

Ewing's Sarcoma of Bone:  
End Results Following Immunotherapy  
(Bacterial Toxins) Combined With  
Surgery and/or Radiation

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## INTRODUCTION

The present study comprises all cases of Ewing's sarcoma of bone with microscopic confirmation of diagnosis who received immunotherapy (at least 11 injections of Coley toxins). Every case of this tumor treated at Memorial Hospital in New York from 1902 through 1955 has been reviewed. Also included are the successes and failures treated by other surgeons.

The apparently beneficial effects of concurrent infection, inflammation and fever on neoplasms have been reported in the medical literature for over 100 years. A total of 222 determinate cases of this type have been recently abstracted and analyzed. Some of these data have been published (49-53; 76-81c; 88-89); others are in preparation.

Most modern surgeons have been unaware of the possible benefit which may occur if infection develops in a cancer patient, but 50-70 years ago the older surgeons such as Wyeth (107) or Da Costa were well aware of this phenomenon. Da Costa stated: ". . . a study of statistics seems to indicate that more cases of sarcoma are cured after operation if the wound suppurates than if it remains aseptic, and it has been proposed to inject deliberately the wound with pus germs to lessen the danger of recurrence. If the wound is large it should not be injected until it is healed. If it is small it may be injected at the time of operation or soon after . . . After removing a sarcoma from any region the patient should be given courses of Coley's toxins." (44)

This statement may come as a shock to present day surgeons who have been trying at all costs to *prevent* infections in their patients. However, experimental evidence is accumulating to prove the earlier surgeons were correct. For example, Christensen showed that rabbits with Brown Pearce carcinoma which were subjected to massive infections with hemolytic streptococci had *no* metastases, while 50% of the controls developed metastases. (13)

Havas has studied the effects of living hemolytic streptococci on ascites tumor cells (Sarcoma 37 and Krebs 2 carcinoma). Three of eight strains of *Streptococcus pyogenes* were highly effective against the tumor cells resulting in reduction of takes as well as reduction of tumor size. *Streptococcus lutea*



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and *fecalis* and *Serratia marcescens* were only partially effective in damaging tumor cells *in vitro*. The striking destructive changes produced by streptococci in tumor cells were recorded by Havas with phase photomicroscopy. (60).

Ruckdeschel et al (92) and a number of other authors in recent years have reported that empyema following surgery for lung cancer significantly increases the survival rate.

Until recently, physicians using bacterial toxin therapy were unaware that streptococci or their toxins are able to stimulate a host response to substances or tissues which do not normally elicit such a response in an animal or patient. (98) Glynn and Holborrow found that four strains of streptococci and a strain of *Staphylococcus aureus*, when grown on agar media gave rise to agar antibodies in antisera prepared against them. (55) Burky found that by combining staphylococcus with lens substance, rabbits were sensitized to lens and developed high precipitin titers for lens tissue. A diverse group of bacteria in addition to streptococci and staphylococci show this property: *Shigella shigae*, *Salmonella typhi*, *Bacillus anthracis*, *Haemophilus influenzae* and *Neisseria meningitidis*. (9)

In order for this to occur the organisms need not be alive, but *must come into significant contact with the target tissue*. These findings suggest a reason why patients receiving at least some of the toxin injections in or near the tumor responded more dramatically than those receiving all injections remote from the tumor. They are also of interest in explaining why streptococcal and staphylococcal infections were responsible for the majority of so called spontaneous regressions of cancer recorded in the literature. (47; 49-53; 76-81c; 89)

Murphy and his colleagues at Rockefeller Institute were apparently the first to make a comprehensive study of the important role of the lymphocyte in resistance to cancer. (76a)

Toolan and Kidd studied the association of lymphoid elements with cancer cells undergoing distinctive necrosis in resistant and immune hosts. They reported: "Tumor cells never exhibit the necrobiotic changes described until lymphoid elements provided by the host accumulate in force about them and attach themselves to first one and then another of the outlying cells adhering closely to them and often curving like crescents about their rims. As they shrink, adjacent tumor cells without attached lymphocytes remain unaltered; . . . cancer cells proliferate for a short time in immune mice, but with the accelerated arrival of lymphoid elements they are promptly overcome as described above." (98a)



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It would seem that the injection of various microbial products, such as BCG and bacterial endotoxins, help to mobilize the lymphocytes in cancer patients, and increase their phagocytic activities. At present many investigators such as Old et al (85-86) are evaluating a wide range of microbial products which may prove to be more stable and effective host-stimulating agents for the treatment of malignant tumors. For example, Nowotny has shown that by sophisticated modern microbiological techniques one may neutralize the toxic effects of bacterial endotoxins while enhancement of resistance does not require toxic action on the host. (83)

In the course of this study of Ewing's sarcoma two cases were found in whom concurrent infection occurred but toxin therapy was not administered. Both these patients recovered and remained well when last traced 31 and 21 1/2 years after onset. Brief abstracts of their histories may be of interest and are given here:

1. MEMORIAL HOSPITAL: P.P., female, age 7 months; Ewing's sarcoma of left femur with mediastinal shadow; onset, began crying constantly due to pain; 7 weeks later Vitamin C given; 2 weeks later swelling lower 2/3 thigh noted, also limitation of motion; aspiration biopsy October 15, 1943; films showed widening of shadow of mediastinum; *febrile episode to 101.8° F.* following incisional biopsy, November 11, 1943; x-ray to femur November 11 to December 6, 1943 (4200 r tumor dose); January 7, 1944 *another febrile episode (101.6° F) due to u.r.i.; 4 more concurrent infections including bronchopneumonia, septic temperature to 102.2° F.; sulfadiazine given, hospitalized 6 months; complete regression femoral and mediastinal involvement; irradiated limb 8 cm. shorter 6 years later; child obese due to compulsive eating (in compensation for deformity due to limb shortening?); n.e.d 1973, 30 years after onset. (73; 82)*

2. LAHEY CLINIC: Mrs. J.F.S., female, 24; Ewing's sarcoma distal left fibula; onset fall 1950, blood counts 4 weeks prior and 24 hours prior to biopsy showed *leukocytosis (12,000 w.b.c., normal differential)*; incisional biopsy January 29, 1951, patient told diagnosis (was an RN); married shortly thereafter, spent honeymoon at Lahey Clinic having x-ray; caused ulceration; became pregnant April 1951; May 18, 1951, mass in left groin; biopsied: *hyperplastic, not metastatic; drainage, suppuration from groin wound; post radiation ulceration proved malignant, November 1951; extensive hematoma, drainage, low grade infection; due to pregnancy no further irradiation given; pregnancy terminated at end of 7th month; x-ray then given to left groin and prophylactically to chest; complete recovery, no further evidence disease; had 6 more healthy children; alive and very well 1973, 23 years after onset. (81, Series C, Group 1, Case 56; 82)*

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Among the toxin treated cases a few patients also developed concurrent infections or had leukocytosis which may have increased their resistance and helped control their disease or increase the survival period: Series A, Case 6; Series B, Cases 5, 10, 46; Series C, Group 1, Cases 9, 10, 21, 46; Group 2, Cases 30, 36.

Lohmann studied the effect of acute inflammation on neoplastic cells, and reported that rat sarcoma cells were destroyed *in vitro* within 10-14 hours after being placed in inflammatory exudate. She concluded that at all costs we must preserve the inflammatory capacity of the body in order to prevent or control cancer. (64)

Martin's finding regarding the deleterious effects of cortisone on possible benefits of combination therapies is of great importance. (67, 68) Kelly reviewed much of the experimental and clinical evidence indicating that corticosteroids usually accelerate the growth and dissemination of malignant tumors. (62) Nauts (1973) reviewed the literature to date and assembled 116 references to the deleterious or dangerous effects of corticosteroids on host resistance to cancer. (unpublished)

Further evidence of the importance of preserving the integrity of lymphoid tissues is discussed by Fowler in an end result study on malignant melanoma. (51) He cited two independent studies on the relative incidence of cancer or leukemia in patients who have had appendectomies or tonsillectomies. (3, 66) McKay concluded that the colon and to a lesser degree the lung, breast, cervix, stomach and pancreas may be organs on which the appendix confers some degree of protection. (66) Bierman confirmed these findings on another large series of cases. (3) No controlled study has been made of the possible influence of appendectomies or tonsillectomies on the incidence or course of Ewing's sarcoma. However, in analyzing the cases in the present study we were impressed with how many of the patients had had these operations. There is increasing evidence that viruses may play a role in the etiology of certain neoplasms in man. The recent study by Ogra concerning the deleterious effects of tonsillectomy and adenoidectomy on nasopharyngeal antibody response to poliovirus is of interest in this connection. He concluded that the complete removal of tonsils and adenoids, particularly in young male children, may deprive them of a valuable source of immunocompetent tissue. (84) Such tissue may play a role in resistance to neoplasms even if they are not caused by viruses.

Fraumeni and Glass recently reported that Ewing's sarcoma is rare among negro children in the United States, as well as in Uganda and Jamaica. (54) They attributed this rarity to genetic resistance. We wonder if it may not



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be partly due to environmental factors such as fewer appendectomies and tonsillectomies and less frequent use of antibiotics among negro children, who may also be exposed to more endemic infections or inflammatory episodes which stimulate their immune responses.

In recent years many investigators have noted the importance of the reticuloendothelial system in resistance to neoplastic disease, or have reported that the functional capacity of the RES may be increased or protected by immunotherapy with bacterial toxins or BCG. (4; 80; 82; 86; 88; 97)

Since there is now considerable evidence indicating that acute bacterial infections, fever or inflammation may cause complete or partial regression of neoplasms, one must question the wisdom of routine use of antibiotics before and after cancer operations. Zwaveling concluded that tumor cells grow less well in an infected milieu. (108) Lohmann found that tumor cells die within 14 hours after being placed in inflammatory exudate. (64)

These findings emphasize the need to avoid the *prior use* of any immunosuppressive agents such as corticosteroids, radiation or extensive surgery which may decrease or inactivate the lympho-reticuloendothelial tissues. However, after preliminary treatment with a host-stimulating agent such as bacterial vaccines, B.C.G. or yeast extracts, has stimulated and protected these vital tissues, one may then administer radiation, surgery or chemotherapy and expect not only protection of these tissues, but potentiation of the response of the tumor to radiation or drugs. (1; 4; 14; 61; 95; 96; 109) This potentiation occurs without increasing the sensitivity of the normal skin. (57)

### **Ewing's Sarcoma, Diagnosis, Prognosis, Results from Conventional Therapy:**

Before reviewing the effects of toxins or infection on Ewing's sarcoma of bone, it may be helpful to mention some of the *characteristics* of this primary malignant bone tumor which was originally designated as round cell sarcoma, later as endothelioma or endothelial myeloma. Ewing defined its clinical, roentgenological and pathological aspects in 1922 (48) and it is now known as Ewing's sarcoma or Ewing's endothelioma.

Certain characteristics are helpful in differentiating it from other primary neoplasms of bone: its predilection for children and adolescents, for males rather than females, for the shaft rather than the ends of the long bones, its roentgenologic appearance, its tendency to metastasize to other bones as well as to the lungs, its marked radiosensitivity, its characteristic histologic pattern and its exceedingly unfavorable prognosis. (15, 16) Fried-



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man and Gold believe that Ewing's sarcoma is a neoplasm of immature reticulum cells. (54a)

The *etiology* remains obscure. However, observers have repeatedly noted cases in which the earliest symptoms and signs suggested an underlying infectious process (fever, leukocytosis). Possibly a viral infection may be a factor in the development of these tumors.

Ewing's sarcoma is so *radiosensitive* that even a single x-ray treatment prior to biopsy has been responsible for errors in diagnosis. The necrotic appearance is interpreted either as osteitis or inflammation. No viable tumor cells are seen.

*Differentiation* from reticulum cell sarcoma is difficult, but these tumors occur at a different age and their prognosis is different. Reticulum cell sarcoma usually occurs in middle or later life and the prognosis is not nearly as grave as in Ewing's sarcoma. (16; 76)

*As to incidence, sex and age*, next to osteogenic sarcoma, Ewing's sarcoma is the most common primary malignant tumor of bone. It occurs more than twice as frequently in males than in females. The great majority of cases occur under the age of 25, the highest incidence being between 10 and 15 years. The bones of the lower extremities are affected more frequently than the rest of the skeleton. (16)

The *symptoms* common to other malignant bone tumors, pain, swelling, or "lump" and disability occur with Ewing's sarcoma. The pain is more variable, and the interval between pain and discovery of the tumor is often shorter than with osteogenic sarcoma. Disability is inconsistent and less notable as an early symptom. Fever of an intermittent type, often with leukocytosis, may be present. The location of the primary lesion is often a diagnostic lead. While it commonly arises in the metaphyseal region of a long bone of the lower extremities, it extends toward the diaphysis which may be quite extensively involved. The progress varies, being exceedingly rapid in some cases, while in others the fatal outcome is long deferred (such cases of long survival usually had concurrent infections or toxin therapy). The average life expectancy is less than two years. (16)

Metastatic neuroblastoma in a long bone may give rise to *diagnostic difficulties*. Barden (2) and Willis (104) noted the similarity of the bone metastases of neuroblastoma to Ewing's sarcoma: both have small rosettes microscopically, both are radiosensitive. Barden states: "It may be that these two are so closely related that they should be considered one complex with varying manifestations. The more likely assumption is that they are distinct

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tumors composed of cells with the same biological attributes . . . Amputation for cure should not be attempted in cases diagnosed as Ewing's sarcoma. It would seem wiser to treat all these patients as if the bone tumor were secondary to a hidden abdominal tumor, since it is so often impossible to determine before post mortem which patients do have primary abdominal tumors." (2)

As to *treatment*, the majority of cases of this type of tumor have been treated by radiation alone or combined with surgery. Unfortunately, despite the control of the primary tumor by such therapy, metastases nearly always develop and although these may yield to further radiation, the patient is unable to tolerate the hopeless struggle to keep up with the widespread disease by such extensive radiation therapy. B. L. Coley stated that no case of unquestioned diagnosis was known to have been cured by radiation alone. He also noted that the results of amputation alone are notoriously poor in Ewing's sarcoma. He suggested that whenever possible resection of the primary should be given a trial, especially in tumors of the fibula, ulna, scapula, radius and humerus. (16)

Wang and Schultz reported that long term survival and presumed cure can be expected in 10% of the cases of Ewing's sarcoma. In fatal cases death usually occurs within two years, but it has been delayed more than five years. (103) The average survival rate is two years.

### **General Information on Cases Comprising the Present Report:**

Since Ewing's sarcoma has such a sinister prognosis when treated by radiation and/or surgery, an analysis has been made of the possible benefits of immunoadjuvants such as bacterial toxin therapy which may stimulate or reinforce the natural resistance of these patients or potentiate their response to radiation.

All known cases of Ewing's sarcoma with microscopic confirmation of diagnosis who received toxin therapy in the period 1894-1955 have been reviewed. Also included are the known cases of this tumor who developed a concurrent infection, fever, or an inflammatory episode. The 114 cases have been grouped as follows:

**Series A: Toxin treated successes, determinate:** 9 cases whose sections were available for review. These patients remained free from further evidence of Ewing's sarcoma from 5 1/2 to 43 years after onset.

**Series B: Toxin treated successes, indeterminate:** 14 cases who were originally designated as round cell sarcoma, but who are now excluded from Series A, either because the sections were unavailable for review or upon review were considered by some pathologists to be some other form of malignant tumor, or because they were traced less than five years.



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**Series C: Toxin treated failures:** Group 1, patients without apparent metastases when toxins were begun, 53 cases; Group 2, patients with metastases present when toxins were begun, 38 cases. Almost all the patients in Series C received considerable radiation prior to toxin therapy, and only one or two brief courses of toxins were administered in most of these cases, often given intramuscularly remote from the tumor areas in small doses insufficient to elicit much febrile reaction.

Of the 9 determinate successes and the 91 failures comprising the present study, there were 19 five year survivals, almost double the expected rate. Ten of these survived for 10 or more years (10%). The 10 year survival rate reported by others is 4%. (59)

If the 14 indeterminate successes had been included, the percentage would have been much higher. Although excluded from the statistics these 14 cases deserve study. Many are quite remarkable, and they give a clearer indication of some of the factors affecting prognosis in patients receiving toxin therapy.

The first case in Series B is one of the earliest examples of cancer developing as a result of heavy radiation. In this case the toxins were not begun until x-ray therapy had been administered steadily *for 10 months*, and metastases had developed. Under toxins alone complete regression of the primary and the metastases occurred. The boy remained well for 10 years, except for extensive radiodermatitis. X-ray cancer then developed in this area and proved fatal 11 years after onset of the Ewing tumor.

Analysis of the technique of administration of the toxins in the successfully treated cases indicates that in most of these patients the toxins were begun before the disease was inoperable and the injections were given either as an adjuvant to surgery, or *in most instances concurrently or before, rather than after radiation*. The dosage of radiation in the successful series was much lower than in the failures, while the duration of toxin therapy was usually much longer.

It may be of interest to note that Scagliatti and Calandriello reported on two cases of Ewing's sarcoma who were given anti-rabies vaccine. The first was a boy of 12 with extensive metastases. He received these injections daily for 10 days. His weight increased, his appetite improved and the tumefaction in his leg decreased in size. Two more courses were given with transient improvement for several months. In the second case, a preagonal boy of 14, transient improvement also occurred. (92a)

At the International Transplantation Congress in Paris in 1967, Wissler



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reported his success in inhibiting the growth of established hepatomas in rats by means of a combined immunization with hepatoma and pertussis vaccine. Growth was consistently retarded and life substantially prolonged. Histologic observations at the border of the tumor and in the spleen were compatible with an immune reaction. "It seems likely that this system, carefully studied, can aid immensely in the search for knowledge of the potentiality and the means of improvement of approaches to an effective immunological control of inoperable malignancies in man," he said, noting that it is not toxic and is directly applicable to the cancer patient. (106)

Wissler's findings are of interest in focussing the importance of *combining* the tumor and the microbial toxin or vaccine. This, we believe occurred in Ewing's sarcoma patients when toxins were given either into the tumor or intravenously *prior* to radiation or ablative surgery. Toxins were apparently *not* able to increase the immune response nearly as effectively if they were given *after* amputation, resection or heavy radiation.

The excellent results obtained by Marcove in recent years (66a) in treating giant cell tumors and osteogenic sarcoma suggest that clinical studies might now be instituted using cryosurgery combined with immunotherapy in an effort to salvage a much higher percentage of patients with Ewing's sarcoma.

As to whether amputation should continue to be used in Ewing's sarcoma, a number of investigators since W.B. Coley have questioned its value (6, 15, 16, 90) Boyer *et al.*, for example, reported in 1967 that a review of their experience at Walter Reed Hospital since 1949, and that of others in this period, has failed to reveal any valid reason for a heroic surgical attack. "Removal of limbs and other portions of the body has become a needless surgical exercise." (6) The recent knowledge that operative stress and surgical trauma may *decrease* the resistance of the animal or patient to his tumor and thus increase the likelihood of metastases must be considered in this connection. (7) W.B. Coley was the first to suggest conservative treatment in sarcoma of the long bones. (21, 29) He succeeded in saving the limb as well as the life in a number of cases of Ewing's sarcoma, reticulum cell sarcoma and giant cell tumor of bone. Following his example a few surgeons such as B.L. Coley and others at the Mayo Clinic and the Willis Campbell Clinic and elsewhere also obtained lasting results using Coley toxins alone or as an adjuvant to radiation or conservative surgery. (15; 16; 34; 41; 42; 63; 74-76; 82; 90; 102)

During the period in which the majority of the patients comprising this study were treated little was known about the deleterious effects of massive doses of x-ray and radium. In many of the failures the resistance of the

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patient was probably seriously affected by such irradiation, thus hastening the dissemination of the disease. fortunately, radiologists have now recognized the dangers inherent in using such large doses, i.e., carcinogenic, sarcogenic or leukemogenic, as well as the fact that in children, skeletal deformity will result, or radiation changes requiring amputation. (31)

Phillips *et al.* recommended that the tumor dose should not exceed 4000 r because they believe that the cure of cancer does not depend solely upon the destruction of cells by ionizing radiation but also involves efficient repair processes by the normal tissues within the irradiated area. As the tissue dose exceeds 4000 r, the normal bone becomes devitalized for longer periods so that its essential role in curing a bone cancer through its power of reparation and restoration of growth can not be fulfilled. (90)

The results described in the present report, and especially in that of Phillips and Higinbotham covering a more recent group of cases, are definitely encouraging. (90) They concluded that the prospect of curing Ewing's sarcoma in children is certainly better today than it was 30 years ago: "Of 54 children with Ewing's sarcoma referred to Memorial Hospital during 1949-1959, 13 survived for five years. Although not statistically significant these results are encouraging when compared with four survivors among 74 patients seen in an earlier period in the same hospital. The reasons for this improvement are applicable to tumors of children in general." (90)

A total of 18 of these 54 cases reported by Phillips *et al.* received toxin therapy as an adjuvant to radiation, of whom 8 (44%) survived five or more years. Six received toxins alone, of whom three (50%) survived five or more years. Of the seven children receiving radiation alone only one (14%) survived. These results suggest that toxins alone may be most effective, but that when given as an adjuvant to radiation they may more than triple the survival rate. Others have also noted that toxin therapy may potentiate the response of even radioresistant tumors to radiation. (12; 51-53; 76; 77-82)

It is hoped that the data herein assembled may help to clarify some of the possibilities and limitations of immunotherapy with Coley toxins, and thus stimulate wider use of such agents and help us achieve greater knowledge of how best to administer them alone or combined with other forms of treatment. It would appear that these host stimulating agents should be used *prior* to other modalities in order to be more effective adjuvants to radiation and conservative surgery. Such techniques should enable us to obtain a far higher percentage of permanent results in Ewing's sarcoma of bone without mutilating surgery or late sequelae from the former immoderate doses of irradiation.



## SERIES A: DETERMINATE SUCCESSES, BRIEF ABSTRACTS

The diagnosis was confirmed by microscopic examination and reviewed in each case. The name following the case number refers to the physician, hospital or clinic handling or reporting the case. The cases are listed according to the bone involved, chronologically as to the date of first toxin injection and type of toxin used. The bones involved were: 1 femur; 2 humerus; 2 tibia; 1 fibula; 1 radius; 2 metatarsal. At the end of each abstract bibliography reference numbers are given. For a brief description of the formulae used in making the 15 different preparations of Coley toxins the reader is referred to references 77 or 79.

Years Traced  
After Onset

1. MAYO CLINIC: N.H., female, aged 11; proximal left femur; onset November, 1928; incisional biopsy April 4, 1929; x-ray January 7, 8; February 16, 27; May 22, 1929 (5500 r in 5 months); toxins (Parke Davis XIII) concomitantly for 6 months, beginning February 1, 1929; pain ceased 2 weeks after first dose; *complete regression; general health improved steadily; no limitation of motion at hip; married 1950; daughter born 1953; small basal cell carcinomas removed from irradiated area in scar 1961, 1964; in excellent health 1973.* (72; 74; 75; 81)

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2. MEMORIAL HOSPITAL: L.L., male, aged 13; recurrent proximal right humerus; child was obese (157 lbs.); had 2 or 3 falls prior to onset, April 1935; tumor size of lemon removed surgically July 3, 1935; August 1935: x-ray (3740 r) to shoulder, supraclavicular, axillary regions causing anemia for which Lextron (Lilly) was given; 2nd cycle x-ray (1500 r) April 1936; recurrence evident when toxins were begun May 14, 1936: (Parke Davis XIII), 20 i.m. and i.v., marked reactions; *gained weight, complete regression* by July 1, 1936; 3rd cycle x-ray July 9, 1936; 2nd and 3rd courses toxins January and July 1937: reactions to 104.6°F., *no further evidence of disease, in excellent health* until May 1962, severe myocardial infarction, recovered well, 2 more coronary occlusions in next 2 years, died of third, November 1964. (5; 73; 82)

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3. PHILADELPHIA NAVY HOSPITAL: C.E.P., male, aged 18; proximal right humerus, in region of deltoid tuberosity; onset December 1952, following slight trauma; January 1953: *concurrent acute frontal sinus and pan-sinusitis*, organism unknown; excisional biopsy, January 2, 1953: toxins at suggestion of Dr. Jesse T. Nicholson, (Sloan-Kettering XIV) daily or every 48 hours i.v., reactions averaged 101.2°-103°F.; maximum 105.5°; after 6 had been given, x-ray begun, (2400 r); toxins resumed 12 in 20 days; *complete recovery* by April 1953; *gained 10 lbs., grew 2 cm. in next year; fractured right humerus April 1958 playing basketball; internal fixation, biopsy, June 1959; hospitalized due to osteomyelitis, prolonged non-*



SERIES A, DETERMINATE SUCCESSES, ABSTRACTS

- |  | Years Traced<br>After Onset |
|--|-----------------------------|
| union, finally required amputation, August 2, 1962 (no evidence of tumor); in excellent health thereafter, except for chronic sinusitis; last traced 1973. (5; 82; 101)  | over<br>20 yrs.             |
| 4. MEMORIAL HOSPITAL: R.W., female, aged 7; right tibia, involving most of shaft; onset December 1916; x-ray, temporary improvement; apparent pulmonary metastases January 1917; x-ray (3 to chest); toxins (Tracy XI) 21/2 weeks, no marked improvement noted; amputation, 8 months after onset; toxins resumed few days later, given nearly 6 months, <i>pulmonary metastases regressed, no further evidence disease</i> , entirely well 1927. (5; 37; 40; 43; 73; 82)   | 10 yrs.                     |
| 5. MEMORIAL HOSPITAL: T.S., male, aged 30, right tibia; (had rheumatic fever, with chorea and polyarthritis at 7); onset September 9, 1936; curettage November 15, 1946, low thigh amputation 3 days later; toxins (Parke Davis XIII) begun 11 days postamputation, 15 i.v., febrile reactions averaged 103°-104°F.; March 1947 second course (14 i.v.); withstood therapy well, despite rheumatic heart; obtained prosthesis, returned to work (on his feet 7 hours daily); <i>no further evidence disease</i> ; alive, well, when last traced 1973. (73; 82)   | 27 yrs.                     |
| 6. MEMORIAL HOSPITAL: W.V.B., male, aged 14; right fibula; October, 1937, trauma at football just prior to onset, right calf, upper leg became swollen, warm, tender, (no redness) temperature 100°F., pain; 4 similar episodes in next 11 months, <i>also contracted mumps in this interval; blood count just prior to biopsy September 1938, 11,900 wbc; incisional biopsy; bone yellow, soft, necrotic, appearance inflammatory</i> ; September 1938: x-ray (4800 r); little apparent benefit; November 7, 1938: toxins (Parke Davis XIII), 8 i.m., 3 i.v., reactions averaged 103°-105°F.; November 21, 1938: upper half fibula resected; <i>complete recovery, no further evidence disease</i> ; married 1948, 2 sons born 1950 and 1954, alive, entirely well 1973. (42; 73; 82) | 35 yrs.                     |
| 7. EINSTEIN MEDICAL CENTER, Philadelphia, Pa.: D.F., female, aged 7; left distal radius, with invasion adjacent muscles; date of onset unknown; January 1954, pathologic fracture, immobilized 6 weeks; indirect trauma May 26, 1954, onset acute pain; extensive biopsy June 7, 1954; cast applied; x-ray (3 cycles totalling 7530 r); toxins (Sloan-Kettering XIV) begun after first cycle x-ray, July 15, 1954; 8 courses toxins given 10-15 injections each, all i.v., reactions averaged 102°-103°F.; <i>no further evidence disease</i> ; but radiation caused considerable deformity of wrist due   |                             |

SERIES A, DETERMINATE SUCCESSES, ABSTRACTS

Years Traced  
After Onset

to decreased growth of radius; became obese (230 lbs.); married; in excellent health 1973, working full time as a computer programmer. (82)

19 yrs.

