

Giant Cell Tumor of Bone:  
End Results Following Immunotherapy  
(Coley Toxins) Alone or Combined With  
Surgery and/or Radiation—66 Cases  
and Concurrent Infection—4 Cases

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## GIANT CELL TUMOR, MARKED BONE REGENERATION

Series A      Femur, 17 cm. destroyed including neck and trochanter;  
Case 8        no traction used; complete recovery, but 14 cm.  
p.44          shortening; 3 cm. bone regenerated.

Series A      Femur; destruction greater and lesser trochanters,  
Case 13       acetabulum, portions of ilium and ischium; in traction  
pp.46-50      5½ months; steady regeneration pelvis, head and neck  
                of femur; no shortening; good function of hip joint.

Series A      Distal radius, involving ulna (see X-rays recording  
Case 36       regression and regeneration during treatment); palmar  
pp.53-58      splint 6 months; X-rays 11 yrs. later reveal normal  
                bone. Traced well 25 years.

Series A      Spine; very extensive involving 5 lumbar vertebrae;  
Table 1       total paraplegia lower extremities, bladder, rectum;  
Case 40       50 lb. weight loss; complete recovery under toxins  
p.38          alone; vertebrae regenerated but fused. Died 46 years  
                after onset, coronary occlusion.

Series A      Sacrum; paralysis right leg; bedridden 6 months; very  
Case 43       severe pain; 90 lb. weight loss; pain controlled in  
pp.60-65      3 weeks; able to walk in a few weeks; regained 50 lbs.  
                during 2 months of toxin therapy. X-rays 2,3 & 5 yrs.  
                later indicated bone regeneration. Traced well 35 years.  
                Died, chronic cholecystitis, diabetes mellitus,  
                arteriosclerotic heart disease.

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## INTRODUCTION

Giant cell tumor of bone is an aggressive lesion prone to recurrence, which will occasionally metastasize. It occurs in the cancellous tissue at the ends of long bones, particularly the distal femur, proximal tibia, distal radius and proximal fibula. It is essentially an osteolytic process which begins beneath the cortex and gradually extends to involve more and more of the bone until the shell of bone remaining may be entirely destroyed. Even when this occurs, the periosteum remains as a limiting membrane. When extension to the articular cartilage takes place, this too offers a considerable barrier to further progress, although at times the cartilage practically floats on a bed of tumor tissue. If weight bearing is permitted, pathologic fracture may cause collapse of the involved portion of bone, with resulting disturbance in the function of the joint. The tumor varies in its cellular composition; the character of the stroma cells determines the aggressiveness of the tumor which has wide individual variations. It is essentially a benign process and should be treated as such until it is established that malignant changes have taken place. (13)

Most giant cell tumors occur in patients between 20 and 40 years of age. Sweetnam stated he had never seen this tumor develop before skeletal maturity. (91) He added that one must regard all giant cell tumors as potentially malignant, for unfortunately a small proportion behave in a most aggressive manner and metastasize to the lungs.

Dahlin, in a study of 195 patients at the Mayo Clinic, reemphasized the female predominance, the predilection for the region of the knee, and the extreme rarity of the tumor in patients with immature skeletons. One case occurred in a patient with Paget's disease. Two patients had two giant cells tumors. (44)

Ewing stated that in giant cell tumors "the natural termination is death from hemorrhage and infection, after the growth has reached large dimensions and caused much destruction of bone . . ." (45, p. 318) "there is little tendency to spontaneous regression in the average case, and yet not a few records exist of a spontaneous cure, some after fracture." (45, p. 147)

### **Treatment:**

In evaluating what may be the best method of treating these tumors, the late Dr. William B. Coley suggested that one must consider which offers the best chance of saving the patient's life and limb, and which involves the shortest period of disability.

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*Surgery:* Primary amputation was abandoned prior to 1935 since it was recognized that the majority of giant cell tumors are of local malignancy. Hence, surgical treatment has come to mean curettage without preliminary biopsy. Although as early as 1854 and 1860, Paget and Nelaton advocated the conservative treatment of giant cell tumors on the ground that these tumors are always benign, their teaching made little impression upon surgeons of the succeeding generation. A review of the statistics prior to 1910 shows that amputation was employed in the majority of cases, both here and abroad. However, Bloodgood accepted the views of Paget and Nelaton concerning the benign nature of giant cell tumors, and strongly advocated the conservative treatment of these tumors. (6) He continued to add more clinical and pathological evidence in support of this premise. Curettage in the hands of Bloodgood, its strongest advocate, yielded excellent results in about 70% to 80% of the cases, with 20 to 30 percent recurrence. W. B. Coley stated: "Many of the recurrent cases can be cured by a second curettage, but in a number of cases, the disease will again recur, and finally by reason of so much bone destruction a pathological fracture will result." (37) Contrary to the belief held by leading pathologists from about 1910 to 1925, W. B. Coley was strongly of the opinion that giant cell tumors are *not* always benign, and that a definite percentage are malignant or develop malignant changes. He believed the percentage to be in the neighborhood of 15 percent. "The disadvantages of surgical treatment so often emphasized by the pathologists, especially Ewing, and also the radiologists are: (a) the danger of acute or chronic infections following this operation which might later require amputation, and (b) the danger of the trauma of operation increasing the chances of benign giant cell tumor being transformed into a malignant metastasizing tumor." (37; 87)

"Both of these disadvantages should be seriously considered, and warning should be given that the curettage of a benign giant cell tumor should never be regarded as a minor operation that can be performed by anyone, but that it is a serious operation, requiring the best and most skillful technique, and should be performed only by someone with large experience in the diagnosis of bone tumors. The macroscopic examination of the gross material is almost as important as the microscopic examination of sections. If the curettage is carefully performed, infection is extremely rare." (37) Coley had no personal cases of simple curettage followed by infection, but one case, in which the wound was extensively fulgurated with the Keating-Hart apparatus for ten minutes, developed a *Welchii Bacillus* infection in the charred muscle. (see Table 3, Case 3)

"It is true that there have been deaths from hemorrhage following curettage, but this is a very rare occurrence; only one case having been reported in the Bone Sarcoma Registry." In most cases, if due care is taken to curette down to healthy bone, there will be very little bleeding, the wound will heal by primary union



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(blood clot) without drainage, and the period of disability will be greatly shortened.

"A simple biopsy without curettage should almost never be done, especially in a giant cell tumor of the long bones. It is difficult to control the hemorrhage without packing and a sinus is apt to follow which will almost certainly be infected." Coley concluded that most of the bad surgical results had occurred prior to 1925, and in the hands of surgeons who had had little experience in the treatment of bone tumors." (34)

Dahlin et al (1970) noted that surgical treatment short of complete resection or amputation was followed by recurrence of benign giant cell tumor in 44.6% of their cases. Adjunctive radiation or cautery did not decrease this rate. (44) Primary en bloc resection or amputation have given excellent cure rates, but usually at the expense of a major disability.

To increase the cure rate of these tumors and avoid resections or amputations, Marcove and his associates recently introduced a new method—cryosurgery, using liquid nitrogen ( $-196^{\circ}\text{C}.$ ) to enhance the benefit of curettage and avoid ablative surgery. Since 1965 they have treated over 100 cases of this tumor by this method, with no deaths. (64) If recurrence develops, they combine further cryosurgery with a second look biopsy. While complications such as infection, fracture or delayed union may occur, it was possible to eradicate these tumors while preserving the joint and avoiding amputation in a far greater percentage of cases than has been possible with former methods of treatment. (64)

Sweetnam advocates very thorough curettage and packing with bone chips for giant cell tumors involving the knee but noted that "the recurrence rate following such treatment approaches 50%." Usually any recurrence occurring within two years is not an indication of malignancy and may if small be treated again by curettage and chip grafting." If the recurrence is large; thorough resection or amputation is usually necessary and certainly any recurrence occurring after five years must be viewed with suspicion of malignancy." (91)

**Radiation:** Radiation is unsatisfactory because giant cell tumors are highly radio-resistant and the dosage needed for eradication often leads to malignant transformation and/or pathologic fractures from radionecrosis. (3; 10; 41; 42; 43; 61; 83; 85; 89)

W. B. Coley stated: "The bad results following irradiation although rarely mentioned, are, I believe, more numerous and far more serious than the bad results of surgery, so often emphasized." Among these are stiff joints, severe burns, late ulceration, occasionally late osteomyelitis, and malignant transformation. Coley stated also "that the length of time required to effect a cure by radiation is often

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much greater than is required by surgery and toxins, and prolonged disability in the case of the working man is a serious consideration." (34) (See below for cases that illustrate these points.)

"The question arises, are the results following the treatment of giant cell tumors by radiation so much superior to those obtained by surgery, or by surgery and Coley's toxins, that they offset the serious disadvantages just mentioned? A study of the cases at the Memorial Hospital, I believe, forces us to conclude that they are not. As a matter of fact, they are not as good as those obtained by surgery alone, and far inferior to those obtained by surgery and toxins." (34)

Sweetnam suggested that radiation may be used in surgically inaccessible sites such as the sacrum but is not advisable elsewhere because of the possibility of malignant change very many years later." (89)

Ordinarily malignant changes in giant cell tumor follow previous disturbances of the tumors by one or more curettages, cauterization and/or irradiation. Copeland noted that the number of giant cell tumors reported in the literature as treated by irradiation with subsequent malignant change is now sufficiently large to contraindicate this form of treatment. (41)

McLeod et al noted that the danger of radiation therapy for benign disease is reemphasized in the fact that nine of the ten patients with a history of benign giant cell tumor at the site of subsequent fibrosarcoma had received radiation therapy. (61)

### GIANT CELL TUMOR RECEIVING RADIATION AS WELL AS COLEY TOXINS, WITH SUBSEQUENT DEVELOPMENT OF A SECOND PRIMARY IN THE IRRADIATED TISSUES: 9 CASES

#### Series A: Successes

*Case 13:* Osteogenic sarcoma pelvic bones 17 years after receiving 40,000 mch. of radium *prior to toxins*, and 9,000 mch. after toxins for extensive giant cell tumor of proximal femur. Death a year later.

*Case 15:* Spindle cell fibrosarcoma in irradiated femur about 23 years after 10 x-ray treatments *prior to toxins* to this area; death a year later.

*Case 16:* Osteogenic sarcoma in irradiated femur 32 years after *concurrent* radium and x-ray (tumor dose 6300 r.)

*Case 20:* A nun, received radium (12,000 mch.) to right distal humerus just after initial 14 injections of toxins. Mammary carcinoma developed in right breast 19 years after onset of giant cell tumor, and proved fatal a year later. No toxins were given for the breast cancer.



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*Case 25:* Basal cell carcinoma (x-ray cancer) in irradiated skin, 39 years after 2 radium packs *given after toxins* for giant cell tumor of tibia; alive and well in 1976, 61 years after onset.

*Case 39:* Thyroid carcinoma and basal cell carcinomas of skin 20 years after radium, *one before, two during toxin therapy* for giant cell tumor sternum and first left rib (about 30,000 mch.) Alive and well 60 years after onset.

*Case 42:* Osteogenic sarcoma pelvic bones, nine years after very large doses of radium over two year period *prior to toxins* for giant cell tumor of ilium, causing death over nine years after onset of the giant cell tumor.

*Case 45:* Basal cell carcinoma bridge of nose 30 years after radium to superior maxilla (28,333 mch. *prior to toxins*), excised, no further trouble. Died atrophic lateral sclerosis, 45 years after onset.

### Series B: Failures

*Case 5:* Malignant fibrosarcoma of femur, acetabulum and pubes irradiated by x-ray (3065 r. *prior to toxins* and 2 more cycles after toxins); also radium pack for recurrence. Caused death 9½ years after onset of giant cell tumor, 8½ years after first x-ray.

### Series C: Infections

*Case 2:* Basal cell carcinoma in irradiated skin of shoulder following radium (30,000 mch. *prior to toxins*) for recurrent giant cell tumor proximal humerus. Alive and well 1975, 46½ years after onset.

