. Louis, Missouri. The incision was made in the median line, exposing a dark, congested tumor which looked almost gangrenous. It was 13 cm. in diameter. Adhesions were freed and there was a flow of dark serous fluid. The tumor was attached to the left ovary with rather a long pedicle. The appendix was also removed. Before the abdominal wound had healed a recurrent mass appeared in the abdominal wall.

TOXIN THERAPY (*Tracy's X*): Injections were begun by Mudd in July 1907 and under continued treatment the tumor disappeared. Details of administration in this case were not recorded, but at this time Coley was advocating intratumoral alternating with intramuscular injections and larger initial doses than in later years. The recurrent mass regressed completely.

CLINICAL COURSE: The patient remained free from any evidence of further recurrence. On May 19, 1915, she was seized with severe cramping pains in the abdomen, and two days later showed evidences of marked obstruction.

SURGERY: An operation was performed under ether, the incision being made a little to the left of the median line. On opening the abdomen a large quantity of dark blood-stained fluid escaped. There presented at the opening a large coil of very dark, much distended small intestine. The nature of the obstruction could not be made out readily. The coil of intestine was delivered through the wound. At the base was a narrow band which constricted the coil so tightly that it was

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almost gangrenous. This band was cut and was found to be the right Fallopian tube wrapped tightly about the gut with adhesions at the end of the tube.

CLINICAL COURSE: The patient made a good recovery and remained well when last traced in June 1919, 12 years after treatment, at which time Mudd cited the case in discussing Coley's paper before the American Surgical Association. He stated: "I report this as merely one more cure of a frightfully malignant condition by Coley's toxins."

COMMENT: It is known that Mudd continued using the toxins in many other cases through 1919, possibly later, but this seems to be the only case of ovarian cancer he treated.

REFERENCES: 11; 25; 99.

CASE 6: Inoperable spindle cell sarcoma of the left ovary, involving the broad ligament, uterus and intestine, conformed by microscopic examination following exploratory laparotomy at the Lewiston City Hospital, Lewiston, Maine. The pathologist reported: "On preparing the patient for operation the condition was found to be so complicated that the surgeon decided to postpone the operation until a microscopic examination could be made of a section of the growth: at the time of the operation they removed only a small piece for me to examine; they were afraid of hemorrhage. The tissue I examined in frozen section, while still on the table, gave a diagnosis of spindle cell sarcoma."

PREVIOUS HISTORY: Female, aged 22, married. The patient's father had died of "inflammation of the bowels", her mother of "general debility, due to frequent childbirth." The patient had always enjoyed very good health until onset. She had had one child. Onset began about November 1907 with a sensation of weight in the pelvis. Although her menstrual periods came at regular intervals, she believed she was again pregnant. A year after onset she consulted Dr. F.L. Tosier, of Washburn, Maine. A small soft boggy growth about the size of a cup was found in the region of the left ovary, which he believed represented a diseased ovary. He kept the patient under observation for three months. By this time the growth had become considerably larger and harder. It was attached to the left broad ligament and uterus and easily movable with the finger in the vagina or rectum. The growth caused much pain and operation was advised.

SURGERY: She was admitted to the Lewiston City Hospital in December 1908, where a biopsy was performed as stated above. Because of the extensive involve-

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ment and fear of hemorrhage, no attempt at removal was made, and after taking a section for biopsy the incision was closed and the patient was sent home to die.

TOXIN THERAPY (*Tracy XI*): Injections were begun by Tosier on her return home in December 1908. The initial dose was 0.5 minim diluted in 10 minims of sterile water, apparently given intramuscularly. This caused chills and a febrile reaction of 103° F., a pulse of 100 to 120. Febrile reactions of 100° to 103° F. occurred following the daily injections and became more pronounced when the dose was increased too rapidly. The first three days 0.5 minim was given, then 1 minim for three days and thereafter the dose was gradually increased as the tolerance of the patient increased, until finally 8 to 10 minims were given. The tumor entirely disappeared. At first the discharge from the laparotomy wound was more like pus, and gradually it became more serous in character, then it soon ceased.

CLINICAL COURSE: Seven months later the patient had gained 60 pounds, her periods were regular and normal, and there was no evidence of further disease. In the autumn of 1910, about a year after the toxins were stopped, she gave birth to a second child. She remained in good health when last traced, over five years after onset.

REFERENCES: 11, 23, 24, 42, 98.

CASE 7: Recurrent inoperable fibrosarcoma of the ovary, confirmed by microscopic examination after oophorectomy.

PREVIOUS HISTORY: M.C., aged 16, of New York City. The family history was non-contributory. The patient had had scarlet fever at the age of six, but had otherwise been well prior to onset. Menses began at 13, and were always regular. In 1909 she fell downstairs, striking her abdomen against the bannisters. Onset, two months later she "noticed a lump" in the abdomen which gradually increased in size during the next year.

SURGERY: It was removed in December 1909, by Dr. Blaslucci, who found a large tumor weighing 6½ pounds involving the left ovary.

CLINICAL COURSE: The patient remained well about five months and then in June 1910, she felt a sharp pain in the left side and found a recurrent lump there. She stated that this "came and went with dieting". At this time a thick yellowish vaginal discharge developed which persisted.

FURTHER SURGERY: A second operation was performed at the same hospital by Dr. Robert T. Morris on February 28, 1911. Morris stated that a large retroperitoneal tumor was found filling up the entire pelvis and lower abdomen. It was entirely

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inoperable, and the wound was closed without attempting to remove the growth. The patient's general condition at this time was bad, she had lost much weight and was cachectic. She was seen in consultation by Dr. William B. Coley on March 7, 1911. He advised the toxins.

TOXIN THERAPY (*Tracy XI*): Injections were begun by Coley one week after this operation, on March 7, 1911, and were administered at first by the family physician. (The technique used as regards site, dosage and frequency is not recorded.) The patient appeared to be very susceptible to the toxins, and severe chills, following rather small doses, occurred. Shortly after the treatment was begun a decrease in the size of the tumor was noted. The injections were suspended on April 10, 1911. On May 2, 1911, although the patient had had no injections for three weeks, palpation revealed that no trace of the tumor remained. She had been running an irregular temperature for two weeks ranging up to 102° or 103° F., but this had gradually fallen to normal. Her appetite was poor and she was slightly anemic. (The continued temperature was apparently due to toxemia from absorption of considerable quantities of necrotic tumor tissue.) The patient returned home and the injections were continued for a week or two, partly by the patient's family physician and partly by her sister.

CLINICAL COURSE: On June 2, 1911, the patient was admitted to Memorial Hospital, stating that during the last few weeks she had diffuse pain all over her body, especially in the joints, the right shoulder, the elbows and the left leg. At this time she was very constipated, requiring an enema every day. She was weak, being scarcely able to walk, and had lost 36 pounds in weight. A blood count showed R.B.C. 3,600,000, hemoglobin, 80%.

FURTHER TOXIN THERAPY: The injections were resumed by Coley on June 7, 1911, and during the next 21 days nine were given intramuscularly in the gluteal region in doses of 1 to 4 minims, causing no reactions. The patient was discharged on July 8, 1911, somewhat improved.

CLINICAL COURSE: The disease was not controlled. Death occurred on September 28, 1911, about two years after onset.

COMMENT: It appears that the toxins may have been given a little too aggressively in the first few weeks, causing such rapid destruction of the growth that toxemia developed from absorption of large quantities of necrotic tumor tissue, which might have been prevented if free drainage had been established through the wound, and carefully maintained. The above case also indicates that when treating far advanced, recurrent growths, it is necessary to continue the injections for some time after all evidence of the tumor has disappeared, in order to prevent recurrence or metastases, rather than give them so briefly.

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REFERENCES: 24;60a.

CASE 8: Mixed cell sarcoma of the ovaries with extensive involvement of the intestines and pelvis, confirmed by microscopic examination after operation. Sections from numerous portions of the intestines and the tumor were examined.

PREVIOUS HISTORY: Mrs. M.M., aged 26. The family and previous personal history were not recorded. The patient consulted Dr. F.R. Calkins of Watertown, New York, in January 1920, for a large painless growth in the abdomen, of about five months duration, which had been diagnosed as a pregnancy. The patient was a strong, healthy young woman, who had been married for four years, but who had not been pregnant. On examination Calkins found a large, firm mass filling the entire pelvis, and extending up for a distance of about 8 cm. above the umbilicus.

SURGERY: On January 29, 1920, under ether anesthesia, Calkins operated through a lower median incision. A large degenerated tumor of the right ovary was found, as well as a double hydrosalpinx also undergoing degeneration and a degenerated dermoid cyst of the left ovary about the size of an orange. An attempt to reduce the size of the ovarian cyst by aspiration was unsuccessful, and the incision had to be enlarged to 8 cm. above the umbilicus. Large masses of cauliflower growth were encountered between the tumor, the cecum, the sigmoid flexure and the rectum. The appendix had taken on this new growth, and was nearly as large as a good-sized cucumber. A bilateral salpingo-oophorectomy, panhysterectomy and appendectomy were performed, but it was impossible to remove all the extensions of new-formed growth attached to the intestines. The patient made a good recovery from the operation.

TOXIN THERAPY (*Tracy XI*): One week later the injections were begun by Calkins and were given daily for the first six months, and after that semi-weekly with occasional intervals of rest for six months longer.

CLINICAL COURSE: The remains of the growth disappeared, and there was no recurrence or metastases. In 1927, eight years after onset, Calkins examined the patient and found her to be the picture of health, working every day. She was not traced subsequently.

REFERENCES: 10; 16.

**SERIES E: INOPERABLE CARCINOMA OF THE CERVIX OR
ENDOMETRIUM TREATED BY COLEY'S TOXINS: 6 CASES
BRIEF ABSTRACTS**

The following six cases are the only known cases of inoperable carcinoma of the cervix treated by Coley toxins with microscopic confirmation of diagnosis. The first two received the Buxton preparations (V and VI), the third Tracy XI and XI F, the others the Johnston XV preparation.

- | | Years Traced
After Onset |
|---|-----------------------------|
| <p>1. STONE: Mrs. L.B., aged 42; onset, May 1895 extensive inoperable epithelioma of cervix, infiltrating broad ligaments; severe uterine hemorrhages, condition very grave; curettage, cautery, November 13, 1895; toxins December 4, 1895; no effects from i.m. injections in scapular region; <i>same large dose injected into outer vagina caused very severe reactions, cessation of hemorrhages and pain, complete disappearance of extensive growth</i>; normal menses April 19, 1896; gained 25 pounds, good color, appetite, vigorous, slept well; remained in very good health 2½ years, then local recurrence, no further toxins, death 6 months later. (24; 90)</p> | 4 (Died) |
| <p>2. GRUVER & SHULL: Mrs. R.G., aged 49; onset 1890; inoperable carcinoma of cervix, extensive metastases small and large intestines, of rapid growth, prognosis grave; nausea, emesis; first operation May 1895; exploratory July 1899, specimen removed; August 1899: toxins given steadily deeply into metastatic masses and i.m.; growth ceased; <i>after 4 weeks regression noted; complete disappearance all evidence of disease; no further metastases</i>; toxins continued 3 years; remained in excellent health; died cardiac congestion, sudden pneumonia at almost 80, January 7, 1929. (11; 16; 23; 24; 64, case 5)</p> | 39 |
| <p>3. GREENLEAF: Mrs. S.P.B., aged 64; onset early spring 1913; inoperable recurrent carcinoma cervix uteri involving entire surface of vagina, also rectum and bladder; recurrence developed following radium therapy, with rectovaginal and vesicovaginal fistulae, marked cachexia, much loss of weight; June 5, 1914: toxins daily with rest periods for 8 months; marked reactions, chills; <i>complete disappearance; regained normal health</i>; died suddenly Christmas 1916, heart condition, no evidence cancer. (11; 16; 99)</p> | 4 |
| <p>4. RICKS: Mrs. E.M., aged 46; onset 1958; inoperable adenocarcinoma of cervix, with metastases involving the pelvis and left hip, left kidney and abdomen, with large inguinal lymph nodes, especially on left side; 32 x-ray; thrombophlebitis of left leg, pain in abdomen, back, pelvis, left groin and leg; becoming progressively worse 1962, morphine addiction; October 10, 1962: toxins intradermally 4 a week for 4 weeks; <i>bone pain</i></p> | |

SERIES E: BRIEF ABSTRACTS

Years Traced
After Onset

decreased 24 hours after first dose; able to walk in a week, no further medication for pain after four weeks; considered herself cured, returned to work; disease reactivated 1963, death September 6, 1963, due to metastases in lungs, bone, fibrous pelvic tissue (autopsy). (11)

5 (Died)

5. JOHNSTON: A.M., aged 68; inoperable carcinoma of cervix with diffuse pelvic involvement, constant bleeding; onset one year prior to toxin treatment; biopsy only; Johnston XV toxins: 81 i.v. in 25 weeks; *no change in symptoms or state of lesions*; died 6 months after toxins were stopped. (48)

18 mos.

6. JOHNSTON: R.C., aged 75; inoperable metastatic adenocarcinoma of the cervix, stage IV; date of onset unknown; hysterectomy; superclavicular nodes were positive when toxins were begun; 22 i.v., 8 i.m. in 8 weeks; *progressive weight loss, no improvement*; died 6 months after toxins were stopped. (48)

? Over a year

NOTE: In the following case there is no detail as to whether the metastasis was examined histologically, nor exactly how long the patient was followed.

MATAGNE: Mrs. V.S., aged 34; metastatic carcinoma of the uterus; hysterectomy 1909, subsequently developed metastasis in left leg; Buxton type (as made by Matagne in Belgium) i.t. and subcut.; *complete regression*; reported as a cure in 1953. (57; 58)

Several

NOTE: Four terminal cases of uterine or cervical cancer are known to have received Coley toxins (probably Buxton product) in 1894-1895. Three were treated by DeWitt and one by Kreider. No details are available as to technique used, or whether diagnosis was confirmed microscopically, so they could not be included for statistical study. DeWitt stated that his very far-advanced recurrent cases were apparently not benefited by the treatment, but that the case of carcinoma of the cervix *was* benefited. The fourth terminal case treated by Coley's toxins was that of Kreider, but little detail was found except that the patient was bedridden, with edema of the right leg and foot. The swelling, pain and bleeding all disappeared entirely in three weeks, and had not returned when Kreider reported the case to Coley. (11; 31)

**SERIES E: INOPERABLE CARCINOMA OF THE CERVIX OR
ENDOMETRIUM TREATED BY COLEY'S TOXINS: 6 CASES
DETAILED HISTORIES**

CASE 1: This case was first diagnosed as a spindle cell sarcoma of the cervix uteri, after microscopical examination of a considerable number of sections by Dr. W.R. Lavender, Professor of Pathology of the Omaha Medical College. The latter reported: "There were distinct groups of round cells with very large nuclei without connective tissue between the cells and small spaces in which were found red blood corpuscles, the walls of these spaces being formed by cells. . . . There was hyperplasia of the uterine follicles at the junction of the cervix with the body of the uterus, but a decided absence of the characteristic invasion of normal tissues usually found in epithelioma." Sections were then examined by Dr. Bertram H. Buxton, of the Loomis Laboratory, Cornell University, and by Dr. E.K. Dunham, Professor of Pathology at Bellevue Hospital, who both stated that the growth was of epithelial origin. It was finally diagnosed as an epithelioma."

PREVIOUS HISTORY: Mrs. L.B., aged 42, of Omaha, Nebraska. The patient was a vigorous woman, of excellent family history, the mother of five children, the youngest of whom was three years old. Onset, in May 1895, she began to have profuse and persistent bleeding from the uterus, but she was not examined by Dr. R.M. Stone until six months after the abnormal flow had begun. At this time she had lost 15 pounds in weight and was very anemic. Examination showed that the cervix was very much enlarged, its inner surface eroded, bleeding easily and open sufficiently to admit the tip of the index finger. The uterus was large and heavy, and there was infiltration of the broad ligament. Stone's clinical diagnosis of malignancy was confirmed by Dr. Charles C. Allison, Professor of Genito-urinary Surgery at Omaha Medical College.

SURGERY: On November 13, 1895, Allison operated. Curettage was done thoroughly and a large portion of the uterine tissue, which was found to be soft and friable, was removed together with the anterior lip of the cervix. Cautery and chloride of zinc were necessary to control the profuse hemorrhage.

CLINICAL COURSE: Recovery was uneventful for 10 days, when there followed a period of 16 days during which there were five almost fatal hemorrhages. The patient's life was despaired of, and her exhaustion profound. The bleeding was only controlled by forcible packing with rolls of absorbent cotton completely filling the vagina. The packing was continued to prevent possible further he-

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morrhages and to allay the patient's nervous tension and fear of further bleeding. Bovinine was the sole nourishment at this time, and the patient's temperature ranged from 100° to 102.5° F. On November 30, 1895, Jonas saw her in consultation. At this time there was decided infiltration of both broad ligaments and no possibility of removing the uterus. The condition was completely inoperable and the prognosis was regarded as very grave.

