been seriously considered until rather recently. However, several investigators have reported the inhibitory effects of intercurrent contagious diseases on tumors in mice or rats (97). Bashford was one of the first to note that mice convalescent from contagious diseases are refractory to tumor transplants (53).

Clinical Course: The patient's condition continued to improve and a series of x-ray pictures taken by Dr H. B. Philips showed the gradual regression of the tumor mass during the next two years. On September 19, 1926, Philips reported: "The irregularity in contour and diminution in size indicates a partial collapse of the tumor. There appears to be considerable regeneration of the posterior ribs, which previously showed marked pressure erosions, and considerable regeneration of the resected portion of the eighth rib has taken place." A month later roentgenological examination showed a normal chest. In February 1928 Dr Leopold Jaches examined the patient's chest and reported: "No evidence of abnormality in the lungs, diaphragm, heart and aorta. The eighth rib shows evidence of previous resection, but it has regenerated almost completely", (film No. 11,846). The patient remained in perfect health and was seen periodically by Pollak and Lilienthal during the next 21 years. She was presented at various medical meetings by Lilienthal, who on one of these occasions stated: "This is not the first time I have noted a continuance of the regression in cases of malignancy after the treatment with Coley's toxins had been discontinued. My experience with this form of therapy in a number of other instances has been so favorable that I would strongly recommend its use in inoperable sarcoma and also as a prophylactic postoperative treatment after surgical removal of operable tumors as well" (66). The patient reported in November 1949 that she had had a son, her first child, $3^1/_2$ months previously and added: "The baby was a natural birth and I had a wonderful pregnancy." Her average weight in 1949 was 150 pounds. The patient was last traced in good health on January 1, 1953, or over 28 years after the toxins were begun. Her only complaint at this time was a low basal metabolism (minus 25) and that she was overweight (165 pounds), her height was 5 feet 3 inches (77).

Note: Pollak's observations of the apparently stimulating effect of the toxins on the rate of healing of the operative wound are of interest, as this effect was also reported by other surgeons using the method, and is apparent in many of Coley's cases, especially osteolytic bone tumors, where extensive areas of bone destroyed by the neoplasm completely regenerated following toxin therapy.

References: 53, 67, 76, 77, 97, 98.

CASE 29: Reticulum cell sarcoma of the tibia, recurrent after amputation, with metastases to bone and soft parts, confirmed by roentgenologic examinations by Dr Frank Liberson, and microscopic examinations by a number of pathologists including Dr Fred W. Stew-

art and Dr James Ewing of Memorial Hospital (Pathological report No. 5677). In 1926 the diagnosis of the Bone Sarcoma Registry was Ewing's tumor or endothelial myeloma; all the members of the Bone Registry Committee agreed that it was a highly malignant tumor (*2*, Case No. 1143).

Previous History and Treatment Other than Toxin: G. B., male, age 32 (in 1926), master mariner. The family history was negative as regards malignancy, tuberculosis, diabetes or venereal disease. The patient had always been in good health until he sustained an injury to the left leg over the tibia on February 25, 1918, while on a voyage to England. He was thrown against a hatch, and the bruise took six weeks to heal, after which the leg appeared normal. Thirteen months later, while again at sea, he began to have severe pain at the spot where the skin had been bruised, accompanied by swelling and fever. The pain, but not the swelling, temporarily disappeared in about a week, followed by recurrent attacks of pain every two or three weeks for a period of three months, during which time the patient was making a voyage from Australia to New York. Shortly after his return to New York he sought medical aid. A roentgenogram of the leg revealed osteomyelitis of the tibia, and an operation was performed at St. Joseph's Hospital, Paterson, New Jersey, on August 19, 1919. He was discharged on crutches, on November 23, 1919, still suffering pain. He remained at home for the next four months, but did not improve very fast. On March 31, 1920, he was admitted to the Marine Hospital at Stapleton, Staten Island. He remained four months during which time he received physiotherapy, which relieved the pain, and a tonsillectomy was performed. He went back to sea and then returned to the hospital for two weeks in March 1921, after which he again went back to sea. On March 3, 1924, he was readmitted to the Marine Hospital for a chronic appendicitis and bilateral inguinal hernia. He was discharged on March 28, 1924, still having occasional attacks of pain in the leg. Six weeks later he was readmitted and remained under treatment $4^1/_2$ months, or to September 25, 1924, receiving baking and ultra-violet rays to the affected leg. At the time of his discharge all pain had gone, there was no swelling and the condition appeared to be cured. However, an x-ray taken on October 2, 1924, showed marked cortical thickening and irregularity of the middle third, and marked periosteal roughening with bony projections, especially anteriorly. At this time the diagnosis was still regarded as osteomyelitis (6, Fig. 1, p. 189). On April 24, 1925, the patient noted a swelling of the tibia a little higher up than the site of the operation in 1919. He was readmitted to the Marine Hospital and operated upon in May 1925. Osteomyelitis was again found, with free pus in the marrow and a sequestrum of dead bone. Two weeks after this operation the bone began to swell and ache just below the knee. An x-ray taken on June 30, 1925 (6, Fig. 2, p. 190), showed marked decalcification of the upper third of the left tibia with only part of the skeleton of bone remaining in the