## SECOND OR THIRD PRIMARIES DEVELOPING IN PATIENTS NOT RECEIVING RADIATION FOR GIANT CELL TUMOR: 6 CASES

Two other patients subsequently developed breast cancer 9 and 23 years after onset of giant cell tumor. *Case 5* recovered following conservative surgical removal of the breast lesion and prophylactic toxin therapy, remaining well 18 years, until death from cardiac failure 29 years after onset of giant cell tumor of the femur. *Case 19*, a nun, developed mammary carcinoma which caused death 21 years after onset of the giant cell tumor of the humerus (no toxins given for her breast cancer).

*Case 12:* A second primary giant cell tumor developed in the other femur seven years after the first. This patient then developed a malignant melanoma of the scalp 34 years after onset of his first tumor, which proved fatal four years later. No toxins were given for the melanoma.

*Case 17:* This patient developed a tumor of the spine 25 years after onset of a giant cell tumor of the humerus, which proved fatal in a few months (no toxins given for second lesion)

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*Case 26:* Carcinoma of the pancreas developed 44 years after onset of her primary giant cell tumor of the tibia, which proved fatal (no toxins given for second primary).

*Case 41:* Bronchiogenic carcinoma developed 63 years after onset of giant cell tumor of D10 vertebra (smoked two packs of cigarettes daily for years). Alive and well eight months after lobectomy.

### CAUSE OF DEATH OTHER THAN A SECOND PRIMARY IN THE SUCCESSFULLY TREATED GIANT CELL TUMORS

<i>Cause</i>	<i>Period of Survival (years)</i>	<i>Age at Death</i>
<b>Coronary occlusion:</b>		
Case 5	29	50
Case 6	10½	60
Case 8	45	81
Case 40	46½	67
Case 42	35	67
<b>Cerebral hemorrhage and/or Arteriosclerosis, uremia, etc.</b>		
Case 22	58	75
Case 23	62	78
Case 37	30½	70
Case 45 (also diabetes, chronic cholecystitis)	35	77
<b>Complications following Surgery or childbirth</b>		
Case 7 (hemorrhage)	9	38
Case 11 (3 days after hysterectomy)	11½	48
Case 26 (after surgery for esophageal hernia; also had pancreas ca.)	44	68
Case 46 (after duodenal ulcer surgery)	47	65
<b>Infections</b>		
Lung abscess	21	62
Pneumonia	17	43
<b>Miscellaneous:</b>		
Diffuse collagen disease	35	66
Atrophic lateral sclerosis	45	61



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*Comparative End Results as Regards Function:* "In the cases of giant cell tumor, especially of the lower end of the femur, treated by toxins and curettage or toxins alone, complete regeneration of function has taken place, whereas many of the cases treated by radiation therapy have shown more or less complete ankylosis." (34) W. B. Coley's method of choice was curettage, followed by a period of prophylactic toxin therapy. In many of the cases after curettage of extensive tumors, the patients have been able to get out of bed in two or three days and leave the hospital in two or three weeks, having the toxins continued at home by the family physician.

In 1935 W. B. Coley reiterated his views that the above method offered the greatest percentage of permanent non-recurrences with the shortest period of disability and the least impairment of function. He summarized his reasons as follows:

- (a) This method eliminates error in diagnosis (which occurs in 20% of cases treated by irradiation without biopsy).
- (b) Because the period of disability following surgical treatment is markedly shorter than following radiation.
- (c) Because the function of the joint is much better.
- (d) Because the number of pathological fractures requiring secondary amputation is much smaller than after primary radiation.
- (e) Because the number of cases which later become malignant osteogenic sarcoma is smaller. (37)

### **Treatment by Toxins Alone:**

Coley believed that a comparison of the results obtained by toxins alone, with those obtained by either surgery alone or radiation alone, would show a larger number of recoveries in the cases treated by toxin therapy. He added, "This raises the question, why has not this method been more widely adopted? I believe it is largely because the results are not generally known and partly because most writers on cancer have repeatedly stated that in the treatment of malignant tumors, there are only two methods to be considered, surgery and radiation, quite ignoring the remarkable results obtained by toxin treatment . . ." (37)

It may be asked why Coley did not advocate the toxins as a primary method of treatment in cases of giant cell tumor. The reason appears logical: He believed that surgical curettage followed by prophylactic toxins was to be preferred to toxins alone, because it appeared to give the shortest period of disability. However, he did use the toxins alone in a few far-advanced hopelessly inoperable cases of giant cell tumor, with complete regression and no recurrence. Some of these had pathological fractures. Union occurred and the regeneration of bone and restoration of function was remarkable. It is important to note that by 1935, Coley was again aware of the value of intratumoral injections in these cases, for he

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stated: "The toxins should be injected directly into the tumor in all cases of inoperable giant cell tumor, especially of the spine and pelvic bone." (37)

### **Prophylactic Use of Toxins:**

W. B. Coley called attention to the fact that Bloodgood's series, in which the toxins were *not* used after curettage, showed 30 recurrences. This percentage of recurrence is probably about what may be expected following surgery alone. In those cases in which toxins were administered, the percentage of recurrences was reduced to about 10 per cent.

A careful analysis of all cases of giant cell tumor in W. B. Coley's published papers, indicated that only three primary operable cases of giant cell tumor were treated by toxins alone. They recovered complete function and remained free from recurrence when last traced, 4, 17 and 25 years later. All three were tumors of the radius. (See cases 34, 35 and 36)

### **Etiology and its Possible Effects on Prognosis:**

Coley believed that most cases of giant cell tumor have a causal relation to some form of trauma: "While Ewing admits that a history of trauma is often obtained in cases of giant cell tumor, he is inclined to doubt if the disease ever arises in a previously normal bone as a result of trauma." On the other hand, Ewing states: "About the knee joint, and in the maxilla, there are unusual elements of mechanical strain which seem to be of importance. In many cases, especially with multiple tumors, the disease arises on the basis of osteitis fibrosa cystica." In the latter event, Geschicter and Copeland are inclined to regard it as a different stage of the same disease, but they were equally convinced of the importance of trauma in the development of giant cell tumor. Looser reached the conclusion that tumors developed from hemorrhages into the bone marrow, with organization or cyst formation of the clot, and reaction on the part of the affected bone. (34)

W. B. Coley stated: "Personally, I believe that trauma plays a much more important part in the development of giant cell tumors than is generally conceded. In my own series of over a hundred consecutive cases of giant cell tumor of the long bones, there was a definite history of antecedent local trauma in over fifty percent of the cases. The history was so precise that it would seem difficult to deny a causal relationship. Again in many instances in which the patient gives no history of trauma, he may have sustained some local injury during the preceding two or three years, which he has forgotten by the time the tumor develops. In other words, I believe that the clinical histories obtained in our series instead of exaggerating the part played by trauma, have really underestimated it." (37)

Virchow, almost 70 years previously, had expressed similar views . . . that is: when local causes, principally traumatic, are added to a certain predisposition which



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may be due to irregular bony growth or pathological processes . . . the local irritation will lead to a proliferating neoplasm which, while it will continue in the direction of the pre-existing tissue, and will not completely change type, will nevertheless produce elementary forms that will develop far beyond the limits of the particular type. Every new irritation, be it local or general, will increase this development . . . also pregnancy will exert a definite influence.

It would seem important, in analyzing the effect of toxin therapy in cases of giant cell tumor, that we should take into consideration the amount of surgical or mechanical trauma in each case and not merely the local trauma which may have occurred. These include: incisional biopsy, incomplete curettage in which the wound was packed with gauze or bismuth paste; drainage tubes; profuse hemorrhage, requiring tight packing to control; any strain or undue exertion resulting in complete or partial pathological fracture before or during treatment, and heavy radiation.

During the past 35 years we have made a careful comparative study of approximately 400 cases of all types of bone tumors, both malignant and benign, treated by toxin therapy or with concurrent infection or fever. This study indicates that when any of the above forms of trauma occur, a more prolonged period of toxin therapy and a more aggressive technique of administration may be necessary in order to produce a permanent result. In several cases, especially with heavy preliminary radiation, a good permanent result could not be obtained by subsequent toxin therapy. (See series of failures.) These cases indicate the unfavorable influence these factors may have on prognosis. In those cases, where there was a minimum of these various forms of trauma and irritation, and toxins were used (either alone or after curettage without packing) the results were excellent and were obtained with a minimum of pain and disability.

Two factors must always be considered in evaluating toxin therapy in giant cell tumors: the quality and potency of the preparations used, and the technique of administration. The same technique as regards dosage, frequency and duration of toxin therapy should not be used for early operable cases of giant cell tumors of the radius, ulna, and fibula and distal tibia, as for tumors of the proximal tibia, femur, humerus and the ilium or for cases that are far advanced and inoperable, or for those who have had any of the immunosuppressive factors mentioned above. In all these more difficult cases, the toxins should be given more aggressively and continued for a longer period, in order to obtain a permanent result.

One other important factor affecting prognosis in toxin-treated cases of giant cell tumor of bone was the use of heavy radiation prior to toxin therapy. Those who have advocated x-ray or radium therapy for giant cell tumors may now wish to reconsider these procedures because the evidence suggests that many patients so treated may develop serious infection or pathologic fracture. What is more im-

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portant, however, is that permanent tissue damage may result, leading in a certain percentage of cases to the development of malignant neoplasms later on, as reported by Arlen (3) and Cahan *et al* (10) and several other investigators in the past decade (41; 42; 43; 61; 83; 85; 89). These reports indicate that as little as 1,500 r. (skin dose) may be enough to evoke a sarcogenic or carcinogenic response several years later. (See above for cases in the present study in which this occurred.)

The following complications other than the development of malignancy may also occur following irradiation of giant cell tumors:

*Successful Series:* Case 8: radiation ulcer, pathologic fracture. Case 18: complete ankylosis of shoulder joint. Case 21: severe radiation damage to skin, unhealed area for 50 years. Case 24: radiation ulcer, osteomyelitis. Case 46: recurrent radiation ulcer, atrophic skin. Case 47: severe radiation ulcer, necrosis, resulting in loss of teeth, requiring morphine for 4 months.

*Unsuccessful Series:* Case 3: extensive radionecrosis. Case 5: pathologic fractures. Case 6: large radiation ulcer required many plastic surgical procedures, extensive damage to normal tissues, bedridden nine years. Case 10: severe infection, persistent sinuses for years.

While radiological techniques have been improved since these patients were treated, there is now a growing awareness of the leukemogenic, sarcogenic and carcinogenic effects of radiation, as reported in the recent literature. (3; 10; 33; 41; 42; 43; 61; 78; 83).

## SUMMARY

In determining the relative merits of various forms of therapy in giant cell tumor of bone, one must consider the period of disability entailed, the permanent result as regards function, and the late effects on normal tissues. The following 66 cases of giant cell tumor comprise all known cases of this type of tumor in which at least 10 injections of Coley toxins were administered alone or combined with surgery and/or radiation. Four additional cases in which acute concurrent infection or fever developed, but little or no toxins were administered, are included in Series C. These four patients were traced 14 to 56 years after onset. The tumor site in the toxin-treated cases is given below.

The diagnosis was confirmed by microscopic examination in all but Case 2 (femur), Case 36 (radius), and Case 39 (sternum) of the successful series. However, the clinical and roentgenological findings in these three cases appeared to justify their inclusion. (Cases 36 and 39 are especially interesting.)



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Tumor Site	A. Successes	B. Failures
Femur	16 (76%)	5
Humerus	4 (50%)	2
Tibia	10	0
Fibula	2	0
Radius	5	
Ulna	1	0
Sternum	1	0
Spine	2	0
Sacrum	1	0
Ilium	1 (33%)	2
Maxillae	4 (50%)	0
Patella	0	1
	<u>47</u>	<u>10</u>

Of the successes, four were malignant giant cell tumor, 12 were inoperable when the toxins were begun, and three others were extensive growths. Seven were recurrent tumors, four once, one twice, and one three times.

Of the failures, 9 of the 10 cases had malignant giant cell tumors. Only two of the failures received reasonably prolonged toxin therapy and these two patients survived 11 and 18 years after onset.

The histories of all these cases have been abstracted briefly in table form, to facilitate analysis. Detailed histories of all these cases are available at the office of the Cancer Research Institute, Inc., 1225 Park Avenue, New York, N.Y. 10028. Six histories were selected from Series A (successes) to be given in detail following the table in order to give a clearer idea of how toxins were administered and how patients responded to treatment.