8. MEMORIAL HOSPITAL: R.P., female, aged 16; right 4th metatarsal; onset April 1949; rest and soaks tried for 8 months; 4 painful episodes in this period; November 30, 1949, toxins (Parke Davis XIII) daily for 13 days i.v., reactions averaged 104°-105°F.; x-ray given concurrently (3300 r); 2nd course toxins February 9, 1950, 13 i.v., reactions averaged 103.4°-104.4°F.; well next 18 mos., then local recurrence; October 4, 1951: 4th metatarsal resected, bone graft from rib; amputation right leg November 22, 1951; obtained prosthesis, worked as secretary; developed lung metastases November 1953; x-ray (2000 r) and toxins (12 i.v.); *costal and subpleural metastases disappeared*; gained weight, returned to work; entirely well, no further evidence disease 1973. (73; 82)

24 yrs.

9. MAYO CLINIC: B.B.B., male, aged 17; recurrent metatarsal bones left foot; onset September 1952; arch supports prescribed; 2 wks. after onset tumor removed; recurred 20 mos. later; biopsied 4 wks. after it developed; reported as Ewing's sarcoma involving metatarsal bones, especially navicular; 2nd incisional biopsy September 30, 1954, amputation mid-to-upper tibia (same day); toxins (Sloan-Kettering Institute XIV) begun 13 days later, 16 i.v.; reactions averaged 102.6°F.; 2 more courses toxins (14 doses each) by family physician; no further recurrence or metastases; married 1963; 3 children born 1964-1968; in excellent health October 1973. (72, 82)

21 yrs.



## SERIES A: DETERMINATE SUCCESSES, DETAILED HISTORIES

**CASE 1:** Ewing's sarcoma of the left femur, confirmed by microscopic examination at the Mayo Clinic. The sections were reviewed by Dr. David C. Dahlin in 1966. He reported it appeared to be a typical Ewing's sarcoma.

**PREVIOUS HISTORY:** N.H., female, aged 11, a farmer's daughter, of Huron, South Dakota. The family history was negative for tuberculosis or cancer, although the child's mother had had a tumor removed from her left side. The patient had had measles, mumps and chicken-pox. There was no history of injury prior to onset, which occurred in early December 1928. The child was brought to the Mayo Clinic on January 3, 1929, complaining of swelling on the anterolateral aspect of the upper left thigh, of one month's duration. The swelling had subsided at the end of the first week, and had recurred two weeks later, accompanied by pain which was throbbing in character and worse at night. There had been no loss of weight. Examination on admission showed a firm fixed tumor of the proximal left femur. The superficial veins were enlarged and there was an increase of 2.5 cm. in the circumference of the thigh. There was no fever. The Wasserman reaction and urinalysis were negative. The blood count showed hemoglobin 73%, w.b.c. 6,700; r.b.c. 4,570,000. X-ray examination showed "a periosteal sarcoma of the femur". Chest films were negative for metastases.

**SURGERY:** An incisional biopsy was performed on January 4, 1929 and confirmed the diagnosis.

**RADIATION:** X-ray therapy was given on January 7 and 8, February 16 and 27, 1929, over the proximal two-thirds of the left thigh through four portals (135 K.V.), filtered through 6 mm. al., focal skin distance of 40 cm., 5 ma. for 30 minutes, each of the four converging beams delivering a dose of 560 r in air. On May 22, 1929, two portals received 550 r each, making a total of 5500 r given in three cycles in a period of five months.

**TOXIN THERAPY (Parke Davis XIII):** Injections of Coley toxins were given by the family physician, Dr. W.H. Griffith, for six months. These were administered at the suggestion of Dr. Henry J. Meyerding of the Mayo Clinic, and were begun about February 1, 1929, after the first cycle of x-ray therapy. During the latter part of treatment only one injection a week was given, the final one being on August 10, 1929. The pain disappeared two weeks after the toxins were begun and the tumor decreased in size. Repeated x-ray examinations showed continued improvement in the condition of the bone. The general health also improved steadily.

**CLINICAL COURSE:** The patient made a complete recovery. She was seen at the Mayo Clinic on three or four occasions in the next 5 1/2 years, and remained in excellent health when examined on August 6, 1934. There was no limitation of

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motion at the hip or knee, but there was some atrophy, i.e. the left thigh was 7.5 cm. smaller in circumference than the right thigh. X-ray examination of the femur showed only slight residual change in the subtrochanteric region. The patient weighed about 100 pounds and was attending school. She married in July 1950 and had one child, a daughter, in April 1953. Her weight in 1957 was 120 to 125 pounds, her height being five feet three inches. Her only complaint was poor circulation in the left leg. A small lesion developed in the irradiated skin of the left lateral thigh, just below the scar of the incisional biopsy. This was removed on March 31, 1961 at the Mayo Clinic. It was reported to be a basal cell epithelioma measuring 1.5 x 1 x 0.1 cm. in diameter. Another was removed in early February 1964. The patient remained in excellent health when last traced in October 1973, over 44 1/2 years after onset.

REFERENCES: 72; 74; 75; 82.

**CASE 2:** Recurrent Ewing's sarcoma of the proximal right humerus, confirmed by microscopic examination by Dr. Fred W. Stewart at Memorial Hospital, and by the Bone Sarcoma Registry Committee (Case #2238), also by roentgenologic examination by Dr. Ralph Herendeen. The films showed a growth extending from the epiphyseal line down the shaft for about 10 cm., involving principally the cortex, externally. The sections and films were reviewed by the Armed Forces Institute of Pathology in December 1959 and coded as a Ewing Sarcoma (see below for report).

**PREVIOUS HISTORY:** L.L., male, aged 13, of Brooklyn, New York. The family and previous history were essentially negative. The patient had had the diseases of childhood including measles, scarlet fever, mumps and whooping cough, with a normal tendency towards colds and sore throats. He never had any fevers or asthma. He had fallen on his shoulder two or three times prior to onset, but gave no details as to possible injuries to the humerus. Onset occurred in April 1935, an aching pain in the proximal portion of the right arm, gradually increasing in severity. On July 2, 1936, Dr. Mac Shevell of Brooklyn was consulted. He found a tumor mass of hard consistency the size of a lemon situated in the upper third of the right humerus. It was not tender and did not affect the mobility of the shoulder joint. Aside from the patient's obesity (he weighed 157 pounds), the remaining physical findings were negative.

**SURGERY:** On July 4, 1935 the tumor mass was removed at the Jewish Hospital, Brooklyn. The wound healed by primary union.

**RADIATION:** From August 6 to 29, 1935, 11 x-ray treatments were administered



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by Dr. J. Kauffman of Brooklyn, totalling 3740 r to the right shoulder, the supra-clavicular and axillary regions.

**CLINICAL COURSE:** To overcome the anemia produced by the radiation, Shevell put the patient on Lexton (Lilly #5). Subsequent weekly examinations revealed a steady rise in the hemoglobin and a steady increase in weight. X-ray examinations on September 16, 1935 showed no activity in the tumor of the humerus. The plates taken April 6, 1936, however, showed a distinct osteogenic change, but no evidence of metastases in the thorax or skull.

**FURTHER RADIATION:** X-ray treatment was given daily from April 20 to 30, 1936, totalling 1500 r to three ports, anterior, posterior, and lateral. The patient was admitted to Memorial Hospital on May 13, 1936. Examination showed an old well-healed scar on the anterior aspect of the right upper arm. Directly under this scar was a firm, nodular recurrent tumor mass, apparently connected with the bone. The entire upper arm was larger than the left. Motion was fairly good, without pain, and there was no pain on palpation or percussion.

**TOXIN THERAPY (Parke Davis XIII):** Injections were begun by Dr. Bradley L. Coley on May 14, 1936, two weeks after radiation was stopped. Six intramuscular injections were given on successive days, in doses of 1 to 6 minims. These caused febrile reactions of 102.4°F. to 103.8°F., accompanied by chilly sensations, headache, and moderate sweating. He was transferred to the Hospital for Special Surgery on May 20, 1936, where he received 14 more doses of the toxins by daily intramuscular and intravenous injections. By July 1, 1936, the patient had gained weight and appeared to be in perfect condition. Palpation of the arm revealed no induration or tumor tissue remaining.

**FURTHER RADIATION:** Between July 9 and 18, 1936, he was given another course of x-ray treatments daily, totalling 2500 r to 3 ports.

**FURTHER TOXIN THERAPY:** On January 7, 1937, he was readmitted to the Hospital for Special Surgery and received another 14 intramuscular injections of toxins, in doses of 1 to 8 minims. A third course of toxins was given in July 1937, consisting of seven intramuscular injections in doses of one to seven minims. The maximum febrile reaction was 104.6°F. A total of 41 injections were given in a period of 14 months in this case.

**CLINICAL COURSE:** The patient was examined periodically thereafter in the Bone Tumor Clinic at Memorial Hospital and no further evidence of disease was found. He was in a serious automobile accident in 1948, and in 1950 was operated upon for a pilonidal cyst. He moved to Florida and became actively engaged in the practice of law. In 1951 he took out some life insurance. He remained in excellent general condition with normal function of the right arm and shoulder. Between

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May 14 and June 10, 1962, he was hospitalized for a myocardial infarction from which he recovered very well. He had two more coronary occlusions in the next two years. The third caused his death in November, 1964, 29 1/2 years after onset. His physician, Dr. Joseph Burns, stated that there was never "any difficulty whatsoever with his arm."

COMMENT: In December, 1959 this case was reviewed by Dr. Lent B. Johnson of the Armed Forces Institute of Pathology, Washington, D.C., who reported as follows: "The x-rays show a pattern that is clearly and unequivocally that of a neoplasm, but the amount of sclerosis through the upper end of the humerus is much greater than is expected with a Ewing tumor. The neoplasm is breaking out of the bone and extensively invading the soft tissues. Microscopically, the material consists only of the surface portion of the soft tissue extension. It has a somewhat papillated structure, with vessels in the centers of the papillae, and medium to small round naked nuclei on the surface of the papillae. Later slides contributed by Dr. Fred W. Stewart showed large sheets of undifferentiated round nuclei compatible with a Ewing tumor. Accordingly, this case is coded as a Ewing tumor, but it should be emphasized that the degree of bone sclerosis seen on x-ray is most unusual for a Ewing tumor of this extent." (82)

REFERENCES: 5; 73; 82

**CASE 3:** Ewing's tumor of the right proximal humerus, confirmed by microscopic examination following excisional biopsy at the U.S. Naval Hospital, Philadelphia, Pennsylvania, and by the Armed Forces Institute of Pathology, Washington, D.C., 1959, (see below for detail)

PREVIOUS HISTORY: C.E.P., male, aged 18, of Mesa, Arizona. The family history was negative for cancer, tuberculosis and diabetes. The patient was born in Texas. He had measles, chicken pox, and mastoiditis as a child, and his tonsils and adenoids were removed. He also had an appendectomy which was complicated by intestinal obstruction (?). He complained of frequent head colds during the last six months of 1952, while he was serving in the U.S. Navy. Onset, following a slight trauma in December 1952, he developed a small localized swelling and tenderness in the right deltoid area. Thereafter the swelling persisted and increased slightly in size.

CONCURRENT INFECTION: He was admitted to the U.S. Naval Hospital in Philadelphia on January 13, 1953, with a diagnosis of "sinusitis, acute frontal sinus, organism unknown, #4115." He stated that he had had a severe cold with fever for two days. Physical and x-ray examination revealed an acute frontal sinusitis, as well as low grade pansinusitis. He was treated by the Ear, Nose and Throat



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Service and responded well to treatment. He did not mention the lesion of the shoulder at this time.

**CLINICAL COURSE:** On February 10, 1953, he was seen in orthopedic consultation and it was recommended that he be transferred to the Orthopedic Service. At this time he first gave the history of swelling and tenderness in the right deltoid area which he had first noticed in December 1952, following a slight trauma. Examination revealed a diffuse fusiform swelling about the size of half a lemon under the right deltoid which was hard, smooth, tender, non-fluctuant, non-pulsating, and which moved with the humerus. X-rays showed a soft tissue mass just distal to the tuberosity. There was marked periosteal reaction along the lateral border of the proximal third of the right humerus. The changes in the cortex and marrow were of a moth-eaten character and stopped rather abruptly at the distal portion of the humerus.

**SURGERY:** On February 13, 1953, an excisional biopsy of this lesion was done and the pathological diagnosis was Ewing's sarcoma. The surgeon reported that the lesion was elevated approximately 1 cm. and was 5 x 8 cm. in diameter. It was gray-white in color, moderately firm to palpation, and the center of the mass exhibited a moderate amount of tissue necrosis which resembled pus grossly. The lesion was rather firmly attached to the cortex of the humerus, and when peeled off the underlying aspect of the humerus appeared pitted, but not osteoporotic. The medullary cavity appeared to be normal. The tumor itself appeared to be well encapsulated and could be separated from the surrounding structures without difficulty. The surgical and pathological reports indicated that the tumor had been completely removed. The x-ray report suggested medullary involvement was apparently a misinterpretation. Most of the tumor was made up of closely packed, small round cells of the kind expected with Ewing's sarcoma. In some areas the cells were swollen, with a water clear cytoplasm. In extremely rare areas these cells went on to the production of chondroid matrix and scant hyalin cartilage. Dr. Lent C. Johnson reported: "This then is a Ewing tumor which shows evidence of attempts at differentiation toward hyalin cartilage. Since these areas are extremely few in number and in an extremely scant portion of the tumor, the staff continued to regard such tumors as Ewing tumors." This tumor was parosteal; the prognosis is much better in these than in Ewing's tumor arising inside the bone. On February 19, 1953, the patient was presented before a Tumor Board. The consensus of opinion was that amputation would be useless, and x-ray therapy was recommended. Dr. Jesse T. Nicholson suggested Coley toxins.

**TOXIN THERAPY (Sloan Kettering XIV):** Injections were begun at the Philadelphia Naval Hospital the next day, the initial dose being 0.1 cc. of a 1 to 7 dilution. This caused transient headache but no fever. The 2nd dose, 0.2 cc. of a 1 to 7 dilution, was given into the tumor area causing a shaking chill about 30 minutes after injection, and a febrile reaction of 102°F. lasting about five hours, also considera-

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ble headache and malaise. Injections were continued daily or every other day, increasing the dose by 0.1 cc. each time. These usually produced chills with febrile reactions of 101.2°F. to 103°F. The maximum reaction 104.5°F. occurred on February 25, 1953. On that date, two distinct reaction curves occurred with chills. The first chill occurred about 50 minutes after injection, subsiding to normal in 6 1/2 hours. Five hours later, another chill occurred, with rapidly rising temperature and in an hour the maximum fever occurred, 105.6°F.; returning to normal 19 hours after injection.

**RADIATION GIVEN CONCURRENTLY WITH FURTHER TOXIN THERAPY:** After six doses had been given in a period of about a week, x-ray therapy was begun, 200 r being given to the right arm daily, to both proximal and distal arm segments through four ports, totalling 2400 r. (tumor dose). On February 27, 1953, a dose of 0.5cc. was given, causing a febrile reaction of 103° F. which returned to normal in about four hours. Due to the rather weakened condition of the patient no injections were given between February 27 and March 2, 1953, at which time 0.1 cc. of the 1 to 7 dilution was given, followed by chills one hour after injection, and a slow rise in temperature over the next three hours to a maximum of 103°F., returning to normal in another three hours. On March 3, 1953, 0.5 cc. (1 to 7 dilution) caused a chill and febrile response of 104°F., 1 1/2 hours after injection, the temperature returning slowly to normal in eight hours. On March 6, 1953, 1 cc. (1 to 7 dilution) caused a febrile reaction of 104°F. about four hours after injection, which slowly resolved to normal in the next ten hours. On March 11, 1953, 0.6 cc. produced a febrile reaction of 104°F. in three hours, which resolved to normal in another three hours. A total of 12 injections was given in 20 days.

**CLINICAL COURSE:** The patient was examined in April 1953 and revealed considerable erythema over the area of the right deltoid from the x-ray therapy, but the skin did not break down. There was considerable limitation of motion of the shoulder joint and pain complained of in this area, and it was difficult to detect any tumor mass. Following resolution under combined toxin and x-ray therapy, no tumor mass was palpable, nor did it recur. However, due to the nature of his condition, the patient was separated from the Military Service. At the time of his discharge, his condition was very good. There was no evidence of disease. However, he was placed on total disability compensation by the Veterans Administration from April, 1953 until April 1, 1954, at which time he was re-examined. Chest films were negative for metastases. Films of the right humerus showed that the 4 cm. long superficial defect of the lateral cortex in the proximal humerus immediately below the greater tuberosity had been filled out by ossified periosteum. In this area the cortical layer of the humerus was thickened and projecting irregularly into the cavity. The radiologist added: "As compared with July 8, 1953, the new formation of bone mass has made some progress which, however, is only slight and reparatory in nature. There is no evidence of recurrence of sarcoma at this time." The patient reported on May 7, 1954, that he was quite healthy,



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having regained his strength and at least 10 pounds in weight in the previous year and that he had grown half an inch. His weight was 152 pounds, his height 5 feet 9 inches. He was again examined in the Veteran's Hospital on August 26, 1955. Chest films were essentially normal. Films of the right shoulder showed the cortical defect in the proximal lateral surface of the humerus, but there had been no change. Urinalysis and the hematology report were essentially negative. The patient stated that he had lost 10 pounds in weight in the previous five months and that he tired more easily. However, there were no palpable masses and no evidence of extension of disease. He was again seen in the V.A. Hospital in Phoenix, where a biopsy of the humerus obtained on October 16, 1957, showed no tumor. He remained well until April 12, 1958, when he sustained a fracture of the right humerus through the area of the previous biopsy, while playing basketball. On June 18, 1958, a new biopsy was performed and internal fixation of the fracture was done with two screws. Biopsy at this time showed no tumor. He was treated with a hanging arm cast until July 1, 1958, when he felt a sudden snap in the arm while working. The fragments had pulled apart so a spica was applied. On September 5, 1958, a new open reduction and bone grafting was done. Biopsy at this time showed no tumor. In March 1959 there developed a draining osteomyelitis of the right humerus and the plate and screws were removed. The patient was readmitted to the V.A. Hospital in Phoenix on April 4, 1959, for continued efforts at treatment of the non-union of the humerus and osteomyelitis. He remained there until January 4, 1960, when he was discharged apparently well. However, the osteomyelitis recurred and finally on August 2, 1962, the arm was amputated because of this condition. Pathologic examination confirmed the absence of tumor. The patient moved to California and obtained a job in a metal works. His only complaints were chronic sinusitis and "nervous stomach" (he smoked). He remained free from recurrence and in good health on October 17, 1973, almost 21 years after onset of his tumor.

**COMMENT:** This case suggests that patients who have received irradiation and excisional biopsies to the humerus should be cautioned against strenuous ball playing or other activities of this type to avoid pathological fracture, osteomyelitis or possible reactivation of the disease.

**REFERENCES:** 5; 82; 101.

**CASE 4:** Ewing's sarcoma of the right tibia, with apparent pulmonary metastases, confirmed by microscopic examination of the primary growth by Dr. James Ewing and the Bone Sarcoma Registry Committee (Case #185).

**PREVIOUS HISTORY:** R.W., female, aged 7, of Toronto, Ontario, Canada. No details were recorded as to the family and previous personal history. Onset, in

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December 1916, a swelling was noted on the mid-shaft of the right tibia, which increased in size. On January 2, 1917, the child was brought to Dr. F.M.G. Starr of Toronto. At his time the tumor involved the proximal third of the tibia. X-ray examination suggested the possibility of a bone cyst.

**SURGERY:** Starr then performed an exploratory operation, curetted out some debris, wiped out the cavity with iodine and packed it. He then became suspicious of sarcoma. This was confirmed by microscopic examination. Chest films suggested the possibility of pulmonary metastases, as there was a shadow in the mediastinum.

**RADIATION:** A number of x-ray treatments were given in January 1917, with temporary improvement but x-ray films of the chest showed a number of apparent pulmonary metastases. The patient was referred to Dr. William B. Coley by Dr. F.N.G. Starr of Toronto on June 20, 1917, and was admitted to Memorial Hospital that day. Further x-ray examination again showed what was believed to be pulmonary metastases. She was given three x-ray treatments over the chest. Examination of the affected limb showed that the tumor involved the greater portion of the shaft of the right tibia. The patient had had an occasional temperature of 102°F. prior to admission, a symptom occasionally seen in this type of tumor.

**TOXIN THERAPY (*Tracy XI*)** Injections were begun by Coley in late June 1917, and were continued until July 26, 1917. No details are recorded as to site, dosage or frequency of the injections, but at this period he usually gave intramuscular injections.

**SURGERY:** As no marked improvement was noted, the leg was amputated at the juncture of the lower and middle thirds of the thigh, approximately eight months after onset.

**FURTHER TOXIN THERAPY:** The injections were resumed a few days after the operation and were continued for nearly six months. The pulmonary metastases disappeared.

**CLINICAL COURSE:** The patient made an uneventful recovery. She remained free from recurrence or further metastases when last traced in 1927, ten years later.

**REFERENCES:** 5, #185; 37, Case 20; 40, Case 6; 43, Case 7; 37, pp. 525-528; 73.



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**CASE 5:** Ewing's sarcoma of the right tibia, confirmed by microscopic examination by Dr. Fred W. Stewart of Memorial Hospital, following incisional biopsy (sauerization) (V 3656).

**PREVIOUS HISTORY:** T.S., male, aged 30, of Laurelton, New York, born in Belgium, a purchasing agent. The family history was non-contributory. At 14 he had migratory arthritis and arthralgia, treated by prolonged bed rest, also onset of heart murmur *de novo*. That year he had a tonsillectomy. A third bout occurred at 21 with migratory polyarthritis. He was hospitalized for six weeks with bed rest. At 23 he had an acute dyspnea after a weight lifting feat, with collapse, and recurrence of a similar episode. In the next seven years he led a completely normal life, married and had a daughter. He had a moderately severe rectal fissure several years prior to admission which responded to treatment and did not recur. Onset about October 9, 1946, four weeks prior to admission the right leg began to ache. A local physician was consulted who prescribed salicylates without benefit. A moderate sized mass was then noted in the right mid-leg. X-rays were taken. A diagnosis of fibrocystic dysplasia and periostitis was made and the patient was referred to Memorial Hospital. Examination on admission on November 9, 1946, revealed a fusiform swelling of the proximal half of the anterior tibia. The swelling was of the same consistency as bone. X-ray examination showed a central lesion of the proximal end of the right tibia with mottled destruction of the cortex, fairly well demarcated. (Pre-operative diagnosis: polyostatic fibrous dysplasia.)

**SURGERY:** On November 15, 1946, a curettage of the bone tumor was performed. The tissue was reported to be Ewing's sarcoma. A low thigh amputation was advised and performed on November 18, 1946. The post-operative course was uneventful, the mental attitude excellent.

**TOXIN THERAPY (Parke Davis XIII):** Injections were begun on November 29, 1946, 11 days after amputation, and 15 were given intravenously in doses of 1/4 to 2/3 minim during the next 21 days. These caused chills except on two occasions, four severe; six moderate, three slight. Febrile reactions averaged 103°-104.2°F. (minimum 102°F., maximum 105.8°F.) On December 2, 1946, a medical consultation was held to ascertain whether toxin therapy might be contra-indicated in view of the history of rheumatic fever. The findings indicated "rheumatic heart disease", probably left auricular hypertrophy; mitral stenosis; compensation stage 1." It was decided to continue toxins but to watch the patient carefully every day. The final dose was given on December 20, 1946. The patient tolerated the reactions well.

**CLINICAL COURSE:** A small hematoma containing about 40 cc. of thin hemorrhagic serum was evacuated on December 20, 1946. The patient was discharged the next

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day. His stump was in excellent condition when he returned for periodic examinations, and he was able to get about very well on crutches. A prosthesis was ordered about March 1, 1947.

**FURTHER TOXIN THERAPY:** He was readmitted on March 5, 1947, and received a second course of 14 intravenous injections of toxins in doses of 1/80, 1/80, 1/60, 1/50, 1/40, 1/20, 1/10, 1/8, 1/5, 1/3, 2/3, 1, 1/4, 2, 2 1/2 minims. Severe chills occurred after three of the injections. Febrile reactions averaged 103° - 104.6°F., (minimum 102°, maximum 105°F.) Again the patient withstood the treatment well despite his rheumatic heart condition.

**CLINICAL COURSE:** He was discharged improved on March 23, 1947. He returned to work in April or early May, having obtained a suction cup prosthesis after attending the Rehabilitation Clinic at the Hospital for Special Surgery. It was noted on February 1, 1950 that he was walking extremely well with it. He worked full time at his former job, being on his feet seven hours daily. He was followed in the Bone Tumor Clinic at Memorial Hospital. In November 1959 he injured his left leg in an auto accident and was hospitalized in Queens General Hospital, Jamaica. His weight in 1962 was 170 pounds, his height being 6 feet, 1 inch. He was last traced in good health, with no evidence of sarcoma, in July 1973, 26 1/2 years after onset.

**REFERENCES:** 73, 82.

**CASE 6:** Ewing's sarcoma of the right fibula, confirmed by microscopic examination at Memorial Hospital and by the Bone Sarcoma Registry Committee (Case #2279). Dr. Fred Stewart reported as follows: "This is one of those cases where it is impossible to decide between Ewing's sarcoma and a small spindle-cell osteogenic sarcoma. (The cells are distinctly spindle shaped, which favors the latter diagnosis, but distortion by curettage sometimes alters the appearance.)" On January 28, 1958, Stewart reviewed this case and reported: "One of three slides only shows the tumor from what I would have to say is a Ewing's sarcoma." In December 1959 the Armed Forces Institute of Pathology reviewed this case, as registered in the Bone Sarcoma Registry, and reported as follows: "The staff would be inclined to interpret this lesion as a synovial sarcoma (or some similar type of encapsulated undifferentiated soft tissue sarcoma) which is secondarily eroding its way into the underlying fibula." (5)



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**PREVIOUS HISTORY:** W.V.B., male, aged 14, of Maplewood, New Jersey. The patient's great-grandfather died of carcinoma of the stomach, a cousin of carcinoma of the throat, but there was no history of bone tumors in the family. The patient had abscessed ears twice during his first year; a tonsillectomy at four, then measles and chicken pox; at nine he had bilateral pneumonia. Onset, in October 1937, he injured his right calf and knee while playing football. There were no external signs of injury and he went about his normal routine until a week later, when the right calf and proximal leg became swollen, warm and tender, but there was no redness. The temperature was 100°F. The boy was kept in bed for a week and the symptoms subsided. During the next eleven months four similar episodes occurred at intervals of two to four months, with temporary swelling and pain, low-grade fever and local heat. In March 1938 the patient had mumps. X-rays taken by the family physician in September 1938 showed a tumor of the fibula and the patient was referred to Dr. Bradley L. Coley. At examination on admission to Memorial Hospital on September 14, 1938, there was a mild non-productive cough, but the chest pictures were negative. There was no weakness or anorexia, and no loss of weight. The breasts were slightly over-developed. Examination of the right limb showed no change in the contour of the extremity, no edema, tenderness, crepitus or deformity, no tenderness over the fibular head, no impairment of knee function and no regional node enlargement.

**SURGERY:** An aspiration biopsy was made on September 14, 1938, but yielded only blood and fibrin. On the following day an incisional biopsy was made over the head of the fibula and the bone exposed. This appeared to be yellow, soft and necrotic, suggesting suppuration and an inflammatory lesion. The bone was curetted, zinc chloride applied, the wound was irrigated with Dakin's solution and then closed up tightly without drainage and the limb elevated. Stewart examined the curetted tissue and reported as above.

**RADIATION:** The patient was given a course of high voltage x-ray therapy from September 20 to October 5, 1938, totalling 1200 r each to three ports over the right fibula, anterior, lateral and posterior, plus 1200 r through two ports, upper and lower. The final x-ray treatment was on October 5, 1938. X-rays taken on October 7, 1938 were reported as follows: "No change in these films . . . as compared with the previous view; with the exception that there may be some increase in the extent of the bone destruction." Further x-rays were taken on November 7, 1938, and the report showed that there was evidence of some slight bone regeneration.

**TOXIN THERAPY (Parke Davis XIII):** Injections were begun on November 7, 1938, and 11 were given in 12 days, the first eight being intramuscular, in doses of 1 to 11 minims, with one chill and average temperatures of 102° to 104.6°F. The maximum febrile reaction was 105°F. after a dose of 8 minims given intramuscularly on November 12, 1938. The final three were given intravenously.