TOXIN THERAPY (Buxton VI): Injections were begun by Stone, December 4, 1895. The initial dose of 3 minims was injected between the scapulae, and no reaction followed. The dose was increased rapidly, and injections were continued daily during the next 16 days, the maximum dose being 17 minims. All of these injections were given intramuscularly in the scapular region and none of them produced reactions. The temperature never rose above 100° F. Nevertheless, the patient's general condition improved, her appetite increased, and she soon slept very much better. The discharge from the uterus was very free at this time and of an offensive odor.

Because no reaction had been produced by injections into the shoulder muscles, Stone decided to go closer to the seat of the disease. However, Coley had apparently not warned him that it was necessary to reduce the dosage for local injections, and so on December 21, 1895, Stone injected 19 minims into the outer vagina. Twenty minutes later a rigor set in, and the temperature soon rose to 101° F. The face became dark purple, the patient delirious, restless and pulseless. Breathing became anxious and labored, and exhaustion profound. Total deafness developed, and suppression of urine. At noon the temperature was 104.5° F. and death seemed imminent. The patient was given stimulants, hypodermic injections of morphine and strychnine. Bovinine was also freely administered. By 12:30 the temperature was down to 103.5° F. At 1 p.m. the pulse was 120 and barely perceptible. The deafness lasted six hours. The patient was nauseated and vomited all afternoon. By 6:30 that evening the temperature had fallen to 100° F. Three days later there appeared a violent herpes on the lips and tongue, absolutely preventing the patient from taking nourishment for two days, and causing very great distress for a week. Sleep was restless and fitful. Intense redness of the face, vertigo and headache were present for 13 days following this injection, apparently due to involvement of the semicircular canals. The patient rallied very slowly from the severe depression of this reaction and for this reason no injections were made until January 2, 1896, an interval of 13 days, when 3 minims was given. On January 5, 6 minims caused a febrile reaction of 102.5° F. and a pulse of 120. Further injections were given on January 10, 13, 14, and 15, 1896, in doses from 2 to 4 minims.

At Coley's suggestion the filtered toxins were used for a time (Buxton V). During the next 44 days, 27 injections were administered in doses ranging from 3 to 23 minims. There were nine chills and the febrile reactions ranged from

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99.5° to 103° F. After a week's rest, the injections of the filtrate were resumed, and made daily until March 24, 1896 in doses of 5 to 30 minims. These were given intramuscularly in the gluteal region, and no reactions resulted except for malaise.

After a rest period of two weeks Stone resumed the injections, using the more potent unfiltered preparation (Buxton VI). Five injections in the gluteal region in doses up to 10 minims produced no reactions other than blueness of the finger nails. On March 11, 1896, the patient insisted that the injections again be made in the vaginal wall. Accordingly, 2 minims were given that day and 5 minims on March 22 without reactions. However, 7 minims injected into the vagina on March 25 caused a severe reaction. Two hours later there was intense headache and delirium, pronounced cyanosis, and very severe pain in the thighs and in a small spot under each breast. There was also diarrhea and vomiting. At 3 p.m., five hours after the injection, Stone found her pulseless and anxious, but clear mentally. The skin was less cyanotic, but was dusky red all over the body. The temperature was 102° F. Herpes labialis appeared the next day.

EFFECTS PRODUCED BY THE TOXINS: During the period between December 4 and 21, 1895, the general condition gradually improved, and the uterine discharge was pronounced and copious, although no fever or chill was produced in this period. By January 21, 1896 the uterine discharge had almost ceased, and Allison and Stone could find no nodules in either of the broad ligaments; granulation tissue was fast disappearing from the amputated cervix. Two days later the patient sat up for the first time, and on February 1, 1896 she walked with support. By February 20, 1896 she was walking up and down stairs.

CLINICAL COURSE: On May 4, 1896, Allison and Stone made a careful examination and were unable to discover any infiltration in either of the broad ligaments. The uterus was very much atrophied and the site of the cervical amputation was clean and entirely healed over. The atrophy of the uterus had been noted in late January and had caused Allison to believe that there would probably be no further menstruation, but on March 5 to 9 and 28 to 31, 1896, there was a show of blood. From April 17 to 22 there was normal menstruation, also from May 16 to 18, 1896. Stone reported on October 21, 1896, that the patient had gained 25 pounds in weight, was rosy, vigorous, ate and slept well, and had neither pelvic pain, tenderness nor dyspareunia. She had resumed all her household duties, and her muscles were hard and her spirits high. The patient remained in good health in June 1898, 2½ years after treatment, with no evidence of recurrence. However, six months later she developed a local recurrence which proved fatal, approximately four years after onset. Further toxins were apparently not administered.

COMMENT: This case emphasizes the following points: 1. The importance of the site of injection as regards the severity of reaction produced. 2. The need of

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teaching those who administer the toxins the importance of the technique of administration, and the dangers of using too large a dose when injecting in or near the tumor in a vascular area of the body. These extremely severe reactions are exhausting and dangerous, and treatment must be suspended until the patient recovers. Most patients would not have the courage to resume treatment following such an experience. 3. The need for continuing the injections for a longer period in such advanced cases, in order to prevent recurrence. Few physicians realized that when recurrence did develop, the disease could again be controlled and a permanent result obtained if the toxins were resumed and given aggressively and steadily for a considerable period.

REFERENCES: 24; 90.

CASE 2: Inoperable carcinoma of the cervix, with metastases in the small and large intestines, confirmed by microscopic examination by Dr. James Ewing of a specimen removed by Dr. Charles Thompson of Scranton, Pa.

PREVIOUS HISTORY: Mrs. R.G., aged 49 (in 1899), of Stroudsburg, Pa. The patient had 10 siblings, three of whom had died in infancy. One sister died of cancer of the intestines at the age of 45, another of carcinoma of the esophagus at 65, another of carcinoma of the breast with metastases at 73, one brother of carcinoma of the stomach at around 44 or 46, and the maternal grandmother of cancer of the uterus at 43 years. The family history was negative for tuberculosis, diabetes, arteriosclerosis or allergies. The patient's previous personal history was non-contributory except for the usual diseases of childhood. Menses began at 18. She was married at 24 and had three children. Onset, at the age of 41 she began to have intense pain in the lower abdomen at intervals of every two days to a week, with much nausea, vomiting and headache. This continued for two years, the symptoms increasing in severity. A diagnosis of malignancy of the cervix was made, and the patient was admitted to New York Hospital, on May 9, 1893. Physical examination at this time showed tenderness on pressure over the left side of the abdomen. The cervix was very hard and the external os was surrounded by a ring of hard nodules.

SURGERY: Dr. William T. Bull operated, removing a growth about 7 cm. in diameter, together with the cervix. A specimen of this growth was reported as "normal cervical tissue". The patient was discharged May 20, 1893.

CLINICAL COURSE: She made a good recovery and remained in good health. During this time menstruation practically ceased, or was irregular, occurring at long intervals. Three years later the abdominal symptoms recurred, with occasional bloody discharge from the uterus. This continued for three years and by

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1899 "there was much nausea, retching and even vomiting of feces," occurring intermittently at intervals of about a week.

FURTHER SURGERY: An exploratory laparotomy was performed by Thompson of Scranton, and a specimen removed and sent to Ewing, who reported it to be carcinoma. The mass in the right lower quadrant was found to be inoperable.

CLINICAL COURSE: The patient was readmitted to New York Hospital on July 18, 1899, and physical examination at that time revealed two metastatic growths, one on each side of the abdomen, attached to the small and large intestines. These masses had been growing rapidly for about six months. The region of the cervix was hard and eroded, the uterus enlarged and firmly fixed. A diagnosis of inoperable metastatic carcinoma of the cervix was made, with a prognosis of not more than 18 months. The patient was discharged unimproved on July 20, 1899. Dr. William B. Coley was then consulted. He confirmed the diagnosis and the prognosis, but nevertheless recommended trying the toxins.

TOXIN THERAPY (*Buxton VI*): The patient returned home and the injections were begun by her son, Dr. Charles D. Gruver and Dr. Joseph Shull of Stroudsburg, Pa. They were made deeply, directly into the masses, and were given twice a week for about six months, and then once a week for over a year. After an interval of rest they were resumed, the total duration of treatment being about three years. The initial dose was 0.5 minim, which was increased to a maximum of about 5 minims. Some injections were given into the abdominal wall and gluteal muscles. In describing the results Gruver stated: "Each injection caused a full reaction: elevation of temperature, redness and swelling, the patient remaining in bed 24 hours. Improvement was noted after the first month of treatment—pain easier, and intervals between painful attacks longer." Gruver added that the growths had been increasing rapidly in size before toxin therapy, and that after the injections were begun they remained stationary and then gradually regressed, being scarcely palpable at the end of a year. There was decided improvement in the general health as well as in the local condition, and the patient was able to resume her normal activity, doing all her own housework.

CLINICAL COURSE: There was never any further recurrence or metastases. The patient remained in unusually good health. During the last five years of her life there was some swelling of her ankles and some dyspnea, but these symptoms did not incapacitate her nor did they require treatment. While visiting her son in Asheville, North Carolina, she was very active during a "flu" epidemic in the household, contracted pneumonia, and died in 72 hours, on January 7, 1929. She would have been 80 years old the following October. This was about 39 years after onset.

COMMENT: This case indicates the importance of sustained aggressive treatment

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in advanced cases. Note that no regression was observed until a month after the toxins were begun.

REFERENCES: 11; 16; 23; 24; 64 (Case 5).

CASE 3: Inoperable recurrent squamous cell carcinoma of the cervix uteri involving the entire surface of the vagina, also the rectum and bladder, confirmed by microscopic examination at the Buffalo General Hospital and at John Hopkins Hospital in Baltimore, Maryland.

PREVIOUS HISTORY: Mrs. S.P.B., aged 64. The patient's mother died of cancer of the breast at the age of 56, otherwise the family history was negative for malignancy, tuberculosis or venereal disease. The patient had seven children, six of whom were living. Onset, she began to have severe hemorrhages from the uterus in the early spring of 1913. A diagnosis of primary inoperable cancer of the uterus was made.

RADIATION: The patient was referred to Dr. Curtis Burnham of Baltimore for radium therapy. She received three treatments at six-week intervals during the summer of 1913, and Burnham stated that the growth apparently disappeared following the first treatment.

INFLAMMATION (BURN): Dr. C.A. Greenleaf first saw the patient in October 1913, when he was called in to treat several severe radium burns on her abdomen. At that time she was having more or less hemorrhagic and coffee-ground colored discharge from the vagina. She also had developed rectovaginal and vesicovaginal fistulae associated with a good deal of discomfort with sloughing.

CLINICAL COURSE: Greenleaf believed that a recurrence had taken place. In March 1914, Dr. Edward Meyer of Buffalo was called in consultation. He and Greenleaf examined the patient under ether. They found a general recurrence in the vagina. At this time there was marked cachexia, and the patient had lost considerable weight. Meyer gave a hopeless prognosis with rapid termination. However, it was decided to try the Coley toxins.

TOXIN THERAPY (Tracy XI): Injections were begun by Greenleaf on June 5, 1914, and were given intramuscularly in the deltoid, the initial dose being 0.25 minim. The dose was increased daily or every other day by 0.25 minim until 5 minims were reached and a reaction obtained. The injections were kept up with occasional intervals of rest for nearly eight months. Chills occurred regularly, the maximum febrile reaction being 102° F. During the latter part of the treatment the Tracy Filtrate was used (Type XIF), and a decided reaction was obtained from

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very small doses. The patient's condition improved markedly. On December 8, 1914, Greenleaf wrote: "The improvement has progressed; the general symptoms have disappeared; and upon examination under ether last month, we could find no evidence of malignancy. The patient rides daily, walks one or two blocks, and as far as one can observe is entirely recovered."

CLINICAL COURSE: The patient resumed her normal activities, which Greenleaf stated included a "great deal of hard work". She remained well and free from recurrence until a few days before Christmas 1916, when she became drowsy. Two days later she became comatose and died the next day. In regard to her condition at that time Greenleaf wrote on January 7, 1917: "Mrs. B. died last week in Medford, Oregon. She was absolutely well and about until four days prior to her death. Two doctors in Oregon examined her carefully on the first day she was taken ill but could find no evidence of a recurrence of the malignant trouble." Her death was apparently due to a heart condition, and occurred nearly four years after onset.

REFERENCES: 11; 16; 99.

Matagne, of Brussels, Belgium, who used the Coley toxins or actually induced erysipelas infections in a considerable number of patients with inoperable cancer, is known to have treated at least three cases of uterine cancer. In reporting these uterine cases he did not give us any details as to the histology so the cases could not be included in the statistics. It is of interest to note, however, the results he obtained in these cases: In one there was marked amelioration, diminution of pain, decrease in size, the improvement lasting four months. Thereafter the disease was no longer controlled. In one case no benefit was noted. In the third, in which the toxins were given after hysterectomy had been performed and metastasis had developed in the leg, complete regression occurred and there was no further evidence of disease.

REFERENCES: 57; 58.

CASE 4: Inoperable adenocarcinoma of the cervix with metastases involving the pelvis, left kidney and abdomen with large inguinal nodes especially on the left side.

PREVIOUS HISTORY: Mrs. E.M., aged 46, bank clerk, of Westminister, California. The family and previous personal history were not recorded. In 1958, the patient was found to have an inoperable carcinoma of the cervix with metastases to the left kidney.

RADIATION: She was given 32 x-ray treatments.

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CLINICAL COURSE: Thrombophlebitis of the left leg followed shortly thereafter. She developed pain in the abdomen, back, pelvis, left groin and left leg. During 1962, the pain became progressively more severe and the patient became addicted to morphine which was given her in California. She was referred to Dr. James R. Ricks early in October 1962. He gave her Sparine (1 cc. every four to twelve hours) and Phenergan (2cc.) intramuscularly to replace morphine for her bone pain. At this time x-ray examination revealed metastases in the pelvis and left hip.

TOXIN THERAPY (*Johnston XV*): On October 10, 1962, intradermal injections were begun by Ricks. The dosage was as follows: 0.5 cc. of a 1:5 dilution 1, 1, 1.5, 2; then a 1:2½ dilution 0.5, 0.8, 1, 1.5; then a 1:1 dilution 1, 1.5, 1.5 cc. These injections were given on Monday, Wednesday, Friday and Saturday for four weeks. They caused febrile reactions averaging 100° to 101° F. Her bone pain decreased after the first 24 hours. By October 17, 1962, a week after the first injection she was able to walk and no longer required the medication for groin and abdominal pain. She took no further morphine, and was given Phenergan (25 mgm.) and Sparine (100 mgm.) every four to six hours. By the time the toxins were stopped she did not require any medication for pain.

CLINICAL COURSE: She returned home "considering herself cured, returned to work and took out new health insurance with everything covered except hospitalization for cancer." No further toxins were administered. The disease reactivated in 1963 and death occurred on September 6, 1963. Autopsy showed undifferentiated carcinoma metastases in lung, bone, fibrous pelvic tissue and adrenals, also focal infarctions of kidneys, small bowel and colon, and acute ulceration of colon with hemorrhage. This was 5 years after onset.

REFERENCE: 11

NOTE: No detailed history is available for case 5.

SERIES F: OPERABLE SARCOMA OF THE CERVIX DETAILED HISTORY

The following case is the only operable sarcoma of the cervix known to have had toxins following surgery to prevent recurrence. The patient remained free from recurrence or metastases, but died of carcinoma of the sigmoid colon 46 years after onset of the sarcoma.

DIAGNOSIS: Operable leiomyosarcoma of the cervix confirmed by microscopic examination.

PREVIOUS HISTORY: Mrs. C.M.F., aged 37. The patient was married but had never had any children. She was about 5 feet 5 inches in height and weighed about 130 pounds. In 1907, she developed a sarcoma of the cervix.

SURGERY: A hysterectomy was performed by Dr. Charles V. Dudley of Chicago, in January 1908.

TOXIN THERAPY (*Tracy XI*): As the patient's husband was a physician, he decided to give her prophylactic toxin therapy following this operation, to prevent metastases. Injections were "given faithfully for a year".

CLINICAL COURSE: The patient remained free from recurrence, and was well and strong on March 1, 1912, when Dr. P.H. Fithian reported the case to Dr. William B. Coley. She enjoyed good health during the next 39 years. She then developed carcinoma of the sigmoid colon, with loss of 30 pounds in weight. Death occurred from metastases on March 27, 1953, at the age of 81 years. This was 46 years after onset of the sarcoma of the cervix.

REFERENCES: 6; 16.