When toxin therapy was first introduced by W.B. Coley, amputation was the usual procedure in giant cell tumors of the long bones. Coley's plea for more conservative treatment led to the use of curettage combined with toxin therapy and/or radiation. Thus it was possible to save the limb in two-thirds of the cases involving the long bones, some of whom were inoperable when the toxins were begun. More patients might have avoided amputation if complications had not developed following preliminary radiation (Cases 10, 25) or inadequate toxin therapy. (Case 4).

The remarkable regeneration of bone destroyed by the tumor following toxin therapy is especially evident in Series A, cases 8, 13 and 36.

While it is possible to cause complete regression of extensive giant cell tumors by toxins alone, as occurred in both inoperable and operable cases, the period

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of disability seems longer than if the toxins are given before and after curettage. In such cases toxins may be resumed a day or two after operation, and continued on an out-patient basis after the patient is discharged from the hospital.

It is hoped that these data will encourage surgeons to try new combinations of conservative surgery (cryosurgery or curettage) with immunotherapy (Coley toxins, *Corynebacterium parvum*, or BCG) in an attempt to cure the largest possible number of giant cell tumors with a minimum period of disability or loss of function.

These data have been assembled in order to give present day physicans and surgeons an objective report on the end results that have been obtained with toxin therapy, alone or combined with surgery and/or radiation in giant cell tumor of bone, both malignant and benign. Similar studies have been made for other types of neoplasms (46-49; 70-79).





TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
OR COMBINED WITH SURGERY AND/OR RADIATION THERAPY: 47 CASES

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
FEMUR: 16 cases						
1. Gerster (13; 14; 22 34)	F. 19 (R.L.)	inoperable giant cell tumor proximal femur, too extensive for hip joint amputation; pathologic fracture after fall May 24, 1898; loss of weight, strength	exploratory operation January 5, 1899; specimen removed; marked increase in size thereafter	none	Coley toxins (Buxton VI) January 25, 1899 in or near tumor for 4 wks.; reactions to 105°F.; lymph nodes in groin became markedly enlarged, patient emaciated, so injections were stopped	tumor slowly grew, general condition worse, then regression occurred, large masses necrotic tumor discharged in few days, greater part of large tumor sloughed; fracture healed; complete recovery; normal function; alive and well 1906, 8 yrs. after onset
2. Matagne (67)	F. 33 (D.A.)	giant cell tumor femur	none	amputation	1916 Coley toxins (Matagne's own preparation using Buxton VI formula) given 4-6 wks. prior to surgery	no recurrence; alive & well 1941, 25 yrs. after onset
3. Green (11; 50; 66)	M. 19 (J.F.D.)	giant cell tumor distal femur; onset October 1906, immediately after fall on dance floor; painful febrile swelling diagnosed as osteomyelitis at first	March 1907 cast applied; November 12, 1907, curettage, cavity washed out with phenol, alcohol, packed with gauze (at Mass. General Hospital)	November 1908 patella freed from adhesions in "attempt to make a new joint"	Coley toxins (Tracy XI) November 20, 1907, subcut. in thigh for 4 wks.; maximum dose 14 minims; wound drained profusely at first, then healed	complete ankylosis knee joint; married, had 3 children, adopted 3 more; in excellent health 37 yrs. then 4-5 attacks cholecystitis in next 10 yrs.; June 1955 emergency cholecystectomy; angina; continued to work; alive and well 1956, 50 yrs. after onset; not traced thereafter

4. W.B. Coley & Vaughan (20; 30; 40)	M. 47 (C.R.S.)	giant cell tumor distal rt. femur; 3 bad falls prior to onset, injuring rt. knee (dislocation twice); very rapid increase in size after 3rd injury February 1910; x-rays in Chicago, Detroit & Ann Arbor in next yr. diagnosed as bone cyst, malignant bone tumor; amputation advised	explored February 21, 1911; egg size tumor found, shell of bone destroyed; more or less necrotic tumor curetted	very profuse extravasation blood after fracture required immediate amputation February 1912	Coley toxins (Tracy XI and Tracy XIF-filtrates) began soon after surgery, 3 a wk. i.m.; 1 very marked reaction July 22, 1911 (106°F., severe chill, very severe herpetic eruption of face, lips); discharge from sinus persisted	steady regression, regeneration of bone, able to walk unaided by crutch or cane; gained 27 lbs. (to 219 lbs.); February 1912 spontaneous fracture occurred, injuring popliteal artery; alive & well February 1921, 11 yrs. after onset
5. W.B. Coley (7; 9; 11; 26; 28; 35; 36; 54; 68)	F. 21 (L.G.)	giant cell tumor distal femur, extensive involvement knee joint with considerable effusion; March 1914 onset pain on going up or down stairs, considerable weight loss	amputation advised by Gibney & Whitman, refused; November 6, 1914 explored by Coley; tumor involved entire distal femur, quite vascular; incomplete curettage; severe hemorrhage required tight packing; limb immobilized in cast	March 1916 curetting of sinus negative; Dakin's fluid irrigations; rapid healing	Coley toxins (Tracy XI) November 11, 1914, 5 days after surgery, daily at first, 73 i.m. in 12 mos. 1-8½ minims; maximum reaction 104°F.; March 1916, sinus became infected, small abscess	complete regression, limb straight, little motion of knee; in good health 8 yrs. then acute mastitis, adenofibroma rt. breast, lesion excised September 1923, small abscesses present; August 1924 another mass of rapid growth; removed October 1924; "malignant cellular carcinoma"; postoperative toxins twice weekly & x-ray (9); N.E.D. in good health; later hypertension, diabetes, died coronary, cardiac failure May 14, 1953, 29 yrs. after onset giant cell tumor, 18 yrs. after onset mammary carcinoma

TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
OR COMBINED WITH SURGERY AND/OR RADIATION THERAPY (con'd)

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
6. W.B. Coley (11; 40)	M. 50 (A.T.)	giant cell tumor distal femur, intense suffering for mos., general condition weak	mid-thigh amputation March 30, 1915 in Ontario "distal femur simply a shell"; morale poor, nervous following surgery	none	Coley toxins (Parke Davis XIII) June 1, 1915 given by sister-in-law, an R.N., every 48 hrs. i.m.; maximum dose 19 minims, maximum reaction 104.4°F.	gained 56 lbs. in 6 mos., desire to live returned; no recurrence but pain in stump due to neuroma; continued to farm until sudden death heart attack February 2, 1925, 10½ yrs. after onset
7. W.B. Coley (11; 28; 30; 34; 40; 68)	F. 29 (C.S.)	very extensive inoperable giant cell tumor distal femur involving all articular surfaces knee joint, 5 cm. of tibia, some areas exceedingly cellular, onset pain, swelling March 1915; fell on knee June 1915, then pain, swelling increased; unable to walk for 5 mos., 25 lb. wt. loss, prognosis guarded	March 1915 poultices, liniments caused swelling to subside; July 1915, limb immobilized in traction; August 1915 in cast for 3½ mos. during which limb shortened 14 cm. amputation advised by several surgeons, but refused; November 20, 1916 explored: whole joint disorganized; curettage, cavity 10 cm. in diameter tightly packed; cast mid-thigh to heel	March 20, 1917 recurrence partially curetted for biopsy; March 21, 1917 radium needles inserted (9,936 mch.); May 2, 1917 radium pack (10,080 mch); May 8, 1917 radium needles (100 mch); June 26, 1917, radium needles (90 mc. in 3 areas, 1 hr each); cast removed each time for radium therapy	Coley toxins (Tracy XI) November 24, 1916, 4 days after surgery, every 24-48 hrs. i.m. in gluteal region for 1st 7 wks., 0.5 to 19 minims; only 1 in 6 days from January 11 to March 17, 1917, total 35 in 3½ mos.; average reaction 100° -101°F., maximum 103°F.	from June 1917 uninterrupted recovery; regeneration of bone, perfect function, in very good health until sudden death hemorrhages from childbirth, July 18, 1924, 9 yrs. after onset



8 W.B. Coley (7; 11; 27; 28; 37; 40; 68)	M. 36 (R.H.)	very extensive inoperable giant cell tumor involving 2/3 shaft of proximal lt. femur, complete destruction proximal 17 cm. including neck & trochanter; also appeared to have pulmonary metastases; onset August 1917 about 6½ mos. after oblique fracture just below trochanter (fell on ice); affected thigh 17½ cm. larger than normal limb; pathologic fracture, prognosis hopeless	hospitalized 20 wks. for fracture; August 1, 1917, diagnosed as inoperable bone tumor	radium packs November 5, 6, 1917 (40,000 mch.); another December 25, 1917 (8,300 mch.)	Coley toxins (Tracy XI) October 30, 1917; 3-4 a wk. alternately in tumor and i.m. for 7½ mos.	in 5 wks. thigh circumference decreased 4 cm., some union of fracture evident; steady improvement, complete regression; wore Thomas splint until 1919; walked with orthopedic shoe due to 14 cm. shortening of limb; fractured same femur 1929 in auto accident; worked until retirement 1949; ulcer developed in irradiated skin of thigh 1955, healed in 6 mos.; herniotomy 1957; in good health except for arthritis and arteriosclerosis; died "kidney condition with uremia, coronary occlusion"; June 27, 1963, 45 yrs. after onset
9. Barss (4; 30; 40)	F. 18 (M.G.)	very cellular, giant cell tumor distal femur; "atypical, likely to recur"; onset March 1915, 6 mos. after local trauma	explored September 4, 1915, curettage, profuse hemorrhage; swabbed with formalin, packed with gauze	hip joint amputation January 17, 1916	Coley toxins (Parke Davis XII, very weak product) begun 2 days after curettage, given 4½ mos. with intervals of rest (site, dosage, frequency or reactions elicited not recorded)	recurrence evident January 1916, uneventful recovery after amputation; alive & well October 1923, over 8 yrs. after onset
10. W.B. Coley (30; 34; 40)	F. 17 (R.S.)	giant cell tumor distal femur; onset February 1918, shortly after a fall	curettage 6 wks. after onset	amputation necessary due to infection	April 1918; Coley toxins (Tracy XI); details of technique or reactions elicited not recorded; 1 month later wound became infected	good recovery; alive & well 1935, 17 yrs. after onset

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11. W.B. Coley (7; 11; 40; 68)	F. 37 (R.H.)	very cellular giant cell tumor distal lt. femur; also had varicose veins, very psychoneurotic; onset pain, swelling, summer 1925, not diagnosed until fall produced cortical pathologic fracture January 2, 1926, considerable joint effusion	January 14, 1926; curettage by B.L. Coley; walking Thomas splint by late February	x-ray (2) July 1926 caused pain relief; August 1926 further x-ray to knee (8) again improved; January 26, February 2 & 5, 1927 x-ray; again June 26, 30, July 30, 1927; amputation at lower 1/3 of thigh after 2nd fracture; specimen contained 2 hemorrhagic cysts, a 3rd filled with grayish semi-necrotic tumor tissue: "very cellular"	Coley toxins (Parke Davis XIII) February 15, 1926, 1 mo. after surgery; 14 i.m. in 18 days, very slight reactions except twice (103° F., 102.6°F.), 3 more i.m. February 4, 6, 8, 1927 (2, 3, 4 minims i.m. in lt. arm); reactions 100.3°-102°F.; cellulitis at site of 3rd injection; wet dressings applied; 1 more i.m. February 15, then 2 i.v. February 17 & 19 (reactions 101.6° & 105°F.); latter caused marked cyanosis, severe chill; 6 more i.m. in March 1927, little reaction	May 24, 1926 evidence recurrence with pain; August 12, 1926 fell causing much pain; January 1927 further reactivation of lesion; improved after i.v. toxins, 2nd pathological fracture early November 1927, adjusted very well to prosthesis after amputation; no further recurrence; well until 1936; multiple uterine fibroids required hysterectomy November 1936; death 3 days later, 11½ yrs. after onset of giant cell tumor