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**SURGERY:** On November 21, 1938, after preliminary radiation and toxins, a resection of the proximal half of the fibula was performed. The perineal nerve was preserved and the dissection was apparently carried well beyond the tumor at all points. The resected tissue was examined by Stewart who reported: "Below the articular surface there is a large area which has eroded through the cortex . . .

4 x 2 cm. The cortex is exposed in this region, disclosing the yellowish gray material. Along the superior margin of this area the bone is soft and a section is taken of this area . . . Pieces of muscle adherent to bone are not invaded by any neoplasm." *The microscopic examination revealed no evidence of residual tumor.*

**CLINICAL COURSE:** The patient made a good post-operative recovery. No further toxins or x-ray therapy were given. He was seen periodically at Memorial Hospital and remained in excellent condition. He went into business for himself. He married in 1948 and two sons were born in 1950 and 1954. He was issued "preferred risk" life insurance in 1951. His weight in 1952 was 150 to 155 pounds, his height being 5 feet 10 inches. (He had been quite overweight and through dieting lost 15 to 20 pounds.) By 1970 he weighed 180 pounds. He remained entirely well and free from recurrence or metastases in January 1973, over 35 years after onset.

**REFERENCES:** 5; 73; 82.

**Case 7:** Ewing's sarcoma of the distal left radius with invasion of the adjacent muscles, confirmed by microscopic examination (following extensive incisional biopsy) by the chief pathologist of Temple University Hospital, Philadelphia.

**PREVIOUS HISTORY:** D.F., female, aged 7, of Longport, New Jersey. The family history was negative for malignancy and the previous personal history was non-contributory. The child had been apparently well until January 1954, when she sustained a pathological fracture of the distal end of the radius. An x-ray was taken which showed a small bone cyst in the fracture line. No particular attention was given to the "cyst". A plaster of Paris cast was applied at the Cooper Hospital in Camden, New Jersey. The limb was immobilized for six weeks with no follow-up x-ray study. The child remained free from disability until May 26, 1954, when she experienced an indirect trauma to the left forearm and wrist (it was twisted by a playmate), with an acute onset of pain. X-ray examination at the Einstein Medical Center in Philadelphia the next day revealed definite cystic formation: an irregular radiolucent area within the distal radial metaphysis. The area of bone replacement appeared to be slightly expansible in nature with some thinning of the overlying bony cortex in the lateral aspect of the distal radius. There was also noted an area of mottled radiolucency within the distal shaft of the radius proximal to the area of cystic change with definite heaping-up of the overlying periost-



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teum and suggested onion-skin layering. There was also erosion of the medial aspect of the cortex of the distal radius. The patient was admitted to the service of Dr. Henry Sigmond at the Northern Division of the Einstein Medical Center on June 3, 1954. A complete bone survey and chest films were negative for metastases. The blood count showed hemoglobin 12.3 gm., r.b.c. 3,670,000; w.b.c. 4,500; differential 43 poly., 57 lymph., 1 eosinophile; blood sedimentation rate 19; 7 mgms. per cc. Urinalysis was negative; the rectal temperature from June 3 to 16, 1954 was 100°-101°F.

**SURGERY:** An extensive excision was performed under general anesthesia on June 7, 1954, through a 10 cm. incision. A large soft tissue tumor approximately 5 x 3 1/2 x 1 cm. in diameter was found overlying the anterolateral aspect of the left radius, 5 cm. proximal to the radiocarpal joint, invading the pronator quadrator muscle which was adherent to the periosteum of the shaft. This massive tumor was removed *in toto* by subperiosteal resection and blocked excision. The remainder of the periosteum of the shaft down to and including the cystic area was elevated, boggy, and was separated from the moth-eaten shaft by a somewhat yellow-white gelatinous material. There was no evidence of fracture of the shaft or distal end of the radius. A section of the periosteum with the attached gelatinous material was also taken as a specimen. The bone under this area was also taken for biopsy. There was marked erosion of the lateral and distal end of the radius with hollowing-out into a cavity in the styloid area. The depths of this cavity produced a yellowish degenerated material. A plaster of Paris cast was applied from below the elbow joint down to and including the distal palmar crease of the left hand with the fingers free.

**RADIATION:** X-ray treatment was given under the direction of Dr. J. Gershon-Cohen daily between June 14 and 24, 1954, through a 10 x 4 cm. portal away from the skin incision, 300 r each, totalling 2,970 r delivered in 10 days. The patient was seen in consultation by Dr. Henry L. Jaffe in New York on June 16, 1954. He advised toxin therapy.

**TOXIN THERAPY (Sloan-Kettering XIV):** Injections were begun by Sigmond on July 15, 1954. The first course consisted of 14 daily injections given intravenously in doses of 1/100, 1/60, 1/50, 1/32, 1/10, 1/5, 1/2, 1, 2, 4, 6, 8 and 10 minims. They caused chills each time lasting 10 to 60 minutes (average 30-35) and febrile reactions averaging 103.4°F-104.4°F. (maximum 105°F.). There was also nausea and headache and occasional abdominal pain.

**FURTHER RADIATION:** A second course of x-ray therapy was given between July 31 and August 7, 1954, totalling 2280 r.

**SECOND COURSE OF TOXIN THERAPY:** Injections were resumed on August 31, 1954, and were given daily for 14 days intravenously in doses of 1/100, 1/80,

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1/50, 1/32, 1/10, 1/5, 1/2, 3/4, 1/2, 4, 6, and 8 minims. The first dose caused no reaction at all, the others causing chills lasting 30 to 160 minutes (averaging being 80-120 minutes) and febrile reactions averaging 103.2°F-104.6°F (maximum 105°F.), also neausea and headache.

FURTHER RADIATION GIVEN CONCURRENTLY WITH FURTHER TOXIN THERAPY: A third course of x-ray therapy was given daily between October 4 and 14, 1954, totalling 2280 r. This was administered concurrently with a third course of toxin injections given daily between October 5 and 15, 1954, in doses of 1/80, 1/50, 1/20, 1/10, 1/5, 1/2, 1/3, 4, 6 and 8 minims, causing febrile reactions averaging 101.8°F (maximum 105°F.), also nausea and headaches. It was noted on October 15, 1954 that x-rays of the radius showed some bone regeneration. Up to that time there appeared to be no local change in the condition of the affected bone. A fourth course of 14 injections was given intravenously between November 30 and December 13, 1954, in doses of 1/80, 1/50, 1/20, 1/10, 1/5, 1/2, 1, 2, 4, 6, 8, 10 and 12 minims. Again there was no reaction to the initial dose, others caused chills lasting 77 to 150 minutes (averaging 100-130) and febrile reactions averaging 102°F.-103°F.(maximum 104°F.) and nausea, headache, photophobia and abdominal pains.

Injections were resumed on February 8, 1955, the fifth course consisting of 14 injections given daily intravenously in doses of 1/80, to 16 minims, with chills averaging 113-125 minutes (maximum 180 minutes) and febrile reactions averaging 103°F.-103.4°F (minimum 101.2°F, maximum 104.°F.)

Injections were resumed on April 26, 1955, after a rest period of two months, (the sixth course) and were given intravenously in doses of 1/80 to 16 minims for 14 days. The febrile response averaged 102.4°F - 103°F., and there was also transient nausea, headache, and abdominal pains.

CLINICAL COURSE: In reporting on the case in May 1962, Sigmond wrote: "The repeated admissions to the hospital for toxin therapy did not interfere seriously with the normal life of this child. The general nutrition remained good and there was no apparent emotional instability." Repeated x-ray examinations of the left forearm, wrist, hand and chest showed no evidence of recurrence or metastases of the Ewing's sarcoma. However, the irradiation caused cessation of growth of the radius while the ulna continued to grow and became 5 cm. longer than the radius. In 1962 the left arm was 10 cm. shorter than the right. In addition to the skeletal deformity, the skin of the forearm over the dorsum and radial surface was quite mottled with marked atrophy and some loss of function of the muscles supplying the hand. These changes were due to the heavy irradiation (7,530 r). A bone graft was considered but it was decided that any bone surgery would be difficult through such devitalized skin. A plastic operation was then done on the wrist as the first stage in rehabilitation.



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**PLASTIC SURGERY:** An abdominal pedicle graft was applied in two stages in August and September 1959, the irradiated skin being excised. By February 13, 1960, the skin had healed well and a trough palmar splint was applied to maintain the wrist-hand relationship and overcome the radial deviation tendency.

**CLINICAL COURSE:** The patient began to become obese prior to puberty, possibly as a neurotic reaction to her crippled left hand. At 12 1/2 years, she weighed 175 pounds. By April 1962 she weighed 230 pounds. Within the next year reconstructive surgery of the left forearm and wrist was performed but without much success in improving the deformity resulting from irradiation; her weight declined to about 185 pounds. She obtained a clerical job prior to 1967, and by 1970 was a computer programmer. Her weight at this time was over 225 pounds. She remained in excellent health on February 15, 1973, 19 years after onset.

**REFERENCES:** 82.

**CASE 8:** Ewing's sarcoma of the right fourth metatarsal, confirmed by microscopic examination of the resected bone by Dr. Fred W. Stewart on October 16, 1951 (51-15218). (Previous aspiration material had been regarded as reticulum cell sarcoma.)

**PREVIOUS HISTORY:** R.P., female, aged 16, of Bayonne, N.J. The family history was negative for familial disease. The patient had had the usual diseases of childhood. She broke her wrist in 1939, with no residual disability. Menses began at 14, were irregular (30 to 60 days) the flow lasting four days. Onset, in March 1949, without known trauma, the patient began to have a sharp, steady throbbing non-radiating pain on the dorsum of her right foot; soon afterwards a swelling developed in this area. Pain was increased by walking, relieved by rest. A local physician was consulted who advised rest and soaking for "arthritis". This caused the pain to disappear in five days. No x-rays were taken. Four such episodes occurred in a period of eight months. The patient treated each of these by rests and "soaks". The local physician was again consulted on November 15, 1949, and x-rays were taken by Dr. W. W. Maver of Jersey City, revealing a destructive lesion involving half the shaft of the fourth metatarsal in its distal portion, and including the medullary, cortical and periosteal portions of the bone. On the lateral aspect of the involvement sun-ray areas of periosteal proliferation were noted. On the dorsal and toward the medial aspect the cortex had broken through and elevated, with fairly extensive new bone formation. Maver regarded it as a low-grade osteogenic sarcoma or an atypical Ewing's sarcoma. The patient was admitted to Memorial Hospital on November 30, 1949. Examination revealed a very slightly diffuse non-pitting swelling over the fourth right metatarsal (dorsum). The area beneath was tender to moderate pressure. There was no swelling or tenderness on the plantar surface. The provisional diagnosis of Dr. Bradley L. Coley and Dr.

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Fred W. Stewart based on smears obtained at aspiration biopsy was either reticulum cell sarcoma or Ewing's sarcoma.

**TOXIN THERAPY (SKI XIV) GIVEN CONCURRENTLY WITH RADIATION:** Injections were begun on November 30, 1949, and 12 were given in 13 days. The initial dose was 1/80 minim which was increased to 2 minims as follows: 1/80, 1/30, 1/20, 1/5, 1/2, 1, 1 1/2, 1 1/2, 2, 2, 2. These produced febrile reactions averaging 104°F. (minimum 102°F. from the first small dose, maximum 105.8°F. from the third injection). Chills occurred after each injection lasting 25 to 30 minutes, with headaches, sometimes severe, and sweating. X-ray therapy was begun the day after the toxins and was given daily between December 1 and 13, 1949 (250 K.V., 300 r each), over the dorsal aspect of the right foot. The total tumor dose at 3 cm. depth was calculated at 2850 r, the skin dose as 3300r. The patient responded satisfactorily to this combined therapy.

**CLINICAL COURSE:** She was discharged home on December 13, 1949, and readmitted for further treatment on February 9, 1950. During that interval she had been in good health. Examination on readmission showed x-ray changes of the dorsum of the right foot.

**FURTHER TOXIN THERAPY:** Injections were resumed on February 9, 1949 and were given daily intravenously for 13 days in doses of 1/60, 1/60, 1/20, 1/10, 1/5, 1/2, 3/4, 1 1/2, 2 1/2, 3 1/2, 4 1/2, 5 1/2, minims. All except the initial dose caused febrile reactions averaging 103.8°F to 104.4°F. (minimum 103.4°F. maximum 104.8°F.). Severe chills occurred after 10 injections, moderate chills after the last two.

**CLINICAL COURSE:** The patient was discharged home on February 22, 1950. She was seen on April 10, 1950. The condition of the foot was excellent. There were practically no residual signs of radiation therapy. Palpation revealed no swelling, no tenderness and there was no lymphadenopathy. Frequent x-ray examinations were made and showed that a favorable response had occurred to combined x-ray and toxin therapy. Within a few months the involved bone had lost the characteristic appearance of a malignant neoplasm and appeared to be fibrotic. This improvement continued until March 1951 when a small fuzzy area could be seen near the superficial cortex. This area slowly increased in size during the summer, but the patient remained symptom-free, except for her usual mild menstrual irregularity (i.e. relative amenorrhea on occasion), and she gained weight. About September 1, 1951 she first noticed mild pain and swelling of the foot after prolonged activity. Further x-ray examination showed that the fuzzy area had slowly increased in size so that by September 24 it was approximately 1 cm. in diameter. There was no soft part involvement. The patient was readmitted to Memorial Hospital on October 1, 1951. She appeared to be very well-nourished and well-developed. There was slight asymmetry of the feet, with evidence of



#### SERIES A, DETERMINATE SUCCESSES, DETAILED HISTORIES

radiation changes over the dorsum and lateral aspect of the right foot. There was a palpable osseous swelling measuring  $2 \times 4.5$  cm. over the distal portion of the fourth metatarsal. An aspiration biopsy was performed that day, but only blood and questionable tissue was obtained.

**SURGERY:** A resection of the fourth metatarsal was performed on October 4, 1951, with inlay of bone graft from the rib. A pathological report on the resected bone was Ewing's sarcoma. On November 22, 1951, the right leg was amputated 8 cm. below the tibial tubercle.

**CLINICAL COURSE:** The postoperative course was uneventful. The patient was discharged five days after amputation. The incision healed *per primum*. She was fitted for a prosthesis three months later. Within two months she was quite expert with it, had no difficulty and was able to dance and walk remarkably well. She was able to do everything other girls her own age can do, including a job as secretary. Physical examination on July 7, 1952 revealed a well healed, well tailored, well proportioned knee stump which seemed to be taking the stress of the prosthesis beautifully. The patient was seen periodically in the Bone Tumor Clinic and remained without symptoms, when she suddenly developed severe pain in the right side of the chest requiring sedation. Films were made on November 13, 1953, and disclosed a lesion apparently arising in the rib (cancelous destruction of the rib), probably arising within bone and compatible with secondary bone involvement, from a subpleural or a lateral pulmonary metastasis. Examination of submitted films showed a 2 cm. nodular density in the mid-lung field, and an oval  $10 \times 4$  cm. density, and there was a slight flattening of the right leaf of the diaphragm with pleural reaction filling the right costophrenic angle. "Conclusion: Nodular deposit right lung, consistent with metastasis. Pleural reaction possible with a metastatic deposit on the right, as described."

**RADIATION:** Deep x-ray therapy (2000 r) was given ending November 19, 1953.

**TOXIN THERAPY (SKI XIV):** The patient was readmitted on December 3, 1953, and injections were given daily for 12 days intravenously in doses of 1/60, 1/20, 1/4, 1/2, 1, 1 1/2, 2, 3, 4 1/2, 6 1/2, 9 and 9 minims. These caused febrile reactions averaging  $103^{\circ}$ - $104^{\circ}$ F. (maximum  $104.4^{\circ}$ F, and minimum  $100.4^{\circ}$ F.) with chills lasting 30 minutes or less. There was some dyspnea during the reactions from the larger doses, also pain in the leg and headache.

**CLINICAL COURSE:** Chest films taken on December 15, 1953, the day the toxins were stopped, showed that there had been marked regression of the subpleural soft mass and some evidence of reossification of the destructive lesion in the right sixth rib, mainly by irregular periosteal new bone production. "Conclusion: Regression in costal and subpleural metastasis." Further chest films taken by Dr. T. Arthur Pearson on February 16, 1954, revealed "no evidence of pulmonary

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parenchymal metastases". Both lung fields were clear. The diaphragm, costophrenic angles, heart, aorta, trachea, mediastinum, and visualized osseous structures were unremarkable. Physical examination on February 16, 1954, by Coley was practically negative. The skin over the area which had been irradiated on the right chest wall was beginning to lose its tan. The patient had no symptoms even on deep breathing. She gained weight, felt well and returned to work as a bookkeeper. She was seen at intervals by Coley and later by Dr. Norman Higinbotham who found no evidence of disease. She remained in excellent health in January 1973, almost 24 years after onset of the primary and 29 years after recovery from the metastatic lesions.

COMMENT: This case is one of the very few who developed metastases to whom further toxins as well as radiation was administered. The result suggests that such combined therapy may be far more effective in gaining permanent control of the disease than further x-ray therapy alone.

REFERENCES: 73; 82.

**CASE 9:** Recurrent Ewing's sarcoma of the metatarsal bones of the left foot, confirmed by microscopic examination after incisional biopsy (Mayo Clinic).

PREVIOUS HISTORY: B.B.B., male, aged 17. The family history was essentially negative. The patient had had the usual diseases of childhood, but no serious illnesses or injuries prior to onset. He developed a painless mass on the medial aspect of the left foot in September 1952; the foot was everted in walking. X-rays taken at this time were negative. Arch supports were prescribed.

SURGERY: Two weeks after onset, a tumor was removed from the medial aspect of the left foot. The diagnosis was not recorded.

CLINICAL COURSE: The patient was told not to worry and no further treatment was given. The growth recurred 20 weeks later.

FURTHER SURGERY: The recurrence was biopsied four weeks after it developed. The diagnosis was "high grade sarcoma, probably Ewing's, involving metatarsal bones left foot (especially navicular)." On August 20, 1954 a second incisional biopsy was performed at the Mayo Clinic and was reported "Ewing's tumor left metatarsal navicular." The left leg was amputated at the junction of the middle and upper thirds that day.

TOXIN THERAPY (S. K. I. XIV): Injections were begun on September 12, 1954, 13 days after amputation and 16 were given intravenously in doses 1/80, 1/50, 1/20, 1/10, 1/10, 1/5, 1/2, 1, 3, 6, 9, 12, 15 minims. These caused febrile reactions



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averaging 102.6° to 103°F. (minimum 101°, maximum 103.6°F.). Two additional courses of 14 injections each were given by the family physician, using similar dosage schedules and producing similar reactions.

**CLINICAL COURSE:** There was no further recurrence. The patient obtained a prosthesis and made an excellent adjustment to it. He finished his education, obtained a job in a bank and in 1963 married. Two healthy sons were born, in 1964 and 1965 and another child in 1968. The patient remained asymptomatic and in excellent health in October, 1973 working regularly. This was 21 years after onset.

**REFERENCES:** 72; 82.

**SERIES B: INDETERMINATE SUCCESSES, BRIEF ABSTRACTS,  
14 CASES**

These cases were formerly classified as Ewing's Sarcoma but were not included in Series A because the pathological, x-ray or clinical material is unavailable for review, or because after review by the Armed Forces Institute of Pathology, the former diagnoses were revised or questioned or because the patients were traced less than five years. The bones involved in this Series are: Femur, 4; humerus, 1; tibia, 3; fibula, 2; clavicle, 3; metatarsal, 1.

Years Traced  
After Onset

1. W. B. COLEY: A.G., male, aged 18; extensive Ewing's sarcoma lower two-thirds of shaft of left femur, extensive metastases pectoral and iliolumbar regions; (no slides available for review); onset November 1901; lost weight, general health deteriorated; exploratory incision, specimen removed February 5, 1902; amputation refused; x-ray therapy to thigh more or less continuously for 10 mos.; gained 20 pounds in weight; December 1902, metastasis iliolumbar region involving ilium (retroperitoneal origin); February 1903: toxins (Buxton VI), 86 i.m. and i.t., in 5 months; *within 4 wks. retroperitoneal tumor softened and broke down, (drainage established surgically, over 1 pint necrotic tumor tissue evacuated);* wound continued to drain well through large tube, healed in few weeks except for small sinus (remained open a year); *complete regression all growths;* sinus in leg remained for several years, also marked thickening of bone; repeated curettings showed no evidence of sarcoma; well 10 yrs. except for radiodermatitis on thigh and pectoral region; March 1912 developed x-ray cancer (epithelioma) in pectoral region, excised week after onset; fall 1912 very large ulcerating area (epithelioma) on irradiated leg 30 × 30 cm.; marked deterioration in general health, portion removed; 12 more doses toxins, no apparent effect; very strong radium ointment given in large doses to overcome very foul odor (no effect); 1 dose colloidal copper injected; January 2, 1913, finally consented to amputation; a week later metastases to lungs and apparently to perineum; *no evidence Ewing's sarcoma at death,* January 6, 1913. Detailed history and pathological reports are of special interest, see below. (20, Case XXII; 23, Case III; 24; 31; 34, Case 41; 37, Case 4 in text, Case 27 in Table 7; 40, p. 13.)

over 11 yrs.

2. W. B. COLEY: J.P.W., male, aged 35; round cell sarcoma involving distal right femur; (sections unavailable for review); onset of pain spring, 1906; amputation 6 months later; toxins (Tracy X) begun as soon as wound had healed, given 6 months; no further evidence disease; well 23 yrs. then health failed; died June 14, 1929, gastric carcinoma. (8; 36; 37; 40; 82)

23 yrs.

3. W. B. COLEY: H.J., male, aged 22; original diagnosis (to 1959) round cell



SERIES B, INDETERMINATE SUCCESSES, ABSTRACTS

Years Traced  
After Onset

sarcoma or Ewing's sarcoma proximal left femur; 1959 diagnosis: A.F.I.P. report: "undifferentiated round cell sarcoma, in which the round cells are much too large for a Ewing's tumor, and do not have the cytologic patterns expected with a reticulum cell sarcoma. In some rare areas there is a vague hint that should the cell have had a chance to differentiate, they would have produced small amounts of chondroid or myxochondroid material. Therefore Ewing's sarcoma is believed unlikely and reticulum cell sarcoma is deemed to be the more probable guess." Onset of pain February 1909; physiotherapy; 1st operation February 1909: tumor chiselled away; 20 days later toxins (Parke Davis XII) i.m., no marked reactions; *did not prevent recurrence; under continued injections some diminution (temporary)*; hip-joint disarticulation December 23, 1909, 10 mos. after onset; (tumor 12 × 7 cm., *large area necrotic, contained leukocytes*); toxins resumed (more potent Tracy XI) for 4 wks.; *no further recurrence*; obtained prosthesis to which he adjusted very well; resumed work; remained well, developed diabetes mellitus, 1937; cholecystectomy, appendectomy 1950; transurethral prostatectomy 1951 (benign prostatic hyperplasia); over the years a perineal fistula *in ano*, of which he had many, would become infected, would drain and close; stump from time to time drained small quantity sanguinous material; 1957, low back pain attributed to lumbosacral arthritis; early 1958, pain, dyspnea due to coronary heart disease, attacks steadily worse; March 31, 1959, acute myocardial infarction; progressed well except for continued severe angina pectoris secondary to ischemic heart disease; another myocardial infarction proved fatal September 10, 1965. (5; 36; 37; 39; 40; 43; 73; 82; 93; 94)

56 1/2 yrs.

4. WILLMOTH: male, aged 28; round cell sarcoma of upper femur (no slides available for review); onset July 1909; exploratory operation 3 months later revealed tumor 10 cm. long; specimen removed; toxins (Tracy XI) begun immediately after operation, given 3 months; *complete regression, normal limb; no further evidence disease*; alive and well when last traced 1925. (33; 37; 40)

16 yrs.

5. MACHID: J.B., male, aged 24; inoperable round cell sarcoma of humerus (no slides are available for review), with pathologic fracture and apparent pulmonary metastases; onset, September, 1917; following severe shoulder strain; considerable weight loss; February 1918, explored; large quantity gelatinous material, pus, blood evacuated; condition regarded as hopeless; toxins (Tracy XI) begun March 1918; dose increased, severe reactions, given 4 months, stopped for 3, resumed with intervals of rest until August 1920 (last part weekly); site: at first i.m. in abdominal wall, arm, "working concentrically toward center;" 1 month after toxins

SERIES B, INDETERMINATE SUCCESSES, ABSTRACTS

Years Traced  
After Onset

stopped pain in shoulder; incision, drainage cup of clear "pus"; toxins resumed; total duration 21/2 years; *pathologic fracture healed, but shoulder was ankylosed; no further evidence disease in humerus or lungs*; returned to work 7 months after toxins were begun; no serious illness, in good health until sudden death, coronary thrombosis, August 12, 1950. (5; 36; 37; 40; 42; 43; 82)

32 Yrs.

6. MATAGNE: Male, aged 16; recurrent round cell sarcoma distal right tibia, metastases in groin; (no slides available for review); onset 1901, following contusion to right tibia; primary removed at operation; recurrence within a few months, involving overlying soft tissues; early February 1902: toxins (Buxton VI formula made by Matagne); in thigh for 2 months; amputation April 1902; metastatic nodes in groin removed; *no further evidence disease; in excellent health, developing normally* 1905; cited as a permanent result 1953. (69; 70; 71).

over 4 yrs.

7. FERGUSON: Male, adult; round cell sarcoma tibia; (sections not available for review;) incisional biopsy; toxins (Buxton VI); *complete regression*: well and free from disease 1906. (20; 42; 73)

over 10 yrs.

8. W. B. COLEY: J. H., male, aged 36; round cell sarcoma right tibia; (sections not available for review;) onset July, 1905; unable to work after December 3, 1905; incisional biopsy 7 months after onset; toxins (Buxton VI) begun April 19, 1906; 48 in 21/2 months, moderate reactions; x-ray (10) given during latter part of toxin therapy; some infection in or near wound before and after toxins were begun; *complete regression, no further evidence disease*; alive and well when last traced, 1917. (42; 73)

12 yrs.

9. WALTON & COLEY: Female adult; inoperable round cell sarcoma right fibula; (sections not available for review); onset March 1894; general health rapidly failed; amputation refused; toxins (Buxton VI) deeply into tumor, reactions 104° - 106°F.; *softening apparent in 6 weeks*, slight discharge; curettage, profuse hemorrhage, week later offensive hard black substance removed; *complete regression; no further evidence disease*; traced well, no disability, 1905, *considered to be 1st case in which limb was saved by use of toxin therapy for a round cell sarcoma*. (18; 41; 42; 102)

11 1/2 yrs.

10. LLOYD: Female, aged 23; round cell sarcoma distal fibula; (sections not available for review); osteomyelitis; onset apparently followed typhoid fever; amputation refused; June 27, 1895, fibula resected; tumor involved soft tissues, adjacent tibia, ankle joint, *wound suppurated*; toxins (Buxton



SERIES B, INDETERMINATE SUCCESSES, ABSTRACTS

Years Traced  
After Onset

- VI) 12 or 15 in 3 weeks; *complete regression*; considerable ankylosis of ankle joint; traced well 1900. (19; 63) over 5 yrs.
11. W. B. COLEY: J. W. H., male, aged 34; round cell sarcoma left clavicle; (sections not available for review); onset shortly after trauma; total excision clavicle May 18, 1908; toxins (Tracy XI) begun 13 days later; considerable infiltration whole lower cervical region (recurrence or incomplete removal); *this gradually cleared up under toxins given in pectoral muscles* (80 i.m. in 18 months); returned to work 31/2 months after first dose, gained 26 pounds; *no further evidence disease*; in excellent health, worked steadily; died May 4, 1933, grippe, chronic myocarditis with dilation, renal complications. (5; 8; 30; 35; 37; 39; 42; 82; 99) 25 yrs.
12. FREEMAN: H.L.S., male, aged 23; inoperable round cell sarcoma clavicle; (sections not available for review); metastases in neck, deltoid; fractured scapula and clavicle February 1907; by April 1908 supraclavicular adenopathy present; 2nd injury June 1908; shortly thereafter rapidly growing tumor over clavicular region extending to spine, metastases in neck and deltoid region size of man's fist; later became a fungating mass; bedridden 4 weeks, 14 lb. weight loss; incisional biopsy, totally inoperable; July 17, 1908: toxins (Tracy XI) given aggressively combined with x-ray; *marked improvement in 6 weeks, tumor masses regressed 50%, much softer*; returned home; severe hemorrhage from necrosing tumor required interscapulothoracic amputation; *complete recovery, no further metastases*; traced well 1917. (35; 42) 10 1/2 yrs.
13. W. B. COLEY: I.M.V., male, aged 18; round cell sarcoma clavicle; (sections not available for review); severe trauma and strain prior to onset, fall 1909; total excision clavicle November 22, 1909; toxins (Tracy XI) begun week later, given i.m., 4 months; *no recurrence or metastases*; served in Army, World War I, drove racing cars thereafter; married 1921; daughter, son born 1925, 1928; in good health until 1945; then pulmonary t.b., with cavitation; hospitalized 3 years, finally recovered 1955; well except for symptoms of prostatism beginning in 1960; duodenal ulcer 1960, responded to treatment; January 1965, basal cell carcinoma of face excised; February 1965, duodenal ulcer reactivated; December 1965, generalized abdominal tenderness and distress, some distention, much gas, enlarged liver, some difficulty in urinating; hospitalized, thorough work up for suspected carcinoma of colon revealed only hiatus hernia, duodenal diverticulum, also diverticulosis of the colon; April 1968, cholecystectomy for chronic cholecystitis with cholelithiasis; also had emphysema and chronic pyelonephritis; traced well 1973. (5; 33; 37; 40; 42; 82)

SERIES B, INDETERMINATE SUCCESSES, ABSTRACTS

Years Traced  
After Onset  
63 yrs.