**SERIES G: INOPERABLE SARCOMA OF THE UTERUS TREATED BY
TOXIN THERAPY: 11 CASES (10 WITH COLEY TOXINS, 1 WITH
STAPH AND STREP TOXINS)
BRIEF ABSTRACTS**

Years Traced
After Onset

1. COLEY: Mrs. M.L., aged 35; inoperable recurrent sarcoma uterus; onset October 1893: menorrhagia, profuse leukorrhea, pain in low back and abdomen, failing health; panhysterectomy for large leiomyoma, June 1893; well 4 months then shooting pains in back and side; 2nd operation attempted December 1893, condition inoperable; January 12, 1894: toxins (Type IV) for 8 weeks i.m.; *considerable regression*; April 7, 1894: exploratory celiotomy, tumor still inoperable; toxins resumed, continued every 48 hours; regression not complete until several months after toxins were stopped; *gradual complete disappearance*; March 1908 large ventral hernia repaired; N.E.D. in abdomen and pelvis; last traced well 1917. (2; 16; 24; 60a) 23
2. WILLIAMS: Mrs. E.Z., aged 37; date of onset not given; recurrent inoperable spindle cell sarcoma uterus, large growth projected about 10 cm. above surface of abdomen; exploratory laparotomy, biopsy April 24, 1896; Buxton VI toxins (7 in 24 days) directly into tumor, very severe reactions (very high dosage for this route); poultices applied, *necrotic tumor tissue drained through sinus 8 cm. deep in center of tumor*; *steady rapid regression, complete disappearance, no further recurrence*; alive and well in 1914. (16; 19; 24) 18
3. WILLY: Mrs. W., aged 42; date of onset not given; recurrent inoperable mixed cell sarcoma uterus, broad ligament, size of cocoon; Buxton VI toxins for 6 wks. into visible parts of tumor in cervix; these *shrank rapidly, entirely disappeared by absorption in 10 days*; toxins not given steadily, *disease controlled under intermittent treatment for 6 yrs.*; weaker Parke Davis IX given last 2 yrs; operation in Switzerland 1903 proved fatal; history indicates important difference in response to local and intramuscular injections. (11; 16; 24) 6 (Died)
4. DUNCAN: Mrs. X., aged 52; date of onset not given; recurrent spindle cell sarcoma uterus following hysterectomy; cystic ovaries and tubes then removed; rapid recurrence in pelvis, size of closed fist; some outlying fragments excised at 3rd operation; prognosis deemed hopeless; toxins given aggressively; *complete disappearance in 2 mos.*; no further recurrence 10 mos. later; end result unknown. (32) ?
5. HUNDLEY: Mrs. A.C., aged 38; onset, fall 1903; recurrent round and spindle cell sarcoma involving entire uterus, size fetal head; removed by supravaginal hysterectomy; later attempt at removal of cervix abandoned;

SERIES G: BRIEF ABSTRACTS

Years Traced
After Onset

- recurrence in right lateral fornix, involving broad ligament, pelvic bone and fascia; January 2, 1904, 33 injections Parke Davis IX toxins directly into fornix and cervix; *complete disappearance growths*; no further recurrence; in good health until sudden severe duodenal ulcer, causing death, July 1933. (16; 19; 24) 29
6. COLEY: Miss M.L.W., aged 42; date of onset not given, recurrent inoperable leiomyosarcoma uterus; following hysterectomy filled whole lower pelvis, involved bladder wall, frequent painful micturition; general health poor; Tracy X and XI Toxins October 1, 1907; improvement noted in 2 or 3 weeks.; *marked cessation pain, softening, decrease in size, improved general health*; toxins suspended during hot weather for 8 wks.; immediate return of symptoms, increase in size; toxins resumed; continued 2½ years; *complete disappearance*; no further recurrence; remained well 35 yrs.; died cerebral hemorrhage, hypertension, aged 80, March 28, 1944. (6; 11; 16; 23; 60a) 37
7. HOWE: Mrs. C. McM., aged 50; date of onset not given; recurrent inoperable round cell sarcoma uterus; infiltrating mass filled pelvis, clinically resembled carcinoma, severe pain, bladder symptoms; general health bad; prognosis hopeless; toxins begun April 7, 1908, 4 weekly; *general condition improved, pain ceased, tumor decreased steadily in size* until toxins suspended during hot weather; severe pains immediately returned; toxins resumed, given steadily, total of 118 in 26 months; *growth completely disappeared*; no further recurrence; in good health until death at 81, 1936, cerebral arteriosclerosis. (6; 16; 22; 24, case 67) 28
8. BEARD: Mrs. W.G., aged 49; onset January 1914; recurrent fibrosarcoma uterus, involving vaginal vault (cauliflower growth); toxins November 5, 1915, i.m. in buttocks for 8 mos., *tumor decreased, softened*; when injections were suspended or dose and frequency decreased, growth would recur or increase; *finally disappeared completely*; some evidence of further growth March 1917; toxins resumed, continued with intervals of rest another 17 months; last traced in good health, September 1918. (11; 16; 99) Over 4½
9. BLUM: Mrs. E.A., aged 37; date of onset not given; malignant myoma weighing 15 lbs. removed surgically; x-ray examination indicated evidence bone metastases to femur, sacrum, skull; Parke Davis XIII toxins July 21, 1927 in massive doses; *complete recovery, gained weight, strength*, no recurrence or further evidence skeletal metastases; alive and well 1933. (16; 26) 6
10. JENNINGS: Mrs. S.L., aged 37; onset about January 1958, during severe dieting for obesity (weight decreased from 257 to 189 pounds); extensive recurrent proliferative sarcoma of endometrium (primary involved the

SERIES G: BRIEF ABSTRACTS

Years Traced
After Onset

uterus, bladder and lateral pelvic wall) with solitary metastasis to right lung; supracervical hysterectomy and bilateral salpingo-oophorectomy May 9, 1958; postoperative ileus; recurrence on right flank extended almost to umbilicus; November 9, 1958: Johnston XV toxins, 15 i.m. in 1st 3 weeks maximum reaction 102.6° F.; *slight decrease in size, softening of recurrence, but lung lesion increased*; injections continued 3 times a week: maximum dose 2 cc.; no really good reactions; disease progressed; death January 15, 1959. (11)

1 (Died)

11. STEWART: Miss D.W., aged 19; inoperable leiomyosarcoma uterus; onset, February 1920, hemorrhages, pain, explored November 9, 1920; hysterectomy impossible, extensive infiltration around urethrae and both fornices; bilateral oophorectomy, pedunculated tumor masses arising from cervix filled vagina, removed by morcellation; vagina packed with gauze dressings from streptococcal and staphylococcal infected leg ulcers, in attempt to induce a local infection; also i.v. (formula unknown); febrile reactions to 104.8° F.; *all bleeding and discharge ceased; infiltrating growth entirely disappeared*; injections continued 7 months; no recurrence; in good health until 1954, then arteriosclerotic and hypertensive heart disease and aortic aneurism; continued working full time until final illness: acute bronchopneumonia and coronary occlusion; death May 3, 1964. (6; 11; 16; 60a.)

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NOTE: Two other cases of inoperable endometrial sarcoma received Coley toxins briefly. The first had neoplastic thrombi occluding the ovarian veins. She received 17 injections in 18 days (12 i.v. and 5 into cervix) at Memorial Hospital in 1953. Since this brief course is considered inadequate, the complete history is not included here but it is of interest that following these injections the stony hard growth softened, became cystic, discharged considerable necrotic tumor tissue within a short time and the remaining tumor was smaller. The patient subsequently was given massive irradiation which apparently caused osteogenic sarcoma of the sacrum with metastases. Death occurred almost 10 years after onset, 6 years after toxins were given. (60a)

The other was a terminal case, treated by Wehrly in California, who received 15 injections in 17 days following small dose of radiation therapy with complete pain relief, able to eat and retain food; sudden death due to hydronephrosis (tumor tissue had blocked ureters). Autopsy showed much less tumor present than at exploratory surgery, no enlarged lymph nodes found. (11)

**SERIES G: INOPERABLE SARCOMA OF THE UTERUS TREATED BY
TOXIN THERAPY
DETAILED HISTORIES**

CASE 1: Inoperable retroperitoneal round cell sarcoma, apparently recurrent from a primary growth in the uterus, confirmed by microscopical examination at New York Postgraduate Hospital.

PREVIOUS HISTORY: Miss M.L., aged 35, seamstress, born in Ireland. The family history was negative for malignancy. The patient first menstruated at 15, and was regular until 1889, when she began to complain of menorrhagia, profuse leukorrhea, pain in the back and lower abdomen and failing health.

SURGERY: In June 1893, a hysterectomy was performed by Dr. Stannard at New York Postgraduate Hospital for a large fibroid tumor. The adnexa were also removed. The patient made a good recovery.

CLINICAL COURSE: She remained well until October 1893, when shooting pains developed in the back and side. She was told she had cancer.

FURTHER SURGERY: A second operation was attempted in December 1893. The incision was made in the left iliac region, but as the condition was found to be inoperable, the wound was closed.

CLINICAL COURSE: She was then referred to Dr. William B. Coley, and was admitted to Memorial Hospital on January 12, 1894, complaining of pain in the back and abdomen. There was no vaginal discharge. Examination on admission revealed two scars, one in the median line and one in the left iliac region.

TOXIN THERAPY (*Type IV, filtered*): Injections were begun by Coley on January 12, 1894, and were made daily or every second day for about eight weeks. The dosage used was not recorded. Because the growth was inaccessible, the injections were made in the thigh and the patient complained of pain and soreness at the site of injection. She also complained of considerable pain in the abdomen and side. The tumor diminished considerably in size during these two months and Coley decided to make an attempt to remove the remains of the growth.

FURTHER SURGERY: On April 7, 1894, he performed an exploratory celiotomy. An incision about 10 cm. long was made in the cicatrix of one of the former incisions. A digital examination of the abdominal cavity revealed a tumor about 7 cm. in diameter in the left side of the pelvis, in close relation to the iliac vessels. It was decided to allow the tumor to remain, as it was considered next to impossible to remove it. The wound was closed. Immediately following this operation the tumor appeared to increase in size.

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FURTHER TOXIN THERAPY: Toxins were resumed and continued every second day until the patient complained of soreness at the sites of injection.

CLINICAL COURSE: She then returned to her home in Ireland and during the next few months the tumor gradually regressed, and she regained her former good health. She remained in Ireland for eight years, and then returned to New York. About February 1, 1908, she noticed a lump in the abdomen, and feared another tumor. She had no pain, however, until one week prior to admission to Memorial Hospital on March 11, 1908. Examination revealed a large ventral hernia on the left lower abdomen at the site of one of the laparotomy incisions.

FURTHER SURGERY: Coley's associate, Dr. William A. Downes, performed a left ventral herniotomy. A careful examination of the abdominal cavity during the operation revealed no trace of tumor either in the abdomen or pelvis. The patient was last traced in good health in 1917, over 23 years after onset.

COMMENT: This is one of the rare cases in which the toxins did not destroy the tumor before the injections were discontinued, and yet the neoplasm ultimately regressed completely. In some of Beebe and Tracy's experiments on animals, the tumors continued to regress and finally disappeared after cessation of treatment. (2) However, in the majority of patients in whom only a brief period of toxin therapy was given the disease recurred. Note that because this was an inaccessible growth, Coley gave no injections in or near the tumor, and therefore regression was less rapid than in cases receiving intratumoral or intravenous therapy.

REFERENCES: 2; 16; 24, case 70; 60a.

CASE 2: Recurrent inoperable spindle cell sarcoma of the uterus, confirmed by microscopic examination.

PREVIOUS HISTORY: Mrs. E.Z., aged 37, of Rochester, New York, born in Canada. Menstruation began at 16 and was regular and normal in amount. The patient had been married nine years and was childless. She had had dysmenorrhea for seven years. She was first seen by Dr. H.T. Williams on April 16, 1891. At this time her health was fair but she had noticed a growth in the abdomen six years before, which had gradually increased in size. A diagnosis of uterine fibroid was made.

SURGERY: On May 31, 1891, a median abdominal incision was made. A large smooth fibroid of the uterus was found, the sound passing 23 cm. There were numerous adhesions, in view of which it was considered best not to do a hysterectomy but to try the effects of sterilization. Both tubes and ovaries, which were large and cystic, were removed as close to the uterus as possible. Catgut was used to ligate the pedicles. The post-operative course was uneventful.

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CLINICAL COURSE: The patient was again examined on November 21, 1891. Bleeding had been much less profuse. The uterine sound passed 13 cm. By May 1892, the sound passed 11.5 cm. The patient had been gaining weight. She was then lost sight of until March 1896, when she again came to Williams complaining of pain in the right side and saying she felt another tumor. Examination showed a large hard tumor about the size of two fists in the right side of the abdomen, and upon vaginal examination it appeared to spring from the right horn of the uterus. The tumor was not very movable and seemed attached to the abdominal muscles.

FURTHER SURGERY: On March 24, 1896, an exploratory incision through the abdomen revealed a large elastic tumor, apparently originating from the right pedicle, extending into the abdominal muscles and adherent to the intestines. It was considered inoperable. A portion was removed for microscopic examination and the abdominal wall was closed with eight silver wire sutures. The wound healed by first intention. The tumor increased rapidly in size and a month after the exploratory incision it projected over 8 cm. above the surface of the abdomen.

TOXIN THERAPY (Buxton VI): Injections were begun by Williams on April 24, 1896, the initial dose being 3 minims injected into the center of the tumor. The reaction was very great, the patient had a severe chill and went into collapse. Brandy and strychnia with saline per rectum and hypodermically were required before she rallied which she did a few hours later. The temperature had risen to 106° F, but dropped to 100° F. in a few hours, and to normal the next day, but the patient felt very exhausted. Four days after the first injection 1 minim was injected into the tumor about 2.5 cm. below the first site. The reaction symptoms were repeated, but were less severe, the temperature rising to 103° F. The patient declined further treatment until May 1, 1896. A dose of 1 minim caused a reaction of 102° F.; 3 minims on May 5 caused a reaction of 103° F., and a slight chill; on May 8 and 14, 1896 this dose was followed by considerable reaction but not much temperature. On May 18, 1896, 4 minims caused a very severe, prolonged chill and 105.4° F. The patient felt extremely weak for several days. After each of the previous injections a slight erysipelatous blush had appeared around the point of injection, which disappeared in a few days. This time a bright red area 8 to 10 cm. appeared. Poultices were applied and in a few days it turned black and a slough about 4 cm. in diameter came away leaving a sinus 6 to 7 cm. in depth in the center of the tumor. The patient then refused to have any further injections. The sinus discharged for several months and the tumor grew rapidly smaller. Six months after the last injection it was about 5 cm. in diameter. Two months later, or by mid-December 1896, it had entirely disappeared, the patient had gained considerable weight and felt fine.

CLINICAL COURSE: There was no further recurrence. The patient remained in good health when last traced on March 5, 1914, 18 years after toxin therapy.

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REFERENCES: 16; 19 (case VI in Table of other surgeon's cases); 24 (Case 8 in Table, p. 151).

CASE 3: Recurrent inoperable mixed cell sarcoma of the uterus and broad ligament, confirmed by microscopic examinations by several pathologists, both in New Orleans and New York.

PREVIOUS HISTORY: Mrs. W., aged 42, of New Orleans, Louisiana, born in Switzerland.

SURGERY: In July 1897, a laparotomy was performed by Dr. Lewis of New Orleans, for what was believed to be sarcoma. The condition was found to be inoperable on account of the extensive adhesions to the intestines.

CLINICAL COURSE: The patient was so weak that Lewis considered the case absolutely hopeless, with a prognosis of a few weeks, but under arsenic internally and methyl violet injected into the tumor, the patient improved somewhat for about six months. Polypous growths then began to shoot out of the cervix very rapidly. Hemorrhages followed and the general condition again declined rapidly.

TOXIN THERAPY (Buxton VI): Injections of the mixed unfiltered toxins were then begun by Dr. J.C. Willy, the patient's husband, and were made three to six times a week in the region of the cervix. Willy stated: "The effect was marvelous. Those polypi—from a bean to half a walnut in size—began to shrink immediately and disappeared entirely in the course of ten days, not by any visible decay of tissue, but by simple shrinkage. Since then I have kept my wife under this treatment, not constantly: six weeks at first, in shorter or longer periods afterwards, whenever I noticed any inclination of the tumor to increase. The patient improved at once with few interruptions: has done her own housework up to September of this year (1900). The tumor which at the time of laparotomy was the size of a good coconut decreased also during the first (course of) treatment. Once I had it down to the size of a small man's fist, particularly the lower portions of the uterus which I could reach by the hypodermic injection were benefited; while the top kept on growing, slowly but surely, principally during the menstrual congestions.

"On September 21 and in October (1900), she had only menstrual moli-men, very little blood but a good deal of mucopurulent secretion, together with severe swelling of the tumor, retention of urine and feces, terrible pains in the back, abdomen and legs, suppurative cystitis, and membranes and bloody discharges with the feces. All these symptoms were alleviated by treatment and stopped almost entirely when in November, a free menstrual flow set in." However, the tumor continued to grow, extending nearly to the navel, and the patient's strength returned very slowly. Willy added: "In the general course of the

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toxin treatment I have arrived at the conclusion that it works all right locally, but not enough on the further end of the tumor. Then I tried the injection at distant parts, went up to 16 and 18 minims, but most of the time without any reaction, while the local injections of 2 or 3 minims into the tumor produced very prompt and regular reactions." He added that "stopping the injections made her worse several times."

Willy's observations clearly indicate the different effects of intratumoral and intramuscular injections remote from the tumor. Although toxin therapy was administered spasmodically, the growth regressed and the patient remained in fairly good condition during the treatment, as evidenced by her attending to her regular household duties, except during the period between September and November 1900, when she was in a serious condition.