12. W.B. Coley (7; 11; 54)	M. 37 (R.P.)	giant cell tumor distal <i>lt.</i> femur; onset 1920 6 mos. after local trauma to knee (proximal tibia); pain rapidly increased; onset giant cell tumor <i>lt.</i> femur September 1927	treated as rheumatism for 6 mos.; abscess above <i>lt.</i> knee incised November 1, 1920, much pus evacuated; specimen removed; amputation refused until November 30, 1920, then performed by Bloodgood; February 1928 x-ray (5) to <i>lt.</i> femur in 4 wks.	May 15, 1928 curettage, lesion in <i>rt.</i> femur; tumor not nearly so vascular (due to preliminary toxins?) posterior splint applied; radium packs June 21, 22, 28, 30 & July 1, 1928, totalling 38,000 mch.	abscess incised above <i>lt.</i> knee November 1, 1920, much pus evacuated; April 19, 1928 Coley toxins (Parke Davis XIII) 11 i.m. in 4 wks. reactions to 102.2°F.; slight sero-purulent drainage; injections resumed 14 days later 1 i.m., 4 i.v. (reactions to 103.2°F.); developed sore throat; so injections stopped	excellent recovery; well 1920-1927, then 2nd giant cell tumor developed in <i>rt.</i> femur; complete recovery following preliminary toxins, curettage & radium; in good health next 25 yrs. then malignant melanoma scalp; excised November 1953; well nearly 3 yrs. then local recurrence, axillary metastases; excised November 1956; 3rd operation for wide-spread involvement below ear & in cervical lymph nodes; disease progressed involving liver, icterus, death September 15, 1957. 38 yrs. after onset 1st, 29 yrs. after onset 2nd giant cell tumor & 4 yrs. after onset malignant melanoma
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13. W.B. Coley (7; 11; 37; 39; 40; 42; 54; 68)	M. 32 (C.K.)	extensive inoperable giant cell tumor proximal rt. femur involving the neck, both trochanters, with complete destruction of acetabulum & portions of adjacent ilium & ischium; onset May 1929, 4 mos. after striking femur on corner of desk, causing severe pain; 2nd injury to same site shortly after onset of pain; pain increased after long motor trip; hip almost ankylosed by September 1929	June 1929; treated by chiropractor as "sciatic rheumatism"; felt better; September 25-October 5, 1929 radium packs totalling 40,000 mch. to anterior & posterior hip	plaster spica applied for fracture & kept on for 13 wks., then walking caliper splint; April 1931 radium pack (9,000 mch.); 15 lbs. traction applied after 2nd pathologic fracture, for almost 5½ mos. (to prevent shortening that occurred in case 8)	Coley toxins (P.D. XIII) September 28, 1929, 3 days after 1st radium, i.m. & i.v. 9 in 1st 20 days; maximum reaction 103.5°; pathologic fracture during severe chill from i.v. injection October 18, 1929; injections resumed November 11, 1929 & 34 more given in next 80 days (12 i.m., 22 i.v.); maximum reaction 103° F.; toxins resumed July 1, 1931, 41 in about 5 mos., i.m. for 3 mos. then i.v. (improvement did not occur until after i.v.)	returned to work February 1930; discarded crutches & walked with cane summer 1930; several bad falls going to work; June 1931 leg began to feel worse, 2nd pathologic fracture due to reactivation of disease; from early November 1931 <i>improved rapidly &amp; steadily; continuous regeneration of bone in pelvis, rt. femur; new head &amp; neck of femur regenerated;</i> returned to work; in good health 13 yrs. then bad sinus infection all winter 1944-45; by April 1945 pain in rt. hip some swelling in inguinal region; improved with hot compresses; recurred 12 days after returning to work; considered synovitis or myositis; x-ray given (3); improved; symptom-free until November 1945, then several attacks pleurisy with fever due to widespread pulmonary metastases from osteogenic sarcoma arising in irradiated pelvic bones; death February 19, 1946, 18 yrs. after onset of giant cell tumor of femur

14. B.L. Coley (68)	M. 15 (T.J.B.)	giant cell tumor distal rt. femur (one of the cartilaginous variants, telangiectatic, few giant cells, much stroma); onset June 1930, 23 mos. after injuring knee in fall	July 1930 curettage; 2nd curettage October 3, 1930	none	Coley toxins (P.D. XIII) begun October 9, 1930, 6 days after 2nd curettage; 12 i.m. in 13 days, little reaction (maximum 100.6°F)	bone regenerated with perfect function, full range of motion; grew quite tall, rt. limb slightly shorter than lt.; alive & well 1942, 12 yrs. after onset
15. B.L. Coley (42; 68)	M. 44 (G.L.O'C.)	giant cell tumor distal lt. femur; date of onset uncertain; July 19, 1930 fell, fracturing lt. femur; fell again while on crutches November 1930 fracturing same site; 3rd fall December 1930, injuring same site; diagnosed April 1931; 51 lb. weight loss in year (normal 220 lbs.)	x-ray (10) ending June 24, 1931 at Bellevue Hospital, no improvement; required crutches to walk; 2 aspiration biopsies at Memorial Hospital unsuccessful; large cystic cavity curetted July 15, 1931, cauterized by zinc chloride; cast applied; groin to toes; severe pain necessitated removal of proximal half of cast, pathologic fracture early August 1931; cast reapplied	none	Coley toxins (P.D. XIII) August 24, 1931; 11 in 20 days, 8 i.m., 3 i.v., only 2 febrile reactions (101.4°F. and 103°F.)	complete recovery; result regarded as extremely gratifying from functional & anatomic standpoint; resumed work on police force; February 1945 broke lt. ankle; healed without incident; asymptomatic 23 yrs. then developed post-radiation medullary spindle cell fibrosarcoma (not bone producing); amputation June 1954; post-operative infection of stump, requiring drainage twice, died metastases May 13, 1955, 11 mos. after amputation, 24 yrs. after onset giant cell tumor

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16. Steiner (89)	F. 20 (J.J.F.)	giant cell tumor rt. distal femur (of conventional histologic pattern); onset November 1930, some joint effusion	large cavity filled with grayish granular material curetted January 1931, cavity filled with bone chips	January 1932 2 radium packs (6700, 9610 mch.); February 1932 x-ray (2900 r.) tumor dose both sources approximately 6300 r.	Coley toxins (P.D. XIII) for about 3 mos. ending January 1932 (technique & reactions not recorded)	complete recovery; well 15 yrs. except for post-radiation skin changes, & marked valgus deformity; amputation advised but refused February 1949; by 1962 extensive osteogenic sarcoma present in irradiated knee; at amputation tumor involved 12 cm. of distal femur, completely obliterated knee joint, extending into tibia; no areas suggestive of giant cell tumor seen; widespread metastases caused death several mos. after surgery; 33 yrs. after onset giant cell tumor, 31 yrs. after radiation
HUMERUS, 4 Cases:						
17. Blake (15; 23; 32; 40)	F. 31 (A.C.)	inoperable, very extensive giant cell tumor lt. proximal humerus involving coracoid process & glenoid cavity of scapula; onset pain 3 days after fall striking <i>rt.</i> side, January 1896; by November 1897 motion of shoulder limited, unable to use arm.	December 24, 1897 explored, all possible masses of large tumor removed; profuse venous & arterial hemorrhage controlled by packing; wound irrigated with corrosive	none	January 18, 1898 Coley toxins (Buxton VI) 25 in 6 mos, maximum dose 12 minims	wound healed remarkably well in 3 wks.; no recurrence; resumed former job as general houseworker; gained 20 lbs. in next few yrs., good function of arm & hand, in excellent health until June 1913 then cerebral hemorrhage with almost complete paralysis; in 1921 developed what was believed to be tumor of spine, died in a few mos., 25 yrs. after onset of giant cell tumor of humerus



18. Barss (4; 11; 40)	M. 15 (A.C.)	extensive giant cell tumor rt. proximal humerus "probably more active than most giant cell tumors"; onset pain May 1914; by January 1915 tumor so large arm could not be raised	January 29, 1915 explored; soft vascular tumor removed from large cavity	none	Coley toxins (P.D. XII) begun 3 days after surgery, given 6½ wks. in gradually increasing doses, then continued at home by family physician	complete recovery; in excellent health, worked in grist mill, married, had 5 healthy children, remained well except for "pleurisy every winter" from 1936-1946; last traced 32 yrs. after onset
19. Calkins (9; 11; 40)	F. 21 (M.M.) (a nun)	extensive giant cell tumor lt. proximal humerus involving joint & acromion process scapula & clavicle; 4 attacks tonsillitis prior to onset (summer 1921) slight enlargement proximal lt. arm; by February 1924 complete restriction of arm; circumference at axilla 45 cm.	1st seen February 1922 immediate amputation advised; refused; returned 1 yr. later; interscapulothoracic amputation February 8, 1923	none	Coley toxins (P.D. XIII) begun immediately after surgery, given every other day for 6 mos., then twice a wk. for another 6 mos.	excellent recovery, entire large wound healed by primary union; March 1935 operated for neuroma of each and brachial plexus which had caused severe pain; later left her religious order; about 1935 developed carcinoma of breast, operated elsewhere, disease recurred causing death October 26, 1941, 21 yrs. after onset giant cell tumor

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20. W.B. Coley & Reid (7; 11; 30; 34; 54; 68)	F. 46 (M.C.) (a nun)	extensive inoperable giant cell tumor rt. distal humerus ("5 members Bone Sarcoma registry regarded it as osteogenic sarcoma, 4 as giant cell tumor, 2 uncertain"); onset 2 wks. after transverse fracture in bad fall downstairs February 21, 1923; pain very intense, edema entire extremity, complete loss of motion at shoulder joint, 5% motion elbow, wrist	explored by B.L. Coley May 7, 1923, specimen curetted; airplane splint, later light cast; tumor slowly increased, great pain	mid-July 1923 radium packs (12,000 mch.)	Coley toxins (P.D. XIII) begun by W.B. Coley June 2, 1923, 3 wks. after surgery; 14 in 35 days subcut. or i.m., mild reactions, maximum 102.6° F.; injections continued by Reid (technique not recorded); injections resumed November 1923, given steadily by Reid that winter & spring	in 4 wks. swelling decreased 2.5 cm.; able to move arm more freely; by September 1923 huge tumor extended over pectoral region nearly to sternum back over scapula; superiors of her religious order refused to let her return to Memorial Hospital; by November 1923 tumor extended into pectoral region infiltrating muscles; slow decrease in size after toxins resumed, general condition improved; complete regression; ankylosis shoulder joint, no recurrence; well until about 1942, then developed carcinoma rt. breast, told no one; late February 1943, severe cold, bronchial pneumonia, causing death March 12, 1943; at death breast cancer had caused nipple to break down, but general health not markedly affected; death occurred 20 years after onset giant cell tumor



21. Owens (22; 39; 81)	M. 7	highly vascular giant cell tumor proximal tibia very hemorrhagic, of very rapid growth; July 1894 fell on knee, contusion, great tenderness, required fixed dressing for wks; again fell causing lameness, same area, plaster of Paris dressing; onset December 1894; tenderness again developed	actual cautery to skin, bed rest; March 28, 1895 curettage; 11 cm. cavity packed with iodoform gauze	early June 1895 drainage established, cavity again packed	Coley toxins (Buxton VI) April 10, 1895; 8 in 13 days subcut. & later into mass of granulation tissue: 31 in 34 days; maximum febrile reaction 105°F.; leg became swollen, pain, temperature, restlessness; June 2, 1895; 24 more in 38 days in outer side of leg; maximum dose 7 minims	wound healed perfectly by June 24, 1895; general health much improved; slept well (before toxins sleep very disturbed); complete recovery, no recurrence; last traced in good health 1913, 18 yrs. after onset (1st case giant cell tumor treated by toxins with limb saved)
22. W.B. Coley (11; 19; 22; 34; 36; 68)	F. 17 (K.K.)	very large recurrent giant cell tumor distal rt. tibia; onset February 1904, 1 yr. after fall, bruising ankle; by October 1904 involved entire distal 1/3, slight effusion in joint, unable to walk, very large recurrence promptly developed after surgery	May 1904 plaster cast; October 1904 explored, 8 oz. thick reddish brown tissue evacuated; Gibney advised amputation for recurrence, refused; January 5, 1907 large mass curetted by Coley (both operations incomplete)	April 1905, x-ray 2 a wk. for 2-3 mos.; caused radiation ulcer; 3 attempts to skin graft failed; 39 yrs. later after infection of foot 1944 & severe influenza 1945 ulcer improved & healed markedly	Coley toxins (Buxton VI) January 10, 1905, 5 days after operation, given 7 mos. in region of wound & in buttocks i.m.; when dose was increased, causing more marked reactions & chills recurrence ceased to grow	slowly steady complete regression, no further recurrence; married that year; healthy son, daughter born 1911, 1914; menopause 1928; nervous breakdown 1929; remained very active working as dressmaker; in good health next 3 yrs. then severe senile arteriosclerosis; died uremia May 29, 1962, 58 yrs. after onset