14. W. B. COLEY: Mrs. E. W. M., female, aged 22; round cell sarcoma metatarsal; (sections lost); onset May 1901; amputation 3 months later; toxins (Parke Davis IX) begun shortly after operation, given 8 months; *complete recovery*; had three children; well 32 years; then rheumatoid arthritis hands; died in sleep, cerebral hemorrhage, 1945. (36; 37; 42; 82)

44 1/2 yrs.



## SERIES B: INDETERMINATE SUCCESSES, SELECTED DETAILED HISTORIES

**CASE 1:** Small round cell sarcoma of the femur, involving the distal two-thirds of the shaft with extensive metastases in the pectoral and iliolumbar regions, confirmed by microscopic examination by Dr. E. K. Dunham, Professor of Pathology at Bellevue Medical School and Dr. B. H. Buxton, Professor of Experimental Pathology.

**PREVIOUS HISTORY:** A.G., male, aged 18. The family history was non-contributory. Onset, a swelling was first noticed in the lower portion of the left femur in November 1901. This gradually increased in size, the patient lost weight and his general health deteriorated. He was admitted to Memorial Hospital February 5, 1902, and at this time there was a fusiform tumor extending from the condyles of the left femur to the junction of the middle and distal thirds.

**SURGERY:** An exploratory incision under ether was made and a specimen removed. Amputation at the hip-joint was strongly advised but refused.

**RADIATION:** X-ray therapy was tried entirely as an experiment, four exposures a week being given for a month, at the end of which time the circumference of the tumor had decreased 2.5 cm. The treatment was discontinued for two weeks, during which time the tumor increased nearly 2.5 cm. It was then resumed, and at the end of another month the circumference had again decreased 2.5 cm. X-ray therapy was continued during the summer and fall until December 1902. At this time the measurements of both legs were the same. The patient gained 20 pounds in weight during treatment.

**FURTHER SURGERY:** There was still some thickening of the lower femur and the old sinus had never healed. This was enlarged under ether and carefully curetted. Examination showed no evidence of sarcoma.

**CLINICAL COURSE:** Towards the end of December 1902, a metastatic tumor developed in the left pectoral region. This grew rapidly until it was 8 cm. in diameter.

**FURTHER SURGERY:** The lesion was partially removed under general anesthesia on February 4, 1903. It was very soft and highly vascular.

**CLINICAL COURSE:** Shortly thereafter there developed a much larger metastatic tumor 10 by 13 cm. in diameter, in the iliolumbar region involving the ilium. This was firm in consistence, and apparently of retroperitoneal origin and was regarded as entirely inoperable. No x-ray treatment was given to this tumor.

**TOXIN THERAPY (Buxton VI):** Injections were begun by Dr. William B. Coley on February 12, 1903, and 86 were given in five months, ending July 25, 1903 in

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doses ranging from 2 to 20 minims. The maximum febrile reaction was 103.5°F. Within four weeks after the first injection the large tumor in the iliolumbar region began to soften and break down. As soon as fluctuation became well marked at the end of two months, drainage was established by an incision over the upper dorsal surface of the ilium, over a pint of necrotic tumor tissue being evacuated. A large tube was kept in the wound which continued to drain well, and then healed in a few weeks except for a small sinus which remained for about a year.

**CLINICAL COURSE:** The growth in the iliolumbar region regressed completely and although the tumor in the leg had also apparently disappeared, there remained a marked thickening of bone and the sinus leading to the broken-down area persisted for several years. Examinations of several curettings failed to show any further evidence of sarcoma. An x-ray examination made early in 1912 showed the presence of an extensive sequestrum. (For photographs of the patient, x-ray pictures and microphotos see 31, p. 100). Coley stated: "The patient went on to apparent cure and remained well over ten years." (31) Aside from the persistent x-ray dermatitis in the lower and anterior portion of the thigh, there was also some x-ray dermatitis in the pectoral region. He was presented before the New York Surgical Society on October 10, 1908, in perfect health. It was noted, however, that some thickening of the femur had persisted. He was again presented before this society on May 8, 1912. Three weeks later Coley noted a small tumor the size of an olive which had just developed in the pectoral region at the site of the x-ray dermatitis. The following week the growth was removed and examined by Dr. James Ewing who reported: "The tumor of the skin proves to be an epithelioma. It is primary in the place it is found and has nothing to do with the sarcoma of the femur." (This was the first x-ray cancer this man developed.) Coley added: "The patient remained well during the summer, but in the latter part of October 1912, when I saw him again, I found a very remarkable change had taken place in the old dermatitis on the lower part of the thigh. There was a very large ulcerating area, fully 2.5 cm. in diameter which showed unmistakable evidence of malignant degeneration, the discharge having the foul odor characteristic of epithelioma. The ulceration rapidly extended until it covered an area fully 30 x 30 cm., and it was constantly increasing in thickness. The general health of the patient also became greatly deteriorated." The appearance of the surface of the tumor was characteristic of tumors originating in old x-ray burns. The disease apparently originated in the skin and subsequently involved the deeper structures; this was confirmed by x-ray examination. A portion of this tumor was removed under cocaine and was examined by Drs. William H. Welch, James Ewing, and William C. Clark. (For complete reports see 31, p. 100.) Coley advised amputation of the leg, but failed to get the patient's consent.

**SECOND COURSE OF TOXIN THERAPY (Tracy XI):** As the patient was anxious to have the toxins resumed, 12 intramuscular injections were administered between November 18 and December 15, 1912, in doses ranging from 0.5 to 5 minims.



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They had no apparent effect upon the progress of the disease.

**FURTHER RADIATION:** During November and December the surface of the tumor was treated with large doses of very strong radium ointment, in the hope of overcoming the very foul odor of the discharge. No effect was noted. He was also given one injection of colloidal copper.

**FURTHER SURGERY:** The general condition grew steadily worse and the patient finally consented to amputation, which was performed on January 2, 1913, under nitrous oxide gas and oxygen. The entire operation, including closing the wound, took 13 minutes and the patient made a very good post-operative recovery.

**CLINICAL COURSE:** About one week after the amputation metastases developed in the lung, and apparently also in the perineum. The disease progressed rapidly. Death occurred on January 16, 1913, over 11 years after onset.

The amputated specimen was further examined by Ewing who reported as follows: "Case of G., April 23, 1913. Tumor of the femur. Specimen consists of a leg amputated through the upper third of the thigh. The skin is absent over the anterior and lateral surfaces of the region of the knee-joint for a distance of 20 c.m., and in its place is a hard modular growth, pale in color and spotted here and there with ecchymotic areas varying in size from a pin point to 4 and 5 cm. in diameter, and small ulcerating areas (0.5 to 1.5 cm.) containing white cheesy-like material.

"On vertical section the tendon and lower portion of the rectus femoris, to within 2 cm. of the patella, is replaced by a tumor mass for a distance of 15 cm. This mass appears quite separate from the periosteum of the femur, a layer of fat being interposed. At its widest point it measured 6 cm. Its upper surface is covered with skin and subcutaneous fat, but the remaining portion has broken through the integument and produces an ulcerating area which is seen on the surface of the limb. The surface of this mass is smooth, white, and glistening.

"At the point of amputation the diameter of the femur is not increased and the compact bone appears to be normal; the medullary cavity contains a reddish-brown marrow. In the lower third of the bone, it measures about 7 cm. in diameter and the medullary cavity has entirely disappeared; the compact bone is atrophied, in places being only a shell. Where the normal marrow cavity ends, there is a small deposit of cancellous bone; just below this, there are two bone cysts, measuring 0.5 and 1.5 cm. in diameter and lined with a glistening membrane. Extending from the cancellous bone, posterior to the cysts, is a mass of ivory-like compact bone which takes in the entire diameter of the femur just below the cysts. Below this compact bone is a sequestrum, 4.5 cm. in length, the remains of what appears to have been a part of the shaft of the femur; this lies in cancellous

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tissue. Just above this condyle in the medullary cavity is a well circumscribed tumor measuring 5 x 3 cm.

"The cut surface is white and granular in appearance and cuts with considerable resistance; the edges are well marked and the tumor does not appear to infiltrate the surrounding tissue.

"The cancellous tissue in the condyles appears normal. Patella shows osteoporosis. The head of the tibia shows atrophy of compact bone. Medullary cavity is normal, except for an area of 5 cm. long by 3 cm. wide, in which the marrow appears to be denser than the surrounding tissue.

*"Microscopical:* The compact tumor measuring 5 x 3 cm. in the marrow cavity of the lower end of the femur, is an adult acanthoma (epithelioma). It is composed of compact masses of stratified squamous epithelium of adult type, with spines and pearls and many large almost cystic areas of hornified material. The stroma is cellular connective.

"The tumor in the rectus femoris is composed of many large and small polygonal and spindle tumor cells, with vesicular hyperchromatic nuclei and prominent nucleoli. These cells invade the muscle tissue in rows, small groups, and diffusely. Muscle cells undergo simple atrophy.

"The origin and nature of this tumor, I am unable to determine. It appears to be of rapid growth and of recent date. Its structure would ordinarily be designated as sarcoma. I do not think it arises from the femur, since the underlying periosteum is intact and separated from the tumor by a layer of fat tissue. The sequelae of the original process in the bone are probably to be found in the cyst, the area of osteosclerosis, and the large sequestrum mentioned in the gross description. It is difficult to determine whether or not these gross lesions can be interpreted as the result of an arrested sarcoma. It would seem possible that they might result from an old osteomyelitis with formation of sequestrum, osteosclerosis, and bone cysts.

"The epithelioma in the medullary cavity may be interpreted as a metastasis from a lesion in the skin resulting from the x-ray, but no such tumor was recognized in the ulcerated surface of the amputated specimen. It is very probable that the tumor of the quadriceps was an extension from the peculiar process on the ulcerated superficial tissues and that it resulted from the long use of the x-ray."

COMMENT: When this patient was first treated in 1903, x-ray therapy had only been used for about a year at Memorial Hospital at Dr. William B. Coley's suggestion and under his direction. Little or nothing was known at that time of



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the dangers of overradiating a case. *This patient received x-ray therapy steadily for 10 months prior to toxin therapy.* Although the primary in the tibia regressed, metastases developed. Following toxin therapy the metastases regressed completely. However, 10 years later the patient developed extensive x-ray cancer both in the irradiated tissues over the primary lesion and on the chest. The latter was excised and did not recur. The former caused his death, 11 1/2 years after onset of his bone tumor. This appears to be one of the first cases of fatal x-ray cancer in this country.

In the discussion following the report of this case before the American Surgical Association in 1913, Welch stated that he and Halsted regarded it as one of the most important cases Coley had ever reported. (31; 40)

REFERENCES: 20, Case XXII; 23, Case III, 24; 31; 34, Case 41; 37, Case 4 in text, Case 27 in Table 7; 40, p. 13; 42.

**CASE 2:** Round cell sarcoma of the femur, confirmed by microscopic and x-ray examination by Dr. F.E. Sondern. (Unfortunately the section was later lost so that it was not possible to register this case with the Bone Sarcoma Registry.)

PREVIOUS HISTORY: J.P.W., male, aged 35. The family history was non-contributory. Onset, in the spring of 1906, the patient first felt pain in the right knee, and was treated for "rheumatism" for a number of months. He later came under the care of Drs. John F. Erdman and Virgil P. Gibney. Physical examination at this time showed a tumor apparently of periosteal origin, involving the whole distal end of the femur.

SURGERY: An amputation was performed six months after onset by Erdman, 10 cm. below the trochanter, and the patient was then referred to Dr. William B. Coley for prophylactic toxins.

TOXIN THERAPY (*Tracy XI*): Injections were begun as soon as the wound had healed, in September 1906. They were continued for four months in gradually increasing doses.

CLINICAL COURSE: The patient made a good recovery and never had any recurrence or metastases. He remained in good health until early in 1929, 23 years after toxin therapy, at which time his health began to fail. Having become a Christian Scientist he did not consult a physician until he became acutely ill about June 1, 1929. Pernicious vomiting developed and he appeared to be on the verge of collapse. Death occurred on June 14, 1929, and was due to carcinoma of the stomach, with pyloric obstruction.

REFERENCES: 8; 36; 37; 40; 82.

**CASE 3:** Undifferentiated round cell sarcoma of the proximal end of the left femur. In 1959 this case was reviewed by the Armed Forces Institute of Pathology. Their diagnosis was reported as follows: "The staff would regard this as an undifferentiated round cell sarcoma, in which the round cells are much too large for a Ewing tumor, and do not have the cytologic patterns expected with a reticulum cell sarcoma. In some rare areas there is a vague hint that should the cells have had a chance to differentiate, they would have produced small amounts of chondroid or myxochondroid material. Therefore, Ewing tumor is believed unlikely and reticulum cell sarcoma improbable. As to the correct diagnosis, the undifferentiated surface of a chondrosarcoma is deemed to be the more probable guess." The Bone Sarcoma Registry Committee, including Dr. James Ewing and later Dr. Arthur Stout (in 1942) classified this as a Ewing's sarcoma. The pathologist at Presbyterian Hospital in 1909 reported on the primary tumor as follows: "Large round cell sarcoma; sections show typical bone without any Haversian system and it is infiltrated with masses of large cells. The nuclei are large and vesicular. The protoplasm is small in amount. These cells infiltrate the bone, there are large masses of them between the spicules of bone. Mitotic figures and multi-nucleated cells are common." Roentgenograms (since destroyed) showed slight thickening of the periosteum about the center of the shaft of the femur, especially on its medial aspect. (See below for Stout's 1942 report.)

**PREVIOUS HISTORY:** H.J., male, aged 22, of New York City. The family and previous personal history were negative for malignancy or tuberculosis. The patient's only childhood disease was measles. During the revolution of 1905 in Russia, the patient was hit in the upper anterior left thigh by a bottle thrown at him in the street. This caused a bruise, but the skin was not broken. A year later the patient came to the United States and worked 10 hours a day in New York City as an engraver. He did not use alcohol, tobacco or coffee. Onset, in February 1909, he first noticed a "squeezing" pain in the medial aspect of the left thigh. It was localized, non-radiating and not severe. It gradually grew worse, however, with intermittent exacerbations, not provoked by any known activity.



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**PHYSIOTHERAPY:** A physician was consulted who gave him a local application of liniment and four injections (probably bichloride). During May and June he was treated at the dispensary of the Hospital for Special Surgery with "electricity".

**CLINICAL COURSE:** About July 1, 1909, three weeks prior to admission to Presbyterian Hospital, the pain became more severe on walking, and spread from the medial to the anterior aspect of the middle third of the thigh. At times it radiated down the leg to the ankle, being worse at night. The function of the knee was normal and flexion and extension of the joint without weight bearing did not increase the pain. There were no other symptoms. Physical examination on admission to Presbyterian Hospital on July 22, 1909 revealed a well-nourished, muscular young man, with no significant findings other than the local lesion in the middle of the left thigh: a palpable mass about  $6 \times 8$  cm., bony-hard, immovable, not tender except to deep pressure and apparently attached to the femur. The overlying skin was normal. X-ray examination revealed a slight thickening of the periosteum about the center of the shaft of the femur, particularly on the medial aspect. The lesion was regarded as chronic periostitis, associated with osteomyelitis and operation was not advised. The patient was discharged on July 27, 1909. He was readmitted on August 23, 1909, as the pain had increased in intensity and frequency. There was no interference with function other than a sense of insecurity in the thigh, but the pain was so severe that it prevented walking. There was no edema. The left mid-femoral region was larger than the right and a hard smooth mass could be felt. It had not grown appreciably, was not especially tender and apparently did not involve the overlying muscles or skin. The blood count showed white cells, 8,750 with 79% polymorphonuclears, and no abnormal white cells.

**SURGERY:** An operation was performed on August 27, 1909, by Dr. John Hartwell. The tumor was approximately 10 cm. long and occupied the internal, anterior, and posterior aspects of the bone. It was fibrous, gristly and attached to the periosteum and underlying bone, from which it was chiselled away en masse, leaving a roughened underlying bone surface. The tumor was soft in places, with plaques of bony hard substance. It was not obviously vascular and contained no pus. The postoperative course was uneventful. All pain ceased and the wound apparently healed.

**FIRST COURSE OF TOXIN THERAPY (Parke Davis XII):** On September 15, 1909 the 20th postoperative day, injections were begun at Presbyterian Hospital, the initial dose being 1/4 minim. There was no local or general reaction. The following day 1 minim was given. The patient was then discharged to the Out Patient Department, where he received 14 more intramuscular injections. He was then referred to Dr. William B. Coley for further toxin therapy. He was admitted to Memorial Hospital on November 9, 1909. Examination of the left lower limb showed a scar about 15 cm. long. The leg appeared normal and was neither swollen nor painful.

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He was given 1 minim in the left thigh, which caused no febrile reaction. On each succeeding day he received injections into the thighs (once into the buttock), the dose being increased by 1 minim a day. Little or no febrile reaction occurred (not over 99°F.) until the 15th injection of 15 minims on November 23, 1909. Injections were suspended for six days and were then resumed for another eight days. The maximum febrile reaction in this series was 102.4°F on December 11, 1909. (This patient's normal temperature was 98°F.) The pain in the thigh returned on November 26, 1909, three days after the toxins were suspended and continued to be severe. However, it was noted that the patient seemed to sleep better on the nights following injections than on days they were not given. There was apparently a recurrence of the growth. Under continued toxin therapy there was evidence of some diminution in size, but later the tumor began to increase and Coley advised immediate amputation.

**FURTHER SURGERY:** The patient was readmitted to Presbyterian Hospital on December 21, 1909. Examination revealed a fusiform swelling occupying the middle third of the thigh. It was hard, bone-like, and rather tender. The overlying muscles and skin were freely movable. The leg was held in a flexed position and could not be straightened voluntarily. At this time it was noted that the patient had acne over his face and back. A disarticulation of the left leg through the hip-joint was performed by Dr. Joseph Blake on December 23, 1909. The pathologist reported: "On removing the extensor muscles of the thigh a soft oval tumor was exposed. It was 12 × 7 cm. and its cut surface was gelatinous, and varied in color from the pale pink to dark red, being evidently of periosteal origin. It was very friable, and adjacent to the bone imparted a gristly sensation. Microscopically, the tumor was found to be composed of medium sized round cells, closely packed together, and supported by very little stroma. The vessels lay in intimate contact with cells which radiated from the vessel walls in a manner suggesting that they originated from the vessels. *There were large spaces in the tumor containing necrotic tissue and leukocytes indicating the effects of toxin therapy.*" (Presbyterian Hospital Accession number 10,087) In 1942 Dr. A.P. Stout reviewed the sections and reported as follows:

"Sections show that the tumor is composed of long cords of cells, which are usually solid and are separated from one another by strands of fibrous tissue. In a considerable number of instances there is a capillary in the center of the fibrous tissue strand. The fibrous tissue in every instance separated the capillary from the tumor cells. Where the tumor masses are large, the cells at the greatest distance from the capillaries are necrotic. The section shows a few spicules of bone. Most of these, in turn, are necrotic, due apparently to pressure from the massed tumor cells which fill the marrow spaces. A few of the spicules suggest new formation of bone. In every instance this is an irritative and not a neoplastic proliferation. The individual tumor cells are, for the most part, rounded, averaging 20 microns in diameter. The nucleus is hyperchromatic, but the nucleoli are,



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for the most part, small and inconspicuous. Mitoses average one in every high-power field, and in some regions are more frequent than this. The nuclei are centrally placed and are surrounded by thin zones of cytoplasm, which is palely stained and inconspicuous. So far as one can tell from the hematoxylineosin stain, there are few or no fibers accompanying the tumor cells, except for the broad septa which separated the cords of cells. This picture is characteristic of the bone marrow tumor, variously classified as reticulocytoma, endothelial myeloma and Ewing's tumor. Pathological diagnosis: Ewing's tumor of the femur." (93)

**CLINICAL COURSE:** The patient was discharged on February 4, 1910. He was readmitted to Memorial Hospital on February 26, 1910, complaining of lancinating pain continually present in the stump of the amputated leg. The appetite was good, the bowels regular, the heart and lungs were negative. He appeared well-nourished and in good physical condition.

**FURTHER TOXIN THERAPY (Tracy XI):** Injections were resumed by Coley on February 29, 1910, in order to prevent further recurrence. The initial dose was 1 minim given into the buttock, which caused no reaction. The following day 2 minims in the buttock caused a temperature of 102°F. an hour after the chill. Injections were continued daily and were all given into the buttocks intramuscularly. The temperature usually rose only one or two degrees, the maximum being 104°F. On March 10, 1910, treatment was suspended for 12 days. A final series of five injections was given between March 22 and 28, 1910. During toxin therapy, he was given Syrup of Hypophosphates as a tonic and a regular diet.

**CLINICAL COURSE:** Because of his amputation the patient broke his engagement to be married. There was no further recurrence. Four months later he was able to resume work as an engraver. In October 1910, 10 months after the operation, he began to walk with his prosthesis. He was then lost sight of until October 2, 1922, when an insurance company to whom he had applied for insurance, requested a report of the hospital findings. Thereafter the patient was followed continuously. Repeated examinations revealed no evidence of recurrence, clinically or roentgenologically. In April 1937 he began treatments in the metabolism clinic at Presbyterian Hospital for diabetes, which developed early that year. He was seen by Dr. Bradley L. Coley at the Memorial Hospital Bone Tumor Clinic on March 11, 1942. At this time he had been using the same prosthesis for 31 years and Coley noted how well he got along with it, considering he had had a hip-joint disarticulation. The patient then moved to California. He was married in 1944 and bought a house in Los Angeles, where he was able to go to his job on the bus, changing once. In 1950 he had a cholecystectomy and appendectomy. During the next year he developed symptoms of prostatism. He was admitted to the County of Los Angeles General Hospital on October 17, 1951. No abdominal masses were noted. The amputation site was well healed without any regional adenopathy or masses in or about the scar. On October 17, 1951, a transurethral

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resection of the prostate was performed. The pathologist, Dr. Waldon Bullock, reported: "benign prostatic hyperplasia". The patient was discharged October 28, 1951. He was seen in the Urology Clinic on February 13, 1952, apparently in good health. It was then noted that "he was able to do all the walking he wished" and that he was "quite active in his garden". He was seen periodically in the Urology Clinic during the next year. In March 1955, he had to give up working due to his age, and his diabetes, for which he had to take 23 units of PGI insulin and a limited carbohydrate diet. He was examined in New York by Dr. Beverly C. Smith on September 15, 1955, while on a trip to the east. His weight at this time with the limb was 154 pounds. His color was good and he looked well. He wore glasses only for reading. His pulse was 70 and regular. His blood pressure 160/75. The lungs were clear. There was no dyspnea. The abdomen was negative. There was a healed transverse RUQ scar at the site of the cholecystectomy. Rectal examination revealed slight prolapse of the mucous membrane without thrombosis or ulceration; also slight internal hemorrhoids. The patient was able to walk about the house without a cane using his prosthesis (a thigh stump socket which he filled with leather and foam rubber, weight bearing the tuberosity of the ischium against the foam rubber which he kept smooth). There was a small furuncle on the buttock in the scar over the tuberosity which recurred at intervals. The prosthesis was held tightly by a belt around the abdomen and shoulder braces attached to the medial upper prosthesis across the perineum. He walked very well in the street with a cane. X-rays of the chest and pelvis September 15, 1955 were negative. His family doctor reported on April 10, 1959, that over the years a perineal fistula *in ano*, of which he had many, would become infected, then drain and close. The stump from time to time also drained a small quantity of sanguinous material. In 1957 he had a few attacks of low back pain which was attributed to lumbar sacral arthritis. Early in 1958 he developed symptoms of coronary artery disease (pain, dyspnea). These attacks became steadily worse and on March 3, 1959, he had an acute postero-lateral myocardial infarction for which he was hospitalized. He progressed well except for continued severe angina pectoris secondary to ischemic heart disease. Finally another myocardial infarction proved fatal on September 10, 1965, 561/2 years after onset. His age at death was 781/2 years.

COMMENT: It is important to note that the weaker commercial preparation of Coleys toxins was given during the first course of toxin therapy following curettage of the primary tumor. None of these injections was given near the site of the former growth, and in the dosage used no reactions were elicited. Toxins thus inadequately administered do not appear to be effective in preventing recurrence. For the second course given after amputation, the more potent Tracy XI product was given somewhat more aggressively and persistently.

This case was regarded by Beverly Smith as the oldest recorded permanent result of Ewing's sarcoma following amputation. The possible effects of toxin



therapy given before and after amputation were not considered in his reports of this case. However, Coley reported that cases of bone sarcoma in which toxins were administered before or after surgery showed less than a third as many recurrences as those in which the toxins were not given. (36) Now that more is known about the technique of administration and as more stable and potent preparations of bacterial toxins become available, this method may prove a more valuable agent in conjunction with surgery or irradiation. Amputation may be avoided in favor of more conservative procedures as has been done in many cases of reticulum cell sarcoma, and some of the Ewing sarcoma cases.

REFERENCES: 5; 36; 37; 39; 40; 43; 73; 82; 93; 94.

**CASE 5:** Inoperable round cell sarcoma of the humerus, with pathological fracture confirmed by microscopic examination. Chest films showed pulmonary metastases. (Bone Sarcoma Registry #412)

**PREVIOUS HISTORY:** J.B. male, aged 24, unmarried, of Calgary, Alberta, Canada. The family history was negative for cancer, tuberculosis or venereal infection. The patient had always been well. He worked for the Canadian Pacific Railroad. On September 10, 1917, while working on an engine, he lost his balance, and caught the running rod to save himself. Although he was able to let himself down to the ground and did not fall or bruise himself, the shoulder was severely strained. He complained the following day of pain in the shoulder and was treated for a month for "rheumatism" by a local physician. During this time a swelling developed in the proximal end of the humerus. This grew rapidly and a pathological fracture occurred. The patient lost considerable weight. He consulted Dr. L. S. Mackid of Calgary in February 1918. At this time the left shoulder was enormously swollen and hard, the overlying skin was drawn tight and the veins were very prominent over the tumor. There was a large area of softening on the posterior aspect of the mass which was tender and painful. There had been considerable loss of weight.

**SURGERY:** Mackid operated, making an incision in the soft area, and evacuated a large quantity of gelatinous material, pus and blood. The condition was regarded as hopeless from a surgical point of view.