PARKE DAVIS TOXINS (*Type IX*): In January 1901, Buxton wrote that he could no longer supply Willy with the Coley toxins and referred him to Parke Davis and Co. The first bottle of their preparation arrived on January 5, 1901, and Willy stated: "It was much thicker than the preparations I had used before and had an offensive smell." This he returned and received a fresh supply. Treatment was then resumed with three to five injections a week, one of which was made locally in the cervix each week, the others being in the gluteal region, as suggested by Coley. The dose was slowly increased from 0.5 to 12 minims. The patient received at least three injections weekly from the spring of 1901 to January 1902, and Willy noted that during December 1901, the tumor seemed to diminish under the influence of large doses. On May 23, 1902, he reported: "Although the tumor is slowly growing it seems to have lost its malignancy; she had gained 22 pounds in 14 months, hemorrhage of bladder and intestines and albuminuria all subsided."

Willy stated that the toxins sent by Parke Davis in 1902 were considerably more effective than the product with which they had supplied him the year before. Willy's final letter to Coley on October 26, 1902 stated that he had given six injections a week for a considerable period. Four of these each week were doses just sufficient to make her feel the effects without producing a chill, the other two being large enough to produce a distinct chill and fever. He stated to Coley that this seemed a better technique to use "in dealing with these refractory cases" than to give only three or four a week as Coley had advised. He added: "The result justifies my supposition: my wife's tumor is certainly diminishing in size; while the top stood somewhat higher than the umbilicus in spring it is now 2 or 3 cm. below. Besides, the patient is in splendid condition, and nobody in seeing her would believe her to be afflicted with cancer. She continued to gain weight and strength and has good color. Of course we go on with the treatment. Fall has always been the dangerous season for her; so I endeavor to get her through it without reverse

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this year." After Willy's death, the injections were continued by Dr. Herman Gessner until sometime in 1903.

CLINICAL COURSE: The patient returned to Switzerland that year, almost six years after the toxins were begun.

SURGERY: Gessner stated that "she was then operated upon by an optimistic surgeon with a fatal result." He added that he considered that the toxins had prolonged her life for several years.

COMMENT: This case indicates the need for more aggressive and prolonged initial course of toxin therapy, using intravenous injections, in order to effect a permanent result. (The first course was only six weeks.) This patient was treated at a period when Buxton's preparation did not appear to be as potent as it was during 1895-7. During the latter part of the treatment, the less potent Parke David IX product was used. (The latter was first made in December 1900.)

REFERENCES: 11; 16; 24 (case 39 in Table, p. 155)

CASE 4: Twice-recurrent inoperable fibromyosarcoma of the uterus, following hysterectomy, double salpingectomy and oophorectomy. The microscopic examination was made by Colquhoun, of the Kyncton Private Hospital, who reported "spindle cell sarcoma"

PREVIOUS HISTORY: Aged 52, married. The patient had never had any children. She menstruated regularly and enjoyed excellent health. Onset, she began to feel discomfort when having a bowel movement, "as if some foreign body was present". Examination revealed a fibromyoma of the uterus the size of a fetal head, which was causing some pressure on the rectum. With this exception the patient was in good health.

SURGERY: The uterus and the tumor were removed in the usual way. The latter proved to be intramural. The ovaries and tubes, being quite healthy, were left. The patient made a quick recovery. The operation was performed in Melbourne, Australia, by Mr. Robert B. Duncan, F.R.C.S., England. She was discharged in the third week.

CLINICAL COURSE: Five months later she returned, complaining of rectal trouble worse than before, and various minor ailments. On examination two almost uniform semi-cystic growths the size of large oranges were found on each side of the pelvis.

FURTHER SURGERY: A second operation was performed, exposing the growths

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which were found to be due to a solid and cystic enlargement of the ovaries with the tubes matted about them. These were easily removed and the patient's recovery was uneventful.

CLINICAL COURSE: The symptoms were relieved for about six weeks, when it became evident that another recurrence had developed. She was readmitted for the third time and examination showed a centrally situated pelvic tumor about the size of a closed fist.

FURTHER SURGERY: The abdomen was opened for the third time and examination revealed a good deal of the growth was due to excessive induration. The iliac colon was adherent to the central stump of the first operation. While some outlying fragments were removed, any attempt to deal with the part which was causing pressure was seen to be futile. The rapidity with which the growth seemed to be spreading and the previous history appeared to render the prognosis hopeless.

TOXIN THERAPY: As soon as possible injections were begun and were administered aggressively. Duncan stated: "Fortunately it seemed to agree with her, and only rarely was there any reaction to delay the treatment. Before many weeks had elapsed she declared herself distinctly better, and in two months all signs of the growth and the induration had disappeared." (Duncan did not state which preparation he used. Three preparations of the unfiltered mixed Coley toxins were available in 1911: Tracy's XI, Parke Davis XII and the English product, Lister Institute VIII. Tracy and Parke Davis also prepared filtrates for use in old, weak patients.)

CLINICAL COURSE: "It is now ten months since the final operation was performed, and she is now to all appearances perfectly well. My colleague, Dr. Groves, who assisted me at the various operations, can confirm my testimony as to the utter hopelessness of the case from the appearance of the parts on the third and final incision when removal was attempted."

This case was reported about 18 months after onset. No further details are known as to the end result.

Duncan added: "Now when Coley's fluid can be obtained in practically any quantity and the fatal results of sarcomatous growths are borne in mind, no time should be lost in giving the patient afflicted with this dreadful malady, the possible benefits of its administration. . . . Coley's results have been nothing less than brilliant, and most hopeful when the nature of the disease is kept in mind. I think it would be most useful in those recurring cases so situated that repeated operations are not attended with any particular risk. I think it is a mistake that the word inoperable has been so prominently used. Whilst it is the only treatment standing

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between the patient and certain death in such cases, it should be used in every case, operable and inoperable. . . . In the light of Coley's experience it would appear that its administration ought to be undertaken as soon as any growth is diagnosed . . . , and whether an operation is performed or not." (Apparently Coley never read this report nor corresponded with Duncan.)

REFERENCE: 32.

CASE 5: Inoperable recurrent round and spindle cell sarcoma of the uterus, confirmed by microscopic examination by Dr. J.L. Hirsch.

PREVIOUS HISTORY: Mrs. A.C., aged 38. The patient had two children, the second born in 1893. Onset, in the fall of 1903, she first noticed "trouble". She consulted her family physician who made a diagnosis of myoma.

SURGERY: In December 1903, she was operated upon by Dr. J.M. Hundley, professor of Gynecology at the University of Maryland. He supposed the condition to be an ovarian cystoma and uterine fibroid. The growth was the size of a fetal head. A supravaginal hysterectomy was performed, leaving the cervix. Microscopic examination proved the condition to be a round and spindle cell sarcoma involving the entire uterus. On January 15, 1904, Hundley attempted to remove the cervix, but had to abandon the operation because of the patient's weak heart action. At this time he detected a recurrent tumor in the right lateral fornix, apparently springing from the broad ligament, the pelvic bone and the fascia. He stated that clinically the condition was undoubtedly sarcomatous in character.

TOXIN THERAPY (*Parke Davis IX*): Injections were begun by Hundley on January 22, 1904, a week after the second operation. They were given alternately into the fornix and cervix through the vagina. The tumors in both regions immediately began to diminish in size. A total of 33 injections were given. The recurrent growths disappeared completely.

CLINICAL COURSE: On September 27, 1904, nine months after the injections were begun, Hundley wrote Coley that to all outward appearances the condition was normal. The patient moved to New York, and Coley examined her at frequent intervals and found her in excellent health; her weight remained normal, and there was no trace whatever of the sarcoma. She remained in good health during the next 28 years. In July 1932, Coley was called to attend her for a severe duodenal ulcer, which proved fatal. At this time there was no evidence of recurrence of the sarcoma for which she had been successfully treated by toxin therapy in 1904. Death occurred 29 years after onset.

COMMENT: A complete regression and a permanent result was obtained in this

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case using the less potent commercial preparation of Coley's toxins. It should be emphasized, however, that an effective technique was used by injecting toxins directly into the recurrent tumors. Also, the disease was not as far-advanced as many of Coley's inoperable cases.

REFERENCES: 16; 19 (case 41 in Table of other men's cases); 24, case 40 in Table, p. 155).

CASE 6: Inoperable recurrent leiomyosarcoma of the uterus, confirmed by microscopic examination by Dr. Mallory, Professor of Pathology at Harvard Medical School.

PREVIOUS HISTORY: Miss M.L.W., aged 42, of Worcester, Mass. The patient's mother had died of a malignant tumor of the uterus, without operation. The patient's previous history had been noncontributory.

SURGERY: On January 8, 1907, she was operated upon at Boston City Hospital for a tumor of the uterus by Dr. Homer Gage of Worcester, Mass. The uterus was removed. The growth was thought clinically to be a fibroid, but proved to be a leiomyosarcoma, following examination by Mallory.

CLINICAL COURSE: During the following summer the patient began to have intermittent attacks of frequent micturition, accompanied by pain. Vaginal examination in September 1907, by Dr. Edward Reynolds of Boston, revealed a mass in the vault of the vagina which had almost doubled in size since the last examination a few weeks before. There was also a reddened surface on the posterior wall of the bladder which by September had developed into well-marked papillomata. Reynolds stated in a letter to Dr. William B. Coley: "I looked on the case as practically hopeless but recommended Dr. Wheeler to send her to you as the one chance remaining." At examination on September 26, 1907, Coley found an infiltrating tumor occupying the whole lower portion of the pelvis, apparently involving the bladder wall. The tumor was hard in consistency, irregular in outline, and had the "feel" of carcinoma, rather than sarcoma. The condition was entirely inoperable. The patient was suffering a great deal of pain and had frequent and painful micturition, and her general health had been seriously affected. Although the prognosis was unfavorable, Coley decided to give her a brief trial with the toxins. She was admitted to Memorial Hospital on October 1, 1907. Bimanual examination on admission showed a tumor infiltrating the anterior wall, involving the bladder wall down to the symphysis and extending as high as the finger could reach. The mass was fixed. There was no ulceration of the vaginal wall. The point of origin was probably in the incision of the old hysterectomy wound.

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TOXIN THERAPY (*Tracy X & XI*): Injections were begun by Coley on October 1, 1907, and were given daily for eight days and thereafter five times a week in doses of 0.5 to 6 minims. These caused moderate reactions, no chills. Definite improvement was noted within two weeks: marked cessation of pain as well as softening and regression of the tumor and improvement in the general condition. The patient was sent home at the end of three weeks, and treatment was continued by Dr. Leonard Wheeler, the family physician, three or four times a week, with occasional intervals of rest. In March and April 1908 one bottle of the Parke Davis unfiltered preparation (Type XII) was used, and from May to July 1909 the Parke Davis filtrate (Type XIIF) was used. The Parke Davis unfiltered preparation (XII) was again used in March 1909 and February 1910. During August and September, 1908, injections were suspended for almost two months because of the hot weather; during this time the former symptoms returned and the growth seemed to increase in size. Injections were resumed and with continued treatment the symptoms again entirely disappeared and the growth became smaller and softer. Injections were discontinued entirely about the end of February 1910, after having been administered for nearly 2½ years. The last year of treatment they were given by a nurse. The patient's general condition was practically perfect the entire time. Coley stated that in this case the dose was never increased beyond 5 minims, which was sufficient to produce a slight malaise and a temperature of 99° or 100° F. three times a week. The low dosage and mild reactions would appear to be the reason why the growth regressed so slowly. In writing Coley regarding the progress of this patient, Reynolds stated in May 1909: "It has struck me as one of the most remarkable cases I have ever heard of. Results have certainly in every way justified the use of the toxins whether they effect a final cure or not."

CLINICAL COURSE: In May 1910, Coley examined the patient and found only "small traces of the original tumor remaining, and what was left, much softer." She had regained her former weight and stated that she had never felt better. Another examination in June 1911 showed no trace of the tumor remaining. The patient weighed more than she ever had and her general health was perfect. She remained well during the next 35 years. She was last heard from in February 1944. Her only complaint at that time was that she was having some trouble with her heart. She died March 28, 1944, of cerebral hemorrhage and hypertension at the age of 80, 37 years after onset.

REFERENCES: 6; 11; 16; 23 (case 3).

CASE 7: Recurrent inoperable round cell sarcoma of the uterus, confirmed by microscopic examination by Dr. Rudolf Steiner, pathologist at the Hartford Hospital, Hartford, Conn.

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PREVIOUS HISTORY: Mrs. C. McM., aged 50, of Hartford. The family and previous personal history was not recorded.

SURGERY: The patient was operated upon for a large tumor of the uterus in the spring of 1907 at the Hartford Hospital by Dr. Harmon G. Howe.

CLINICAL COURSE: The tumor recurred and the patient was referred to Dr. William B. Coley for consultation early in April 1908 as a totally inoperable case. Examination at that time revealed an infiltrating tumor which filled the whole pelvis and which was so hard that clinically it resembled carcinoma, rather than sarcoma. The patient had severe pain, her general health had markedly failed and bladder symptoms had developed. Coley regarded the prognosis as hopeless and told Howe that all that could be expected was to hold the disease temporarily in check.

TOXIN THERAPY (*Tracy XI*): Injections were begun by Howe under Coley's instructions on April 7, 1908, and were continued four times a week. Gradually the frequency was reduced to twice a week. The patient's general condition soon began to improve, the pain disappeared, and the tumor diminished steadily in size until August 1908, when the injections were suspended for two weeks. Immediately the severe pains returned. Howe resumed the toxins, giving injections every other day through September, then twice a week, then once a week, and finally once in ten days. On December 14, 1908, after eight months' treatment, the patient wrote Coley reporting her condition. At this time the infiltrating growth had entirely disappeared. She stated: "I feel so well that I can hardly believe myself, and on all sides people are congratulating me." Although the disease had apparently entirely regressed, the injections were continued for a total of 26 months, during which time she received 118 injections.

CLINICAL COURSE: The patient was presented by Coley before the Clinical Congress of Surgeons of North America on November 12, 1912. She was examined periodically by Howe, and remained free from further recurrence. She was again presented before the Clinical Congress of Surgeons of North America by Coley in 1933, at which time she was in excellent health. She was last traced by Coley in January 1935 and was well at that time. She died on July 7, 1936, at the age of 81, of cerebral arteriosclerosis, over 29 years after onset, having never had any further recurrence.

COMMENT: This case and the preceding one seem to indicate the danger of suspending the injections or decreasing the frequency too soon in far-advanced cases as recurrence may develop. Note that the toxins stopped the pain in these cases and that when the injections were suspended the pain and other symptoms returned at once. By resuming treatment for a prolonged period, final control of the disease occurred.

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REFERENCES: 6; 16, case 3; 22; 24, case 67.

CASE 8: Recurrent fibrosarcoma of the uterus, involving the vault of the vagina, confirmed by microscopic examination following biopsy.

PREVIOUS HISTORY: Mrs. W.G., aged 49. Following laceration and pyosalpinx some 20 years before, the patient had had considerable endometritis, which culminated in malignancy. This was confined to the uterus, and was not far advanced when discovered in January 1914.

SURGERY: A complete hysterectomy was performed at once, from which the patient made an excellent recovery.

CLINICAL COURSE: She remained in the best of health until September 1915, 21 months after operation, when a slight discharge appeared. Speculum examination revealed a rather pronounced ulcer surrounded by infiltration 2.5 cm. in diameter in the vault of the vagina, transverse induration, the ulcer being at the point of suture of the broad ligaments. A wedge was removed from the wall of the ulcer for microscopic examination. The incision was closed a week later, and hemorrhage ceased. The patient's general health was good and she led an active life. She was referred to Dr. Charles G. Beard of Sterling, Illinois, by Dr. Charles H. Mayo of Rochester, Minnesota, for toxin therapy.

TOXIN THERAPY: Injections were begun about November 5, 1915. On January 26, 1916, the patient's husband, Dr. William Gardner, an osteopath, wrote to Dr. William B. Coley as follows: "The results we had hoped for from the mixed toxins seem to be eluding us." He stated that for a month or more Beard had administered the toxins daily, until he had reached a dose of 15 minims, and a reaction of something less than 104° F. had occurred two or three times. He added that the induration had softened nicely. However, about January 1, 1916, he reduced the dose to 10 minims given only once a week, and these doses caused a reaction of 101° to 102° F. each time, usually lasting 12 hours more or less. Beard made a digital examination on January 24, 1916, and found that though the tissues were soft and mobile, the tumor nevertheless had increased a third in size in the preceding three weeks. Heretofore, Beard had been much gratified with the results of treatment, but at this time he seemed to doubt the possibility of producing a complete and permanent regression. (The increased growth in the tumor occurred following a decrease in dosage and frequency which reduced the weekly amount of toxins administered from 70 to 10 minims.)

Apparently some of the injections were given in the gluteal region, because Gardner reported that a dose of 5 minims given into the buttock, on January 30, 1916, caused an induration about 4 cm. in diameter, painful and slow to subside.