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23. W.B. Coley (11; 19; 30; 34)	F. 16 (C.M.R.)	giant cell tumor proximal rt. tibia, onset September 1909 following fall from bicycle bruising leg, pain continued for 7 mos.	April 2, 1910 curettage	none	Coley toxins (Tracy XI) soon after surgery, 2 a wk. for 3 mos., then 1 a wk. for another month, treatment did not interfere with normal routine; only remained in bed 2-3 hrs. after each injection	gained weight, general condition improved; used crutches for 6 mos. to avoid pathologic fracture during regeneration of bone; complete recovery, no recurrence; married 1914, 2 children 15 mos. apart, 1914-1916; at age 40 very sudden menopause, after husband's death 1934, hypertension; phlebitis 1942, after extraction of teeth, arthritis of spine, bedridden 7 mos.; recovered, in perfect health, working 6 days a wk.; remarried 1953; in good health until July 1969, then complete heart block, hospitalized 8 wks.; pacemaker worked well; had arteriosclerosis; November 15, 1971 cerebral hemorrhage, paralyzed rt. side; unable to speak; death December 30, 1971, 62 yrs. after onset giant cell tumor

24. Barss (4; 11; 39)	F. 17 (T.F.)	giant cell tumor proximal rt. tibia; onset October 1915, 1 yr. after fall from runaway horse, bruising ankle	March 4, 1915 soft, vascular cellular tumor curetted; whole cortex eroded; cavity packed with gauze	none	Coley toxins (P.D. XII) begun immediately after surgery in increasing doses to 9 minims; 2nd course April 28, 1915; 3rd August 18, 1915, total 6 mos., with intervals of rest; toxins resumed February 1916 for 2 mos.; continued after recurrence appeared	pain ceased, rapid improvement, gained weight, in excellent condition until February 1916, when soft area appeared in center of scar; recurrence regressed completely after continued toxin injections; no further evidence disease; married 1919; had 5 children in 15 years., in excellent health 1976, 60 yrs after onset (has 6 grandchildren, 8 great-grandchildren)
25. W.B. Coley (7; 11; 28; 30; 35; 36; 40)	F. 17 (C.F.)	extensive malignant giant cell tumor, involving proximal rt. tibia; dysmenorrhea every other period; onset February 1915, 2-3 mos. after taking job at which she sustained repeated mild trauma to rt. knee (pressing lever of printing press)	amputation strongly advised by Whitman; late July 1915 curettage of 13 cm. tumor mass; limb immobilized in cast, wound dressed through window	March 3, 1916 recurrence size of hen's egg curetted, wound packed; radium pack April 1, 1916, July 22, 1916; 1950 scar tissue excised from knee by B.L. Coley (reported negative); basal cell carcinoma excised from irradiated area 1954	Coley toxins (Tracy XI) begun 4 days after surgery (August 1, 1915) daily increasing doses, reactions 102°F-104°F.; toxins discontinued January 10-24, 1916 during attack of gripe; resumed for recurrence alternately i.m. in buttocks, i.t.; injections continued with rest periods summer 1916; 350 in 14 mos.	cavity filled with healthy granulations, general condition excellent during treatment, gained weight, strength, marked regeneration of bone seen in x-rays; N.E.D. December 27, 1915; recurrence soon apparent after toxins stopped; regression apparent in 6 days, but not complete, then began to increase; general condition improved, sinus gradually healed, gained 24 lbs. in 7 wks.; symptom-free 9 yrs., then osteomyelitis, required 3 curettages; recovered; again had osteomyelitis proximal tibia for 2 mos. ending September 28, 1954; sinus persisted; chronic radiation ulcer progressively larger, required further hospitalization, May 1955, pinch grafts; January 1956 diabetes, controlled by diet (reduced from 154 to 135 lbs.); last traced well 1976, 61 yrs. after onset



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26. W.B. Coley & Allen (11; 30; 34; 54)	F. 23 (M.C.)	extensive giant cell tumor proximal lt. tibia involving entire knee joint, with pathologic fracture; had typhoid fever year prior to onset; fell July 1920, injuring lt. knee, 2-3 days severe pain, then swelling	regarded as tuberculous, in plaster cast 3 mos.; explored December 4, 1920, curetted, cavity packed; limb immobilized in plaster spica, under traction 2 wks.; then cast to trochanter applied	sinus remained open, discharging very slightly, filled rapidly with granulation tissue; several times this was cut back & cauterized by Allen; slight curettage of recurrence October 11, 1921; x-rays showed entire articular surface tibia destroyed, very little cortex remained; was very anemic; few days later radium pack; amputation necessary due to life-threatening infection	Coley toxins (Tracy XI) begun December 6, 1920, 2 days after surgery resumed 8 days later i.m., causing large indurations in buttocks, slight febrile reactions (99°-100°F.); some in deltoid region; given 5 mos. with intervals of rest; 1 mo. later resumed, 36 more in next 120 days small i.m. doses; when frequency decreased summer 1921 proximal tibia swelled whole knee larger; toxins resumed by Coley October 1921; severe staph. albus infection wound 5 days after radium, fever to 106°F	recurrence apparent by early October 1921, recovered well after amputation; obtained prosthesis, married, in good health except for lt. hip fracture, March 1959, until April 1964 then rt. back pain radiating up & down legs; also nausea, constipation; large paraesophageal hernia found; at transthoracic approach to repair it, spleen lacerated, requiring splenectomy; death June 17, 1964; pulmonary renal & cardiac failure; autopsy revealed extensive adenocarcinoma pancreas, metastases to celiac & iliac lymph nodes, liver, lungs; calcified leiomyoma uterus; this was 44 yrs. after onset giant cell tumor
27. Lilienthal & Nadel (7; 22; 60)	F. 22 (A.L.)	giant cell tumor distal lt. tibia; no trauma prior to onset (date not recorded)	explored March 1922, tumor 7½ cm. long, curetted, fat implant inserted in cavity	none	Coley toxins (P.D. XIII) shortly after surgery every 3 days for 9 mos. i.m., reactions 100°-101°F.	complete recovery, no recurrence; in good health 1930, 8 yrs. after onset; not traced thereafter

28. Stone (7; 34; 40; 68)	F. 35 (M.G.)	giant cell tumor proximal tibia; (some pathologists considered it to be an osteogenic sarcoma) onset July 1921, 2 mos. after fall, injuring lt. knee & rt. hand	December 1921 baking, massage for 3 wks.; March 1927, limb in cast for 8 wks.; June 1923 x-ray & radium (6249 mch)	amputation June 5, 1924	Coley toxins (P.D. XIII) June 26, 1923, 3 days after radium, 13 in 17 days; maximum reaction 101.8°F., average 100°F.	patient not seen again until May 1924; tumor had increased markedly to 30 cm., little motion of knee, joint involved; prosthesis January 1926; general condition improved considerably; in good health 9 yrs.; died lung abscess March 17, 1937, 16 yrs. after onset
29. W.B. Coley (7; 68)	F. 23 (S.B.)	giant cell tumor lt. proximal tibia; shortly prior to onset August 1927 fell, small stick penetrated lt. leg; wound healed but considerable pain in lt. knee, then swelling	January 25, 1928 thorough curettage, cavity packed with gauze	July 1928, radium packs (53,249 mch.); November 1928, 2 radium packs (16,000 mch.); leg immobilized in cast; brace applied Spring 1929, mid-thigh amputation September 14, 1929	Coley toxins (P.D. XIII) February 4, 1928 (10 days after surgery); dose increased to produce reactions to 104.8°F. wound discharged yellowish exudate beneath exuberant granulation tissue for 2 wks. then discharged purulent material; Dakin's solution applied; healed in 11 wks.; symptom-free 3 mos., then swelling, pain, pulsation recurred; July 9, 1928, injections resumed i.v.; 14 in 30 days, September 10, 1928; injections resumed i.m. 46 in 4 mos., ending November 3, 1928; toxins resumed December 1928 & January 1929 i.v.; June 1947 revision of stump (redundant soft tissue)	following radium, areas of softening increased, condition worse; amputation advised; refused; 3-4 wks. after toxins resumed Fall 1927, tumor decreased, pulsation ceased; pain, swelling recurred November 1928 after toxins stopped; comparatively well until June 1, 1929, then pain, swelling recurred complete pathologic fracture head of lt. tibia; prosthesis obtained; able to work; married 1934; child born 1938, alive & well 1947, 20 yrs. after onset

TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
OR COMBINED WITH SURGERY AND/OR RADIATION THERAPY (con'd)

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
30. W.B. Coley (7; 40; 54; 68)	M. 41 (E.B.)	giant cell tumor involved almost entire lt. proximal tibia (his job required working on his knees as a painter); onset January 1928, 30 lb. wt. loss in 10 wks.	bed rest; curettage October 8, 1928 by Whitman; packed with vaseline gauze; limb immobilized in spica cast	irrigated daily for 3 mos.; January 1929 overhanging roof of bone removed, attempts at skin grafting by Coley	wound infection, considerable suppuration (greenish pus); Coley toxins (P.D. XIII) early November 1928; 8 i.m., 10 i.v.	wound took 8 mos. to heal after 1st surgery; normal function, in excellent health 20 yrs., then headaches & other symptoms due to large infiltrating neoplasm in lt. cerebellar hemisphere seen at craniotomy; death May 29, 1949, 4 days after surgery, 21 yrs. after onset giant cell tumor
FIBULA: 2 cases						
31. B.L. Coley (7; 11; 68)	M. 16 (H.L.N.)	recurrent malignant giant cell tumor shaft lt. fibula; onset May 1925, 5 mos. after influenza, rapid loss of weight, strength; then trauma to lt. calf while sledding; May 1925 sprain while playing baseball; lost 10 more lbs., very weak; recurrence early 1927 infiltrating muscles, much pain	mass following 2nd injury explored June 1925 by family physician; tumor found, muscle & part of fibula resected by Munson, electric cautery used; postoperative course stormy, high fever; 3 x-ray treatments; August 1925; gained 75 lbs. that summer; x-ray for 3 mos. early 1927 for recurrence, no effect; amputation by Coley June 1927, 25 mos. after onset	furuncles incised yielded bone wax	Coley toxins (P.D. XIII) August 10, 1927, almost daily i.m., continued at home by family physician for about 6 mos.; pain, suppuration	fall directly on stump, dislodging bone wax, causing large sore furuncles for a month (pain, suppuration, local heat); gained 50 lbs. in 10 months. after amputation & toxins; prosthesis satisfactory; married 1941, 2 children 1941, 1946; very good health 1976, 50 yrs. after onset



32. W.B. Coley (7; 11; 68)	F. 31 (I.L.)	malignant giant cell tumor lt. proximal fibula; developed in osteitis fibrosis cystica of 13 yrs. duration; chronic sclerosing osteomyelitis 1921; onset July 1930, constant dull ache	incisional biopsy October 16, 1930; "malignant bone tumor"; 4 radium packs (80,000 mch.) October 21-25, 1930; amputation October 29, 1930	none	Coley toxins (P.D. XIII) November 7, 1930 every 48 hrs. i.m. for 9 days, little reaction; 2nd course March 3, 1921 given intensively every 48 hrs. for 1 mo., good febrile reactions	gained weight, strength; obtained prosthesis, in excellent health except for hay fever; became pregnant 1939 (age 40), also had myomata; hysterectomy, rt. salpingo-oophorectomy, appendectomy May 1939; only complaint chronic eczema rt. elbow, labia majora, for which 8-10 x-ray given (25r. daily); numerous squamous papillomas on neck, 7 removed April 1935 also smooth papule in tongue; 1947 multinodular goiter; 1957, pulmonary fibrosis, emphysema, probable bronchiectasis, hospitalized for lt. lobar pneumonia; 1960 cerebrovascular insufficiency, angina; rheumatic arthritis of hands, cervical spine, degenerative arthritis spine, polyarteritis; diffuse collagen disease, butazolidine, prednisone, physiotherapy; death July 26, 1964, 35 yrs. after onset giant cell tumor
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#### RADIUS, 6 Cases