**TOXIN THERAPY (Tracy XI):** Injections were begun by Mackid in March 1918, and the dose was increased to the point of producing very severe reactions, some of which were alarming. At the time toxins were begun chest plates showed what was believed to be a metastatic growth in the lung. (36, Case 29, Fig. 30) A few weeks later a second x-ray picture showed that the disease had not increased in the lungs, but had decreased somewhat, and the discharge from the shoulder was less profuse. At the end of two months another x-ray examination showed that the

disease was apparently under complete control. There was no further increase in the size of the tumor and it gradually regressed. The pathological fracture reunited, the wound healed and the patient regained partial use of his arm. His general health returned to normal and there was rapid gain in weight. Injections were continued until July 1918, when they were stopped for three months. They were then resumed and continued with intervals of rest until August 1920, a dose of 7 minims being given once a week. The patient was able to return to work in the machine shop in November 1918. In regard to the technique of administration, Mackid stated: "We started inoculations into the abdominal wall and into the arm and worked concentrically towards the center, starting with a dose of one minim and increasing according to the severity of the reaction." (82)

**CLINICAL COURSE:** On September 29, 1920, about a month after the toxins were stopped, the patient again developed some pain in the shoulder. Mackid made an incision along the outer margin of the scapula and evacuated about a cupful of clear "pus" (no gelatinous substance).

**FURTHER TOXIN THERAPY:** At Coley's suggestion the toxins were resumed for two or three months. The initial dose was one minim and injections were made every five days, increasing the dose as before. The wound healed and the injections did not interfere with the patient's work. Toxin therapy was given with intervals of rest for 21/2 years.

**CLINICAL COURSE:** He remained in excellent condition, the only disability being a more or less ankylosed shoulder joint. He was able to adapt himself to certain types of work, and continued working until 1943. He never married. In 1945 he developed orchitis, with no history of injury or infection. He again consulted Mackid who reported the case to the Cancer Clinic. They advised orchiectomy. This was refused, however, and during the next year the condition subsided considerably. When the patient was examined in February 1946, although the testis was a good deal larger than normal, it was not giving any discomfort. He was examined at the Central Alberta Sanatorium (Division of Tuberculosis Control) on March 24, 1947, which reported as follows: "When this man was first seen there were no signs found of active tuberculosis. He weighed 147 pounds, temperature 98°, pulse 72, height 5'5". Mantoux positive 1/20 mgm. O.T. . . . He has apparently complete ankylosis of the left shoulder joint. Present weight 151 pounds. No history of any serious illness since 1918 . . . chest examination: no signs of clinical disease. X-ray: unchanged from October 1947. The same large calcified areas are seen below the left clavicle. These appear to be within the lung tissue. Mr. B. looks reasonably well. States that he has had good health. No other signs of disease found." He remained in good health until his very sudden death, while on a fishing trip, of what was considered to be coronary thrombosis. He ran a very high blood pressure for some time before his death, but responded to treatment which consisted of rest, and he "thought he felt well enough to go



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fishing." Death occurred on August 12, 1950, at the age of 56, 33 years after onset of the sarcoma of the humerus.

REFERENCES: 5, Case #412; 36; 37; 40; 42; 43; 82.

**CASE 6:** Recurrent round cell sarcoma of the distal end of the right tibia, with metastases in the groin, confirmed by microscopic examination of both the recurrent tumor and the groin metastases following the second operation.

**PREVIOUS HISTORY:** G., male, aged 16, of Brussels, Belgium. The family and early personal history were not recorded. In 1901, prior to onset the boy suffered a contusion of the right tibia. A hard tumor then developed.

**SURGERY:** This was removed surgically. A few months later the lower portion of the tibia lost its normal contour and a soft tumor invaded the region. The patient was admitted to the Hôpital St. Pierre in Brussels.

**TOXIN THERAPY** (*Buxton VI formula, as made by Matagne himself*): Injections were begun by Dr. J.H.J. Matagne, of Brussels, early in February 1902, and were given for about two months, in the thigh. Matagne's usual technic was described as follows: he always made the injections daily into the tumor tissue when this was possible, gradually increasing the dose each day or every other day until a febrile reaction of 102.2° to 103° or even 104°F. was elicited. The reaction usually consisted of a violent chill which began about 30 minutes after injection and lasted 30 minutes. Matagne stated that there was no set maximum dose. He increased the dose in each patient according to the febrile reactions elicited.

**CLINICAL COURSE:** In April 1902 a mid-thigh amputation was performed and the metastatic nodes in the groin were extirpated. There was no further recurrence or metastases. The patient was presented as a cured case before the Société Médico-chirurgicale du Brabant in Belgium by Matagne early in 1905. It was noted at this time that the wounds in the stump and groin had remained well healed and that the patient was in excellent health and had developed very well since his treatment and operation three years before. This case was cited as a permanent result by Matagne in 1953.

REFERENCES: 69; 70; 71.

**CASE 9:** Inoperable extensive round cell sarcoma of the right fibula, confirmed by microscopic examination.

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**PREVIOUS HISTORY:** Female adult, of Reidsville, North Carolina. The patient's general health, with the exception of an attack of rheumatism as a child, had always been good until a year prior to onset. In March 1894 she first complained of pain and soreness in the leg, and in June, about three months later, she noticed a small swelling on the calf of the leg, associated with lancinating pains. The swelling was confined to the central portion of the calf, being a hard, large, smooth, globular tumor with distended veins over its surface. The affected limb measured 5 cm. more than the normal one. The joints were not involved. Following onset, the general health rapidly failed, from pain, inability to sleep, anorexia, etc. She consulted a well-known Virginia surgeon who pronounced the condition sarcoma, and advised an amputation at the lower third of the thigh. Dr. J.C. Walton then saw the patient and concurred in the diagnosis. The patient refused operation. For this reason the toxins were tried.

**TOXIN THERAPY (Buxton VI):** Injections were begun on May 18, 1895 and were made *deeply into the tumor*, commencing with one drop, increasing to four, the maximum dose tolerated. These caused severe chills and high fever, the temperature rising to 104° and 106°F. with nausea, emesis, a weak rapid pulse, muscular twitching and more or less collapse. The injections were continued until August 1, 1895, a total duration of 10 weeks. The general condition appeared gradually to deteriorate under treatment. The tumor became circumscribed with redness of skin, pain, etc. In July, about *six weeks after the injections were begun* the growth first began to soften, with slight discharge.

**SURGERY:** Walton then cut down on the tumor and curetted away a part of the mass. Owing to the hardness it was impossible to remove much of it. The tumor being very vascular, the hemorrhage was profuse. In the middle of December a second operation was performed, and in January 1896, a third, removing this time a large quantity of marrow-like, gelatinous substance, and a large portion of the shaft of the fibula. A week after this operation a secondary hemorrhage occurred, which nearly proved fatal before Walton was called. A few days later, he removed a hard black substance the size of a hen's egg, which was very offensive. From this time on the patient's health rapidly improved. The cavity soon filled with healthy tissue, and in a short time she was discharged as cured.

**CLINICAL COURSE:** Walton reported the case in May 1898 before the Medical Society of North Carolina at which time the patient was in good health and able to walk without a cane, suffering no inconvenience, except a little weakness in the limb from loss of bone. The site of the former growth presented a normal appearance. She was last traced well and free from recurrence in December 1905, over 11 1/2 years after onset.

**REFERENCES:** 18; 41; 42; 102.



## SERIES B, INDETERMINATE SUCCESSES, DETAILED HISTORIES

**CASE 10:** Round cell sarcoma of the distal end of the fibula involving the tibia and ankle joint, confirmed by microscopic examination by Dr. H. T. Brooks, pathologist of the New York Post Graduate Hospital.

**PREVIOUS HISTORY:** Female, aged 23, of Troy, New York. The family history is not recorded. The patient fell eight years prior to consulting Dr. Samuel Lloyd, injuring her ankle, but not sufficiently to confine her to bed, and in three days she was able to walk. However, for the next six or seven years she complained of more or less pain in the region of the injury. Four years after the injury she had typhoid fever, and on recovery noticed that the joint was swollen and much more painful. Pain from this time on became constant and increased on walking.

**SURGERY:** The swelling about the joint also increased, and in 1894, the tumor was incised and "pus" evacuated, but there was no involvement of the joint. The wound healed promptly but the tumor continued to grow, sometimes appearing to be larger than at other times. The patient was referred to Lloyd on June 23, 1895. Examination revealed a tumor of considerable size involving the lower end of the fibula and malleolus. At the lower margin and also across the upper border, eggshell crackling could easily be made out. Lloyd advised amputation above the knee, but this was refused by the patient. He therefore resected the entire fibula on June 27, 1895 at the New York Post-Graduate Hospital. Lloyd believed this was the first case of total excision of the fibula for malignant disease: at that time, when malignancy was suspected, amputation was always performed. At operation the growth was found to spread out from the fibula and involve the soft parts as well as the periosteum and adjacent surface of the tibia. All of this was cut away when it was found that the ankle joint was also involved. The joint was then opened and all of the diseased tissue carefully and freely removed. It was impossible to accurately approximate the lower portion of the wound because of the amount of tissue that was removed, so this portion was packed.

**WOUND INFECTION:** The wound suppurated, apparently due to defective catgut, and when this was discarded suppuration ceased, although three sinuses did not heal until late in the summer.

**TOXIN THERAPY (Buxton VI):** Injections were begun on July 24, 1895, the initial two doses being 3 and 5 minims, which caused no reactions. The third dose of 8 minims on July 29, 1895, caused a febrile reaction of 101°F. and a pulse of 112 two hours later. At the end of six hours the temperature was 102.2°F., the pulse 96. There was no chill or local induration. (The site of injections is not recorded.) The patient received a total of about 12 or 15 injections in a period of three weeks, and no severe reactions occurred until after the seventh injection. The latter, a dose of 30 minims, caused a chill lasting 15 minutes with marked cyanosis and emesis, the temperature being 104°F., the pulse 120, 11/2 hours after injection.

## SERIES B, INDETERMINATE SUCCESSES, DETAILED HISTORIES

**CLINICAL CURSE:** The patient was discharged on August 16, 1895, with three sinuses in different parts of the cicatrix. On the inner aspect of the ankle there was also a small abscess cavity leading backward and upward. These sinuses rapidly healed after her return home. On January 26, 1898, the patient was presented at a meeting of the Medical Society of New York at Albany, in good health, and with no evidence of disease. This was over five years after onset. The leg was useful, although there was considerable ankylosis of the ankle joint. She walked with a slight limp and stated that the leg was perfectly comfortable. She was not traced subsequently.

**REFERENCES:** 19; 63.

**CASE 11:** Round cell sarcoma of the left clavicle, confirmed by microscopic examination by the Bone Sarcoma Registry Committee (Case #597), as well as by Dr. W. F. Whitney, Professor of Pathology at Harvard Medical School, who stated that the growth was composed of "round cells of a rather irregular size with a little fibrillated intercellular substance and traversed here and there by strings of connective tissue." He added that the greater part of the clavicle had been destroyed by the growth.

**PREVIOUS HISTORY:** J. W. H., male, aged 34, of Dismount, Maine. The patient's father died of cancer of the stomach, but otherwise the family history was negative for malignancy or tuberculosis. In January 1908, the patient was struck on the left clavicle and almost knocked down by a plank. Shortly thereafter a swelling appeared at the site of the injury. This grew rapidly, with mild pain. The patient consulted Dr. W. L. Hunt, of Bangor, Maine, on March 23, 1908, who made a diagnosis of sarcoma. This was confirmed by Dr. S. W. Johnston of Belfast, Maine, who then referred the patient to Dr. Maurice K. Richardson of Boston. Examination at this time revealed a hard irregular growth about 8 x 13 cm. in diameter, extending from the coracoid process to the sternal notch and upwards slightly behind the sternomastoid. There were enlarged veins in the overlying skin.

**SURGERY:** A total excision of the clavicle was performed by Richardson on May 18, 1908, at the Deaconess Hospital, Boston. The tumor occupied the middle and inner third of the clavicle and the operation was most difficult. The subclavian vein was adherent to the growth but was freed without injury. The patient was then referred to Dr. W. B. Coley for toxins. Richardson believed the prognosis so grave from operation alone that he stated that "if this man made a permanent recovery, entire credit was to be given to the toxin treatment."



## SERIES B, INDETERMINATE SUCCESSES, DETAILED HISTORIES

**TOXIN THERAPY (Tracy XI):** Injections were begun by Coley on June 1, 1908, 13 days after the operation. At this time there was considerable infiltration in the whole lower cervical region, suggesting either a recurrence or incomplete removal. This gradually cleared up under treatment, and at the end of two months had entirely disappeared. He returned home where the injections were continued by the family physician Dr. H. L. Truworthy. The dose was gradually increased to 20 minims and some severe reactions were produced, with chills. The injections were made in the pectoral muscles, at first every other day, then twice a week and finally once a week, over 80 being given in 18 months. The patient was able to return to hard work as Postmaster in September 1908, 31/2 months after the toxins were begun.

**CLINICAL COURSE:** On January 22, 1909, Richardson wrote Coley stating he was very much pleased with Mr. H. and added: "If he recovers permanently, it will surely be due to your toxins rather than my operation. I will adopt your method as a routine after all my operations for this disease." There was no recurrence. Coley examined him in February 1909, and found him entirely well, having gained 26 pounds in weight. On July 19, 1915, the patient wrote: "I am in excellent health. I feel fine, eat and sleep well, weigh nearly 200 pounds against 163 when you last saw me, and work 15 to 17 hours daily. Have not taken any vacation during the last five years. Do not suffer from any of the old pains and feelings that I did previous to my operation. Several local surgeons including Dr. S. W. Johnston of Belfast, Maine, have examined me during the past two years and are not able to discover any symptoms or any recurrence of the tumor." (42) The patient continued to attend to his work as Postmaster until six weeks before his death, which occurred on May 4, 1933, 25 years after onset, following an attack of grippe. The cause of death was listed as "chronic myocarditis with dilation, due to renal complications."

**REFERENCES:** 5; 8; 30; 35; 37; 39; 42; 82; 99.

**CASE 12:** Inoperable round cell sarcoma of the clavicle confirmed by microscopic examination, with metastases in the neck and deltoid region.

**PREVIOUS HISTORY:** H.L.S., male, aged 23, of Cora, Oklahoma. The patient sustained a fracture of the scapula and clavicle in February 1907. Onset, in April 1908 enlarged nodes appeared above the clavicle, and two months later the patient had another injury, falling upon his back. Shortly after this second injury a rapidly growing tumor appeared over the right clavicular region, extending nearly to the spine. There was also a metastatic tumor in the neck as large as a fist, and another of equal size in the deltoid region, which had ulcerated and from which projected a fungating mass. The lymph nodes in the left cervical region were also enlarged. The patient had been bedridden for four weeks and had lost

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14 pounds in weight. He was first seen by Dr. Leonard Freeman of Denver, Colorado, on July 17, 1908.

**SURGERY:** A specimen was removed for microscopic examination. The case was regarded as entirely inoperable, even as regards interscapulothoracic amputation.

**TOXIN THERAPY (*Tracy XI*) COMBINED WITH RADIATION:** Injections were begun by Freeman on July 17, 1908, and were given aggressively. Some x-ray therapy was also given, but the details are not recorded. By September 1, 1908, six weeks after the injections were begun, marked improvement had occurred. The tumors had decreased to half their original size and were much softer.

**CLINICAL COURSE:** The patient then returned to his home in Oklahoma. Shortly thereafter he had a severe hemorrhage.

**FURTHER SURGERY:** An interscapulothoracic amputation was performed in Wichita, Kansas. The patient made a good recovery from the operation.

**CLINICAL COURSE:** He remained free from recurrence or metastases when last traced by Freeman in November 1918, over 10 1/2 years after onset.

**REFERENCES:** 35; 42.

**CASE 13:** Round cell sarcoma of the left clavicle, confirmed by roentgenologic and microscopic examination by Dr. James Ewing and other members of the Bone Sarcoma Registry Committee, who reported: "There were no giant cells, the tumor was laminated without new bone production and of very rapid growth." (Case #508)

**PREVIOUS HISTORY:** I.M.V., male, aged 18, of Brooklyn, New York. The family history was negative for cancer or tuberculosis. The patient had had the usual diseases of childhood, and had not been too healthy. He broke his leg at the age of three, and about a year later he apparently had spinal meningitis. He was a thin, nervous child. Early in October 1909, he slipped while going downstairs, and in trying to save himself caught hold of the banisters with his left hand, thereby bringing himself to a sudden stop with a jerk. This caused a good deal of strain on the left shoulder and clavicle. Shortly after this he was riding a motorcycle which broke down. He was obliged to push it a distance of ten miles, using his left arm almost entirely. Onset, within three weeks he felt pain and soreness in the region of the left clavicle. A week later a swelling was noted at this site. On November 20, 1909 Dr. Alfred Potter was consulted. He found a fusiform en-



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largement of two-thirds of the inner portion of the left clavicle Roentgenograms showed a typical round call sarcoma, the outline of the periosteum being nearly lost. The patient was referred to Dr. William B. Coley and from clinical and roentgenological evidence he made a positive diagnosis of sarcoma, urging immediate surgical removal. The tumor was about the size of an English walnut. There were no enlarged lymph nodes, little pain, and the patient was in excellent general condition. Coley stated that the clinical history, the x-ray photograph and the physical signs made the diagnosis sufficiently certain to warrant removal without subjecting the patient to an exploratory operation.

**SURGERY:** Accordingly, two days later, on November 22, 1909, a total excision of the clavicle was performed by Coley. The wound was closed leaving a small cigarette drain. The patient made an uninterrupted recovery, the wound healing by primary union.

**TOXIN THERAPY (*Tracy XI*):** On December 1, 1909, about a week after the operation, Coley began the injections, which were then continued at home by the family physician for about four months after the patient was discharged. They were given intramuscularly in the gluteal region, in doses sufficient to produce good febrile reactions with chills.

**CLINICAL COURSE:** There was no recurrence. Almost no deformity resulted from the operation, and the patient regained complete functional use of the arm. During 1916 and 1917 he drove racing cars for the Hudson Auto Company. He served in the U.S. Army during World War I. He married in 1921 and a daughter was born in 1925, a son in 1928. He was seen periodically by Coley until 1936. He reported in November 1945 that he was in good health, working long hours. He stated that his only trouble had occurred about two years previously. His car was rammed from the rear, causing a whiplash neck injury. X-ray examination showed no evidence of fracture or displacement. However, shortly thereafter, all his hair fell out. The hair had been brown, but it grew in white, later darkening. His physician believed this was due to the shock of the motor accident.

**TUBERCULOSIS:** The patient remained perfectly well until early November 1946 when he became hoarse and two weeks later he had a slight hemoptysis following steam inhalations. He had streaked sputum for about five days and then expectoration disappeared but the hoarseness persisted. He consulted an otolaryngologist who advised an x-ray examination of the larynx. The latter was done at the north Shore Community Hospital and a chest x-ray was also taken. Definite pathology was found in the lungs. He was therefore admitted to the Nassau County Tuberculosis Hospital, Farmingdale, Long Island, on November 29, 1946. He was placed on modified bed rest. X-ray revealed medium productive infiltration in the upper third of the right lung, and dense exudative infiltration with large cavity in the upper half of the left lung. The patient was fairly well and

## SERIES B, INDETERMINATE SUCCESSES, DETAILED HISTORIES

his only symptom was fatigue. Gastric washings were positive on concentrate and culture for tubercle bacilli . . . The general condition improved. In April 1947 a left thoracoplasty was performed, with removal of three ribs. The postoperative course was rather stormy for the next month with increased infiltration and elevation of temperature. Further surgery was abandoned in the fall of 1947 due to the reactivation of the disease, and the poor general condition. The patient was discharged on February 17, 1948, at his own request, the prognosis being regarded as fair. The cavity in the left lung slowly increased until it was the size of a lemon. On November 8, 1948 he had another hemorrhage. At one time there were also two cavities in the right lung. In 1952 streptomycin and another drug were tried. He did not react satisfactorily. (He was allergic to them.)

**CLINICAL COURSE:** During 1953 the large cavity in the lung healed. In December 1953 he was severely injured in an auto accident, and one of the lumbar vertebrae was broken. He was hospitalized for several months, but recovered completely and returned to work for the state, as director of automobile racing. In June 1955 he weighed 184 pounds, his height being 5 feet 11 inches, and he was in very good health. Periodic chest films showed no further evidence of tuberculosis. All the lesions in his lungs remained healed. He remained in excellent health except for symptoms of prostatism which began in 1960. That year he also developed a duodenal ulcer which responded to treatment. In January 1965 he had a basal cell carcinoma of the face excised. In February 1965 his duodenal ulcer reactivated. In December 1965 he developed generalized abdominal tenderness and distress, some distention, much gas, an enlarged liver and some difficulty in urinating. Thorough work-up at a Florida hospital for suspected carcinoma of the colon revealed only hiatus hernia, duodenal diverticulum and diverticulosis of the colon. He was readmitted on April 1, 1968 with chronic cholecystitis and cholelithiasis. A cholecystectomy was performed on April 4, 1968. The patient was also suffering from emphysema and chronic pyelonephritis. On June 17, 1968 he was readmitted because of digitalis poisoning. Digoxin was stopped and thereafter he was carried on sparine, Compazine and Kaon. Within a few days his symptoms subsided. He remained well when last traced in January 1973, nearly 64 years after onset of his Ewing's sarcoma.

**REFERENCES:** 5; 33; 37; 40; 42; 82.

**CASE 14:** Round cell sarcoma of the metatarsal bone, confirmed by microscopic examination by Dr. James Ewing.

**PREVIOUS HISTORY:** Mrs. E.W.M., female, aged 22. The family history was negative for cancer or tuberculosis. The patient had had the usual childhood diseases, measles, mumps, scarlet fever, and at the age of 15 or 16 she had a severe attack of inflammatory rheumatism. She seldom had colds and there were no allergies.



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Her menstrual history was normal. She was an actress on the New York stage. There was no history of antecedent local trauma. Onset, in May 1901 pain developed in the right foot and a month later the patient first noticed a slight swelling on the dorsum of the foot. The pain became very severe, requiring morphine. The condition was treated for a number of weeks as rheumatism. Dr. William B. Coley first saw the case in consultation with Dr. Alexander Lambert in August 1901, three months after onset.

**SURGERY:** An immediate amputation was advised, which was performed by Coley three days later, at the junction of the middle and lower thirds of the tibia.

**TOXIN THERAPY (*Parke Davis XI*):** Injections were begun soon after the operation and were given in doses of three or four minims for eight months. They caused moderate reactions and there were only one or two chills. The patient made a complete recovery.

**CLINICAL COURSE:** There was never any recurrence. She subsequently had three children and remained in good health until 1933-34 when she had a prolonged rheumatoid attack which left her with an arthritic condition in her hands. Menopause occurred without incident at the age of about 45 or 50. The patient died in her sleep apparently from a cerebral hemorrhage on October 20, 1945, at the age of 66. This was 44 1/2 years after onset.

**REFERENCES:** 36; 37; 42; 82.

## SERIES C. FAILURES 91, CASES

The failures were divided into two groups, the first comprising 53 cases *without* apparent metastases when toxin therapy was begun. The bones involved were: femur, 17 cases; humerus, 5; tibia, 8; fibula, 5; ulna, 1; radius, 1; scapula, 2; clavicle, 4; rib, 3; ischium and/or ilium, 5; sacrum, 1; pubis, 1. The average survival in this group was 31 months. (The expected survival is two years or less)

In the second group of failures were 38 cases *with* metastases when toxin therapy was begun. The bones involved were: femur, 14 cases; humerus, 1; tibia, 2; fibula, 3; scapula, 2; clavicle, 2; rib, 7; ilium, 3; pubis, 4. The average survival in this group was 21 months, or about one or two months less than the expected rate.

It is of interest to note that 9 patients in group 1 of the failures survived from 4 1/2 to 11 years after onset and in almost all these 9 cases the duration of toxin therapy was much longer than the others, i.e., several courses of from 3-17 months, or the patient had concurrent infection or fever.

In group 2, three of 38 patients survived from 5 to 7 years after onset, and in these cases two to four courses of toxin injections were given and the patients also had fever, infections, inflammatory episodes and two had appendicitis concurrently.



SERIES C, GROUP 1, FAILURES WITHOUT METASTASES WHEN TOXINS WERE BEGUN:

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
1. W.B. Coley (29; Case 16; 37; 42)	F. 13 1906	Distal 1/3 rt. femur	explored; amputation 3 days later	Parke Davis IX begun 6 wks. after amputation, given 3 mos. i.m.	well over 3 yrs.	recurrence in rt. hip involving spine, no pulmonary metastasis. Death, Dec. 1910, 4 1/2 yrs. after onset
2. W.B. Coley (21, p. 339; 22, p. 135; 37)	M. 10 1906	central 2/3 lt. femur 27 cm. in length, episodes very severe pain for 6 mos. prior to evidence of tumor	none prior to toxins; x-ray (5), March 1907	November 1906; Tracy X into tumor, prior to & after x-ray	pain disappeared after 2nd injection, decrease in size in 2 wks.; gained wt.; when dose decreased growth increased; when dose increased growth decreased 5 cm.; this occurred several times, initially rbc decreased then rose from 4 to 5 million; n.e.d. 10 mos. after toxins begun	then developed metastases to both orbits, death few mos. later, about 2 yrs. after onset of pain
3. Le Breton (42; 99)	M. 8 1/2 1907	rt. proximal femur (inguinal nodes enlarged)	explored Dec. 1907	Tracy X i.m., some in tumor, marked reactions for 6 wks. begun 1 wk. after exploratory operation.	tumor increased in size involving entire femur, ulceration	disease progressed rapidly; death Feb. 18, 1908, 11 mos. after onset
4. W.B. Coley (8; 42; 73)	M. 18 1914	distal 3/4 lt. femur, 18 x 33 cm.	explored Oct. 1915, amputation refused; Jan. 1916: 4 radium treatments at 2 wk. intervals; Jan. 1919: further radium, no effect; amputation	Nov. 24, 1915 Tracy XI, 12 in 27 days, in chest or in tumor, reactions 102-103°F (given prior to radium)	tumor stationary for 2 wks. then increased slowly in size; radium caused extensive burns, ulcers; almost complete regression; in good condition, worked 2 1/2 yrs.: then recurrence, wt. loss, pain	metastases to lungs, spine; death June 11, 1919, 5 1/2 yrs. after onset

5. R. Whitman (41, p. 70)	M. 14 1922	proximal 1/2 lt. femur, inguinal nodes enlarged	explored; radium (50,000 mch.)	Feb. 1923: Parke Davis XIII i.m. for 6 wks. during radiation	complete regression during toxin therapy; shortly thereafter metastases developed	extensive metastases to skull, jaw & other regions; rapid course, death June 1923, 9 mos. after onset
6. W.B. Coley (5, #798; 42; 73)	M. 16 1926	proximal rt. femur (onset followed strain); severe pain; had concurrent tuberculosis rt. femur	in traction 6 wks. explored, mass about 15 cm. in diameter chiselled from femur, Dec. 1926; 3 radium packs (18,000 mch.); amputation, Feb. 26, 1927; stump incised April 1927; liter cheesy material evacuated: parietal metastases excised; 2 radium packs to skull (5000 mch.); 7 radium packs to lt. iliac metastasis; x. ray June 1928	P.D. XIII begun 5 days after surgery, i.m. daily for 5 days, resumed after radium, 27 in 2 mos., mild reactions; 3 more in June 1927; final course 7 i.v. (reactions 103.2*) caused some regression metastases	evidence some degeneration in tumors, no effect on tuberculosis; metastasis lt. parietal area evident 3 wks. after amputation; metastasis lt. iliac bone September 1957; felt well after i.v. toxins, good appetite; marked regression of metastases following x-ray, June 1928	disease progressed, pulmonary metastases, death March 31, 1929, 2 1/2 yrs. after onset
7. W.B. Coley (5, #999; 73)	M. 20 May 1927	mid-third rt. femur	considered inflammatory, local applications for pain; Feb. 1928 x-ray (5-6) no effect; 12 more in 3 mos. ending Aug. 4, 1928; 2 more cycles x-ray Oct., Dec. 1928; amputation 6 days after pathologic fracture; radium packs to stump recurrence (16,000 mch.)	P.D. XIII May 17, 1928: begun during 2nd cycle of x-ray, 33 i.v. in 81 days; 5 more very small doses i.v. in 5 wks. after amputation; moderate reactions	definite improvement, general condition excellent; Nov. 1928: tumor began to increase in size: pathologic fracture, Jan. 1929; recurrence in stump regressed very little after radium	disease gradually progressed locally extensive neoplasm in soft parts of thigh, destruction of femur; death Nov. 20, 1929, 2 1/2 yrs. after onset



SERIES C, GROUP 1, FAILURES WITHOUT METASTASES WHEN TOXINS WERE BEGUN (con'd.)