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Next day Beard aspirated the exudate. This was stained and examined and found to be chiefly serum, no *Bacillus coli* or other micro-organisms, and very little debris. (This is the only known instance in which the site of a subcutaneous injection was subsequently aspirated and examined microscopically. It is apparent that such injections produce very slow and incomplete absorption, and it is not surprising that they are less effective in producing regression than the intradermal or intravenous route combined with intratumoral injections.)

Injections were continued steadily, at least one a week being given. On April 4, 1916, Beard wrote that "the desired effects were arriving." Gardner reported: "Beard gave her a thorough digital and speculum examination on March 28, 1916, and to his manifest surprise and delight he found the tumor greatly reduced in size." He added that when he took the tumor between his fingers it felt very much like a fold of physiologically normal vaginal wall, soft and smooth. He found no induration except a negligible ray of it extending into what had been the pedicle of the tumor. He found that red but sound cicatricial tissues marked the point at which the wedge was removed for pathological examination. Beard continued the toxins, giving 4 minims once a week, which caused only a one degree rise in temperature. He stated that the patient's endurance, activity and general health were better than for a good many years. As Gardner expressed it: "To all appearances she would pass for a thoroughly well woman, better than the average. . . . I had not known a time during the past 25 years when she had so few aches and pains to complain of." Injections were continued until June 1916, a total duration of eight months.

CLINICAL COURSE: Gardner stated: "Thorough examination in October 1916 revealed no return of the disease. Every trace of the ulcer in the vaginal vault had disappeared, even the scar tissue from the biopsy. There was no induration whatever, no peduncle: the entire vaginal wall was pink, tonic, perfectly normal and physiological. The only thing to indicate there had been a tumor was a loose fold of the wall which could be gathered in the fingers. Even this was entirely free from the substructures. Beard commented upon her grit and perseverance in going on with the toxins all through the winter and spring, according to Coley's directions . . . , as also upon her present color, energy and every mark of perfect health."

SECOND COURSE OF TOXIN THERAPY: Coley advised another course of injections, which were given in October 1916 for three or four weeks, in doses of 1 to 5 minims. The maximum febrile reaction was over 101° F.

CLINICAL COURSE: The patient remained free from the disease for some months but on March 18, 1917, examination revealed injection and arborization over a space of about 2.5 cm. in the vault, not amounting to ulcerization though seem-

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ingly tending that way. "The area felt rough, suggestive of cauliflower." The general health remained good.

THIRD COURSE OF TOXIN THERAPY: Injections were immediately resumed, increased daily by half a minim. They were continued with intervals of rest through September 1918.

CLINICAL COURSE: Coley's records contained no further notes on this case, and it has not been possible to follow her since 1918. The history is included because of the detailed descriptions of the effects produced by the toxins, indicating the importance of maintaining the dosage and the frequency of injections so that the growth may be controlled.

REFERENCES: 11; 16; 99

CASE 9: Malignant myoma of the uterus, confirmed by microscopic examination by Dr. R.R. Simmons, of Des Moines (Iowa Methodist Hospital Pathological Report # 8890), and by Dr. J.E. McWhorter, Pathologist of the Hospital for Special Surgery, New York. There were also skeletal bone metastases in the femur, pelvic bones and skull, confirmed by roentgenological examination by Drs. Ralph Herendeen and Duffy at Memorial Hospital, New York.

PREVIOUS HISTORY: Mrs. E.A., aged 37, of Des Moines, Iowa. The patient had had measles, pertussis, influenza, tonsillitis and pneumonia (twice). One child, a son, was born when she was 19, a normal delivery. There were no other pregnancies. Three years after this child was born her appendix was removed at the Mayo Clinic, also adhesions were cut and a retroversion of the uterus was corrected. In 1922, the patient was in an auto accident sustaining internal injuries and indefinite head and skull injuries, but no skull fracture. Two years after this accident she had been examined and told she had a fibroid uterus. In July 1927, she consulted Dr. David M. Blum, of Des Moines, Iowa, because of weakness and a growing mass in her abdomen which had been noticed for four years. The tumor had varied in size during this interval, but had recently been of rapid growth, associated with attacks of weakness, anorexia and periodical bearing-down pains not unlike labor pains, occurring about every 20 minutes. There was also a dependent edema when she remained on her feet.

CONCURRENT INFECTION (?): Two weeks prior to observation she had an attack of gastro-enteritis, associated with pain, cramps, vomiting and diarrhea, without mucus or blood in the stool. After this attack she was unable to digest her food and vomited frequently. Two weeks prior to observation she also had a uterine

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hemorrhage while at stool (an estimated loss of a pint of blood), and thereafter there was a leukorrheal discharge while she was on her feet. There was unremitting pain in the lower lumbar region and in the region of the right hip, unrelated to motion. There was also loss of weight and a paroxysmal tachycardia at times. Physical examination was negative except that the sclerae were slightly yellow, the lips and skin waxy pale. The tumor of the lower mid-abdomen was the size of a full-term pregnancy and was somewhat fluctuating and very tender when touched, contracting at intervals like a mild labor pain. No fetal heart tones or bruit were heard. The extremities were somewhat swollen and edematous. Pelvic examination was negative, except for the old laceration of the cervix and a ballooning out above the cervix in all directions, filling the pelvis, a soft fluctuating, tender mass. Urine and Wassermann examinations were negative. Blood examination showed hemoglobin 50%; red blood cells 3,240,000; white cells 15,400; 96% polymorphonuclears and 4% lymphocytes. While under observation, albumin and pus appeared in the urine and the blood count continued to fall to 35% hemoglobin, 2,030,000 red cells, and the differential count varied between 14 and 81% polymorphonuclears and the lymphocytes from 36 to 19%. Large lymphocytes were present to the extent of 18% on one occasion. There was variation in the size and shape of the red cells. X-ray examination showed beginning bone destruction around the lesser trochanter of the femur, and similar areas about the sacro-iliac joint and the skull. Two days prior to operation she was transfused with 500 cc. of whole blood, which caused general reaction with aching pains.

SURGERY: On June 30, 1927, Blum operated, removing the uterus which weighed 15 pounds. Upon section it showed a degenerated massive fibroid which was undergoing malignant changes, and which had broken down so there was considerable pus at the cervical end of the uterus. There were many adhesions about the uterus between the intestines and the peritoneum which were separated. The ovaries were cystic and about the size of a small egg and were left untouched. Recovery from the operation was uneventful, but due to the malignancy of the condition found in the uterus and the skeletal metastases, a hopeless prognosis was made. She was put on a liberal diet including green vegetables, liver, iron and hydrochloric acid.

TOXIN THERAPY (Parke Davis XII): In view of the multiplicity of the metastases, it was thought inadvisable to submit her to x-ray or radium treatment, and so on July 21, 1927, the toxins were begun by Blum, the initial dose being 2 minims (four times more than Coley usually advised as an initial dose.) This was repeated the next day. July 23, 1937, she received 7 minims in the morning and 10 minims in the afternoon, but not until July 24, when the dose was increased to 15 minims, was there a severe febrile reaction, 105° F. On July 25 she received 23 minims; July 26, 20; and on July 27, 25 minims. Following these injections her temperature varied from 100° to 102.4° F. Only nine injections were given, but the amount

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at each dose was a great many times larger than Coley had ever given in so short a time. Due to financial problems the patient had to be transferred to the State Hospital, where no further treatment was given. At the University of Iowa further x-ray studies were made, which confirmed the diagnosis of multiple bone metastases, but no further treatment of any kind was given.

CLINICAL COURSE: The patient regained her health and strength and returned to work, and by November 30, 1927, she was well enough to motor 100 miles. She remained in good health, working as a stenographer when last traced in July 1933, six years after onset.

COMMENT: This case indicates that even rather weak preparations of the toxins can produce permanent results if given aggressively from the beginning, in sufficiently large doses to compensate for their lack of potency. It is possible that Blum did not make very deep injections, for he reports the formation of several sterile abscesses in the buttocks which opened spontaneously and drained for several days. These large intramuscular doses may have been absorbed slowly, with a cumulative effect sufficient to produce a permanent result. In analyzing this case it must be remembered that very few cases remained free from recurrence with such a short period of treatment. The effect on the disease of the toxins generated by the attack of gastro-enteritis and beginning infection near the cervix just prior to operation should also be considered because some enteric organisms produce toxins of high tumor-destructive potency.

This case greatly impressed Coley, who compared it with Christian and Palmer's famous case (12), and Lilienthal's case (54). Coley stated: "(These cases) lead me to wonder whether I have not been too timid in some cases in pushing the dosage to the limits of tolerance." (26)

Brooks and Thomason have reported a case of malignant myoma of the uterus with metastases to the upper left femur. In summarizing their case the writers stated: "Sarcoma of the uterus is a rare neoplasm, probably occurring in not more than one per cent of patients who are operated on for uterine fibromyomas. Metastases from sarcoma of the uterus are most common in the lungs, peritoneum, lymph nodes, liver and kidneys. Little has been written concerning metastases of uterine sarcoma to bone. We were able to find only three cases reported, and we know of one questionable case through personal communication." (26)

REFERENCES: 16; 26.

CASE 10: Recurrent proliferative sarcoma of the endometrium of the uterus, with a solitary metastases in the right lung, confirmed by microscopic examination

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following operation at St. Paul's Hospital, Dallas, Texas.

PREVIOUS HISTORY: Mrs. S.L., aged 37; the family history was not recorded. Menses began at 12, a regular 27-28 day cycle, lasting four to seven days. The patient had two pregnancies, both children were born by Caesarian section, the tubes were ligated. In November 1957 because of excessive weight gain, she consulted a physician and was put on a reducing diet: she was 5 feet 3 inches and weighed 257 pounds. During the next six months she lost 68 pounds. Onset, in this period, despite the weight loss, her abdomen increased in size and she had a sense of pressure in the pelvis. Following her menses in late April 1958, she had a pinkish discharge which persisted. She was admitted to St. Paul's Hospital in Dallas, Texas on May 4, 1958 with a clinical diagnosis of ovarian tumor. Examination on admission revealed the abdomen was distended by a firm, hard, irregular mass extending almost to the scyphoid which did not impinge on the vaginal fornices and was slightly movable. There was no particular tenderness. The pinkish discharge from the os was reported as Class II on smear. The patient's movements were definitely restricted by the size of the mass. Chest films revealed a 1 cm. circular density in the middle lobe of the right lung.

SURGERY: An exploratory operation was performed on May 9, 1958. The tumor involved the uterus, the bladder and the lateral pelvic wall. Because of technical difficulties, a supracervical hysterectomy and bilateral salpingo-oophorectomy was performed. The ovaries contained multiple simple cysts. Her postoperative course was complicated by ileus but she was discharged improved on the 12th postoperative day.

CLINICAL COURSE: During the next six months the sarcoma recurred in the right flank. By November 1958, there was a firm irregular mass extending almost to the umbilicus.

TOXIN THERAPY (*Johnston XV*): Injections were begun on November 9, 1958, by Dr. Mary A. Jennings of Dallas. They were given five out of seven days for three weeks. The maximum febrile reaction was 102.6° F. Chills were of very variable occurrence. There was some slight decrease in size and softening of the recurrent mass, but the lung metastasis increased in size. Injections were continued thrice weekly after her discharge from the hospital, the dose being increased to 2 cc. undiluted, without producing really satisfactory febrile reactions or chills.

CLINICAL COURSE: The disease progressed causing death on January 15, 1959, two months after the first toxin injection was given and about a year after onset.

COMMENT: Only a few very obese patients have received toxin therapy. They do

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not seem to respond as well. Note that in this case treatment was delayed until an extensive recurrent mass was present as well as pulmonary metastasis.

REFERENCES: 11.

CASE 11: Inoperable leiomyosarcoma of the uterus, confirmed by microscopic examination at Knickerbocker Hospital. The report stated: "The uterine tissue consists of fine fibrous stroma densely infiltrated with atypical irregularly-shaped and staining cells, some round and some spindle, showing numerous mitotic figures. Both ovaries showed fibrosis and follicular cysts but no tumor infiltration."

PREVIOUS HISTORY: Miss D.V.W., aged 26, social worker. The patient's father had died of cancer of the stomach at the age of 63. Otherwise the family history was negative. The patient had measles as a child. The menses began at 12 and occurred irregularly at five to six week intervals. Early in 1918, the patient had typhoid fever, the ambulatory type, being ill for about five or six weeks.

SURGERY: This was complicated by intestinal obstruction, for which a laparotomy was performed in May 1918, by Dr. Douglas H. Stewart.

CLINICAL COURSE: Onset, in February 1920, the patient developed a sticking pain in the left flank, radiating to the small of the back. The pain prevented deep breathing. Shortly thereafter the patient became aware of a thin watery vaginal discharge which was often bloody between periods. She was advised to have an exploratory operation but nothing was done for several months. The discharge persisted and there were several hemorrhages. Dr. West was consulted and stated that the condition was inoperable.

SURGERY: Finally, in early November 1920, Stewart decided to perform an exploratory operation. The patient was admitted to Knickerbocker Hospital on November 8, 1920. Abdominal palpation revealed marked tenderness over the lower abdomen. The vagina was filled with masses of tumor, apparently originating in the uterus. An exploratory laparotomy was performed on November 9, 1920, through a midline incision. The right ovary was found attached to the abdominal wall, and being cystic was removed. The left ovary was also cystic and was removed. The uterus was the site of a tumor which had invaded the supravaginal portion of the cervix and extended down to fill the vagina. Hysterectomy, which had been planned, was found to be impossible. The abdomen was closed. The vagina was explored and a pedunculated tumor mass arising from the uterus was delivered and removed by morcellement. This was chiefly for purposes of biopsy, since there was extensive and widespread involvement surrounding the

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urethrae, extending up into fornices and into the uterus. There was no involvement of the abdomen.

INDUCED INFECTION: On November 9, 1920, in the hope of producing a local streptococcic infection, Stewart packed the vagina with gauze dressings removed from infected leg ulcers. This packing was left in for six days. On the fourth post-operative day the temperature rose to 102° F. and it did not subside to normal until the eighth post-operative day. (The records do not state whether a true streptococcus infection occurred.) Further dressings were placed in the vagina on the 6th, 9th, 10th, 11th, 13th, 16th, 20th, 21st, 24th and 27th post-operative days. Apparently there was some septic absorption because during this period the patient was pyretic, the average rise in temperature being one or two degrees, the maximum 102° F.

On January 7, 1921, intravenous injections of toxins were begun by Stewart, the initial dose being 18 minims. This caused a febrile reaction of 104.8° F., and the temperature did not reach normal for three days, when a second injection was given. This caused a fever of 100.8° F. No injections were given during the next week, and thereafter injections were continued two or three times a week, gradually increasing the dose. The sixth injection of 32 minims on January 21, 1921, caused a febrile reaction of 103.8° F., with a chill within four hours after injection. However, 35 minims on January 24 gave no reaction until the following day when the maximum temperature was 102° F. The maximum febrile reaction of the entire treatment occurred on February 9, and was 105.2° F., with a chill.

During the course of local and systemic treatment all bleeding and discharge ceased and the infiltrating growth disappeared completely. The patient was discharged from the hospital on February 27, 1921, much improved. Injections were continued at home, the total duration of therapy being seven months.

CLINICAL COURSE: The patient regained her former health, and remained entirely well for the next thirteen years. In May 1933, at the age of 38, she developed pain radiating down the back of the right leg and also some pain in the back. She also developed some constipation requiring enemas. There were no bladder symptoms, no weight loss and no change in the patient's strength or endurance. She continued her regular activity as a probation officer. Examination on admission to Memorial Hospital on August 1, 1933, showed a well-nourished and well-developed woman of 38 in good general condition. There were no palpable masses in the abdomen, but there was extensive induration by nodular masses from 1 to 1½ cm. in diameter extending throughout the right parametria and also posteriorly. Otherwise the examination was negative. The provisional diagnosis of Duffy was recurrent sarcoma of the uterus. Dr. William J. Hoffman also saw the patient and stated that he was not convinced that she had a recurrence, but that possibly the induration might have been a normal virginal cervix thickened by

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scar tissue and the fibrous remains following regression of the extensive inoperable sarcoma under toxin therapy in 1920.

FEVER THERAPY & RADIATION: However, it was decided to try fever therapy, since the patient had responded so well to toxin therapy twelve years before, and since it could not be determined whether she had a recurrence or not. During the next 15 days she received eight artificial fever treatments with simultaneous radiation over the pelvis (4800 r. through 4 different ports). The temperature reached 102° to 104° F. by mouth, 103.4° to 105.4° by rectum. The patient tolerated the treatment well and was cooperative. One treatment caused a good deal of discomfort from hot spots in the fever therapy bag. The patient was discharged on August 19, 1933.

CLINICAL COURSE: She returned for examination on November 21, 1934, or 15 months later. Dr. William T. Healy reported at this time that she did not need further radiation. Palpation still revealed multiple nodular masses crossing over the vaginal vault out into both broad ligaments, firmly fixed, very hard. The right groin appeared to contain a node.