33. W.B. Coley (19; 23; 40)	F. 31 (L.M.L.)	giant cell tumor distal lt. radius size of orange; onset Fall 1905 pain in hand, wrist; mass apparent January 1906; September 1906 pathologic fracture, considerable displacement	treated as rheumatism several mos.; amputation September 14, 1906, 11 mos. after onset	none	Coley toxins (Tracey X), immediately after amputation, given 4 mos.	complete recovery; in good health when last traced 1918, 13 yrs. after onset
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TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
OR COMBINED WITH SURGERY AND/OR RADIATION THERAPY (con'd)

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
34. W.B. Coley (11; 19; 20; 22; 30)	F. 26 (M.F.)	giant cell tumor lt. distal radius, with pathologic fracture; fell, spraining wrist twice; onset after 2nd injury (date not recorded, probably early 1908); general condition poor, anemic	May 1, 1908 Stewart & Pool: incomplete curettage, fractured edges approximated; no union; Hartley & Pool advised amputation; patient absolutely refused	none	Coley toxins (Tracy XI) May 22, 1908, 4-5 a week i.m. chiefly in pectorals or deltoid for 5 wks.	swelling slowly subsided, mobility decreased, union gradually took place; complete recovery, in perfect health until death pneumonia 1925, 17 yrs. after onset
35. W.B. Coley (22; 30; 36)	F. 25 (F.S.)	giant cell tumor distal rt. radius (8 cm.) onset pain in thumb, swelling distal radius August 1910; fungating mass protruding from incision, considerable serosanguineous discharge, great pain	treated as sprain, arm immobilized in cast; 2nd physician regarded it as tubercular; February 13, 1911 explored, biopsy	none	Coley toxins (Tracy XI) February 23, 1911, 10 days after exploratory surgery; i.m. 1st wk. then alternately into tumor & i.m., marked reactions for 6 wks.	radius returned to normal size, fungating mass entirely disappeared in 1 month, wound healed in 3 wks.; no recurrence, complete restoration of function; last traced in perfect health, 1914, 4 yrs. after onset
36. W.B. Coley (7; 11; 28; 29; 34; 38)	M. 28 (L.d'G.)	extensive giant cell tumor distal lt. radius (7½ cm.) involving ulna; 1909, sprained wrist; onset November 1917, sharp pain, 2 mos. later lost power lt. hand, enlargement distal forearm; amputation advised if no response to toxins	untreated	arm kept in splints during early part of therapy; after tumor had regressed cast applied, hand abducted, to avoid deformity during bone regeneration	Coley toxins (Tracy XI) April 25, 1918: all i.m. except 1 in tumor (caused reaction 104°F. herpes labialis); given every other day, reactions 102°-104°F; continued on ambulatory basis for 9 mos.	very little improvement 1st 2-3 wks.; after 9 wks. swelling had nearly subsided, frequent x-ray examinations showed gradual regression, then steady bone regeneration of the 7½ cm. radius & portion of ulna which had been totally destroyed; new bone not entirely solid by Spring 1919; but patient returned to work in grocery; normal function, little deformity; x-rays showed normal bone; in perfect health; last traced 1942, 25 yrs. after onset.

37. W.B. Coley (7; 9; 11; 30; 32; 54; 68)	F. 40 (M.F.)	recurrent giant cell tumor involving entire rt. distal radius with pathologic fracture, for 3 yrs. prior to onset worked in factory winding silk; onset June 1919, pain, swelling; couldn't work after July 1, 1919	curettage December 1, 1919, only small area posterior wall intact; cavity washed with pure phenol, alcohol	arm splinted; radium packs July 2, 4, 5, 1920 (about 29,000 mch) 2 more radium packs August 6, 1920; 2 more on August 29, 30, 1920; 2 more October 1, 1920 (total dose 68,250 mch. in 4 mos.)	Coley toxins (Tracy XI) December 11-16, 1919 (2 or 3 doses) i.m., injections resumed January 20, 1920, dose increased daily to 14 minims, produced moderate reactions for 1 mo.; toxins resumed October 1920, given steadily for 4 mos.	pathologic fracture occurred mid-December 1919, evidence of recurrence; 2-3 days after daily toxin injections January 1920, tumor began to decrease in size, steady regression; pain ceased almost immediately; in 3 wks. circumference decreased 4 cm.; May 20, 1920, 3 mos. after cessation of treatment, 2nd recurrence of rather rapid growth ( $4\frac{1}{2} \times 8\frac{1}{4}$ cm.); tumor increased considerably; good deal of swelling after 2nd course radium, then some improvement, but pain soon returned, recurrence considerably larger; affected wrist 25 cm. in circumference by September 24, 1920, hand practically useless growth 14 cm. in diameter, further steady increase in size despite massive radium therapy; immediate steady improvement after toxins resumed & given steadily for 4 mos.; gradual regeneration of bone, complete regression, good function of wrist & fingers; in good health, no further recurrence until death at 75, January 29, 1950, hypertensive cardiovascular disease, cerebral hemor- rhage, 30½ yrs. after onset
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TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
OR COMBINED WITH SURGERY AND/OR RADIATION THERAPY (con'd)

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
ULNA, 1 Case						
38. Wetherall (7; 11; 31; 32; 38; 40)	M. 15 (E.M.I.)	extensive giant cell tumor proximal half lt. ulna (originally regarded as Ewing's tumor); January 1908 fell, fracturing & dislocating lt. elbow, reduced 2 hrs. later, reset 4 days later; onset July 1908, 6 mos. after injury, pain at fracture site, marked weight loss (to 102 lbs.)	amputation July 8, 1908	none	Coley toxins (Tracy XI) begun 12 days later, given for 3 mos. under W.B. Coley's direction; all but 2 in rt. arm, several marked reactions (to 104.5°F.)	no recurrence; gained 30-40 lbs., returned to school, then college, married 1914; 3 sons, in very good health, running 300 acre farm, working outdoors, hunting, etc.; got driver's license 1916, driving 12,000 miles yearly; played baseball, tennis, active in community; never wore prosthesis; prostatectomy 1972; skin cancer 1973; freak accident damaged circulation to rt. hand, rendered it useless; in good health 1976, 68 yrs. after onset

# STERNUM AND RIB: 1 Case

39. W.B. Coley (1; 7; 11; 32; 68; 88)	F. 19 (H.M.)	inoperable giant cell tumor sternum & 1st lt. rib 7½ cm., extending to lt. apex, metastases to lung roots; at 1st regarded as osteogenic sarcoma; diagnosis based on clinical & x-ray findings; recurring attacks neuritis lt. scapular region for 2 yrs. prior to onset; April 1916 influenza; onset very severe pain below lt. clavicle while riding a horse summer 1916; February 1917, 1 wk. after another episode of pain, diminished resonance in lt. lung, effusion at base; growth between jugular vein & heart; prognosis hopeless	radium pack March 27, 1917	radium pack May 17, 1917 to sternum & rib for 1 hour; as precaution 1 more March 1918: 10,000 mch.	Coley toxins (Tracy (XI) April 1, 1917, 5 days after radium; i.m., increasing dose to 8 minims; May 25, 1917, severe reaction & chill: 104°F.; at first 2 or 3 weekly, then 1 a week for 5 mos.; later injections caused little or no reactions	within 3½ wks. considerable regression, general condition good; marked improvement seen on x-rays early August 1917, 4 mos. after toxins begun; able to exercise, lead normal life; complete regression, no recurrence; married 1923, son born 1925; spontaneous abortion 1927 in 6th month of gestation; 1933, iritis; 1934, psychic stress; leukorrhea, cervix eroded; squamous cell carcinoma diagnosed clinically; no evidence malignancy found at panhysterectomy, appendectomy; 1936, again iritis; thyroidectomy for carcinoma invading tracheal surface, September 1937; in good health, working as college professor until retirement; 1957: 2-3 carcinomas appeared in irradiated skin on back, chest, excised; in very good health, working as antique dealer 1976, 60 yrs. after onset
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TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
OR COMBINED WITH SURGERY AND/OR RADIATION THERAPY (con'd)

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
SPINE AND SACRUM: 3 Cases						
40. W.B. Coley Wachsmann & Pollak (7; 11; 14; 22; 40; 53; 54; 68; 72)	M. 21 (D.G.)	very extensive inoperable giant cell tumor involving 5 vertebrae: D8 to L3; 14 cm. in diameter; wrenched back while wrestling prior to onset, autumn 1898 causing pain; this recurred at site of injury, unable to walk by April 1901; chronic cystitis for 6 mos., recurred Fall 1901, sporadically all 1902, then total paraplegia lower extremities, bladder, rectum, 50 lb. weight loss, general emaciation; prognosis absolutely hopeless	in Home for Incurables beginning April 3, 1901; exploratory operation February 18, 1902	immobilized in plaster jacket during bone regeneration	Coley toxins (Buxton VI) February 22, 1902, i.m. in buttocks daily; marked reactions, usually 103.2° -104.2°F., maximum 108.8° F. April 14, 1902 (may have pricked a vein?) daily at 1st, every 1-3 days for 3 mos., despite discontinuing injections daily rise in temperature May 15-June 5, 1902, due to absorption huge quantities necrotic tumor tissue	2 days after 1st dose could move toes for 1st time in a year; steady decrease in size; by September 1902 fair motor power and ability to walk, reflexes normal, areas of sensory disturbances diminished in intensity & extent; complete recovery, resumed regular occupation, married 1905, had 3 sons; in very good health 33 yrs.; (involved vertebrae regenerated but fused); diabetes 1935; coronary heart disease 1943, sudden death August 19, 1944, coronary occlusion, nearly 46 yrs. after onset



41. Harmer (7; 11; 14; 22; 53; 54; 66)	M. 16 (A.J.McL.)	recurrent, inoperable giant cell tumor D10 vertebra: highly cellular, composed of spindle cells with numerous giant cells, very atypical cells, scattered necrotic areas; onset, May 1912, 2 mos. after injuring spine in fall; by June 10, 1912 10 cm. in diameter; no tactile or pain sense over rt. anterior crural distribution	June 26, 1912, aspiration biopsy; dry tap; explored that day, transverse process removed mass curetted; profuse bleeding due to vascularity, cavity tightly packed; in very poor condition post-operatively, required stimulation	none	Coley toxins (Tracy XI) July 2, 1912, 6 days after surgery, 15 i.m. in abdominal wall, twice weekly, 1 marked reaction; injections resumed for recurrence, given directly into growth, causing violent reactions; continued 7 mos.	1st course of toxins did not prevent recurrence 13 × 9 × 5 cm., causing paresis of leg on lying down, pain in spine at slightest jar; recurrence entirely disappeared by mid-January 1913 (following intratumoral injections mass sloughed in several areas); gained steadily in weight, strength; no further recurrence, scars soft, not adherent to underlying tissues; in excellent health, married, had 1 child continued to work as mechanic until he retired in 1960; in very good health 1974, routine chest film showed asymptomatic bronchogenic carcinoma June 1975 (smoked 2 packs cigarettes daily for years); lobectomy June 1975; excellent recovery; alive & well February 1976, almost 64 yrs. after onset
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TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
OR COMBINED WITH SURGERY AND/OR RADIATION THERAPY (con'd)