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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
8. W.B. Coley (5, #1067; 42)	F. 7 Oct. 1928	distal 1/2 shaft rt. femur; trauma prior to onset	tonsillectomy April 1929; incisional biopsy, radium pack, June 1929	3 febrile episodes (103-104°F, followed by improvement; P.D. XIII after 1st radium (8 i.m. in 14 days); 5 more i.v. in 7 days after 2nd radium; continued at home few wks. longer	great improvement, general health excellent; well 1 yr.	metastases summer 1930, death January 1931, 2 1/4 yrs. after onset
9. B.L. Coley (5, #1459; 41; 73)	M. 21 1930	proximal lt. femur following chronic osteomyelitis (foot ball injuries)	explored July 1931; curettage, Aug. 1931; x-ray Sept. 1931 (11) all prior to toxins; further x-ray (17); Oct. 1932: appendectomy, long section collapsed gut (volvulus) resected; x-ray to vertebral lesion after biopsy and before toxins (1500 r); x-ray to knee, ankle, 1934	P.D. XIII, Aug. 31, 1931, (9 i.m., 13 i.v. in 54 days) after x-ray, slight reactions; superficial staph. infection, necrosis, gangrene, Jan. 1932, 2nd course i.v. toxins, 1 before, rest after x-ray; October 1932 acute appendicitis, volvulus; March 1933 erysipelas, purulent discharge from old wound for wks.; December 1933 toxins for vertebral lesion, 17 in 25 days, i.m. & i.v. alternately; 4th course: 15 in 28 days, i.m. & i.v., only 1 marked reaction: continued i.v., 1 a wk.	general & local condition improved markedly, complete recovery; well 6 mos., July 1932 fell, fracturing femur; gained weight (to 200 lb.); 12 days after appendectomy, rt. sacroiliac pain, due to lying on brace, subsided Dec. 1933; well next year; metastases to L5 vertebra; pain in lt. knee, tibia; again marked pain relief from toxins (painfree 3 mos.) N.E.D. April 28, 1934	complete paraplegia from sacroiliac metastasis; metastases to skull; death Nov. 2, 1934, 4 1/2 yrs. after onset

10. B.L. Coley (5, #2088; 73)	F. 12 March 1935	proximal lt. femur; psychoneurotic, somewhat obese; (had had a tonsillectomy)	pituitary extract for leukorrhea prior to onset; salicylates; Nov. 1935, x-ray (2400 r), marked pain relief; aspiration biopsy after x-ray negative; further x-ray (4500 r to proximal 1/3, 2400 r to middle 1/3); some pain relief; 2nd aspiration biopsy negative; 3rd aspiration after toxins negative: spicules of dead bone; Jan. 1936: incisional biopsy & repeated aspirations remained negative; 2nd incisional biopsy, Feb. 1937: Ewing's tumor	P.D. XIII, Dec. 31, 1935: 14 in 22 days during 2nd cycle x-ray (12 i.m., 2 i.v.); febrile reactions averaged 102°F; staph. aureus chronic osteomyelitis, thrombophebitis; toxins resumed Feb. 1937: 31 in 41 days (13 i.m., 18 i.v.): reactions averaged 102°-103°F; 3rd course April 1937 (5 i.m. in about 14 days)	remained very neurotic, though combined therapy well tolerated	by mid-June 1937 had lost weight, strength; disease progressed; death October 17, 1937, 2 1/2 yrs. after onset
11. B.L. Coley (73)	M. 15 prior to Aug. 1935	lt. mid. femur	Aug. 1935, operated at another hospital for large "hematoma," x-ray (12); aspiration, incisional biopsies, Sept.-Oct. 1936; x-ray Oct. 1936: 4500 r to proximal & distal lt. thigh; i.m. injections liver extract	pus evacuated, Oct. 1936; postoperative lobar pneumonia; P.D. XIII Nov. 1936, following x-ray: 21 in 30 days (6 i.m., 3 locally, 11 i.v.)	disease not controlled	death Jan. 25, 1937 about 16 mos. after onset
12. B.Coley (73; 82)	M. 9 Dec. 1935	Lt. mid. femur	linament applied, swelling disappeared, but not pain; March 1936: radium packs (60,000 mch.), caused ulcer; May 1936, transfusion	P.D. XIII, Feb. 28, 1936: 3 i.m. prior to radium, resumed during latter part of radium therapy: 10 i.m. in 14 days; moderate reactions; April 1936: Lilly product given i.m., few i.v.; 7 more P.D. XIII, i.m. (total of 60 in 73 days) no marked reactions	symptom-free May 1936, good range of motion, ulcer almost healed, gained 32 lbs.; radiation ulcer healed in 1 yr., symptom free.	lost wt. early 1938, severe pain soon bedridden, death Sept. 19, 1938 2 3/4 yrs. after onset.



SERIES C, GROUP 1, FAILURES WITHOUT METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
13. B.L. Coley (5, #2278)	M. 24 April 1936	proximal lt. femur	curettage July 1937 then x-ray (12,000 r); Jan. 1938, x-ray to occipital region (900 r), to lt. pelvis (6,000 r); Feb. 1938 transfusion	P.D. XIII, Sept. 1937 after x-ray; 15 in 15 days (13 i.m., 2 i.v.) persistent low grade fever, unknown cause; transfusion reaction (104°F)	no apparent benefit; painless metastases rt. sacroiliac, rt. femur, lt. scapula, ilia, ribs, skull, liver, exophthalmos lt. eye; latter decreased, vision improved after x-ray; general condition deteriorated after radiation to pelvis	bedridden, very ill for 4 mos., death Sept. 1938, 17 mos. after onset.
14. Un. of Cal. Hosp., San Francisco (82)	M. 10 1937	lt. femur	amputation, Dec. 1937	P.D. XIII begun 8 days after surgery: 12 in 26 days	general health suffered during toxin therapy, rapidly returned to normal	died metastasis and endocarditis Oct. 17, 1940 over 3 yrs. after onset
15. B.L. Coley (73)	F. 13 summer 1938	rt. proximal femur; (psychoneurotic, very obese; question of thyroid disease)	treated as arthritis (diathermy); aspiration biopsy negative; Feb. 23, 1939 x-ray given concurrently with toxins (10,500 r), March 1939 incisional biopsy "no viable tumor"; Sept. 1939: x-ray for recurrence; x-ray to rt. temporal region (2000 r), x-ray 6 times weekly for generalized metastases, 1940	Feb. 1939 P.D. XIII 3 i.m. in 4 days concurrent with x-ray, large doses, marked febrile reactions; 15 days later resumed, 2 i.m., 5 i.v.; unexplained febrile episode Feb. 1940 (102.4°F.); toxins resumed after disease had generalized, given concurrently with x-ray; 4 i.m. & i.v., marked reactions	felt very well for 1 month after combined therapy, pain-free; pain recurred after fall, ceased after further x-ray; twisted leg, fracturing proximal femur; metastases to ribs, rt. eye, skull at angle of jaw, rt. clavicle, rt. ribs (5th to 8th with pathologic fracture of 5th); very severe pain; also to rt & lt. occiput & lungs	blood count declined, general condition did not improve, death August 31, 1940 2 yrs. after onset

16. B.L. Coley (73)	M. 33 Sept. 1948	lt. femur	heat caused relief of pain; osteomyelitis suspected, so 900,000 units penicillin given daily for 1 wk., pain persisted intermittently; incisional biopsy Jan. 19, 1949; x-ray (18,000 r through 6 portals) given during toxin therapy	Jan. 25, 1949 P.D. XIII or Sloan Kettering XIV begun 1 day after x-ray, 12 i.v. in 15 days, moderate or slight reactions	disease not controlled	disease progressed rapidly after toxins were stopped, metastases to lungs, spine, brain, death May 25, 1949, 8 mos. after onset
17. Mayo Clinic (72)	M. 14 June 1954	lt. femur	incisional biopsy Sept. 30, 1954; x-ray concurrent with toxins (23); x-ray to rt. lung Jan. 1955 (7)	Oct. 1, 1954; S.K.I. XIV, 16 i.v. in 16 days, febrile reactions averaged 103.6° -104.8°F. given during x-ray	femoral lesion healed, metastases rt. lung evident Jan. 1955	disease progressed, death Oct. 12, 1955, 16 mos. after onset.
18. W.B. Coley (21; 37; 42)	F. 13 August 1906	proximal rt humerus	explored; amputation refused	Parke Davis IX Nov. 1907 for 3 wks.	tumor decreased in size during 1st 10 days, no further improvement	disease progressed death less than 1 year after onset
19. W.B. Coley 25, case 2; 26; 37, case 81 in table; 41)	F. 15 late 1906	very extensive involving proximal 2/3 rt humerus	treated as rheumatism for several wks. Feb. 1907; x-ray (4) during toxin therapy, July 3-10; interscapulothoracic amputation, July 11, 1907; axillary and subclavian veins nearly blocked by tumor, axillary nodes involved	Parke Davis XII June 14, 1907, small doses, 28 in 42 days, mostly in or near tumor or in upper margin lt. breast; adequate febrile reactions; toxins resumed Oct. 1907 for recurrence, 38 in 78 days, moderate reactions	at first slight decrease in size, then increase; gained 19 lbs. following amputation; recurrence evident Oct. 1907; recurrence disappeared in 4 wks. during toxin therapy, gained 16 lbs. in 4 mos.; well until March 1908	metastases to lungs, breasts, face; death May 10, 1908 18 mos. after onset



SERIES C, GROUP 1, FAILURES WITHOUT METASTASES WHEN TOXINS WERE BEGUN: (con'd.)

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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
20. Campbell Clinic (5, #1828; 11)	F. 20 Fall 1931	lt. humerus, pathologic fracture after slight fall	tumor, evident when splint removed Dec. 1933, severe pain, fever, delirium; several similar episodes 1934; incisional biopsy Jan. 1935 x-ray (7 cycles totalling 15,900 r in 15 mos.); June 1936 proximal 3/5 of humerus resected, fibula grafted; union occurred; physiotherapy, fair function	Jan. 1935 P.D. XIII begun 9 days after x-ray, given 3 times weekly i.m. with rest periods of 2 wks. between courses; 7 courses in 15 mos. ending about May 1, 1936	excellent response to combined therapy: tremor, pain, soreness & local heat all subsided fairly rapidly; slight recurrence of symptoms June 1935, but x-rays showed progressive healing & solidification of humerus; another episode of pain & local heat Dec. 1935, but x-rays negative; Jan. 1937, agonizing pain rt. hip	disease generalized to lt. ilium, rt. femoral neck, further pathologic fracture and soft tissue mass at site of primary; disease progressed rapidly, death April 28, 1937 5 1/2 yrs. after onset
21. Memorial Hospital (73)	M. 9 Nov. 1947	rt. humerus (lumps in lt. arm apparent Nov. 1946, disappeared spontaneously); rt. humerus lesion increased in size with pain & tenderness following trauma	aspiration, incisional biopsies July 1948; x-ray concurrently with toxins (4200 r)	developed ring worm infection June 1947, scarlet fever winter 1947-48; toxins (SKI XIV); 14 i.v. in 14 days, reactions averaged 102° - 104°F.	complete regression during 2 wks. combined therapy; symptom-free 16 mos., then backache; Jan. 1950, sudden rt. hemiplegia in 1 wk. due to spinal metastases, no evidence brain involvement	terminal pneumonia death July 6, 1951 3 1/2 yrs. after onset
22. B.L. Coley (73)	F. 36 July 1947	distal 1/3 rt. humerus (had received psychiatric treatment several years before)	fluoroscoped, x-rayed; aspiration and incisional biopsies Oct. 3 and 6, 1947; Oct. 8, 1947; x-ray (3500 r tumor dose) concurrently with toxins; requested psychiatric advice Dec. 1947, (considerable anxiety); rt. axillary metastatic node excised March 15, 1948; x-ray to chest (9600 r), to rt. axilla, (1750 r)	P.D. XIII begun 2 days after x-ray, given concurrently: 14 in 14 days reactions averaged 103° - 104°F.	apparent regression, in excellent health, n.e.d. in humerus, suspicious area in skull noted but disappeared spontaneously, node in rt. axilla; bilateral lung metastasis present by March 15, 1948, but completely disappeared following radiation, only symptom thereafter dyspnea, due to radiation fibrosis	died pneumonia, Sept. 8, 1948 15 mos. after onset

23. Family Physician (37, case 59; table 7; 42; 73)	F. 12 Nov. 1912	rt. tibia	specific treatment for fairly positive Wasserman; 2 incisional biopsies, Dec. 1912, Jan. 1913, amputation Feb. 3, 1913	Tracy XI toxins by family physician for few wks. i.m.	not recorded	metastases developed, death over 3 1/2 yrs. after onset
24. Gottlieb & W.B. Coley (37, case 62, Table 7; 42; 73)	F. 22 Feb. 1915	entire proximal rt. tibia; onset just after confinement, severe pain wt. loss	explored June 1915 tissue negative; very rapid increase in size; amputation refused; curettage, August 1915; x-ray during toxin therapy, radium inserted in cavity Dec. 13, 1915; no benefit; amputation March 9, 1916	fever, discharge from sinus following 1st exploratory; Tracy XI during x-ray, marked reactions, 1st by Gottlieb, resumed by Coley, Oct. 22, 1915, i.m. 29 in about 8 wks.; reactions marked during latter part; 4 more given 3 wks. after amputation	gained weight, strength under x-ray & toxins; unimproved by further therapy; recurrence in stump 6 wks. after amputation, metastases to pelvic bones	disease progressed, death spring 1917, over 2 yrs. after onset
25. W.B. Coley (37 case 63, Table 7; 42; 82)	F. 8 June 1916	lt. mid. tibia	explored Oct. 24, 1916 radium pack (3000 mch.) Nov. 14, 1916 during toxin therapy; further radium pack January 15, 1917 (2500 mch.); 3rd radium pack May 28, 1917 (4700 mch.)	Tracy XI Oct. 28, 1916, i.m. & into tumor alternately every 48 hrs.; during Jan.: 8 i.t., 1 i.m. during Feb. 8 i.m., 9 more April 15-May 18, 1 i.t. others i.m. (total 63 in 6 1/2 mos., 33 of which were i.t.) 8 more injections July 19-Aug. 14, 1917	wound discharged necrotic tumor tissue beginning 4th week after toxins begun; very rapid decrease in size, partly by sloughing, mainly by absorption, little evidence of tumor left by January 1917, gained 15 lbs.	pulmonary metastases evident Oct. 1917, apparent recurrence in tibia; disease progressed, death autumn 1918, 2 1/2 yrs. after onset
26. Harmer (59)	F. 15 Nov. 1911	rt. tibia following injury	confined to bed; amputation Feb. 10, 1912	Parke Davis XIII begun 9 days later, given i.m. every 48 hrs. for 25 days; injections resumed for 1 month after recurrence, every 48 hrs. i.t., sharp reactions	recurrence in stump 4 mos. later; intratumoral injections caused it to increase in size and become very soft; general condition deteriorated	bedridden all summer, death Nov. 18, 1912 metastases, pneumonia and pleurisy, 1 yr. after onset



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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
27. Besley (5, #339; 43)	M. 11 Dec. 1922	tibia	incisional biopsy; amputation refused; x-ray begun 2 mos. after toxins, given weekly during toxins	P.D. XIII subcutaneously for several mos. beginning May 1923; no febrile reactions	marked decrease in size, gained 10 lbs., improved in every way; by Nov. 1923 tumor had regressed 2/3, believed to be getting well	death Jan. 1924, about 14 mos. after onset
28. W.B. Coley (5, #2286, 42)	M. 18 April 1927	rt. tibia following a fall; 10 lb. wt. loss in 2 mos.	cast applied at another hospital without benefit; incisional biopsy July 20, 1927; amputation 10 days later; hemorrhage followed removal of drain, sero-sanguinous discharge for 2 wks., required tight dressings; x-ray to rt. chest & skull for metastasis, Jan. 1928	P.D. XIII begun 20 days after amputation 24 i.m. in 56 days (7 caused reactions 102°-103°F, remainder only 1°-2° rise); resumed January 1928 (14 i.v. in 49 days)	soon after toxins begun stump cleared up rapidly, discharge decreased; general condition improved; gained 30 lbs., strength, appetite good; January 1928 metastases to rt. lung, skull, posterior rt. ilium	disease progressed, became bedridden March 1928, death June 20, 1928, 14 mos. after onset
29. Campbell Clinic (5, #1743; 10, case 13; 82)	F. 12 May 1929	lt. tibia, ulcerated, severe pain (involved distal 25% of tibial shaft)	incised Nov. 1930 and in 1931: "osteomyelitis"; amputation May 20, 1931; x-ray as prophylactic: 4 cycles beginning August 14, 1931, over stump, chest, pelvis, abdomen (no metastases present); x-ray to chest for metastases March, Aug., Nov., Dec. 1939	P.D. XIII, June 10, 1931; 3 wks. after amputation; 4 courses, 3 a wk. for 3 wks., in 17 mos., no reactions from final course	uneventful recovery; menses ceased after x-ray, n.e.d. for over 7 yrs.; began to feel badly Oct. 1938; pulmonary metastases present March 1939; gained 4 lbs. after x-ray to chest; married against advice August 1939; gained another 4 lbs. fall 1939	disease then progressed, death April 28, 1940, 11 yrs. after onset

30. B.L. Coley (5, #2073; 73)	M. 8 Nov. 1936	proximal lt. tibia aggravated by fall 2 mos. after onset	aspiration biopsy Feb. 17, 1937; x-ray for 1 month beginning Feb. 15, 1937 (7200 r); amputation, March 20, 1937; prosthesis obtained that fall; March 1941, x-ray to rt. lung (4050 r); April 1941, further x-ray to <i>rt.</i> tibia (2500 r); May 1942 x-ray to frontal skull (2100 r)	P.D. XIII March 27, 1937 1 wk. after amputation; 17 in 32 days (8 i.m., 9 i.v.) 2nd course, July 1937 (13 i.m. in 13 days); 3rd course (prophylactic), April 1938, good reactions; 4th July 1938 (12 in 14 days, 8.i.m., 4 i.v.) reactions averaged 103°-104°F; Shear's polysaccharide March 1941 (11 i.m.), 2 severe reactions (106°F): 11 more May 1941 (5 i.v., 6 i.m.); 5th course Coley toxins (P.D. XIII) Jan. 1942, 10 in 13 days (7 i.m.)	tumor seemed smaller 1 wk. after x-ray begun; general condition poor in early May, but wound in excellent condition; gained wt., attended school, in excellent condition for 2 1/2 yrs; late Feb. 1941, chest pain, wt. loss; considerable improvement after x-ray, Shear's polysaccharide; metastases to <i>rt.</i> tibia; pain ceased after Shear's polys., gained wt., symptom-free until August 1941	tibial lesion reactivated, lung metastases recurred Sept. 1941, <i>rt.</i> tibial metastases regressed gained another 8 lbs.; child lost hope Feb. 1942, though appearing very well, refused further therapy until May 1942 then metastases to skull irradiated; disease progressed, much pain, cough, hemoptysis, death, 6 yrs. after onset
31. W.B. Coley (37, case 74, Table 7; 42; 73)	M. 12 July 1921	rt. fibula	biopsy; radium packs 10 & 14 days after toxins begun (7808 & 8052 mch.)	Sept. 1, 1921. P.D. XIII, 30 in 86 days, i.m., only 9 reactions over 101° F, maximum 104.2°F.	tumor 7 cm. smaller by mid-Oct. 1921; pulmonary metastases present Nov. 1921	disease progressed, death 11 mos. after onset



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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
32. W.B. Coley & Henkle (5, #2281; 42; 73)	F. 18 Nov. 1932	rt. fibula	pain relieved by hot baths until severe injury July 1933; tonsillectomy Oct. 1933, pain vanished for 2 wks. then mass apparent; incisional biopsy Nov. 29, 1933; Dec. 1933, x-ray (12); amputation refused, 3 more x-ray (900 r); July 1934, wound curetted & debrided; special support to overcome foot drop; April 17, 1935, 4 radium packs totalling 32,000 mch. in 4 days; partial excision of fibula May 1, 1935 (resected specimen showed no evidence tumor); foot drop, full leg cast; indolent radiation ulcer removed; deep ulceration still present; pinch grafts Oct. 1935; femoral node excised, Feb. 1936; 8 radium packs to rt. groin, abdomen, March 2-9, 1936 (60,000 mch.); x-ray to 12th dorsal vertebra (1500 r):	March 1, 1934 P.D. XIII 9 i.m. (reactions to 105° F); further toxins continued at home by Henkle i.m. little reaction, 2 a wk. until March 1935; April 20, 1935, given daily or every other day, i.m. mild reactions; 3rd course May 16, 1935 (13 in 18 days i.m.), mild reactions;	severe herpes labialis following maximum febrile reaction; n.e.d. except for some limitation of motion (contraction of Achilles tendon); pain recurred, increased in severity shortly after toxins were stopped; also pain in proximal lt. humerus; radiation ulcers intractable; pain over lt. kidney region, Sept. 1935; lymph node metastasis rt. femoral area, Jan. 1936, shortly after radiation to abdomen and chest, also in dorsal spine; recurrence in fibula followed x-ray	pulmonary metastases apparent by April 1936; disease progressed; death June 8, 1936; over 3 1/2 yrs. after onset

33. B.L. Coley (5, #1496; 73)	F. 7 June 1931	rt. fibula 8 x 4 cm.	x-ray 1524 r July 1931, 2 wks. after onset; incisional biopsy after x-ray: "chronic osteitis" 300 r more x-ray in late July 1931; well 21/2 yrs.: then tenotomy performed for double equinus; 2 wks. later fibula reactivated, aspiration biopsy, May 16, 1934 positive; further x-ray (1200 r to fibula, 800 r to mandible, 800 r to rt. femur, 800 r to lt. humerus)	May 24, 1934, P.D. XIII 15 in 15 days (10 i.m., 5 i.v.)	metastases developed, condition deteriorated, except for lesion in lt. gingivus which disappeared.	lost much weight, disease progressed, death July 22, 1934, over 3 yrs. after onset
34. B.L. Coley (73)	M. 14	distal epiphysis fibula (6 cm.)	Dec. 9, 1939, excision; ultra violet treatments post-op.; x-ray March, April 1941 (3500 r), prior to & during toxins; 2 transfusions April 1941; fibula resected June 1941; bone graft from other tibia; 3rd transfusion; incision ulcerated, remained open March 1945; x-ray to chest (2500 r distal, 2400 r proximal)	P.D. XIII March 31, 1941, 6 i.m. in 10 days, reactions averaged 101° -102°F; 2nd course Oct. 1941, 9 in 16 days (4 i.m., 5 i.v.)	ulcerated wound improved markedly during 2nd course toxins; regained full motion; grafted bone in fibula enlarged; symptom-free 3 yrs., struck in chest by basketball January 1945; fluid in rt. base, metastasis; n.e.d. after chest x-ray	disease reactivated, very ill by June 1, 1945; death August 30, 1945, 5 3/4 yrs. after onset



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35. B.L. Coley (73)	M. 21 July 1947	proximal rt. fibula; trauma 6 mos. prior to onset; 20 lb. wt. loss; (psychoneurotic hysterical features, possible narcotic addiction)	heat treatments caused severe burn lasting 2 mos.; treated for osteomyelitis by injections penicillin (300,000 units daily for 11 days ending Sept. 1947); resection head of fibula under tourniquet, Dec. 1947; cast applied; paralysis, anesthesia entire leg from tourniquet site distally; referred to B.L. Coley; aspiration biopsy Jan. 19, 1948; amputation Jan. 22, 1948	P.D. XIII January 30, 1948; begun 8 days after amputation, 14 i.v. in 15 days, reactions averaged 102.2-103.4°F.; unexplained febrile episode March 1948	gained 7 lbs. after toxin therapy; stump healed perfectly	disease progressed death May 19, 1948, 11 1/2 mos. after onset; autopsy revealed metastases to parietal and visceral pleura, vertebrae, ribs, sternum, lungs & skull
36. W.B. Coley (37, case 101, Table 7; 73; 82)	M. 8 1919	lt. ulna following injury	"medicinal" treatment for 2 mos.: explored July 17, 1919, radium packs, August 2, 1919 (19,846 mch.); 3rd radium pack Sept. 24, 1919 (7,895 mch.); 4th radium pack April 1920 (11,920 mch.); 5th & 6th on June 24, 1920 (20,000 mch.), 5 more in August 1920 totalling 40,000 mch.	Tracy XI August 9, 1919, 7 days after radium: 9 i.m. in 19 days, 1 moderate febrile reaction; 2nd course August 1920, 6 i.m. in 14 days, little reactions; continued at home by patient's brother for 6 mos. & after a 3 mos. interval a 3rd course lasting 3 mos., all i.m. reactions to 104°F, total duration with intervals of rest, 2 yrs.	tumor barely palpable by August 30, 1919 after combined treatment; pain recurred spring 1920, n.e.d. on readmission; recurrent tumor apparent in Aug. 1920 disappeared under prolonged toxin therapy; remained well until Sept. 1921 (1 mo. after toxins were stopped)	metastases to lungs liver, disease generalized; death Dec. 14, 1921 2 1/2 yrs. after onset

37. Mt. Sinai & Memorial Hospitals (42; 73)	F. 14 Nov. 1918	rt. radius	radium packs Dec. 1919 (12,761 mch.); Jan. 1920 10,530 mch.); 2 in May 1920 (19,624 mch.), 2 in July 1920 (11,529 mch.); 1 in Aug. 1920 (8,224 mch.); Sept. 1920 3 doses Salvarsan, sodium cacodylate; incisional biopsy Oct. 1920; 4 more radium packs Nov. 1920 (7,600 to 8,268 mch. each); a total of 112,935 mch. of radium in 1 yr.	P.D. XIII Nov. 1919 for 2 wks. i.m. no febrile reactions	no effect from toxins; almost complete regression few weeks after initial radium; became ill, colitis, nervous collapse, anemia, Sept. 1920; soon after incisional biopsy 1920 developed double vision, recurrence, general condition declined, anemia more marked; metastases to scalp; nosebleeds almost daily; recurrence fungated through scar: metastasis on ulnar surface	studded with metastases, disease progressed rapidly, death Jan. 1, 1921, 26 mos. after onset
38. B.L. Coley (73)	M. 16 Nov. 1 1949	lt. scapula, 40 x 43 cm. (played tuba, carried over lt. shoulder)	chiropractic treatment for 2 wks., no benefit; aspiration & incisional biopsies, Dec. 1949; Dec. 20, 1949 x-ray concurrent with toxins 8100 r, causing burn, scapulectomy Jan. 23, 1950 (tumor showed extensive necrosis); thoracentesis yielded malignant cells, April, 1950	P.D. XIII 15 in 15 days (13 i.v., 2 into tumor); spiking fever postsurgery for 2 days (to 101.4° F).	tumor visibly smaller after 3 injections & x-ray treatments; after 1st i.t. dose could move arm more, felt better; less pain; no further regression; considered excellent result from surgery; rt. pleural effusion April 1950	disease progressed rapidly; death June 6, 1950, 7 mos. after onset