The patient was given four more x-ray treatments in March 1935, 600 r. each to 4 areas: left, right, anterior and posterior. There was no change in the condition. Except for being somewhat apprehensive about her health, the patient remained well until about 1954 when she developed hypertensive and arteriosclerotic heart disease and an aortic aneurism. She continued to work as a probation officer in Brooklyn until her final illness, acute bilateral bronchopneumonia. She died in Doctors Hospital, three days later, May 2, 1964, at the age of 64. Three or four hours before she expired she had a coronary occlusion, but death was regarded as due to the pneumonia. It occurred 44 years after onset of her neoplasm.

REFERENCES: 6; 11; 16; 60a.

**SERIES H: EPITHELIOMA OF THE VULVA TREATED BY COLEY
TOXINS: 1 CASE
BRIEF ABSTRACT**

Only one case of epithelioma of the vulva with microscopic confirmation of diagnosis appears to have been treated by Coley's toxins. One case was observed of epithelioma of the vulva in which a concurrent streptococcus infection developed causing complete regression without recurrence or metastases (16).

COLEY & DAGGETT: Mrs. E.I., aged 49; epithelioma of the vulva with metastases in the left groin. Date of onset unknown; chronic suppurative Bartholinitis for 2 yrs.; complete excision May 16, 1913; metastasis on left iliac fossa with constant burning sensation; x-ray to this area for several weeks early 1915; Coley biopsied area prior to Tracy XI toxins April 9, 1915: 29 i.m. in 52 days; mild reactions; toxins continued by Daggett with marked regression by mid-June 1915; *gained a pound a week for several weeks that summer*; recurrent lesions developed; first regressed, 2nd given x-ray treatments, September 1915; further toxins September-October (14 in 48 days); mass in left groin dissected out October 25, 1915; abscess in wound; i.m. toxins in hips resumed by Daggett; *definite softening and narrowing of recurrent area following marked febrile reaction*; injections caused hard indurations on hips; *pain lessened when toxins were given*; *general condition remained good*, but disease was not controlled, death July 27, 1916. (16)

5

**SERIES I: CASES INVOLVING THE CERVIX, UTERUS OR VAGINA
WITH CONCURRENT INFECTION, INFLAMMATION OR FEVER
BRIEF ABSTRACTS**

Years Traced
After Onset

INOPERABLE CHORIOEPITHELIOMA: 5 cases infected spontaneously.

1. VON FRANQUE: L.M., aged 25; malignant chorioepithelioma uterus, onset 8 weeks post-partum; hemorrhages or bleeding for 6 months; very anemic; June 1897: curettage, carbolated alcohol injected into uterine cavity; *marked fever, sepsis lasting 11 days*; 2nd curettage 18 days after sepsis subsided; *no trace of malignant elements found*; no recurrence; had two more normal pregnancies; last traced 1903. (101) over 6

2. LANGHANS: Adult; recurrent chorioepithelioma vagina, primary nodule size of walnut developed following normal confinement 1900; removed with sharp spoon, base cauterized; local recurrence 14 days later; *suppuration; necrotic tumor mass discharged, healing*; well and free from recurrence 10½ months after onset. Not traced subsequently. (52) ?

3. NOBLE: Mrs. D., 24; inoperable chorioepithelioma; onset followed miscarriage; growth filled pelvis, infiltrated omentum, bladder; November 17, 1900: incomplete removal; *convalescence was febrile for 6 days*, (type of infection unknown); *remains of growth on fundus of bladder disappeared*; end-result unknown. (77; 85) ?

4. HÖRMANN: Mrs. H.E., aged 36; inoperable chorioepithelioma uterine body infiltrating surrounding tissues, 2 metastases in vaginal wall (confirmed microscopically); incomplete curettage; prognosis hopeless, symptoms of pulmonary metastases; cachectic; metastatic nodule on in-troitus excised; April 30, 1901: *post-operative infection*, chills, fever (41° C. at first, for weeks it was 38-39° C.), constant mucopurulent discharge; only treatment constant uterine irrigation; *complete disappearance all evidence disease*; regained normal health; became pregnant 12 months later, normal pregnancy and confinement; last traced alive and well. (28; 45) Almost 3

5. HEARIN: Aged 28; malignant chorioadenoma destruens of the uterus with pulmonary and pelvic metastases; onset, intermittent spotting late November 1957, continued until curettage January 15, 1958; uterus size of 5 month gestation; large amount grape-like material evacuated; considerable bleeding; 2nd curettage March 23, 1958; persistent trophoblastic tissue; *postoperative infection, chills, fever 103° F. or more for over 2 weeks*, antibiotics given; readmitted April 9, 1958; 3 × 3 cm. stony hard mass in left adnexa; metastases present in both lungs; transfusions; panhys-

SERIES I: BRIEF ABSTRACTS

Years Traced
After Onset

terectomy, bilateral salpingo-oophorectomy, April 12, 1958; large tumor on posterior uterine wall and another large nodular mass in region of bladder extending to pelvic wall; latter could not be completely removed; *it slowly decreased in size*; by August 16, 1958 the multiple nodular lesions in lung had mostly regressed; "*amazing improvement, complete regression occurred*"; patient entirely well 1976. (11; 43)

18½

INOPERABLE CARCINOMA: 3 cases were found in which acute erysipelas or sepsis caused complete regression in inoperable cancer of the uterus, but as there was apparently no microscopic confirmation of the diagnosis in these cases, they have not been included. They were reported by Mosengeil (63), Bidlot (5) and Mazzoni (60). Another case of uterine carcinoma reported by Lomer recovered following incomplete removal. This patient sustained a severe third degree burn. This case history has been abstracted in detail. (56)

OPERABLE CARCINOMA: 8 operable cases of cervical or uterine cancer (7 carcinoma, one sarcoma) were found in which an acute infection or fever developed before or after operation. All eight remained free from recurrence 5-20 years later. However, it is not clear whether the diagnosis was confirmed microscopically in three of these cases, and so only five have been included. It may be of interest to cite them all briefly.

The first, in 1878, was reported well 20 years afterward by Freund and cited by Lomer (1903) as an example of the effects of post-operative infection or inflammation on prognosis. (See below Case 1.) (37; 56)

Lomer cited Lewer's case, a squamous cell epithelioma of the papillary type in which there was a pre-operative infection (pyometra) and during operation the whole operative field became inundated with very fetid pus. This case remained free from recurrence when last traced five years later. (See below Case 2.) (52; 56)

Lomer also cited Thorn's experience; he had three cases, in two of which, because there was inflammation in the parametrium, a high amputation of the cervix was performed rather than a total extirpation. In one of these parametritis flared up after operation, lasting four weeks. These three cases remained well and free from recurrence when last traced 6½ to 8½ years later. In all three fever to 39° C. occurred. (56)

MALARIA: Jovin (1933) reported two cases of pavement cell epithelioma (one of the vagina, one of the cervix) in which malaria developed, causing complete

SERIES I: BRIEF ABSTRACTS

regression. The patients remained well and free from recurrence when last traced three years later. (50)

UTERINE MYOMA: Gray reported a case of multiple myomas of the uterus with concurrent respiratory and urinary infections and septicemia (*Escherichia coli* and *Salmonella suipestifer*) with fever to 105.4° F. Gray stated he had never seen such changes in uterine myomas; most of them contained extensive suppurating areas of necrosis. (40)

UTERINE SARCOMA: A case of inoperable sarcoma of the uterus, in which concurrent fever and urticaria developed was observed at Memorial Hospital in an adult: inoperable myosarcoma uterus; date of onset not given; exploratory operation; condition hopeless, tumor had spread through whole pelvis and in mesenteries, soft, very vascular, hemorrhagic; biopsy; radium bomb; no evidence of radiosensitivity; mass failed to regress at all; just before completion of treatment and within almost a matter of hours, a dramatic change occurred: *patient developed high fever, urticarial rash, high eosinophilia, and within a few days lost kilos of tumor and ascitic fluid; tumor entirely disappeared.* About 5 years later developed some insignificant lesion of cervix; received small amount of radium; again showed hypersensitive reaction: alive and free from disease at least 10 years after regression under fever and intense inflammatory reaction. (89)

SERIES I: DETAILED HISTORIES

INOPERABLE CHORIOEPITHELIOMA:

CASE 1: Typical malignant chorioepithelioma of the uterus. (See ref. # 101 for detailed report.)

PREVIOUS HISTORY: Mrs. L.M., aged 25. The patient had been delivered of a child on January 17, 1897. Onset, eight weeks later she had a uterine hemorrhage. Bleeding continued until the patient was admitted to the hospital on June 15, 1897, about three months later. At this time she was highly anemic and cachectic, the anemia being regarded as "different from the type seen in myoma." The cervical canal was dilated sufficiently to admit the index finger. The uterus was retroverted and enlarged, and the uterine cavity contained soft, easily bleeding, crumbling pieces of tissue, similar to placental tissue. Clinically the condition was regarded as "definitely malignant".

SURGERY: A curettage was performed under anesthesia and the uterine cavity was injected with 20 percent "carbolic alcohol."

CONCURRENT INFECTION: On the day of the alcohol injection there was a rise in temperature, chills and icterus. The following day there was marked sepsis, the temperature being 41.4° C., the pulse 172. The prognosis was regarded as hopeless. The uterine cavity was douched with lysol and alcohol (50%). The patient remained septic until the eleventh day when the temperature returned to normal.

CLINICAL COURSE: Because of the microscopic findings, a second curettage was performed 18 days after the infection subsided, on July 17, 1897, and it was found that the uterus had become very small and mobile, and there was very little tissue to be curetted; there was "no trace of the malignant elements which had been present prior to the infection", and the uterine mucosa was in a state of regeneration and cicatrization. Microscopic examination showed "round cell infiltration and transformation into fibrillar connective tissue". Von Franque believed that the combination of the curettage and the sepsis had destroyed the neoplastic cells before they could produce metastases. By July 24, 1897, the patient was regarded as cured and was discharged. She was seen periodically and remained in good health when last traced in 1903, over six years after onset. In these six years she had two more children.

In reporting this case Von Franque cited a similar one observed by Zagorjansky-Kissel. This patient had "chills and bloody sputum" which ceased later. She remained well 15 months after operation and infection. Von Franque stated that he believed that even when tumor cells had reached the blood stream and have caused metastases, these may also regress following operation and sepsis,

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the reason being the "organism's defense mechanism." He gave 41 references to the literature on chorioepithelioma and uterine cancer.

REFERENCE: 101

No detailed history is available for Case 2.

CASE 3: Inoperable chorioepithelioma which had perforated the fundus uteri, confirmed by microscopic examination following hysterectomy.

PREVIOUS HISTORY: Mrs. D., aged 24. The patient had had two pregnancies; the first had ended in miscarriage in the fourth month in November 1899, and the second in the sixth week, on August 15, 1900. The previous history was noncontributory. The menses were normal from the age of 13 to 23 years. During the year prior to admission they had been irregular (three to six weeks), and there had been marked pain one week before and also during flow. Since the last miscarriage the flow was constant, being profuse during the first two weeks. The patient was admitted on November 14, 1900. A tumor having the general characteristics of a fibroid was found connected with the cervix.

SURGERY: A supravaginal hysterectomy was performed on November 17, at which time it was apparent that the condition was malignant. The growth filled the pelvis, having a dark bluish, matted appearance resembling a hematocele covered by a membrane. The omentum was adherent to the bladder, and apparently the tumor had infiltrated both. It was impossible to remove a portion of the growth on the fundus of the bladder. The prognosis was regarded as hopeless. Gauze drainage was employed.

APPARENT CONCURRENT INFECTION: Convalescence was febrile until the sixth day, after which it was uninterrupted. No details as to the type of inflammation or infection present were given.

CLINICAL COURSE: The patient regained her former health. The remains of the growth regressed slowly and completely. She remained well in September 1902, two years after onset, when the case was reported by Dr. Charles P. Noble, Surgeon-in-Chief of the Kensington Hospital for Women, Philadelphia.

REFERENCES: 77; 85.

CASE 4: Inoperable chorioepithelioma of the uterine body with metastases in the vaginal wall, confirmed by

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microscopic examination of two metastatic nodules which were found to consist of typical chorionic giant cells and residual masses which penetrated deep into the muscular structure and produced atrophy and destruction of the muscular fibers. There was clinical evidence of pulmonary metastases. A second microscopic examination was made in May 1901, of the final curettage and metastatic nodule by Professor E. Albrecht, who reported "undoubtedly chorion epithelioma."

PREVIOUS HISTORY: Mrs. H.E., aged 36. The patient had had four children. Her periods had been irregular since July 1, 1900. After a lapse of two months she had an excessive hemorrhage from the uterus on September 15, 1900. Three days later she passed lumps of tissue and masses like portions of skin. She was treated for subinvolution of the uterus following abortion, with hot douches, etc. Hemorrhages ceased, but recurred six weeks later, and on November 12, 1900, there was a very active hemorrhage. The uterus at that time was the size of an orange, its surface smooth.

SURGERY: A curettage was then performed, and the microscopic examination was: endometris post-abortionum, definite islands of deciduoma malignum and granular hypertrophy.

CLINICAL COURSE: After the curettage the hemorrhages ceased for a considerable period, but ultimately returned in irregular form. They frequently contained dark brown fragments of tissue, sometimes masses of whitish substance. The uterus was again the size of an orange. The patient was admitted to the University Gynecological Clinic in Munich in March 1901, at which time she complained of constant hemorrhage, pain in the back, dyspnea and a dry cough. The examination showed two nodules the size of cherries on the anterior aspect of the abdominal wall, somewhat to the right, with necrotic surfaces and livid discolored margins. These had the appearance of metastases. The uterus was larger than a man's fist, resting on the anterior vagina wall, and corresponded to a firmly fixed mass felt above the symphysis, which on palpation was found to have nodular outlines. A radical operation was considered impossible because the surrounding tissues appeared to be infiltrated, the uterus involved and firmly fixed.

FURTHER SURGERY: Therefore the two vaginal nodules were removed with a cutting Paquelin and a curettage of the uterine mucosa was performed. The uterine cavity was found to be greatly enlarged, the surface raw and during dilatation, bloody brown masses as well as proliferative tissue resembling mucosa were extruded from the uterus, and the greater masses were removed with the

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curette and examined microscopically as stated above. An absolutely unfavorable prognosis was given.

CLINICAL COURSE: Following this operation there was pain in the lungs, constant dry coughing, cramps, dyspnea, and marked cyanosis of the face. These symptoms were regarded as being due to pulmonary metastases. She was allowed home on request on the 16th day. She became rapidly cachectic, with blood in the sputum at one time, and was confined to bed.

FURTHER SURGERY: On April 29, 1901, she was admitted to the Krankenhaus r.d. Isar, where a metastatic nodule the size of a cherry was removed from the introitus, apparently a recurrence of one of the earlier nodules. The uterus was very large, reaching to a point half way between the symphysis and the umbilicus.

CONCURRENT INFECTION: At this time the patient apparently had some form of post-operative infection, with repeated chills and a temperature of 41° C. On May 4, 1901, another curettage was performed, and another vaginal nodule was excised. The fever continued for some weeks at 38° - 39° C., gradually subsiding. At first there was constant hemorrhagic mucopurulent discharge from the uterus. The only treatment given was constant uterine irrigation. The discharge from the uterus gradually decreased, the appetite and the general condition improved. The uterus gradually decreased in size and the cervix contracted.

CLINICAL COURSE: At the end of eight weeks the patient was able to leave her bed, and in three months she was in fairly good health. The uterus was reduced to the size of a pear, was mobile, retroflexed and the parametrium and adnexa were free from disease. The hemorrhagic discharge had long since ceased and no evidence of disease was present. In early August 1901, about three months after the infection, menstruation began to occur regularly at the usual period, lasting two days. A year later, on August 11, 1902, the patient again became pregnant. The pregnancy was normal in every way and on May 22, 1903, she gave birth to a mature fetus weighing 3,750 grams. The placenta and membranes were absolutely without pathological change. The puerperium was without incident. The periods returned six weeks after confinement. The patient was again examined by Hörmann on July 21, 1903. He found her in perfect health, holding a strong young baby in her arms. Her appearance and general nutrition was extremely good. Over the entire pulmonary region there was pure vesicular breathing, the heart tones were good. The abdominal wall was soft, with absolutely no resistance over the symphysis. A vaginal examination showed the vaginal wall to be perfectly smooth with no evidence of tumor or scars. The portio was in the spinal line, the cervix a closed transverse cleft. There was a small amount of mucofluor cervicalis. The uterus had undergone complete involution, being slightly larger than a hen's egg, of good consistency, lying on the anterior vaginal wall and absolutely movable. In the anterior vaginal wall there were three or four small myomata the size

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of peas. The adnexa were free from inflammatory changes. This was almost three years after onset.

REFERENCES: 28; 45.

CASE 5: Chorioadenoma destruens of the uterus with pulmonary and pelvic metastases, confirmed by microscopic examination following panhysterectomy and x-ray examination of the lungs.