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
42. W.B. Coley (22; 40)	F. 30 Mrs F.	inoperable malignant giant cell tumor lt. ilium; onset April 1908, 2 mos. after bad fall on ice striking buttock & ilium; very severe often excruciating pain, markedly emaciated, anemic, bedridden; 3 sinuses near sacroiliac up to 15 cm. deep, kept open by catheter; leg could not be extended	Spring 1908 operation by McCosh; sinus persisted; x-ray post-operatively; June 1909, radium by Abbe for recurrence in large doses (2300 mch), continued during 1910 in Paris; radium tubes inserted in tumor; tendency to toxemia much increased after radium (largest dose ever used); pain very severe requiring large doses morphine	early September 1911, large incision made, 8 oz. necrotic tumor curetted, very severe hemorrhage; 18 cm. cavity packed with gauze; late January 1912 sinuses again enlarged under ether; much necrotic tissue evacuated with some trabeculae, free drainage established no viable tumor seen; further severe toxemia April 1912 required 3rd operation to reestablish drainage, large part of sacrum also involved making drainage, very difficult	1908-1910 sinus became blocked occasionally causing septic fever; early 1911 large swelling over whole dorsal ilium above trochanter extending to crest, finally broke into old sinuses, about a litre of purulent material drained; temperature 101°F by April 1911; Coley toxins (Tracy XI) May 2, 1911; afebrile next day, remained so for several wks. except during reactions to toxins; injections given 4 mos. stopped early Sept. 1911	both local & general improvement apparent very soon after toxins begun, continued steadily, very striking during July 1911 gained weight; in 3 mos. only 1 sinus remained, tumor continued to decrease in size, then began to break down more rapidly than possible for it to drain, causing toxemia from absorption Sept. 1911; rapid recovery after evacuation of tissue, condition improved, gained 20 lbs.; late January 1912 sinuses again became blocked; April 1912 more severe attack toxemia, pain again severe requiring morphine, condition serious; began to improve June 1912, sinuses gradually healed, pain ceased, gained 30 lbs. <i>complete regression by November 1912; in excellent health, regained erect posture; well 5 yrs. then died of what was considered as abdominal &amp; pelvic metastases but which is now regarded as osteogenic sarcoma arising in the heavily irradiated pelvic bones</i>

43. W.B. Coley (11; 33; 40; 54; 58; 68)	F 32 (L.T.)	extensive inoperable giant cell tumor sacrum, paralysis rt. leg; (had received x-ray to ovaries for obesity 1924, causing radiation menopause, also dieted, took thyroid); weighed 185 lbs. 1926); bad fall down iron stairs, caused severe back injury 18 mos. prior to onset; late April 1928, following a cold, onset sudden pain in rt. leg, regarded as sciatica; by October 1928 pain very severe, 90 lb. weight loss; by January 1929 shadows in both lung roots, the left suggesting a mass; pain excruciating	2 epidural injections novocaine caused increased pain; massage, passive exercise diathermy for 7 wks.; no improvement; October 12, 1928 explored at Lenox Hill Hospital; several pieces of tumor curetted for biopsy	October 16-23, December 18-24, 1928 x-ray to sacrum: 5 anteriorly, posteriorly, laterally, 7 to rt. pelvis; severe radiation sickness, nausea, complete anorexia: "subsisted on small quantities of caviar and little else for some time"; January 15-21, 1929: 4 radium packs (30,000 mch)	Coley toxins (P.D. XIII) October 15, 1928, 3 days after surgery; 11 subcut. in 15 days, 7 caused reactions (to 106°F.), 5 caused chills, some severe (at Lenox Hill Hosp.) referred to Coley January 7, 1929 in excruciating pain; toxins resumed, i.m. & i.v., reactions to 104°F.; not given during radium, resumed January 21, 1929: every other day for 6 wks.	18 days after toxins begun x-rays showed some filling of involved area especially at superior margin; no further regeneration seen December 21, 1928, had lost 10 more lbs.; by January 9, 1929 shadows in both lung roots; 3 wks. after Coley began more aggressive toxin therapy, pain began to ameliorate, then gradually subsided; 2 wks. later began to walk (had not done so for 7 mos.), gained 50 lbs in 3 mos. complete regression, bone regenerated, lungs cleared; no further evidence disease; resumed work as actress; in excellent health; 1939-40: nervous breakdown, severe neurodermatitis (cleared after 16 sulphur baths); September 1961, severe coronary thrombosis, hospitalized several wks., weight declined to 120 lbs; death May 27, 1963, chronic cholecystitis, diabetes mellitus, arteriosclerotic heart disease, 35 yrs. after onset
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TABLE 1, SERIES A: GIANT CELL TUMOR SUCCESSFULLY TREATED BY IMMUNOTHERAPY ALONE  
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Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate & Final Result; Years Traced After Onset
MAXILLAE, 4 Cases (Note: two other maxillary cases were excluded as they were primary operable benign lesions which could have recovered from surgery alone)						
44. Leavy & Whitley (11; 22; 40)	F. 19 (E.W.)	inoperable giant cell tumor superior maxilla, involving frontal sinuses, ethmoid, posterior orbit: "abundant spindle cells with hyperchromatic nuclei, prognosis guarded"; date of onset not recorded	November 1911 incomplete removal: posterior wall of orbit soft & destroyed, frontal brain exposed; much of tumor remained	none	Coley toxins (Tracy XI) begun immediately after surgery, given into tumor & gluteal region maximum dose i.t. 6 minims. i.m., 20 m.	remains of growth regressed completely, partly by sloughing, partly by absorption; lost 25-30 lbs during first part of treatment, after 2 mos. began to gain (30 lbs); all symptoms of brain involvement ceased; in perfect health, married, had 2 or 3 children; last traced 1931, 20 yrs. after surgery, in best of health
45. W.B. Coley (7; 11; 40; 68)	F. 16 (M.D.)	recurrent giant cell tumor lt. inferior maxilla: "much spindle cell tissue"; (Ewing regarded it as malignant osteogenic sarcoma of type seen in jaw); onset January 1917 after having had tooth capped	cap removed, replaced, tooth finally extracted; swelling then noted, rapid increase in size; April 1917, inferior maxilla resected from symphysis to 2½ cm. beyond angle leaving only skin, subcut. tissues of cheek	radium packs October 1917 (18,000 mch); explored November 28, 1917; inoperable, so radium inserted in mass; pain, swelling increased; necrotic tumor & pus evacuated; radium January 18, 19, 1918 (1,932 & 8,400 mch)	Coley toxins (Tracy XI) June 11, 1917 about 8 wks. after surgery for 5 wks.; resumed mid-December 1917, some i.t. some i.m., maximum reaction 104°F., 63 in 3 mos.	recurrence October 1917, 3 × 3 cm. in posterior end of scar; complete regression, excellent function (speech, swallowing), in excellent health; married 1928, never pregnant; basal cell carcinoma bridge of nose excised 1947; coronary thrombosis January 1948; curettage for hyperplastic endometrium April 1948; castration dose radium, August 1948; January 1953, x-ray (3) for thyroiditis; 1954, capsular cataract rt. eye, also changes in lt. eye; atrophic skin on tip of shoulder frequently ulcerated; excised 1957; atrophic lateral sclerosis, downhill course, death April 1962, 45 yrs. after onset

46. W.B. Coley Nicholson (11; 40; 68)	F. 16 (W.P.)	inoperable 3 times recurrent giant cell tumor rt. superior maxilla; (Ewing regarded it as a fibrosarcoma); onset August 1918, rt. check swelled, gradual occlusion rt. naris; 20-30 lb. wt. loss spring 1920; (inner wall of deep cavity lined by nodular 3rd recurrence when 1st seen by Colley)	March 18, 1919 rt. superior maxilla resected, disease very extensive, 2 cm. sinus remained in roof of mouth, recurrence removed 8 mos. later (knife, curette, cautery); again rapidly recurred; 3rd operation January 1920; radium inserted March 5, 1920, increased swelling of face, slight earache	none	fever to 102.4°F. for 2-3 wks. after radium; Coley toxins (Tracy XI) April 21, 1920, daily; reactions to 103°F., chills; injections continued for several mos. in deltoid muscles; reactions 102°-103°F.	cavity clean 9 days after toxins were begun; lost another 9 lbs; all recurrent growths sloughed off, complete regression; gained 20 lbs; no further recurrence; in very good health working steadily 1976, 57½ yrs. after onset
47. Johnston (11; 40)	M. 18 (C.F.B.)	extensive inoperable giant cell tumor inferior maxilla; onset January 1928, after 2 teeth extracted; (to see if they had caused the swelling); in 2 mos. lower face frightfully deformed due to tumor mass; severe pain, morphia for wks. rectal feeding; 80 lb. wt. loss (also had Recklinghausen's disease)	incisional biopsy; radium to gum (1,200 mch.); severe radio-necrosis caused all but 4 lower teeth to fall out	none	Coley toxins (Parke Davis XIII) every other day for 2 mos., marked reactions	tumor became necrotic after toxins were begun, small pieces sloughed, general condition improved rapidly; <i>complete regression in</i> <i>3½ mos.</i> leaving jaw flat, sinus in mouth persisted a yr.; no recurrence; in good health; neurofibromas on torso; 15 excised 1920-1944; married, 3 normal children 1942-49; injured rt. knee early 1944; bone cyst distal femur removed April 1944; in excellent health 13½ yrs.; 1960: thoracotomy for lesion in lung, excised; neurofibroma; severe pain at site of wound persisted; psychiatric problems; death December 29; 1972, 47 yrs. after onset



**DETAILED HISTORIES, SERIES A: SUCCESSES**  
**6 CASES SELECTED AS BEING OF SPECIAL SIGNIFICANCE**

**CASE 8:** Inoperable very extensive giant cell tumor of the femur, confirmed by clinical and x-ray examination at Memorial Hospital, New York. X-rays taken on admission to Memorial Hospital showed complete destruction of the bone, including the neck, the trochanter and the upper 13 cm. of the shaft of the femur, as well as what was believed to be pulmonary metastases. (For photographs of the patient and roentgenograms, see 27, Fig. 19-21, or 32, Fig. 14-16.)

**PREVIOUS HISTORY:** R.H., male, age 36, of Bridgeport, Conn. The family history was negative for malignancy, tuberculosis or specific disease. The patient had been entirely well until he fell on the ice on January 27, 1917, sustaining an oblique fracture of the left femur, just below the trochanter. At this time x-ray examination showed no evidence of a pathological condition. The patient remained in St. Vincent's Hospital, Bridgeport, for about 20 weeks. After several complaints about the length of time he was being hospitalized, a brace was ordered, and the patient was allowed to go home on crutches. About eight months after his discharge, the thigh began to swell considerably. The patient was again seen by the local physician, who stated that he was either exercising the limb too much or not enough. This disgusted the patient and he then consulted Dr. Herman Fischer at Lenox Hill Hospital, New York. X-ray examination at this time showed a tumor which was considered inoperable, the condition being regarded as hopeless. The patient was then referred to Dr. William B. Coley. Physical examination on admission to Memorial Hospital October 20, 1917, revealed a huge tumor occupying two-thirds of the shaft of the left femur. The circumference of the inner portion of the affected thigh was  $17\frac{1}{2}$  cm. larger than the normal limb, and longitudinally the tumor extended for a distance of 17 cm. X-ray examination at this time showed a pathological fracture and almost complete destruction of the bone including the neck, and trochanter and the proximal 13 cm. of the shaft. The condition was regarded as entirely beyond hip-joint amputation by several surgeons at Lenox Hill Hospital, as well as those on the Bone Service at Memorial Hospital.

**TOXIN THERAPY (Tracy XI):** Injections were begun on October 30, 1917, and were continued three or four times a week, alternating intramuscular injections with those made locally into the growth. Severe reactions were produced. The maximum dose injected directly into the tumor was  $\frac{3}{4}$  minim, the maximum remote from the tumor intramuscularly was  $4\frac{1}{2}$  minims

**RADIATION:** The radium pack was applied on November 5 and 6, totalling about 40,000 mch. at 10 cm. distance. By December 10, the circumference of the thigh



## SERIES A: SUCCESSES, SELECTED DETAILED HISTORIES

had diminished 4 cm., and there was some union of the pathological fracture. The radium pack was again applied on December 25, 1917, 8,300 mch. each over two areas.