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39. B.L. Coley (73)	M. 24 Jan. 1950	lt. scapula 4 x 8 cm. 10 lb. wt. loss	aspiration biopsy July 1950 x-ray July 17, 1950 concurrent with toxins (3500 r tumor dose); further x-ray September 6, 1950 to metastases in L3 (808 r); caffeine cacodylate improved symptoms; x-ray to skull (375 r) & to scapula (300 r)	P.D. XIII begun same day as x-ray 14 i.v. in 15 days, reactions averaged 102° - 104°F.	marked regression evident in 48 hrs., 75% regression in 5 days; complete disappearance in 3 wks. combined therapy well tolerated; 2 wks. after cessation of treatment, low back pain; Sept. 4, 1950 assaulted, brutally beaten (knocked out), severe psychic as well as physical trauma, taken by ambulance next day to Memorial Hospital; metastases in 2 wks.; 10 days later recurrence in scapula	vertebral lesion progressed rapidly, complete paraplegia, death Dec. 4, 1950, 11 mos. after onset
40. W.B. Coley (8; 31; 35, case III; 37, case III, Table 7; 42)	M. 12 early Dec. 1912	recurrent rt. clavicle (2 wks. after local trauma)	total excision of clavicle Dec. 20, 1912 tumors had extended almost into mediastinum, filling space above sternum; evidence of local recurrence within 10 days, radium given (details not recorded)	Dec. 30, 1912 Tracy XI daily i.m. for 2 wks. 2nd course given in March for 1 mo.	swelling disappeared in 2 wks.; rapid wt. gain; during the 6 wks. when no toxins were given local recurrence again apparent, also 2 other nodules, of very rapid growth	disease not controlled, metastases to chest, cervical nodes, appeared shortly after radium; death, Jan. 1914, 1 yr. after onset
41. University Hospital, Philadelphia (82)	M. 10 autumn 1922	rt. clavicle pathologic fracture (repeated falls in football)	"osteomyelitis" incised, drained Nov. 15, 1923; growth resected Jan. 5, 1924; granulation tissue biopsied; 4 x-ray treatments; Dec. 2, 1924, block of necrotic tumor excised	Jan. 18, 1924, P.D. XIII (2 wks. after resection); i.m., no reactions, duration not recorded; injections resumed Sept. 1924 given in region of recurrence, details not recorded; 3rd course begun 2 days after excision of necrotic tissue; given in or near tumor area, daily without reaction	wound healed in 2 mos. well 9 mos., then recurrence; local injections caused it to "melt down"; recurrence again evident in 2 mos.; metastatic nodules developed in pectoralis major, in lt. ilium; clavicle lesion recurred by Jan. 1925, some of metastatic nodules broke down, rt. arm greatly swollen	disease progressed, death March 1, 1925, 2 1/2 yrs. after onset

42. W.B. Coley (5, #504; 37; 73)	F. 11 Feb. 1924	clavicle, of very rapid growth infiltrating soft tissues, shortly after falling on hard floor	total excision of clavicle May 15, 1924; bare tubes radium implanted in wound; massive dose radium applied for recurrence	June 2, 1924, P.D. XIII, 2 wks. postoperative, 4 i.m. in 11 days, one good reaction (103.6° F), continued at home by child's uncle; further toxins after radium & in Oct. 1924	slight recurrence evident by August 1924	disease not controlled, death Nov. 28, 1924, 11 mos. after onset
43. University of Wisconsin Hospital (82)	F. 14 Dec. 1954	recurrent, lt. clavicle	resected Nov. 3, 1955; local recurrence Jan. 1956 also resected; aspiration biopsy of iliac mass, July 1956; cobra toxin given for 7 days, August 1956; palliative x-ray Sept. 1956 (13,600 r) in 10 wks.; terramycin, aspirin, demerol, codeine, thorazine & dramamine for radiation sickness	Johnston XV January 20, 1956: 15 in 45 days, good febrile responses; injections resumed July 25, 1956, 13 in 14 days excellent febrile responses	got along fairly well until metastases developed in rt. ilium July 1956; condition deteriorated, mass larger, pain more pronounced, initial regression of metastatic tumor clinically	disease then progressed, metastases to skull, dura, ribs, ilium, sacrum & lungs, death Dec. 5, 1956, 2 yrs. after onset
44. B.L. Coley (82)	M. 26 June 1929	rt. 8th rib, 4 x 5 cm.	Sept. 18, 1929: x-ray caused pain relief, but mass increased; 2nd x-ray Oct. 16, 1929, 3rd Nov. 20, 1929, without much effect, except wt. gain; 4th x-ray Feb. 1930, no improvement; by March increased swelling and pain; 5th x-ray March 6, 1930; pain became unendurable thereafter; March 14, 1930 radium pack (12,000 mch.)	March 14, 1930 P.D. XIII, begun same day as radium & after x-ray over a 6 mo. period; 10 in 19 days (8 i.m., 2 i.v.)	2 days after toxins begun pain less, general improvement evident; continued to improve under toxins, tumor regressed completely in 1 mo., symptom-free, returned to work; well 4 mos. then pain recurred, lost wt., diffuse metastases in lungs	disease progressed causing death January 19, 1931, 19 mos. after onset



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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
45. B.L. Coley (73)	M. 11 March 1935	rt. 7th rib, extension to pleura (onset followed u.r.i. & trauma)	thoracentesis (3) for traumatic rt. pleural effusion, March 1935; another Feb. 1936, 7th rib then resected, pleural tumor biopsied; radium packs March 1936 (48,000 mch.) during empyema, fever 101° - 102.8°F); ultra violet radiation to whole body April 1936 (10); transfusion April 10, 1936; Dakinization of wound; huge chunks necrotic tumor removed; further radium packs April 1936, thoracentesis July 1936; x-ray (15), Aug. 1936	Feb. 1936, staph. albus empyema; fever (103.8° F.) remained febrile 2 mos.; mixed toxins (special Lilly product) April 22, 1936; 12 in 14 days (10 i.m., 2 i.v.) little reaction except from i.v.	considerable discharge from wound during radiation; empyema cavity closed during toxins; in good condition, no complaints for 2 1/2 mos. July 24, 1928 fever, abdominal pain	disease then progressed rapidly, death August 29, 1936, 16 mos. after onset

46. Memorial Hospital (73)	M. 23 March 1945 (while in army in far east)	rt. 9th, 10th 11th ribs, 15 x 10 cm.; 14 lb. wt. loss	area strapped, relieving pain after 2 1/2 mos.; symptom free 21 mos.; pain recurred, mass appeared, remission in hot weather; again recurred Aug. 1947, increased rapidly; aspiration biopsy, Sept. 10, 1947; x-ray (2400 r); artificial pneumothorax, Sept. 29, 1947; ribs resected; transfusion; complete sterilization of tumor had occurred; x-ray to right lung Feb. 1953 (2500 r); HN <sub>2</sub> March 1953; further x-ray to lung March 1953 & Nov. 1954 (2600 r); x-ray to lt. ischium Dec. 1955; thoracentesis attempted Jan. 1, 1956	u.r.i. Sept. 1947 spiking fever to 101.6°F, continued after operation (100-101.6°F); unknown cause; P.D. XIII Oct 7, 1947, 16 i.v. in 16 days, reactions averaged 103.8° - 104.8° F) pleural effusion during x-ray, fever to 105.6°F continued Feb. 12-25, 1953	gained weight, well, strong, asymptomatic for 3 yrs., then "tired" but n.e.d. until July 1952, pain in rt. lower chest after swimming, due to multiple lung metastases; 3 attacks "flu" in 9 mos. ending Jan. 1953; by Feb. 1953 had intermittent fever, weakness; considerable improvement after chest x-ray; metastases regressed slightly, then increased for awhile after 2nd cycle x-ray; general condition remained excellent, relatively symptom-free, gained 15 lbs.; after almost complete disappearance, lung lesions recurred, March 1954, asymptomatic until Nov. 1954; again symptom-free after further x-ray (33% regression lesion in rt. lung), symptom-free another yr.; then metastases to lt. ischium	Dec. 30, 1955, sudden fever, dyspnea, pleural effusion; disease progressed steadily; death January 17, 1956, over 10 1/2 yrs. after onset
47. Memorial Hospital (73)	M. 16 early Aug. 1938	lt. ischium onset 1 wk. after spraining lt. hip	aspiration biopsy Aug. 28, 1938; x-ray Sept. 9-21, 1938 (4500 r)	Sept. 16, 1938 (1 wk. after beginning x-ray) P.D. XIII: 17 in 20 days (10 i.m., 7 i.v.) reactions averaged 102.4 - 104.6° F.	Dec. 1938, pathologic fracture	metastases to D8 vertebra, skull; death Dec. 8, 1938, 5 mos. after onset



## SERIES C, GROUP 1, FAILURES WITHOUT METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
48. B.L. Coley (73)	M. 7 Sept. 1947	lt. ischium & ilium	incisional biopsy Dec. 1947; x-ray Dec. 22, 1947 (2900 r); 2 transfusions, Dec. 30, 31, 1947; May 1948 x-ray to chest (6000 r) & to ischium (2000 r); antibiotics for sore throat including penicillin; transfusion, amethopterin June 1948; required medication for pain; another transfusion July 19, 1948 & 2nd course amethopterin; palliative x-ray to abdominal mass & Amin-an-fol Aug. 1948 (no benefit)	febrile episode day before x-ray (103.2°F); wbc 14,000; toxins begun Jan. 3, 1948, during x-ray: P.D. XIII (14 i.v. in 14 days) reactions averaged 103° - 105°F.; febrile reactions after chemotherapy & radiation Aug. 1948	pain, tenderness disappeared after combined therapy, clinically well, pain-free, gained 10 lbs., hemoglobin increased from 64-78%; well entire April 1948, then pulmonary metastases several hemoptyses June 1948, diminution in lung metastases; some further improvement after amethopterin; leukopenia (to 2500 wbc); pain increased, condition slowly deteriorated, marked emaciation	disease progressed metastases in epigastrium, lt. lower abdomen, lt. lung, lobar pneumonia; death August 20, 1948, 11 mos. after onset. Autopsy showed metastases to lungs, skull, vertebrae
49. Memorial Hospital (73)	M. 20 May 1948	rt. ischium & ilium, 10 x 15 cm. (25 lb. wt. loss in 4 mos., had weighed 213 lbs.)	incisional biopsy, Sept. 14, 1948, x-ray (5000 r) begun that day, given concurrently with toxins; further x-ray to rt. chest & lumbar spine (1800 r each) without improvement, nauseated; x-ray Oct. 1948 (50 & 85 r) to rt. & lt. skull caused more severe pain	P.D. XIII begun same day as x-ray: 13 i.v. in 14 days; reactions averaged 103.4 - 104.8°F	pain relieved somewhat in 4 days, no longer limped in 10 days; pain in scapular region noted day toxins were stopped, due to metastases in posterior rt. 8th rib, & in region C7, 8 & T1 vertebrae, also metastases in lungs; severe generalized headache by Oct. 16, 1948 during 2nd cycle x-ray due to metastases in frontal skull; primary lesion in ischium remained unchanged but other lesions appeared in both ilia and femora	rapid downhill course, death Jan. 1, 1949, 9 mos. after onset

50. B.L. Coley (73)	F. 25 Oct. 1945	inoperable lt. ilium (4 episodes throbbing pain radiating lt. ilium to knee, lasting 4-5 days; insidious pain, tenderness Jan. to mid-June 1947)	mid-June 1947 tenderness ceased after penicillin (501,000 units every 3 hrs, for 5 days); June 25, 1947, aspiration biopsy; 2 days later x-ray (4500 r); Dec. 29, 1949 x-ray to lt. chest (4800 r); mass over lt. scapula excised Jan. 3, 1949; lt. thoracenteses June & July 1949, nitrogen mustard i.v. July 1949, no benefit, severe leukopenia (wbc 600); penicillin, chloromycetin aureomycin; lt. thoracotomy Aug. 1949: morcellement of tumor, lt. pleural space filled with huge tumor masses	P.D. XIII June 26, 1947, begun 1 day prior to x-ray; 14 i.v. in 14 days; reactions averaged 103.4 - 104°F.; 2nd course Sept. 1947: 11 i.v. in 11 days (similar reactions); 3rd course Sept. 1948, 10 i.v. in 10 days; similar reactions; 4th course Dec. 30, 1948, during x-ray to chest: 12 i.v. in 17 days (1st 3 P.D. XIII, last 9 S.K.I. XIV; latter caused more marked febrile reactions); persistent fever July 1949 after chemotherapy & antibiotics	symptom-free, looked well after combined therapy, returned to medical school, clinically well, but x-rays revealed small lung lesion Aug. 1947; this disappeared after toxin therapy, recurred by Dec. 29, 1948, also soft tissue metastasis over lt. scapula; combined therapy caused disappearance lung metastasis, but recurred; graduated from med. school; May 1949, slight pain in lt. tibial region: June 1949, tired more easily, cough, pleural effusion	rapid downhill course following chemotherapy & antibiotics, death Aug. 29, 1949, almost 4 yrs. after onset
51. Memorial Hospital (73)	M. 18 early Aug. 1953	lt. ilium 20 x 27 cm.; anemic, severe & disabling pain	gold injections, butazolidine, rest; slight improvement temporarily; March 6, 1954, explored: 3 transfusions March 1954; HN <sub>2</sub> ; x-ray to lt. pelvis (5152 r) April 23, 1954; x-ray to upper dorsal spine (2500 r); June 17, 1954: x-ray to skull (850 r), to rt. shoulder (400 r), to lt. lower ribs (400 r), to rt. pelvis, hip & thoracic spine (400 r each); cortisone given for several days	S.K.I. XIV begun 2 days after HN <sub>2</sub> & 1 day after 1st x-ray: 15 i.v. in 17 days reactions averaged 104° - 105°F	marked decrease in size of mass, dramatic relief of pain, ambulatory, relatively pain-free after combined treatment; symptom-free for 10 days after discharge, then u.r.i., sore throat, lt. ear ached; metastases to T3 vertebrae by mid-April 1954	disease progressed rapidly, generalized bone pain, especially in region lt. eye; weakness, anorexia, wt. loss, emaciation; death July 23, 1954, 1 yr. after onset.



SERIES C, GROUP 1, FAILURES WITHOUT METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
52. B.L. Coley (73)	M. 17 Feb. 1931	sacrum inoperable	aspiration biopsy, June 10, 1931; radium packs June 16-29, 1931 (80,000 mch.) caused some relief; Oct. 9-21, 1931 2nd cycle radium given as a precaution (80,000 mch.); 3rd cycle March 1934 (80,000 mch.); 4th cycle April 1935 (68,000 mch.); Sept. 1935 5th cycle (60,000 mch.) Dec. 11, 1935 aspiration biopsy scapular lesion; Dec. 19, 1935 radium to scapula (42,000 mch.); 20 micrograms radium chloride i.v. Dec. 21, 1935	P.D. XIII, June 27, 1931 after 1st radium therapy; 13 in 21 days, (6 i.m., 7 i.v.); 6 marked reactions; May 1935 2 i.m. little or no reactions;	felt fine on discharge July 1931; in excellent condition, resumed activities as fruit dealer; then 3 mos. later lost job (depression); n.e.d., progressive bone regeneration; April 1932, pain, gynecomastia of lt. breast: gained wt., remained in excellent condition until Sept. 1933, then pain down thigh after work, became symptom-free during 3rd cycle radium, remained so for 8 mos. except on movements of pelvis; improved after obtaining sacro-iliac belt, recurrence again apparent April 1935, improved very much after further radium and toxins; symptom-free 2 mos., then pain recurred, dysuria, obstipation; again relieved by further radium; Nov. 1935, metastases to scapula, regressed markedly after radium	somewhat incontinent by Jan. 1936, disease progressed rapidly, death March 22, 1936, over 5 yrs. after onset

53. B.L. Coley (73)	M. 20 April 1946 (while in Navy)	pubis, 5 × 3 cm.; pain increased in severity for 5 mos. causing limp	aspirin, heat lamp; sitz baths; incisional biopsy Oct. 8, 1946; x-ray Oct. 17, 1946 begun 2 days prior to toxins (4200 r) April 1947 codeine for pain; x-ray July 1947 to chest 6,000 r, & to lt. pubis (2,100 r) Nov. 1947 chordotomy for pain; massive doses dropterin, Dec. 1947, (no apparent benefit); x-ray to pelvis (300 r) to lt. chest (2,800 r); transfusion, Dec. 20, 1947	Oct. 19, 1946 (15 i.v. in 44 days); 1st 9 P.D. XIII, last 6 S.K.I. XIV; 6 good reactions (103° - 105.4°F; 2nd course Jan. 7, 1947; 14 i.v. in 15 days; reactions averaged 103° - 104.6° F; reaction, chill & hives following transfusion.	2 wks. after combined therapy was begun pain disappeared; remained in good health, returned to college, well until April 8, 1947, then sudden pain radiating down lt. leg to knee required medication, metastases to lt. lung evident by July 1947 also reactivation of primary, considerable pain relief following further x-ray, returned to college; lung lesions diminished considerably in number & size; pain recurred by mid-Nov.; general condition improved after transfusion	disease progressed, bedridden by March 1948, severe pain, death April 28, 1948 2 yrs. after onset
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SERIES C, GROUP 2, FAILURES WITH METASTASES WHEN TOXINS WERE BEGUN

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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
1. W.B. Coley (42; 73)	M. 15 1904	extensive distal 2/3 lt. femur, metastases to inguinal nodes (trauma)	biopsy of metastasis; x-ray during toxins (15 in 2 wks.)	Parke Davis IX, very small i.m. doses, no reactions	no improvement	death less than a yr. after onset.
2. B.L. Coley 5, #869; (73)	M. 10 winter 1926-27	generalized, involving femora, skull, rt. ischium, apparently primary in rt. femur (trauma)	tonsillectomy July 1927; thereafter rapid loss of strength & weight (18 lbs.); explored, x-ray: 7 to femur, 3 to skull, mostly prior to toxins	Parke Davis XIII, 15 i.m. in 15 days, no marked reactions: had several acute respiratory infections	peculiar intermittent type of fever; no apparent benefit from x-ray or toxins	disease progressed; death, Feb. 1928, about 1 yr. after onset
3. W.B. Coley 5, #898; (8; 42; 73)	M. 2 1/2 1927	distal 2/3 rt. femur metastases to lt. ulna (trauma)	x-ray for 2 mos. prior to toxins; mass almost disappeared, ulnar lesion developed; 2 radium packs (18,000 mch.) given after toxins, no effect	P.D. XIII, Jan. 1928: 29 in 35 days, 1st few in tumor, mostly i.m., mild reactions	some decrease in size during beginning of toxin therapy, later no effect	metastases to entire skeletal system; death April 21, 1928, 8 mos. after onset.
4. A. Whitman (5, #1105; 8; 42; 73)	M. 15 May 1928	distal rt. femur, metastases to lt. distal ribs, lt. orbit, lungs	amputation Dec. 10, 1928; x-ray to chest; radium packs to temple for metastases	P.D. XIII begun 5 days after amputation, 6 i.m. in 2 wks., little or no febrile reaction; 5 more i.v. after radiation	patient lost wt. in first 3 wks. after amputation, generalized pain in back, chest, dimness of vision in lt. eye; by Jan. 2, 1929 metastases on external aspect lt. orbit pushed eye inward & forward; marked improvement immediately following combined toxins and radiation but prognosis believed hopeless, patient discharged	disease progressed rapidly; death April 9, 1929; 11 mos. after onset

5. W.B. Coley Mayo Clinic (72; 73; 75, case 4; 82)	M. 24 summer 1928	recurrent distal lt. femur, pulmonary metastases; 10-12 lb. wt. loss; (4 episodes pain, swelling, fever, chills)	aspirin, local heat; diathermy gave some relief; 6 surgical procedures in 5 mos.: biopsies, curettages, excision; amputation; Dec. 1929: x-ray to stump, chest, all at Mayo Clinic prior to toxins; 8 more x-ray after toxins	P.D. XIII, March 3, 1930, 3 i.m., 6 i.v. by Coley, rest i.v. by family physician; further toxins for stump recurrence	lung metastases regressed 50%, general condition improved markedly, symptom-free; some further regression lung lesions; in good condition 2 mos., then stump recurrence	disease not controlled, dyspnea, cyanosis, terminal pneumonia, bedridden only 5 days: death Jan. 29, 1931 2d yrs. after onset
6. Memorial Hospital (5, #1351; 73)	M. 23 Aug. 1930	proximal shaft lt. femur, pathologic fracture, metastases to skull, pelvis, lt. humerus, lungs	4 teeth removed, physiotherapy; explored, Aug. 1931, x-ray to femur (2260 r), to chest (2000 r), all prior to toxins; further x-ray to pelvis, femur, humerus (totalling 8000 r); 2 blood transfusions; x-ray to skull (800 r) to lumbar region (600 r)	P.D. XIII, Sept. 12, 1931: 8 i.m., 2 i.v. in 20 days, 2 adequate reactions (103.8°-104.6° F); 4 more i.v. 24 days later	lung metastases disappeared, no further pain or cough but general health declined: metastasis to lt. skull, Nov. 1931; in good condition when discharged that month	disease then rapidly progressed, paralysis of face, inability to swallow, death Jan. 1932, 17 mos. after onset
7. Memorial Hospital (73)	M. 16 Jan. 1931	proximal 1/3 rt. femur, pathologic fracture; involved entire rt. ilium, some destruction sacrum, (onset 6 mos. after fall downstairs)	aspiration biopsy, Jan. 1932; x-ray to femur (900 r); 2nd cycle x-ray, March 1932, 3rd cycle to femur (2100 r) June, 1932; 4th cycle Aug. 1932; to rt. femur (1500 r), to chest (3000 r), to scalp lesions (500 r each)	P.D. XII, after x-ray to femur, 40 in 90 days: 5 i.m., 15 i.v., 20 in tumor through window cut in cast, 7 adequate febrile reactions	mass much smaller 3 wks. after 1st x-ray & toxins; in good condition until June 1932, then cough, wt. loss; 1 month after further x-ray, severe pain in lumbar region, rt. shoulder & arm	disease progressed, much wt. loss, pain; death Dec. 1932, 23 mos. after onset



SERIES C, GROUP 2, FAILURES WITH METASTASES WHEN TOXINS WERE BEGUN (con'd.)

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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
8. Memorial Hospital (73)	M. 9 Sept. 1934	very extensive involving proximal 3/5 rt. femur, pathological fracture; metastases to lumbar spine (fell 11 mos. after onset); 10-15 lb. wt. loss	heat; "pills" for rheumatism; aspiration biopsy; x-ray, Nov. 1935 (6000 r to proximal 3960 r to distal femur); 5 doses radium chloride i.v., Dec. 1935, all prior to toxins; x-ray to spinal metastases during toxins; blood transfusion Jan. 1936	P.D. XIII, after x-ray & radium, 26 in 40 days (12 i.m., 14 i.v.); reactions averaged 102° - 104° F. (maximum 105.2° F)	firm union of fracture evident 19 days after toxins begun; marked clinical improvement after transfusion; progressive healing of primary lesion, vertebral lesion disappeared, but another appeared on skull; 8 days after toxins stopped, severe pain	became blind in lt. eye; disease progressed, bilateral exophthalmos, blindness, edema of foot, death April 12, 1936, 19 mos. after onset
9. Memorial Hospital (73)	F. 10 March 1936	rt. proximal femur, metastases rt. deep iliac region, lungs, (trauma)	x-ray 5 days after onset of pain (4800 r); very intense reaction; infection denuded skin, several deep necrotic radiation ulcers, intense pain; hip joint disarticulation Jan. 1936, Dakinization of wound, x-ray to iliac metastases (2250 r), caused regression but lung metastases occurred, May 1938: x-ray to lungs (3500 r); June 1939 (3200 r); x-ray r.l.q. mass June 1940 (3600 r); final x-ray begun 10 days after toxins, to hip (3600 r)	P.D. XIII, August 30, 1937 when lung metastases present, 16 in 19 days (11 i.m., 5 i.v.) good reactions; resumed May 1938: 19 in 19 days (11 i.m., 8 i.v.); given during further x-ray, good reactions from i.v. only; 3rd course toxins begun day after further x-ray: 19 in 19 days (16 i.m., 3 i.v.); 4th course: 18 in 21 days (9 i.v., 9 i.m.) total duration 2 1/4 yrs.	lung lesion vanished 2 mos. after toxins begun, well all winter; recurred May 1938, again disappeared after combined therapy; in excellent health, gained 20 lbs.; bilateral lung lesions present June 1939; lt. lung improved, rt. did not from further x-ray; r.l.q. mass did not respond to x-ray, believed to be 2nd primary: osteogenic sarcoma pelvic bones	death April 1941, diffuse pulmonary metastases, over 5 yrs. after onset

10. B.L. Coley (5, #2280; 73)	M. 30 1934	recurrent rt. femur with large metastases in rt. groin (onset 4 mos. after injury to rt. thigh); very severe pain, 28 lb. wt. loss, pathologic fracture	March 1935 Ober operation, diathermy; injections (?); 2nd operation 1936; finally referred to Memorial Hospital (7th hospital); April 1936 x-ray (4500 r); pain-free in 2 wks.; 2nd cycle x-ray June 1936 (12000 r); marked vesication; gained 6 lbs, symptom-free for 3 mos., Oct. 1936, x-ray for recurrence (1500 r); lost 10 lbs.; pain persisted, pathologic fracture (radiation necrosis); Feb. 1938 x-ray to groin metastasis (1800 r) all prior to toxins; May 1938 hip joint disarticulation to alleviate severe pain	Dec. 1936 local inflammation, heat, Feb. 1938, thigh red, hot, swollen, fever (101° F); March 1938: P.D. XIII 17 in 18 days (8 i.m., 9 i.v.) reactions averaged 102-103° F.	improved after irradiation & inflammatory reactions; felt better after toxins	large local recurrence, pulmonary metastasis; death Oct. 29, 1938, 4 yrs. after onset.
11. B.L. Coley (8; 73)	M. 19 July 1938	rt. femur, metastasis to parietal region of skull, blurring of vision, headaches; (onset followed bronchitis)	July 1, 1939 explored; July 17, 1939, x-ray (200 r); limb immobilized to prevent fracture; parietal metastases resected May 1940; x-ray to area post-operatively; Jan. 1941 parietal metastases again removed (1200 gms, involved brain, meninges, skull & scalp); further x-ray to entire scalp; x-ray to chest	P.D. XIII begun during x-ray, 22 in 25 days (7 i.m., 15 i.v.); reactions averaged 102.4° - 104.4° F.	decrease in size, then recurrence; parietal metastases extended 8 cm. into brain; pain relieved after excision & x-ray; all cerebral signs ceased after final operation & x-ray; pulmonary metastases responded to x-ray	Feb. 1941, generalized metastases including lung, spine; death Sept. 9, 1942, 4 yrs. after onset.