PREVIOUS HISTORY: Aged 28. The patient had been married eight years with no pregnancies. Her menstrual periods had been regular, but she did not menstruate after October 1957, except for spotting on and off for two weeks prior to admission and rather bright bleeding on the day of admission of December 3, 1957. That day she also complained of pain in the lower left side. It was thought that the patient had a uterine pregnancy with threatened abortion, and the possibility of a left tubal pregnancy. She was discharged three days later, and was readmitted on January 14, 1958 because of continued bleeding and because of the rapid growth of a hydatidiform mole was suspected. On this admission several attempts were made with a pit drip to empty the uterus without success.

SURGERY: On January 15, 1958, evacuation of the uterus was carried out under anesthesia. A uterus the size of a five months gestation was found, a large amount of grape-like material was removed and gentle curettage was then performed. Considerable bleeding was present and a 5 cm. uterine pack was inserted. The patient received 1000 cc. of blood. The pathological report was hydatidiform mole—Hertig Grade III. No evidence of malignancy.

CLINICAL COURSE: The patient was discharged on January 19, 1958. On March 3 and 21, 1958 the frog test was still positive for pregnancy.

FURTHER SURGERY: On March 23, 1958 she was readmitted for a second curettage. Pathological report at this time was "persistent trophoblastic tissue following hydatidiform mole."

POSTOPERATIVE FEVER AND INFECTION: The patient had a temperature of 103° F. on the second postoperative day, lasting about 24 hours. After her return home she had high fever for several days and was given antibiotics by her family physician. She complained of chills and fever and low backache and pain in the left lower quadrant and down the inner aspect of her left leg when admitted on April 9, 1958. At this time there was a definite tender mass 3 × 3 cm. in the left adnexa which was stony hard. She was given erythromycin (500 mg. q.i.d.). Her temperature was 102° F. on admission and it remained between 102° - 103° F. for four days. There was no cough and no respiratory symptoms, but chest films on April

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12, 1958 revealed a great deal of abnormal density in the lungs highly indicative of metastatic chorioepithelioma. The hemoglobin on admission was 9.9 grams and transfusions were given prior to surgery.

FURTHER SURGERY: On April 12, 1958, a total hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus showed a large bluish area of probable tumor on the posterior wall in the region of the left uterine vessels. There was also a large nodular mass separate from the uterus in the region of the bladder extending out to the pelvic wall. The ovaries and tubes were grossly normal. It was impossible to remove all the implants under the bladder and on the left lateral pelvic wall. The pathologist reported it was a malignant hydatidiform mole (*chorioadenoma destruens*).

CLINICAL COURSE: The patient's temperature returned to normal the day after surgery and remained normal. On April 29, 1958, the frog test was still positive. On June 12, 1958, the patient weighed 109 pounds, her hemoglobin was 13 grams, she had no pulmonary symptoms and the left adnexal lesion was smaller though still palpable. The frog test was still positive on June 20, 1958. By August 2, 1958, she had gained seven pounds and her hemoglobin was 13.8 grams. Chest films on August 16, 1958 showed a very ill defined nodule projected at the level of the third anterior rib. Tiny fibrotic scars were seen in the lung, but the multiple nodular lesions seen four months previously were gone for the most part. The radiologist noted that "the chest showed amazing improvement in view of the past history." The patient was feeling well and had returned to work. The chest continued to be essentially negative in April 1959; there was no evidence of any infiltration in the lung nor any metastatic nodules; all the nodules previously present had disappeared without scarring and even the small ill defined nodule in the left lung present in August 1958 had completely disappeared. At this time two male frog tests were negative and a female frog was also negative for the first time. The patient remained in good health in April 1965. This was 7½ years after onset.

REFERENCES: 11; 43.

INOPERABLE CARCINOMA:

DIAGNOSIS: Inoperable carcinoma of the uterus confirmed by the clinical and macroscopic findings at incomplete operation by Drs. Lomer, Schrader and Niemeyer who stated that its malignancy was undoubted, due to the extensive infiltration into the parametrium.

PREVIOUS HISTORY: Frau R., aged 31. Onset, in November 1892, she began to

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have irregular hemorrhages from the uterus. The whole vagina was filled with soft carcinoma tissue, which bled easily when touched. The extent and origin of the growth could not be determined without an exploratory curettage. The patient was admitted September 9, 1893, 10 months after onset.

SURGERY: Dr. R. Lomer of Hamburg, Germany, attempted a hysterectomy. The growth had to be removed by morcellement. It was found that it had infiltrated behind and around the vagina, as well as into the right parametrium. Lomer believed the operation should be terminated, but the hemorrhage was so abundant that he decided to go on. The growth was very soft and friable and repeatedly the instruments "were torn out", and on the right side a large opening in the parametrium was made with ragged, crumbling walls. The operation was then terminated and the vagina packed with iodoform gauze. The patient left the operating room pulseless and therefore hot water bottles were placed on her legs.

POSTOPERATIVE BURN: From one of these bottles she received (while still anesthetized), a deep third-degree burn almost the size of one's hand. The postoperative course was uneventful. Two weeks later the burned area was covered by a hard dry leathery scab. The patient had not felt any great pain, nor complained, and the nurse had successfully hidden the burn from Lomer's attention during these two weeks. However, she could neither stand nor walk because of this burn. For many weeks Lomer attended the patient at her home, after she was discharged. The burn was dressed with camphor compresses and the limb was elevated.

CLINICAL COURSE: On March 13, 1894, she was again seen by Lomer, who stated that he was "surprised to see her not only alive but flourishing and to find that the scar was absolutely free from recurrence." She was again examined in September 1899, stating that she had never been in better health and had not needed a doctor since her recovery. She worked hard, delivering bread, arising at 4:00 a.m. and climbing many stairs, and she stood this strenuous life well, and had become fat. Lomer found the vagina smooth, and the abdominal region entirely free from recurrence or metastases. The scar of the former burn had shrunk to a diameter of 11 by 6 cm. This patient was last examined on July 30, 1903, or over 10½ years after onset. She was in good health and free from recurrence. Drs. Schrader, Niemeyer and Seeligman also observed this patient and confirmed the observation. This case was cited by many oncologists including Meyer (62) and Ewing.

COMMENT: In reporting this case Lomer wondered if the burn had had a beneficial effect on the carcinoma, citing the fact that severe burns produce toxins. He asked if such toxins may be antagonistic to cancer. He studied the whole literature on burns, concluding that red blood cells are destroyed by burns and other profound alterations of the blood are produced. Lohmann noted that cancer cells are

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destroyed by inflammatory exudates. (55) This factor may play a role in the beneficial effects of burns in patients with cancer.

REFERENCES: 55; 56.

OPERABLE CARCINOMA:

DIAGNOSIS: Epithelial carcinoma of the portio vaginalis, confirmed by microscopic examination by Binswager, who also published the case. He reported: "Carcinoma of the portio vaginalis, also in isolated carcinomatous ulcer in the fundus." This is particularly important because the disease spread by leaps and bounds. "Exploration revealed a carcinoma of the portio which was not extensive and apparently the surrounding tissues were not affected, but on microscopic examination it was found that the portio was completely involved by the carcinoma. There were deep ulcerated craters and these were covered with fatty soft tissue masses and the surrounding tissues were greatly indurated—a coarse nodular structure. The destructive process extended to the mucosa but not quite to the os uteri nor to the vagina. The lower uterine mucosa was greatly swollen but completely free from carcinoma. However, in the fundus there was a round ulcer 2 cm. in diameter with hard-walled margins with a firm nodular base. Microscopically here again there was the distinct character of carcinoma."

PREVIOUS HISTORY: Aged 37, an accountant. She had had regular menses, three abortions and six full-term pregnancies. The last confinement had occurred 14 months previously with much loss of blood. Since this time she had had hemorrhages every two weeks and finally, during the last four months, steady hemorrhages. She had abdominal pain and a foul vaginal discharge and had lost weight. At examination there was found an ulcerated cancer of the portio vaginalis.

INFECTION: Prior to operation the patient had a remittent fever, the evening temperature being 38.6° C.

SURGERY: On July 28, 1878, she was operated upon by Professor W.A. Freund, of Strasbourg, Germany. The uterus was only slightly enlarged. There was a sudden hemorrhage from the uterine artery which was controlled by compres-

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sion. A hysterectomy and left oophorectomy were performed. The operation lasted three hours.

POSTOPERATIVE INFECTION: That night the patient had a temperature of 37.9° C., pulse 92 and profuse sweating. Two days after operation she became quite ill, with fullness, aching and severe pain in the abdomen. The dressings were removed and the wound appeared to be healing normally at the upper part, but in the lower portion the skin was red and infiltrated. On the fifth postoperative day this area developed into an extensive abscess. Necrotic grayish black masses appeared in the wound, and fistulous channels led upwards. The necrotic masses were removed and the fistulae were drained. There was no further trouble and the convalescence proceeded uneventfully. The abscess wound granulated and discharged copiously. Four weeks after operation the wound had healed except for three small granulating areas. The abscess had filled in and the fistulae had closed.

CLINICAL COURSE: The patient returned to work at this time and remained well and free from recurrence when last traced by Freund in 1898, 20 years after treatment. Freund stated that this case resembled the first such operation with (abscess?) reported by Heidemann-Volkmanns (Klin. Vortrage, # 122.) He added: "It would be well to consider if this (infection) might have prevented recurrence." (56, p. 353) He also stated that if in this case an amputation of the cervix uteri had been performed, one would have thought that one had operated on a healthy individual, and would have been very much surprised to have seen a prompt recurrence in the fundus. This case indicates the absolute necessity of removing the diseased organ in toto, as in malignancy in other organs." (56)

Lomer cited this "famous case of Freund's as an example of the effects of post-operative infection or inflammation on prognosis." He added that "Freund's case was often reported as the clearest case of a spontaneous cure of abdominal carcinoma." He added: "Fever should be considered as a remedial factor in carcinoma." (56, p. 341)

REFERENCES: 37; 56.

DIAGNOSIS: Large cancer of the cervix, confirmed by microscopic examination by Mr. Targett, of the Clinical Research Association, who reported it to be a "squamous cell epithelioma of the papillary type. There is a considerable amount of keratoid change in the epithelial processes." (See 53, p. 14 for photograph of gross specimen and microphoto.) It is of interest to note the areas of granular degeneration. Possibly these changes were induced by the pyometra.

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PREVIOUS HISTORY: Aged 55. The patient was married and had had six children in the preceding 17 years and two miscarriages, both prior to the last confinement. Menopause had occurred at the age of 50, four years prior to onset. Since then there had been no menstrual discharge, but beginning in August 1894, there was a constant red discharge from the vagina, and in May 1894, for three weeks prior to operation it was offensive. The patient felt ill and worn out at the time the vaginal discharge commenced, stating that for some time she had suffered from continuous pain in the lower abdomen (exact date of onset could not be determined). She had been getting thinner rapidly. On examination by Dr. Arthur H.N. Lewers of the London Hospital, London, England, on May 17, 1895, nothing abnormal could be felt in the abdomen. On vaginal examination a large cauliflower growth was felt springing from the vaginal portion of the cervix. The uterus seemed freely movable and the body of the uterus seemed considerably larger than normal for a woman past menopause.

CONCURRENT INFECTION: The patient was admitted to a nursing home for operation. At this time her evening temperature was about 100° F.

SURGERY: On June 1, 1895, a vaginal hysterectomy was performed. Lewers stated: "At one stage of the operation the whole field became suddenly inundated with horribly fetid pus. This came from the body of the uterus and had been let out by a laceration about the junction of the cervix and body caused by traction with the volsella. The pus had previously been pent up in the body of the uterus by occlusion of the os internum, constituting the condition known as pyometra. In spite of the fact that the whole region of the wound was fouled with this fetid pus the convalescence was quite uninterrupted. (For photograph of the uterus and extensive cauliflower growth from the cervix, extending up the cervical canal to the internal os, see 53, p. 15. This also shows that the cavity of the body of the uterus had been enormously dilated due to the pyometra.)"

CLINICAL COURSE: There was no recurrence or metastases. The patient moved to Australia, but was followed periodically by Lewers. She was last traced on June 11, 1900, six years after onset, at which time she remained entirely well.

NOTE: In one other five-year survival reported in Lewers' series (Case 8), the patient had fever for over two weeks following operation. The details seemed a little too vague to include this as a separate case.

REFERENCES: 53; 56.

MALARIA:

DIAGNOSIS: Pavement cell epithelioma of the vagina, confirmed by microscopic examination.

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PREVIOUS HISTORY: Aged 35. The patient was of a robust constitution and in excellent general health. She developed an extensive cancer of the upper right aspect of the vagina which did not involve the cervix, and with no adenopathy.

RADIATION: Radium was given to three ports totalling 31 r. in five days. Ten days later the patient left the hospital.

CLINICAL COURSE: Although cautioned to return soon for further treatment, she did not return for 10 weeks, at which time she was in a weakened general condition, complaining of bloody discharges. Examination revealed that some regression had definitely taken place in the vaginal lesion, but there still existed bleeding nodules especially on the right side.

SURGERY: A biopsy of this area showed that the tumor was not undergoing radionecrosis as had been believed, but that the epithelioma was almost intact, having the same histological characteristics as the primary growth with few pyknotic figures. Dr. J. Jovin, chief of the Centre Anti-Cancéreur at Bucharest, Roumania, accordingly decided against further radiation.

CONCURRENT INFECTION: Shortly after this the patient developed a continuous fever which was at first attributed to a septic complication in the vaginal lesion. After the daily fever had lasted three weeks, the patient was much weakened. A blood examination revealed she had malaria, which was very prevalent in the district. Specific anti-malarial remedies caused prompt cure.

CLINICAL COURSE: Much to Jovin's surprise, vaginal examination revealed that the epithelioma had regressed completely, leaving the tissues soft, supple and with no trace of the former lesion. The patient remained well and free from disease three years later, when Jovin reported the case.

REFERENCE: 50

DIAGNOSIS: Inoperable non-differentiated pavement cell epithelioma of the cervix, confirmed by microscopic examination.

PREVIOUS HISTORY: Aged 42. The patient consulted Dr. J. Jovin, Chief of the Centre Anti-Cancéreur at Bucharest, Roumania, for a cancer of the cervix which had invaded the right cul de sac and juxta-uterine portion of the parametrium on the right side. Radium therapy was advised, but the patient returned home under pretext of urgent family matters.

CONCURRENT INFECTION: The patient then developed intermittent fever which for

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a long time was attributed to parametritis. Four weeks after onset of the fever a blood examination was made which proved she had malaria.

CLINICAL COURSE: Seven months after the initial examination Jovin again saw the patient and was surprised at the remarkable regression which had occurred in the cervical cancer. The induration in the cul de sac had completely disappeared. The cervix, which had been nodular, appeared almost normal, and no longer bled when touched. Another biopsy again revealed the presence of epithelioma.

RADIATION: At this time radium therapy was given, resulting in cure.

CLINICAL COURSE: The patient remained well and free from recurrence three years later, when Jovin reported the case.

REFERENCE: 50.

UTERINE MYOMA:

DIAGNOSIS: Myomas of the uterus confirmed by microscopic examination at Johns Hopkins Hospital, following hysterectomy, with concurrent prolonged septicemia from *Salmonella suipestifer*, with abscesses within the myomas.

PREVIOUS HISTORY: Negro, aged 36. The family and previous personal history were not recorded. The patient had had a tumor mass in her lower abdomen for eight months.

CONCURRENT INFECTIONS (RESPIRATORY, URINARY, E. COLI, SALMONELLA SUIPESTIFER, SEPTICEMIA): She developed a slight cold, sore throat, vomiting, diarrhea and urinary frequency. Five days after onset of these symptoms she was admitted to Johns Hopkins Hospital. She was dehydrated and weak. Her temperature was 101.4° F. The nasal mucous membranes were congested, the throat infected and moist rales were heard in the left base. Slight tenderness was present over the left kidney and bladder. The fundus of the uterus was replaced by an adherent nodular tumor extending half way to the umbilicus. The Wassermann was positive. A catheterized specimen of urine showed numerous white cells and a culture revealed *Echerichia coli*. Palliative treatment was instituted for the respiratory and urinary tract infections. After eight days cytoscopy was performed. The bladder appeared diffusely injected. The ureters were not catheterized. Following this procedure the temperature rose to 105.6° F. Blood cultures showed *Salmonella suipestifer*, as proved by agglutination. Urine culture again showed *E. Coli*. The temperature gradually subsided, to rise again a week later to 105.4° F. At this time there was definite evidence of bronchopneumonia. Three other

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blood cultures were sterile. Several transfusions were given, and there was a long course characterized by low grade fever.

SURGERY: Laparotomy was performed 111 days after admission, by Dr. Thomas S. Cullen. Numerous adhesions were found about the nodular uterus. One subserous nodule was densely adherent to the transverse colon. In freeing this nodule a cavity present within the myoma was entered and several cc. of grayish yellow purulent material was evacuated. A culture was taken. It was necessary to sacrifice a part of the outer coat of the bowel wall to free the suppurating myoma. Supravaginal hysterectomy was performed and the abdomen was closed. Convalescence was uneventful except for some drainage from the incision.