anterior upper third of the tibia, appearing like a bone dissolving under corrosive fluid. Shortly afterwards, injections of sodium iodide were begun, and given every third day intravenously, until a total of 50 grams had been given. Another x-ray, taken September 13, 1925 (6, Fig. 3, p. 191), shortly after the sodium iodide treatment, showed further advance of the erosion, with pathologic fracture at the junction of the upper and middle thirds of the tibia. (Coley stated that this picture was quite characteristic of endothelial myeloma.) On September 11, 1925, a piece of bone was removed which was reported as "Myelosarcoma, very cellular, with slight fibrosarcomatous structure." A mid-thigh amputation was performed on September 21, 1925. The wound healed in two weeks, but pain in the stump continued. A roentgenogram taken 60 days after the amputation showed the periosteum intact, the cortex and medulla sharply demarcated and no evidence of recurrence (6, Fig. 5, p. 194).

On December 12, a nodule was noted beneath the skin just above the umbilicus. A biopsy was made, and the growth reported to be metastatic. On January 5, 1926, examination revealed that the head of the femur-amputated stump had a tumor mass the size of a man's fist on its inner aspect, with an additional growth about the size of a lemon over its outer aspect. The skin of the stump appeared to be quite healthy. There was a mass in the left inguinal region which was about two inches long, one inch wide and two inches thick. There was a supra-umbilical mass which involved the skin about $^3/_4$ of an inch in diameter. The circumference of the stump was 19 inches.

Toxin Therapy: (Parke Davis XIII). Injections were begun by Christian and Palmer on January 5, 1926, the initial dose being $^1/_4$ minim. The dose was increased daily by $^1/_2$ minim until the patient was receiving $6^1/_2$ minims, all injections being given intramuscularly in the gluteal region, alternating sides. Palmer stated: "There is little local reaction at the site of the injection." He added that he gave a few of the first injections "directly into the tumor mass" (76, p. 347). In describing the effects of the treatment Palmer stated: "Each injection would be followed by a severe reaction. About an hour after the injections he would have a violent chill, lasting 10 to 15 minutes. Four to six hours later the temperature would be around 104° to 106° F., accompanied by sweating and restlessness. Then in 4 to 6 hours it would be normal again and the patient would feel fine (76, p. 348). Subsequent series of injections, after the patient had established tolerance for the toxins, did not produce such reactions even with large doses (see below). On January 22, 1926, or three weeks after the toxins were begun, the circumference of the stump had decreased two inches, the mass in the groin had disappeared, and the supra-umbilical mass was decidedly smaller, softer and lighter in color. The patient looked paler, apparently due to the effects of absorbing large quantities of necrotic tumor tissue. The dose was held at $6^1/_2$ minims from January 25 to February 2, after which it was increased by one minim daily to a maximum

of 18 minims given daily. The site at this time was the muscles of the buttocks, the shoulders and occasionally the lumbar region. On February 20, the injections were discontinued because of the extreme weakness of the patient. At this time the stump appeared to have taken on a new growth, associated with considerable edema on both the good leg and the stump.

Clinical Course: A roentgenogram taken February 23, 1926 (6, Fig. 7, p. 195), showed the stump of the femur undergoing dissolution. There was hardly a skeleton of the cortex seen, with the bony substance, primarily the calcium, disseminated into the soft structure in all directions, as if transported by lymphatics and veins. By March 17, there were three small vesicles on the stump. The supra-umbilical growth had increased considerably, being the size of a large lemon.

Further Toxin Therapy: On March 27, 1926, 2 minims of the toxins were injected directly into the tumor mass on the stump. The dose was gradually increased each day until the patient was receiving 5 minims directly into the tumor. Each of these injections was followed by considerable febrile reaction. Apparently the injections were suspended during the next few months.

Clinical Course: On May 5, 1926, several small nodules were felt under the skin of the abdomen. During May and June the patient grew steadily worse with metastatic growths appearing in many parts of the body, including considerable involvement of the right clavicle, and multiple tumors in the scalp, cranial bones and cervical vertebrae. About this time the maximum growth in the tumor of the stump was attained, the circumference being 31 inches. The end of the stump had broken down over an area about five inches in diameter, from which there was a foul profuse ichorous discharge.