SERIES C, GROUP 2, FAILURES WITH METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
12. B.L. Coley (73)	M. 14 May 1945	rt. femur, metastasis to rt. inguinal nodes, pathologic fracture at football, 1945	incisional biopsy, August 1945; x-ray for 6 wks.; inguinal metastases excised; Feb. 1946, transfusion, x-ray to skull, mandible (2000 r each)	P.D. XIII Jan. 1946: 17 i.v. in 20 days, dosage much larger than usual, average reactions 103.4 - 104° F.	16 days after toxins begun metastases on forehead & below 2nd molars; felt fine briefly, then pain due to multiple metastases to foot, hips, arm, head, jaw; lesions on skull regressed spontaneously	disease progressed, further metastases to tibia, ribs, dorsal & lumbar spine, skull; death Sept. 1946, 16 mos. after onset.
13. B.L. Coley (73)	F. 33 June 1947	lt. femur, terminal; metastases in occiput, lt. great toe, 5th dorsal vertebra, lung; (onset after muscle strain-was professional dancer general condition deteriorated	incisional biopsy when extensive soft tissue involvement already present; Nov. 1947 x-ray (4200 r), slight regression; January 1948 HN <sub>2</sub> into femoral artery; x-ray (16,000 r through 14 portals); complete regression in 2 wks.; head aches, photophobia; generalized metastases irradiated; teropterin, rapid relief of headache; radiation ulcer, extensive fibrosis; then referred to B.L. Coley, incisional biopsy lt. metatarsal; x-ray to skull (1650 r), to lt. foot (2400 r) to skull (1500 r); nupercaine ointment for radiation ulcer; cobra venom helped final severe pain	Sept. 28, 1948, P.D. XIII: 16 i.v. in 23 days, marked reactions	pain in foot ceased after 3rd dose of toxins; headaches improved, diplopia subsided	condition slowly deteriorated; very severe pain; death March 6, 1949, 21 mos. after onset

14. Wehrly (82)	F. 17 Oct. 1953	lt. femur, metastases to lungs; pleural effusion, marked wt. loss	incisional biopsy Feb. 1954; then x-ray (3,135 r tumor dose), given before and during toxins	S.K.I. XIV, Feb. 25, 1954: 17 in 42 days (2 i.m., 15 i.v.) reactions averaged 104.2°-104.8° F	general condition deteriorated markedly during March 1954, improved in April, then severe back pain, paraplegia	death, May 7, 1954, 7 mos. after onset
15. W.B. Coley & Margolis (42; 82)	M. 20 March 1932	32 lt. humerus, extensive pulmonary metastases (had rotated joint markedly while fencing)	treated as neuritis; osteomyelitis, bursitis; rapid increase in size; punch biopsy; 2 cycles x-ray (12 & 8 each); by Oct. 1932 extensive metastases present in lungs, dermatitis to chest, lt. arm & face; further x-ray Jan. 1933	after 2 cycles of x-ray P.D. XIII i.m. begun Oct. 12, 1932, little or no reactions; continued at home by Margolis, 2 severe reactions, rest moderate; became febrile Feb. 1933 (99° -102° F)	marked improvement in humerus, pulmonary metastases disappeared; returned to college	pulmonary metastases recurred, also primary lesion in humerus; death April 6, 1933. 1 yr. after onset
16. Bloodgood (42; 82)	M. 17 Oct. 1909	recurrent rt. tibia infiltrating soft parts; metastases to groin, iliac region, scalp, 15 lb. wt. loss	curtettage, Nov. 1909; explored April 29, 1910; partial removal, cauterization; 6 injections tumor emulsion; drainage of abscess	abscess in 1 of injection sites of tumor emulsion; Tracy XI June 6, 1910, 8 in 60 days in or near wound, febrile reactions to 103° F at first	gradual regression metastases in groin; anemia, loss of strength; mass on scalp became enlarged	disease progressed, death Nov. 3, 1910, 13 mos. after onset
17. B.L. Coley (42; 73)	M. 20 Feb. 1929	rt. tibia, metastases to lungs	incisional biopsy Nov. 1929; amputation refused: radium packs Feb. 4, 1930 (60,000 mch. in 10 days), x-ray (2); x-ray to chest March 1930 (2); x-ray to scalp mass, March 1930; 2 more to chest late March, to 2nd metastasis on skull, April 1930; x-ray to cervical lesion & to chest May 1930 (7); July 1930 x-ray to ilium; scalp & popliteal metastases excised	P.D. XIII Jan. 15 1930; 9 i.m. in 11 days, good febrile reactions; acute respiratory infection, fever (104° F); bronchopneumonia; 1 i.v. Feb. 17, 1930; reaction 103.4° F next day; further toxins March 10, 1930, 26 i.v. in 29 days; 4 more i.v. May 1930; infected toe, so no further toxins given	considerable improvement under toxins alone; pain less, some regression after radiation; metastases to thyroid disappeared under further toxins; felt greatly improved, no evidence of primary tumor March 31, 1930; scalp nodule vanished after x-ray, excellent appetite, 2nd scalp nodule disappeared after x-ray; another appeared in lt. cervical region	began to lose ground, May 1930, metastases to skull, ilium, scalp, disease progressed, death Sept. 15, 1930 20 mos. after onset



SERIES C, GROUP 2, FAILURES WITH METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
18. Mayo Clinic (42; 73; 82)	F. child	rt. fibula extensive pulmonary metastases entire rt. lung, probable pleural effusion, also in lt. upper lobe	explored, May 22, 1914; aspiration of chest showed blood in pleura	Tracy XI June 1, 1914, continued all summer	considerable amelioration of symptoms, especially the pain	death from pulmonary embolus Sept. 14, 1914, at least 1 yr. after onset
19. B.L. Coley (73)	F. 12 Nov. 1938	rt. fibula 5 × 6 cm.; metastases in rt. base	aspiration biopsy Feb. 1939; Feb. 14, 1939 x-ray (12,000 r); given concurrently with toxins, x-ray to lungs begun 2 days after final toxin injection (2200 r), x-ray to lumbar lesion (1500 r), to lt. chest (3200 r) ending Oct. 28, 1929; x-ray to fibula Jan. 1930 (1800 r); x-ray to sacroiliac (1400 r)	Feb. 14, 1939: P.D. XIII 17 in 30 days (6 i.m., 11 i.v.)	clinical evidence improvement of primary in 14 days, leg less swollen, mass less palpable, evidence bone regeneration in 4 wks.; no change in lung lesions until x-ray given, disappeared by April 5, 1939, in excellent condition, gained weight; April 1939 metastases to 3rd lumbar and to lt. lung improved under x-ray; symptom-free, gained 12 lbs.; recurrence in fibula Dec. 1939; pain in leg ceased after x-ray, symptom-free; lost 10 lbs. Spring 1940, severe pain sacroiliac, metastases to skull	disease progressed, death August 10, 1940, 21 mos. after onset
20. B.L. Coley (73)	M. 6 Nov. 1950	proximal lt. fibula, multiple pulmonary metastases (12)	fluoroscoped foot; aspiration biopsy negative; bed rest, warm soaks, empirin; incisional biopsy Dec. 14, 1950; x-ray Dec. 12, 1950 4500 r prior to toxins in Miami; x-ray to chest Jan. 24, 1951, 9760 r in 17 days; Feosol	Jan. 17, 1951 S.K.I. XIV, 16 i.v. in 16 days; reactions averaged 103° -104.6° F; given before & during chest x-ray	some lung metastases became much larger, others disappeared, general condition excellent, but by April 1951 new lesions present in lungs	disease progressed, death May 30, 1951, 7 mos. after onset

21. Memorial Hospital (73)	M. 25 March 1934	rt. scapula, 23 × 23 1/2 cm. metastases to rt. axilla & rt. pleura; repeated trauma to area in his job as auto mechanic	aspiration rt. thoracic cavity Nov. 1934, aspiration biopsy of tumor, Nov. 1934, further thoracentesis yielded 20 cc., & later 1200 cc., 1500 & 1200 cc.; x-ray Nov. 23, 1934 (2000 r to scapula, 4500 r to chest) in 6 wks.; further thoracentesis March 20, 1935; x-ray to pelvis (1400 r), to chest (about 6400 r) ending April 22, 1935; 5 doses radium chloride i.v.	P.D. XIII Jan. 8, 1935, 17 in 18 days (7 i.m., 10 i.v.) moderate reactions	fluid in chest ceased 4 days after x-ray begun, felt greatly improved, dyspnea ceased; tumor decreased 50% in size prior to toxins; skin recovered well from radiation; n.e.d. by Feb. 1935, returned to work early March 1935, disease reactivated promptly, very ill in 2 wks., marked dyspnea, recurrence, metastases in lungs, ischium; dyspnea diminished after further x-ray; no benefit from radium chloride	disease progressed, pain unbearable by August 1940, further metastases to skull, death May 22, 1941, about 3 yrs. after onset
22. B.L. Coley (73)	M. 9 June 1938	lt. scapula, 20 × 10 cm. metastases to mediastinum (1 mo. after fall downstairs)	osteopathic treatments for 5 wks. Jan. 1939; aspiration biopsy June 1939; scapulectomy June 28, 1939; x-ray July 1939 to chest (2400 r) prior to toxins; x-ray April 1940 to head (1400 r), palliative x-ray over skull (1000 r), rt. mastoid (1000 r), lt. & rt. posterior neck (1000 r each) ending Sept. 23, 1940	chronic pharyngitis; P.D. XIII July 19, 1939 begun 3 days after last x-ray; 13 in 14 days (9 i.m., 4 i.v.) reactions averaged 102°-103° F; 2nd course Feb. 22, 1940 9 in 9 days (4 i.m., 5 i.v.) same reactions; 3rd course April 1940, 14 i.v. in 15 days	tumor increased rapidly after osteopathy; no complaints following surgery, x-ray & toxins until mid-January 1940 (about 6 mos.), then pain rt. hip & knee, wt. loss; symptoms subsided spontaneously; well until April 1, 1940, then brain metastasis, diplopia, wt. loss; improved temporarily under combined treatment April 1940; metastases to skull diminished after x-ray, August 1940	disease progressed, pain unbearable by August 1940, further metastases to skull, death May 22, 1941, about 3 yrs. after onset



SERIES C, GROUP 2, FAILURES WITH METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
23. W.B. Coley (30, Case 7 in text, #58 in table; 35; 73)	M. 13 Jan. 1905	rt. clavicle metastases in neck back of sternomastoid	June 1905, partial resection of clavicle at Mt. Sinai Hospital; metastatic node excised by Coley April 1906	Buxton VI Feb. 5, 1906 for recurrence 15 i.m., in 20 days in 1st course, resumed in 10 days, to June 10, 1906 (85 i.m. in about 4 mos.) some marked reactions; 3rd course Sept. 6, 1906: 6 i.m. in 10 days, 4th course Oct. 1906 12 i.m. in 23 days; final course Jan. 1907 (4 i.m., no marked reactions)	further metastatic nodes in supraclavicular region and near midline apparent by Sept. 1906; increased in size by Nov. 1906 despite toxins	disease not controlled, death May 1, 1907, almost 2 1/2 yrs. after onset
24. Presbyterian Hospital (82)	M. 25 Feb. 1930	rt. clavicle, 9 x 7 cm., metastases to skull, chest	palliative x-ray Nov. 6, 1930 to skull and chest	Oct. 30, 1930: P.D. XIII begun 8 days prior to x-ray; no further toxins until Nov. 11, 1930 then given every 2 or 3 days i.m.	no apparent improvement	disease progressed with multiple bone metastases, death Feb. 1931, 1 year after onset
25. B.L. Coley (82)	F. 20 Oct. 1926	11th & 12th ribs, recurrent with pulmonary metastases possibly also present in rt. lumbar region	resection of distal 1/3 of 12th rib Feb. 1927; mid-March 1927 x-ray (2); definite recurrence by April 1927; x-ray (6 more), marked radiation sickness for days; recurrence disappeared, but severe pain persisted, pulmonary metastases by June 1927; local recurrent nodules; July 13, 1927 radium pack over scar (8000 mch.)	July 4, 1927 P.D. XIII 16 i.m. in 22 days, only 3 adequate reactions;	local recurrences present during week toxins were begun, but lung lesions disappeared in 12 days; became very ill after radium pack treatment, in 6 wks. complete paraplegia	disease progressed rapidly, death Jan. 12, 1928 15 mos. after onset

<p>26. Memorial Hospital (82)</p>	<p>M. 18 April 1935 pain; (Nov. 1936, tumor)</p>	<p>rt. 8th rib, 11 × 6 cm.; extra-pleural metastases; 13 lb. wt. loss</p>	<p>aspiration biopsy March 31, 1937; radium packs April 8-17, 1937 (72,000 mch.); pneumothorax instituted April 28-May 14, 1937; block removal 7th, 8th, 9th ribs and pleura; extrapleural metastases could not be removed; further radium pack treatments daily June 1-15, 1937 (112,000 mch.); patient somewhat exhausted by it; metastases in lt. supraclavicular fossa, August 1937; x-ray over supraclavicular fossa, August 1937; thoracentesis twice, late Sept. 1937; x-ray over supraclavicular lesion Sept. 1937 (1500 r) also to skull, scapula, cervical region &amp; lt. chest, Oct. 1937</p>	<p>August 9, 1937 P.D. XIII, 20 in 30 days (10 i.m., 10 i.v.) reactions more marked with i.v.</p>	<p>condition considerably worse after toxins; metastasis to skull, and lungs</p>	<p>disease progressed, death Jan. 14, 1938, 14 mos. after onset of mass, 2 3/4 years after onset of pain</p>
<p>27. B.L. Coley (5, #1772; 73)</p>	<p>M. 11 Oct. 1933</p>	<p>rt. 6th rib, pleural, pulmonary metastases, pleural effusion.</p>	<p>liniment for pain; radium packs daily for 7 days ending Feb. 14, 1937 (60,000 mch.); caused remarkable regression; radium packs April 20-27, 1934 (60,000 mch.); 3rd cycle radium packs June 1934 (60,000 mch.) - a total of 200,000 mch. in 4 1/2 mos.</p>	<p>March 3, 1934: P.D. XIII, 11 in 20 days, 6 i.m., 5 i.v., 2 good reactions (102.8-104.4° F); given after 1st cycle radium</p>	<p>metastases considerably smaller 5 days after toxins begun, well 2 wks. then lost 10 lbs. in 4 mos.; pain recurred but disappeared after radium; lung lesions increased, new masses projecting from mediastinum by August, frequent nose bleeds, but general condition was maintained</p>	<p>death occurred Sept. 15, 1934, 11 1/2 mos. after onset</p>



SERIES C, GROUP 2, FAILURES WITH METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
28. B.L. Coley (73)	M. 7 Jan. 1935	4th lt. rib, extensive, inoperable involving pleura; onset after pneumonia of lt. lung with fever for 2 wks. (extremely bad home conditions)	thoracentesis shortly after onset; incisional biopsy; x-ray March-April 1935 (2000 r); very marked regression by April 8, 1935; pneumothorax attempted, Feb. 1946; disease still present Jan. 1936, extensive involvement; further x-ray ending Feb. 10, 1936 (2700 r); transfusion Feb. 7, 1936; further x-ray July 1936 (3600 r to chest)	April 13, 1935: P.D. XIII, 22 i.m. in 34 days, 11 reactions 102°-104.8° F.; special formula tried Feb. 1936 (9 i.m. in 10 days); mild reactions; measles, May 1936, pertussis July 1936	improved after toxins, symptom-free, in excellent condition all summer & fall, remarkable regression primary & metastases; discharged improved after further x-ray & toxins; continued to gain weight; disease reactivated July 1936, extensive lung metastases	steady deterioration, widespread metastases, including cutaneous lesions on scalp, extreme cachexia, exophthalmos, death Dec. 10, 1936, 2 yrs. after onset
29. B.L. Coley (73)	F. 8 July 1935	lt. 6th rib with pathologic fracture, metastases to lt. lung; (trauma to chest wall 11 mos. before; recurrent u.r.i., tonsillitis; tonsillectomy, 11 days prior to onset of pain; febrile (101° F), slight wt. loss	partial pneumothorax induced; radium packs Aug. 3-8, 1935 (48,000 mch.), causing rapid decrease in tumor; artificial pneumothorax Oct. 25 & 27, 1935; lt. 4th, 5th & 6th ribs resected anteriorly, showed incomplete regression; thoracentesis Nov. 8, 1935; radium packs July 15-30, 1935 (60,000 mch.)	August 10, 1935, P.D. XIII, 20 in 24 days (8 i.v., 12 i.v.); pleural effusion, fever Nov. 3, 1935; toxins resumed July 29, 1936: 12 i.m. in 16 days, moderate reactions	considerable regression in primary & lung metastases, symptom-free, in excellent condition, gained 10 lbs. in 3 wks.; regression of primary complete by Oct. 22, 1935, further wt. gain; condition continued to improve; in excellent condition, symptom-free next 8 mos., but chest films showed metastases in lt. base, July 1936; gained 5 lbs. after treatment in July, some diminution in metastases	disease progressed, bedridden, Sept. 1935, very severe pain in legs; death Dec. 10, 1936, almost 2 1/2 yrs. after onset

30. B.L. Coley (73)	F. 11 March 1948	recurrent lt. 7th rib, metastases to femur, skull, rt. tracheal region (kicked in lt. chest 5 mos. prior to onset)	explored, curettage, July 7, 1948; recurrence evident, Oct. 1948; x-ray (1) caused "resolution of mass;" further x-ray (30) Nov. 17-Dec. 23, 1948: (femoral metastasis); March 1949 metastasis to rt. parietal region; April 27, 1949 x-ray to rt. proximal femur (3,000 r), to rt. parietal region (1,500 r) to lt. parietal region (1,600 r) to lt. chest (800 r); November 1949, x-ray to lt. parietal (1,800 r); Jan. 1950, x-ray to lt. anterior iliac spine (1,700 r) to lt. parietal region that summer (no benefit); x-ray to rib caused large recurrent mass to regress; further x-ray to lt. face caused regression; another lesion 1952 cleared up under further x-ray; terramycin for appendicitis	April 25, 1949, P.D. XIII begun 2 days before & given concurrently with further x-ray: 15 i.v. in 15 days, reactions averaged 103.8°-104.6° F; 2nd course Nov. 10, 1949: 12 i.v. in 12 days (reactions averaged 103.8-104.6° F), several respiratory infections early 1941; acute appendicitis, high fever April 1953 (wbc 18,000)	no complaints after concurrent toxins and x-ray: symptom-free 2 1/2 mos.; then metastasis lt. parietal at spot traumatized few wks. before; it practically disappeared within 10 days after resuming toxins & 8 days after 1st x-ray; lung lesions evident in 4 wks., also in skull, L3 vertebra, rt. femur, lt. iliac spine; patient well-nourished, good color, no complaints, did remarkably well though rib lesion recurred, others increased in size; pathologic fracture Nov. 1950; healed; continued to do well, gained wt.; by 1953, another recurrence over rib; compressed fracture of spine, healed by Feb. 1953	April 1953 mesenteric metastases (?); terminal lobar pneumonia, death May 8, 1953, 5 1/2 years after onset
31. B.L. Coley (8; 73)	M. 21 Jan. 1949	lt. 10th rib, skull metastasis (also had 2 episodes severe low back pain rt. sacral region just prior to onset—may have been metastatic?)	local heat for 1st episode sacral pain caused it to subside: April 1949, 2 ribs resected; back pain then recurred; May 1949, testosterone, x-ray to skull	febrile before & after resection (to 102° F); P.D. XIII May 1949, 16 i.v. in 17 days, reactions averaged 103.2°-104.6° F; frontal headache noted during toxin therapy	pain in iliolumbar region recurred after rib resection; considerable pain relief after toxins; metastases to skull or brain (exophthalmos) June 1949, relieved by x-ray; then pain in rt. thigh, partial hemiplegia	disease progressed migrating pains to all joints, soft tissues; death April 15, 1950, 14 mos. after onset



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Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
32. B.L. Coley (5, #1546 73)	M. 6 June 1933	lt. ilium, metastases to rt. skull, unable to walk (onset after kick on lt. pubic spine)	x-ray to lt. ilium August 1933 (6400 r) prior to toxins; to rt. fronto-temporal metastases prior to and during toxins (800 r); September 27, 1933, x-ray to lt. skull, lt. zygoma (400 r each)	August 23, 1933: P.D. XIII begun after completing radiation to primary: 15 i.m. in 30 days, little or no reaction until 6 m. dose then moderate; 1 more Oct. 17, 1933 (104° F), spiking temperature 1 wk. after this dose - to 104.6° F	improved, good function during therapy, then pain in lt. hip, lt. temporal, lt. zygoma	disease progressed, bedridden, rt. temporal lesion increased markedly death Jan. 3, 1934, 7 mos. after onset
33. B.L. Coley (73)	F. 8 July 1928	extensive lt. ilium, metastases to rt. lung (6-8 recurrent episodes pain in 1st 8 mos., almost constant after April 1940); 8 lb. wt. loss; anemic	July 18, 1940, aspiration biopsy; 4 days later incisional biopsy plaster spica applied July 26, 1940: x-ray (6,000 r) prior to toxins; Sept. 9-20, 1940: x-ray to lt. lung (9,000 r); Jan. 15, 1941 (5,600 r) given concurrently with toxins; i.m. liver injections; p <sup>32</sup> ; transfusion, Feb. 7 1941; March 7, 1941: x-ray to lt. femur (3,000 r); vitamin A; x-ray mid-May 1941 to lt. sacroiliac region (900 r) & few more in June-July 1941	August 15, 1940, P.D. XIII begun day after last x-ray: 16 in 19 days, 9 i.m., causing considerable pain in rt. buttock, mild reactions; 6 i.v., no marked reactions, 2nd course Jan. 22, 1941 begun 8 days after x-ray - concurrently with p <sup>32</sup> : 7 in 12 days (4 i.m., 3 i.v.) only 2 moderate reactions febrile episode mid-April 1941 (103.2° F)	lung metastases tripled in size by August 11; 1940 then disappeared; symptom-free, no limitation of activities, felt fine until mid-Jan. 1941 when pain in lt. hip recurred following influenza; metastases in lt. lung then apparent; during further x-ray fever recurred (to 102° F); felt well for 2 wks. after combined therapy, then pain in lt. hip recurred, radiating down rt. leg; improved after x-ray; symptom-free, gained wt. until mid-April 1941, metastases in lt. sacro-iliac joint	metastases to lt. mandible; disease progressed rapidly July-August, death August 29, 1941, 2 3/4 yrs. after onset

34. Memorial Hospital (73)	M. 20 Jan. 1946 (in Navy)	extensive rt. ilium, metastases to frontal bone and lungs	diathermy; Sept. 11, 1946; resection of all bone which appeared to be necrotic & all localized abscesses; sulfanilamide in wound; placed in cast; adreno-cortical extract given after operation; x-ray to sacro-iliac joint Sept. 29, 1946 for 24 days, 4000 r; 2 wks. later 600 r more; Jan. 21, 1947, 1600 r to ilium; x-ray to lungs 2000 r) May 1947; x-ray to rt. frontal bone, June 1947 (1800 r); HN <sub>2</sub> , 1 more course x-ray (unknown amount)	postoperative fever to 104° F, remained febrile 14 days; June 28, 1947; P.D. XIII, 14 i. v. in 14 days; further toxins advised but patient returned to west coast & none were given	4 days after fever began, pain ceased; general condition remained good but bilateral lung metastases evident by May 12., 1947, these regressed after x-ray June 4, 1947, metastasis to rt. frontal bone, regressed somewhat after x-ray, further regression during toxins	lost 40 lbs. following final x-rays & HN <sub>2</sub> ; disease progressed, death Feb. 13, 1948, 25 mos. after onset
35. W.B. Coley (42)	F. 18 Nov. 1938	pubic bone, pathologic fracture; metastases to lungs, wt. loss	plaster cast, brace applied; August 1928: x-ray (dose unknown) some improvement; further x-ray Nov. 9, 1928 (dose unknown); Dec. 15, 1928 radium (dose unknown)	P.D. XIII Oct. 1928, after 2 mos. of radiation; 10 i.m. in 16 days; Dec. 3, 1928, 2nd course; 6 i.m. in 15 days	primary tumor did not increase during radiation or toxins but another lesion appeared in lung; these appeared to be disintegrating by Dec. 6, 1928, but 2 wks. later they were increasing and primary tumor was also larger	April 1929 rapid loss of weight, general condition decidedly worse, increasing emaciation, bronchopneumonia, death May 5, 1929, 10 mos. after onset



## SERIES C, GROUP 2, FAILURES WITH METASTASES WHEN TOXINS WERE BEGUN (con'd.)

Physician or Hospital (References)	Sex, Age Date of Onset	Site and Extent of Tumor When Toxins Were Begun; Trauma	Other Therapy Before, During or After Toxins	Type of Toxin Used; Site, Duration; Concurrent Infection	Immediate Result	Final Result Period of Survival
36. Memorial Hospital (73; 82)	M. 13 May 1945	rt. pubic bone, lung metastasis (1st episode pain in rt. groin 5 yrs. previously, continued for 5 yrs.)	explored May 3, 1945; then x-ray (4000 r emaciation rt. pubic bone) 2nd cycle Jan. 31, 1946 (4200 r); appendectomy late Feb. 1946; July 15, 1946: x-ray to pubis 3000 r; Oct. 23, 1946 x-ray to lt. chest (2100 r); April 1, 1948; x-ray to lt. chest (4200 r), to skull 1600 r; Dilantin begun Nov. 8, 1949 (1 gr; t.i.d.); March 30, 1950: x-ray to chest (2560 r); further x-ray to lt. lung August 9, 1950 (3000 r); Dilantin again given Jan. 1951 & attacks of impaired vision ceased; April 3, 1951: x-ray to chest (2620 r) July 1951, x-ray to lt. shoulder for pain	purulent discharge from exploratory incision prior to x-ray; brief febrile episode mid-Oct. 1945; Jan. 30, 1946; P.D. XIII (14 i.v. in 15 days) reactions averaged 103° - 104° F (begun 1 day before 2nd cycle x-ray), acute appendicitis late Feb. 1946; 2nd course June 13, 1946; 12 i.v. in 14 days (reactions averaged 103.2° - 103.8° F); 3rd course during x-ray to chest Oct. 28, 1946, 9 i.v. in 17 days; reactions averaged 102° - 102.4° F; u.r.i. Nov. 1947; 4th course toxins Dec. 31, 1947: 7 i.v. in 7 days, reactions averaged 102.6 - 103.2° F; tonsillitis June 1949	gained 8 lbs. after initial x-ray, child very active that fall, had 2 dizzy spells, Dec. 1945, fatigue, recurrent pain in groin; slight decrease in lung lesion, symptom-free by Feb. 15, 1945; severe pain recurred following appendectomy; but by April 26, 1946, symptom-free; early July slight pain, new lesion in lt. lung; symptom-free after further x-rays; attended school; large 6 cm. lesion in lung became scarcely visible following concurrent toxins & x-ray; remained well, strong, n.e.d.; Sept. 1947 blurred vision, headache, some speech difficulty; symptoms subsided in Oct.; hard fall at football, Nov. 1947 fractured lt. clavicle; u.r.i. that month; hit by basketball between eyes, stunned; 2nd & 3rd episodes similar to that in Sept. 1947, in Jan. & March 1948; partial blindness, steady headache, nausea, vomiting, aphasia; partial deafness believed possible due to metastases in lt. occipital-temporal parietal region; these attacks occurred weekly after x-ray to chest, then	worked most of summer, 1951, then pain in lt. scapula, metastatic node above lt. clavicle, retastases to rib; rapid downhill course, death Oct. 17, 1951, about 7 yrs. after onset

37. Nicholson (82)

F. 26  
Sept.  
1956

rt. pubic ramus,  
mediastinal metastases

incisional biopsy June 5, 1953;  $\text{HN}_2$  i.v. for 4 days, July 1953 also x-ray to rt. groin (3000 r); Jan. 3, 1954: x-ray to mediastinum & lt. lung (3300 r) ending Feb. 10, 1954; April 5, 1954: x-ray to rt. inguinal region (300 r) & to pelvis (3050 r); blood transfusions July 1954; x-ray to liver mass June 17, 1954 (900 r), to mediastinum, June 22-25, 1954 (550 r), to spine (D7-S1) June 28, 1954; antibiotics for pneumonia, August, 1954

June 7, 1953 SKI XIV: 14 i.v. in 14 days; Sept. 18, 1953: 12 i.v. in 12 days, 4 good reactions; Nov. 1953: 12 i.v. in 12 days, 4 good reactions (over 103° F); March 17, 1954: i.v. & i.t. in pubic ramus; August 1954, pneumonia

ceased; active in all sports 1948-1949, gained 13 lbs., grew 3 in.; another convulsive epileptic episode Nov. 1949; also dull ache in lt. chest during Oct. 1949; in excellent health until March 1950, then further lung metastases & chest pain; disappeared following x-ray; reactivated by July 1950; symptom-free after further x-ray, well until Jan. 1951, then difficulty in voiding, wt. loss; returned to school, active, also worked Saturdays; wt. declined to 100 lbs., Jan. 1951 pubic lesion reactivated, also lung lesions; apparently palliated by further x-ray, then pain in splenic region radiating to shoulder

subjective improvement but pathologic fracture occurred about July 6, 1953 & lung lesion increased slightly; improved after x-ray, gained 10 lbs., pubic lesion filled in, lung lesion enlarged; mediastinal mass slowly increased during summer & fall 1953 but it almost disappeared following x-ray by March 1953; mass in pelvis disappeared; metastases in liver June 1954; improvement after pneumonia

disease progressed, death August 15, 1954, 23 mos. after onset



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38. Memorial Hospital (73)	M. 14 April 1943	metatarsal, multiple metastases to cervical dorsal, lumbar spine, frontal bone, pelvis, rt. femur; edema legs, decubitus ulcer over sacro-coccygeal region, 40 lb. wt loss	treated for arthritis elsewhere; July 29 & 30, 1943; 2 transfusions; July 26, 1943; x-ray to lt. foot (1200 r), to lt. leg (1200 r). to cervical spine (800 r), to dorsal spine ( 1200 r), to lumbar spine (800 r); further transfusions	August 2, 1943, decubitus ulcer suppurated, fever to 103.6° F, August & Sept. 1943; P.D. XIII August 13, 1943 after x-ray; 14 i.m. in 20 days	no improvement after x-ray; cranial masses began to regress markedly after toxin injections; no further improvement after toxins were stopped	disease progressed; death Oct. 1943; 6 mos. after onset

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