The nodular fundus of the uterus measured $13 \times 9 \times 7$ cm. On the superior surface over one nodule 4 cm. in diameter was a roughened area containing several small irregular sinuses. On section these led into an abscess cavity which almost completely replaced a small myoma. The abscess contained thick yellowish purulent material and had a thick ragged greenish-yellow lining. There were many other myomas through the wall, from 2 to 4.5 cm. in diameter, the centers of most of which were occupied by the same greenish-yellow necrosis. A few of the myomas, however, had the usual typical white appearance. The microscopic sections showed that the many necrotic appearing myomas were largely hyalinized about the margins, but the centers contained polymorphonuclear cellular debris. Surrounding the undulating hyalinized borders, a most intense chronic inflammatory reaction was seen, made up of plasma cells, round cells and foam cells. Within the inflammatory areas between the myomas were many minute abscesses containing polymorphonuclear leukocytes. This inflammation had infiltrated through the uterine wall. There were a few scattered large giant cells here and there between the diffuse round cells and plasma cells. Small groups of cells contained bright yellowish-brown granular pigment. Also there were a few scattered crystals of bilirubin, of the typical brownish starlike granules. As the uterine cavity was approached the inflammation became less intense, so that beneath the endometrium there were only a few areas of collections of round cells. The endometrium itself was covered by two or three layers of columnar cells, and had a dense cellular stroma containing a few scattered round cells and plasma cells. The glands were tubular, non-secreting and many were greatly dilated. No organisms were found in sections of the uterus. The appearance of the uterus on section was quite unusual: The myomas had greenish-yellow necrotic centers. Dr. Cullen stated that he had never seen such changes in myomas of the uterus studied in that clinic. The original source of the infection was not determined. The illness began with upper respiratory infection, gastrointestinal and urinary symptoms. It is possible that the patient had food poisoning. *S. suipestifer* is known as a common cause of food poisoning.

COMMENT: This case appears to be the only known case in which an acute concur-

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rent infection occurred in uterine myomas, causing necrosis and acute inflammatory reaction.

REFERENCE: 40.

UTERINE SARCOMA:

DIAGNOSIS: Inoperable, very vascular myosarcoma of the uterus with metastases throughout the pelvis and in the mesenteries, confirmed by microscopic examination after biopsy.

PREVIOUS HISTORY: Adult. The family and early history are not recorded.

SURGERY: At exploration by Dr. George W. Pack, the patient had a soft very vascular and hemorrhagic tumor which was wholly inoperable, being spread through the whole pelvis and in the mesenteries. A biopsy was performed.

RADIATION: Dr. Fred W. Stewart, in reporting the case, stated: "The patient was treated by a radium bomb, and as might have been expected nothing happened. There was no evidence of radiosensitivity and the mass failed to regress at all."

FEVER AND URTICARIA AND ASCITES: "Then just before the completion of treatment and within the course of almost hours, a dramatic change occurred. The patient developed a high fever, an urticarial rash, a high eosinophilia, and within a few days lost kilos of tumor and ascitic fluid. The tumor completely disappeared. What I assume happened was that some alteration occurred in the tumor protein of this patient and she became sensitized to her own protein, thus provoking an intense immune reaction."

CLINICAL COURSE: Five years later the patient developed "some insignificant lesion of the cervix for which she received a small amount of radium."

FEVER, URTICARIA, ETC.: She again repeated the hypersensitive reaction.

CLINICAL COURSE: The patient remained well when last traced at least 10 years later.

REFERENCE: 89.

**SERIES J: MISCELLANEOUS VACCINES, SERUMS OR PLANT
EXTRACTS
BRIEF ABSTRACTS**

RABIES SERUM: Inoperable or terminal uterine or cervical cancer treated by anti-rabies serum. Three cases were found in which anti-rabies serum was used. The first, because the patient had been bitten by a rabid dog, had the Pasteur treatment, recovered completely and remained well 10 years before recurrence developed. (29) The result in this case led De Pace (1902) to administer anti-rabies serum in a series of cases of inoperable or terminal cancer.

SCHMIDT'S VACCINE, prepared from pure cultures of a protozoan parasite isolated from human neoplasms. 3 Cases.

1. SCHMIDT: Aged 48, inoperable ovarian cancer recurrent 4 months after bilateral oophorectomy; numerous growths throughout peritoneum up to size of fetal head; exudate had been withdrawn eight times; marked edema right leg; metastases in pleura, patient bed-ridden, cachexia, vomiting, retention of feces; prognosis 8 weeks; Schmidt's vaccine: *pain, nausea, edema disappeared at once*; pleuritic effusion accumulated, dyspnea, paracentesis; raspberry-colored exudate aspirated twice with numerous carcinoma cells; *abdominal tumors softened, became fluctuating*; three were aspirated, yielding $\frac{3}{4}$, $1\frac{1}{2}$ and 3 litres of necrotic tumor tissue; *general condition improved, tumors continued to break down; general condition excellent 6 months after treatment begun*; end-result unknown. (86)
2. SCHMIDT: Adult, inoperable carcinoma body of uterus, firmly embedded in pelvis, hard, immovable, hemorrhages; biopsy; 4 series vaccine injections; uterus became mobile, no further hemorrhages, *complete regression; general condition improved*; final course given 18 months later to prevent possible recurrence; alive and well 13 years later. (86)
3. SCHMIDT: Adult, extensive ulcerated carcinoma, $\frac{2}{3}$ of cervix destroyed, extending into vagina and rectum; nodules in region of sphincter; free discharge, hemorrhages, violent pains, bedridden; complete course given; in 4 weeks pain, hemorrhages, discharge ceased, general health much better; *complete regression*; no recurrence; in good health 5 years later. (86)

GOAT SERUM: The following cases of uterine or cervical cancer received goat serum. Wilson used this because he had been told by a veterinary surgeon that goats never suffered from cancer, whereas the disease occurs in most other animals.

SERIES J: BRIEF ABSTRACTS

1. WILSON: Aged 68, 1899; inoperable terminal cancer of cervix; patient in dying condition; 6 oz. normal goat serum injected into basilic vein, severe general reaction, fever 102° F.; *offensive bloody discharge soon ceased, pelvis mass decreased, roof of vagina healed, patient up and about in 6 to 8 weeks; well and free from recurrence*; died 2 years later at 70, of unrelated causes. (105)
2. WILSON: Adult, 1923, advanced carcinoma involving body of uterus, acute pain, ascites; 2 injections of normal goat serum caused *complete relief of pain*; no further details given. (105)
3. WILSON: Adult, 1925, advanced uterine carcinoma uterus, villous growth protruding from cervix, acute pain; 2 injections of normal goat serum caused *complete relief of pain*; no further details given. (105)
4. WILSON: Adult, 1925; advanced uterine carcinoma with lymph node metastases; uterus and later a kidney removed; large recurrent abdominal mass, hemorrhage, fetid vaginal discharge; after 3 or 4 injections normal goat serum *mass became much smaller, pain completely relieved, patient died shortly thereafter*. (105)

PLANT PROTEINS: A few cases of cancer of the female genitalia were treated by "Autolysin" (vegetable nucleoproteins) by Beebe and Williams with apparent benefit. (3, 4, 104)

**SERIES J: MISCELLANEOUS VACCINES, SERUMS OR PLANT
EXTRACTS
DETAILED HISTORIES**

RABIES SERUM:

DIAGNOSIS: Extensive inoperable carcinoma of the portio vaginalis, confirmed by microscopic examination following biopsy.

PREVIOUS HISTORY: Aged 60, Italian. The family and previous personal history were not recorded. Apparently no treatment was given for the enormous malignant growth which was regarded as inoperable because of the age and general condition of the patient.

ANTIRABIES TREATMENT: At this time she was bitten by a rabid dog and received the antirabies treatment in Bologna, Italy.

CLINICAL COURSE: Immediately thereafter she consulted Dr. N.G. DePace, a well-known gynecologist, in regard to the enormous mass in her vagina. She did not mention to him at this time that she had been bitten by the mad dog nor that she had received antirabies serum. DePace advised against operation, regarding the prognosis as hopeless, but the patient insisted on "any cure".

QUININE THERAPY: Before attempting to remove a part of the tumor, DePace administered a series of quinine injections (Jaboulay's method) as a palliative. After about 40 days' treatment, the patient disappeared. During the quinine treatment the vaginal discharge diminished and finally ceased altogether.

CLINICAL COURSE: DePace reports: "She came back in about a year when I thought she had died." He was greatly surprised to find that the mass which had filled the vagina had disappeared. The neck and the body of the uterus were reduced to a minimum because of senility, and there remained no trace of tumor in the cervix. A vaginal examination showed that on the posterior lip a portion was redder and DePace believed this was all that remained of the former growth. The exterior orifice was very narrow. The remains of the tumor were excised and examined microscopically in various clinics, the diagnosis being confirmed by Professor Schron. In January 1912, ten years later, the patient again consulted DePace, because she had a return of her former symptoms: loss of blood, fetid discharges, pain, etc. He examined her and found all the walls of the vagina invaded by an infiltrating neoplasm, ulcerated in places, which he regarded as undoubtedly of epithelial type. There were metastases in the inguinal lymph nodes on both sides, some being the size of nuts.

Because of the importance of the case and because the recurrence was the

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best proof of the malignancy of the former growth which had regressed ten years before, DePace wished to present the patient before the Italian Society of Obstetrics and Gynecology before sending her to the Hospital of Professor Pestolozza. He urgently advised the patient to have another course of antirabies serum and quinine injections, but she absolutely refused. In reporting the case he stated that he hoped to persuade her to have the treatment at home and that he would report the final result later.

We have not found a further reference to this case. The end-result is therefore unknown. However, the case is of interest as it appears to be the only one in the literature in which a patient with far-advanced cancer of the portio vaginalis was bitten by a rabid dog, received antirabies treatment and quinine, followed by complete regression and freedom from recurrence for a period of ten years.

In evaluating the result in this case DePace stated that several hypotheses were possible: (a) that the case was one of the rare instances of spontaneous regression; (b) that the regression was due to "the neoplasm being subjected to the virus of rabies, with its own degree of virulence or to the effects of the antirabies vaccine (each one associated with quinine)". As regards the latter he then cited the fact already recognized, that certain acute infections, such as erysipelas had modified the development of cancer or sarcoma. He mentioned the cases of Bruns, Fehleisen, Durante and the attempts of other investigators including Coley to inoculate virulent cultures and filtrates of streptococcus erysipelatis and Bacillus prodigiosus. (29)

Having observed the apparently complete regression of an enormous carcinoma of the portio vaginalis in the above case following the administration of rabies vaccine following an attack by a rabid dog, DePace treated nine cancer patients with injections of antirabies serum:

CASE 1: Terminal cancer of the liver: treatment was begun a few weeks before death, and only a few injections were given, without effect.

CASE 2: Inoperable cancer of the cervical lymph nodes in a hopeless condition with a prognosis of a few months, hemorrhages, pain, etc. As soon as antirabies serum was begun, *there was a marked improvement: the pain and hemorrhages ceased, and pieces of necrotic tumor were discharged. The general condition improved and after two weeks the patient was able to return to work as a cook.* The improvement lasted for some time. About 70 injections were given at intervals of 8 to 10 days. Between injections the symptoms returned, but not as strongly. The patient lived for two years in fairly good health. The end result is not recorded.

CASES 3 & 4: Cancer of the uterus, very advanced terminal cases. *There was great*

SERIES J: DETAILED HISTORIES

improvement during the first ten days, necrotic tumor tissue was eliminated, and there was a relief of pain and cessation of hemorrhage, improvement in respiration, digestion, etc. After a short while both patients became worse again and died within two to four months. These patients had only about 15 injections each.

CASE 5: Epithelioma of the cheek. No effects noted.

CASE 6: Cancer of the cervical canal, very advanced. Although the treatment was stopped at the end of 20 days at the patient's request, there was *diminution of the pain and of the fetid, bloody discharges.*

CASE 7: Cancer of the portio vaginalis, diffused, inoperable. After a few injections the patient refused further treatment.

CASE 8: Cancer of the portio vaginalis, diffused, inoperable; 30 or 40 injections were given. *She remained well for two years.* At the time the case was reported her health was failing, however.

CASE 9: Ulcerating, infiltrating cancer of the anterior portion of the vagina (peri-urethral), involving the portio. Urination became difficult, and it was necessary to catheterize the patient almost daily; 30 injections of antirabies serum were given in two series; the first of 20, the last of ten, with a week's rest in between. *During treatment there was an improvement in the general condition.* The patient then lost bladder control. The disease was fatal in five months.

In evaluating these cases DePace stated he did not believe that these few trials would allow us to form an opinion of this method which was discovered by coincidence. However, he stated that in all the gynecological cases, in addition to the evacuation of large pieces of necrotic tumor tissue, it was noted from the beginning of the rabies serum therapy that the general condition improved, the hemorrhages were controlled and the pain diminished. This improvement continued for a certain length of time and then the disease was no longer controlled and proved fatal. In Case 2 there was especially marked improvement. DePace believed that the rabies serum, with or without the administration of quinine, had had a cytolytic effect on the neoplastic cells in these cases.

REFERENCES: 29; 30.

SCHMIDT'S VACCINE:

CASE 1: Recurrent inoperable carcinoma of the ovaries, confirmed by microscopic examination after exploratory operation. There were multiple metastases throughout the peritoneum.

SERIES J: DETAILED HISTORIES

PREVIOUS HISTORY: Aged 48. The family and early personal history were not recorded. The patient had had both ovaries removed for cancer, and four months later, recurrence had developed. Six months after the operation, examination disclosed numerous small and larger tumors up to the size of a fetal head throughout the peritoneum. Ascites had been withdrawn on eight occasions. There was marked edema of the right leg. The patient was bedridden, as the general condition was very bad, with distinct cachexia, considerable vomiting, and retention of feces. The case was entirely hopeless. The surgeon and family physician estimated that the patient might live about two months.

SCHMIDT'S NOVANTIMERISTEM VACCINE: (Prepared from pure cultures of a protozoon parasite isolated from human neoplasms.) With the first injections pain and nausea disappeared. The edema in the right leg vanished. The patient reacted to injections in dilution "C" with temperatures of 101°, 102° and twice 102.2° F. Following this the general condition deteriorated. Dr. Wolfgang Schmidt apparently treated this case personally.

PLEURITIC EFFUSION: Originating in a metastasis in the pleura, a pleuritic effusion accumulated. There was dyspnea and an exploratory puncture revealed a raspberry-colored exudate with numerous carcinoma cells. "On account of the reactions in the tumors, caused by the injections, nausea and abdominal pains reappeared and ascites necessitated a fresh withdrawal of fluid. After the reaction had subsided, it was noted that the tumor which had been the size of a fetal head had softened and become fluctuating. Pain and dyspnea disappeared. The patient now had a good appetite, was cheerful, and able to be up for two hours daily. No further exudation accumulated.

FURTHER VACCINE THERAPY: The injections repeatedly had to be suspended on account of frequently recurring febrile reactions (temperatures up to 100 ° F.). Of the numerous tumors in the peritoneum, three could be punctured after complete liquefaction and yielded 3/4, 1½ and 3 litres, respectively. The general condition remained good.

CLINICAL COURSE: Six months after treatment was begun, the continued breaking down of the remaining tumors could be confirmed, and the general condition was excellent. The end-result is unknown, as the case was published at this time.

REFERENCE: 86.

CASE 2: Inoperable carcinoma of the body of the uterus, confirmed by histological examination after biopsy.

PREVIOUS HISTORY: Adult. The uterus was firmly embedded in the pelvis, hard

SERIES J: DETAILED HISTORIES

and immovable. The patient had hemorrhages. A biopsy was performed. Radical operation was impossible.

SCHMIDT'S NOVANTIMERISTEM VACCINE: Injections were given by Dr. Schmidt. The patient appeared to be cured after the fourth series had been completed. The uterus was mobile and there were no further hemorrhages. The general condition was excellent. The patient was given another course of injections 18 months after this in order to make sure there would be no recurrence.

CLINICAL COURSE: The patient was traced well and free from recurrence 13 years after treatment was begun.

REFERENCE: 86.

CASE 3: Inoperable ulcerated carcinoma of the cervix, confirmed by microscopic examination.

PREVIOUS HISTORY: Adult. The patient had an extensive cancer which had destroyed two-thirds of the cervix and extended into the vagina and rectum. There were large open ulcers around the cervix and carcinomatous nodules in the region of the anal sphincter. There was a profuse discharge, hemorrhages, violent pains and the patient was bedridden.

VACCINE THERAPY: Schmidt's "Novantimeristem" vaccine was used, and a complete course was given by Dr. Schmidt. After the first four weeks the general condition was much better; the pains, hemorrhages and discharges ceased. Eight weeks later the tumor was clean and showed a tendency to cicatrize. Some of the nodules were considerably smaller, others had disappeared. The patient was then able to exercise. In another three weeks complete healing took place with disappearance of all the remaining nodules. The patient was completely healed and in better health than ever 4½ months after beginning treatment.

CLINICAL COURSE: She remained in good health and free from recurrence when last traced five years later.

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