Third Course of Toxin Therapy: The injections were resumed on August 5, 1926, the initial dose being 2 minims, which was increased by one minim a day until the patient was receiving 17 minims daily. The dose was held at this point until September 4. The effect of this series of injections was a marked improvement: the edema of the good leg and the stump decreased very much and the stump almost healed by September 4. The supra-umbilical mass had practically disappeared as well as the clavicular tumor. The area in the scalp had regressed completely. After a two weeks' rest period the injections were resumed on September 19 and continued for three weeks. Palmer stated that the September—October series of injections (as well as the final course in 1927) were not followed by marked febrile reactions such as had occurred during the first and second series in 1926. He added: "Very rarely would there be a fever. (Sometimes one to two degrees.) The depression, however, was marked and more pronounced than in the earlier series. Within a few hours after a large dose he would begin to feel badly, but would have no chill or fever. He would feel 'all knocked out'—having no appetite, and feel restless and irritable. This would last about 10 hours, and

then he would feel better again. Of course, after several weeks of this reaction, he would lose considerable weight and get terribly weak so that we would have to discontinue the injections to allow him to recuperate. In the later series it never seemed that we reached the maximum of toleration. We could have given larger doses than 30 to 35 minims, but this seemed enough. The marked depression seemed to tell us when to stop. I should like to emphasize again the difference in the type of reaction when the sarcoma was still present and later when all evidences of sarcoma had disappeared" (76, p. 349). (Note that during the first series some of the injections were made into the tumor mass, apparently the stump tumors, and that this may have partly accounted for the difference in reaction noted by Palmer.)

Clinical Course: By November 22, the general condition of the patient was excellent, his weight being 147 pounds, or 30 pounds more than it had been the previous January. The stump was 17 inches in circumference, a decrease of 14 inches. The old discharging wound on the stump had healed although the skin was quite leathery, and underneath it was a tough fibrous mass believed to be scar tissue. The growths on the abdomen had regressed completely; just above the umbilicus there was an area of pigmentation of the skin $3^1/_2$ inches long by $2^1/_2$ inches wide corresponding to the site of the former metastatic growth. Areas of involvement in the scalp and skull could no longer be detected, although there remained some degree of thickening and roughening of the right clavicle. The patient was discharged from the Marine Hospital on December 5, 1926, apparently cured (6).

Final Course of Toxin Therapy: The case was reported to Dr William B. Coley and at his suggestion, as a precautionary measure, in order to prevent further recurrence or metastases, the patient was given two more courses of toxin injections in the spring and fall of 1927. Between February 23 and March 27, an injection was given every third day, beginning with 3 minims, the dose being doubled each time until 30 minims was given each time. The final course was given between October 23 and December 7, 1927, when the injections were given every third day in doses up to 30 minims.

Clinical Course: Christian and Palmer presented the case at a Memorial Hospital Bone Tumor Clinic in December 1927. On this occasion Coley stated: "I believe this is one of the most remarkable cases of malignant tumor of the long bones that has ever been published, and I am quite willing to admit that, had the patient been under my care, he would probably not have been alive today. In the first place, I am almost certain that I should not have continued the treatment after three months when not only no improvement had been noticed, but marked increase had taken place in the metastatic tumors and especially in the recurrent tumor of the stump. (An increase of from 17 to 31 inches.) In the second place I am quite

sure that I should not have dared increase the dose to such a large amount (30 minims). However, it was not until these large daily doses were given that the improvement continued until all the tumors had disappeared. I have learned more from this one case than from any other that I have personally treated, and I feel that many of the past failures might have resulted otherwise had larger doses and more frequent injections of the toxins been given" (6, p. 196).

The patient was presented before the New York Surgical Society by Coley on March 13, 1929, in the best of health; at this time he weighed 140 pounds, the stump was normal, and he was wearing an artificial limb (36). Since this time he has not used the limb, but gets about on crutches (76).

The patient was examined periodically by Coley for several years. He remained well and free from further recurrence or metastases when last traced on January 1, 1953. He had no illnesses other than an occasional cold in the 27 years following toxin therapy (77).

References: 2, 6, 35, 36, 37, 38, 73, 76, 77.

CASE 30: 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 St. Luke's Hospital, New Bedford, St. Ann's Hospital, Fall River, as well as by Dr Fred W. Stewart, of Memorial Hospital, New York, and Drs John E. McWhorter and D. A. De Santo, Pathologists at the Hospital for Special Surgery, New York, who reported on March 28, 1935:

"*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 sagitally. 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 subdivisions 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 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." (Note: In February, 1949, Dr Sophie Spitz of Memorial Hospital reviewed the sections on this case and also reported it was a papillary adenocarcinoma of the ovary.)

Previous History and Treatment Other than Toxin: Mrs G. L., female, age 38 (in 1933), of Pawtucket, Rhode Island. The family history was negative for