**FURTHER TOXIN THERAPY:** The toxin injections were then continued without further radiation during the winter and spring, until June 23, 1918, a total of over 7½ months. Coley stated that the entire staff at Memorial Hospital pronounced this a malignant tumor and during the prolonged treatment criticized him for keeping the hospital bed occupied for so long by a "hopeless case". By June 1918 the circumference of the affected limb had decreased 8 cm., although there was still marked mobility at the site of the pathological fracture.

**CLINICAL COURSE:** Improvement continued steadily during the months following cessation of treatment. On October 8, 1918, the patient was re-examined at Memorial Hospital. At this time the general health was good. Physical examination showed complete disappearance of the extensive tumor of the femur, but there was 14 cm. shortening. The circumference of the limb at the level where the tumor had been was still 9½ cm. larger than the other leg. X-ray films taken at this time showed no evidence of tumor remaining. The proximal portion of the femur had been drawn upward to the region of the trochanter, and there was an attempt at union due to formation of new bone. X-ray examination of the chest was negative. The patient continued to wear a Thomas splint until 1919. He was kept under frequent observation during the fall and winter of 1918-1919. On February 24, 1925, Fischer wrote Coley regarding this case: "Our friend H. is surely one of the most remarkable cases that I have ever seen treated by you. If I had not seen the result you obtained with my own eyes, I am afraid I would still be among the number of doubting Thomases." The patient remained in excellent condition and was presented before the Clinical Congress of Surgeons in October 1925. At this time Coley stated that he was able to walk without a crutch or cane. He wore an orthopedic shoe due to the marked shortening caused by the complete destruction of bone which occurred during his illness. In the spring of 1926 he had double vision in his right eye, and in the spring of 1948 in his left eye. This was corrected by glasses. In 1929 the patient was in an automobile accident in which this same leg was fractured below the knee. In three months he was able to return to work, and he continued to work until the early summer of 1949. He reported in November 1949 that since the previous spring he had had trouble with his *right* leg. This limb, being almost 12.5 longer, had borne most of the patient's weight for 32 years. The family physician stated that there was very little fluid in the joint and that the cartilages were brittle and dry. This caused a good deal of pain, especially when bending the knee, so the patient had to give up work. He reported on October 30, 1950, that the condition of the right knee remained unchanged, and was causing pain and discomfort. At the family physician's suggestion, the patient kept off his feet as much as possible, only taking a little walk each day, wearing his orthopedic shoe and using a cane. At this time he was given diathermy and massage by Dr. Arthur S. Griswold of Bridgeport, Conn. He reported in October 1951 that the trouble in the right knee had disappeared, and

he was feeling "pretty good", his only complaint being that he was approaching 70 years of age. In 1954 he moved to Florida to avoid the northern winters. In March 1955, a "sore spot" appeared on the left leg between the hip and the knee. Dr. Irvin S. Leinbach of St. Petersburg, Florida, found that the "bed sore" had developed in the area which had been treated by radium 38 years previously. This sinus was about 1.5 cm. deep and 1.5 cm wide, and there appeared to be a pus pocket beneath it. By May 31, 1955, the sinus was getting smaller but it had not healed. It healed during the summer, about six months after it developed. In the spring of 1955 the patient developed a hernia, requiring a truss and early in 1957 an operation. He remained in reasonably good health except for some arthritis and arterosclerosis. He retired to a rest home in North Carolina where he died at the age of 83 on June 27, 1963, 45 years after onset. Death was due to a kidney condition with uremia and a coronary. There was never any evidence of recurrence of his giant cell tumor.

**COMMENT:** It should be emphasized that alternate intratumoral and intramuscular injections remote from the tumor were given in this case, which appears to be an effective technique, and they were continued steadily for a considerable period. A comparison with other cases of extensive osteolytic tumors with pathological fracture indicates that if the affected limb is placed under traction at the beginning of toxin therapy and kept there until complete union and healing has taken place, there may be no shortening of the limb, with its resulting inconveniences. (For an example, see the case of Carl K., Male, age 32, also a giant cell tumor of the femur, treated in September 1929 with Type XIII toxins. In that case there was complete destruction of the acetabulum and 10 cm. of the adjacent ilium, the femoral neck and part of the giant trochanter. The patient was kept in a plaster cast, and later a walking caliper splint. There was continuous regeneration of destroyed bone, including a new head and neck of the femur, and the patient regained very good function with surprisingly little shortening. See next case)

**REFERENCES:** 7; 11; 27; 32; 40; 54; 68

**CASE 13:** Extensive inoperable giant cell tumor of the proximal femur, involving the neck and both the greater and lesser trochanters, with complete destruction of the acetabulum and portions of the adjacent ilium and ischium. Dr. William B. Coley stated that the clinical evidence and the x-rays pointed to its being a malignant bone tumor. Following microscopic examination, the Bone Sarcoma Registry Committee and Dr. Fred W. Stewart classified it as a benign giant cell tumor.



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**PREVIOUS HISTORY:** C.K., male, aged 32. The patient's mother had died of cancer of uterus. The patient struck his femur against the corner of a desk in January 1929. Severe pain was felt in the region of the greater trochanter for several days. This gradually subsided and he was able to walk without any difficulty. Onset, in May 1929, the pain returned and was felt especially when making the first few steps. The patient then had a similar injury to the same site, resulting in increased pain and lameness. A chiropractor was consulted, who made a diagnosis of sciatic rheumatism. After several treatments the leg began feeling a little better. In August 1929 the patient drove his car to New Hampshire and back for his vacation. There was increased pain following this trip, and a physician was consulted who referred him to Dr. Armitage Whitman. He was admitted to the Hospital for Special Surgery in September 1929. Clinical and x-ray examinations revealed a tumor of the proximal femur involving the neck and part of the greater trochanter, of such rapid development as to suggest a malignant type. In view of its location it was regarded as inoperable, and the patient was referred to Dr. William B. Coley for toxin therapy. There was no evidence of metastases seen in the film of the lungs taken September 27, 1929, but a large area of destruction was noted in the neck of the right femur. The hip was almost ankylosed, it being impossible to move it without moving the pelvis. Adduction and abduction were almost absent. The patient was transferred to Memorial Hospital.

**RADIATION:** Between September 25 and October 5 a total of 40,000 mch. of radium in the form of a pack was applied over two aspects of the hip, anterior and posterior, at 10 cm. distance.

**TOXIN THERAPY (*Parke Davis XIII*):** Injections were begun by Coley on September 28, 1929, three days after the first radium treatment and were given intramuscularly in doses up to  $4\frac{1}{2}$  minims, and intravenously in doses of  $1/60$  minim. The maximum febrile reaction was  $103.5^{\circ}\text{F}$ . A total of nine were given in the first 20 days. On October 18, 1929, the patient had a severe chill following an intravenous injection, during which a pathologic fracture of the neck of the femur occurred.

**CLINICAL COURSE:** The patient was then transferred to the Hospital for Special Surgery, where Whitman applied a plaster spica.

**FURTHER TOXIN THERAPY:** Injections were resumed on November 11, 1929, after a lapse of 23 days, and during the next 80 days 34 were given, 12 intramuscularly (maximum dose  $3\frac{1}{2}$  minims), and 22 intravenously (maximum dose  $1\frac{1}{2}$  minims). The maximum febrile reaction was  $103^{\circ}\text{F}$ . X-ray examination at the end of this course of toxin therapy, January 30, 1930, was reported as follows: "Extensive destruction of the lower two-thirds of the femoral head, and apparent almost complete absence of the femoral neck, with a marked upward displacement of the shaft and the trochanters, the greater trochanter reaching well above the upper margin of the acetabulum. The appearance differed from the characteristic ap-



pearance found late after a fracture of the femoral neck, in the amount of the destruction of the femoral head. This usually remains intact in cases of fracture.” (54)

CLINICAL COURSE: The patient was kept in a plaster spica for 13 weeks, after which he was fitted with a walking caliper splint. With this he was able to get about quite well and after a month's rest he resumed work. During the summer of 1930 he discarded the crutches and walked with a cane. He had several bad falls going back and forth to work. He was a commercial artist, and once he got to work he could sit all day. Films taken April 13, 1931, showed what Lewis interpreted as either active giant cell tumor or osteitis fibrosa cystica. The patient's general health was good.

RADIATION: At this time the radium pack was again applied, (6 cm. distance, 9,000 mch.).

CLINICAL COURSE: In the latter part of June 1931, the leg began feeling worse again and the patient made arrangements to return to Memorial Hospital. The day he was to be admitted another pathological fracture occurred. (This patient had three pathological fractures in the course of his illness.) An aspiration biopsy was performed at this time by Dr. Bradley L. Coley. The tissue was examined by Dr. Fred Stewart, Pathologist of Memorial Hospital, who pronounced it benign giant cell tumor of bone. Roentgenological examination at this time revealed that the proximal end of the femur, the greater and lesser trochanters, the head of the femur, the acetabulum, portions of the ilium and ischium adjacent, were involved in a destructive process which appeared to be a giant cell tumor. The condition was entirely inoperable.

FURTHER RADIATION: During July and August 1931 a total of 54,000 mch. of radium was applied in the form of a pack, at 10 cm. distance over the anterior and lateral aspects of the hip. The patient also received three exposures of high voltage x-ray (750 r.) over the left pelvis anteriorly and the right pelvis posteriorly.

FURTHER TOXIN THERAPY (*Parke Davis XIII*): Injections were resumed about July 1, 1931, and 41 were given in the next five months. During October 1931 intravenous injections were given, but the dosage and frequency are not recorded. The patient remained in the Memorial Hospital from July 6 until December 24, 1931, and during almost this entire period traction was applied to the leg by moleskin straps, using 15 pounds weight. This was done to prevent the contraction of the muscles from producing marked shortening, owing to the extensive areas of the destroyed bone in the proximal femur. There was little or no improvement during the first four months of treatment, but from about November 1, 1931, the condition improved rapidly and on December 24, 1931, the patient was dis-

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charged walking well with crutches. (It is of interest to note that the improvement occurred following the intravenous injections of the toxins.)

**CLINICAL COURSE:** He resumed work, and frequent physical and roentgenological examinations showed steady improvement. A film made in June 1932 showed the neck of the femur being formed. *Films made during the next year showed continuous regeneration of bone in the pelvis and right femur, with formation of a new head and neck of the femur.* The patient continued to carry on his regular work. He was examined periodically at Memorial Hospital. An x-ray examination in January 1942 showed no interval change: "good repair and no evidence of activity in the right femur." The patient remained in good health from 1931 to December 1944, when he developed a bad sinus condition which persisted all winter. On April 8, 1945, he noticed pain in the right hip area, with some swelling in the right inguinal region, which was thought to be an acute process. He was seen by Dr. Walker E. Swift at Memorial Hospital and advised to use hot compresses, and the symptoms improved. He returned to work about 12 days later, and the symptoms recurred. Swift was again seen and advised radiation, believing the condition was synovitis, or myositis.

**RADIATION:** Three x-ray treatments were given over the right pelvis, beginning on April 26, 1945, and by May 2, 1945, the patient felt much better, except for considerable nausea.

**CLINICAL COURSE:** During the next few months he felt quite well, with only occasional hip pain, especially at night. He was symptom-free, able to work, and in good condition when seen at the Memorial Hospital on October 24, 1945. An x-ray examination at this time showed no alteration in the hip region. He was last seen at the hospital on November 21, 1945. The report stated: "complains of difficulty in getting about and doing his work. He was advised to try out a period of rest. He remained in bed from about December 1, 1945. On January 6, 1946, his wife reported that he had several attacks of "pleurisy with fever" in the previous six weeks, but that the pain in his hip was easing up somewhat, due perhaps to rest in bed. He died on February 19, 1946, having been bedridden for about three months. X-ray examination of his chest prior to death showed widespread metastases, but views of the upper end of the right femur showed no evidence of disease. No post-mortem examination was made. Death occurred over 18 years after onset.

**COMMENT:** In reporting this case in 1936, Coley stated that he did not know of any other case of giant cell tumor of such extensive involvement that recovered under treatment, adding that the condition had been regarded as hopeless by many of the surgeons who had seen him before treatment was begun. The period of disability in this case was considerably longer than in those in which the toxins were used steadily for a longer period without heavy radiation. This case indicates



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the danger of allowing a patient with such an extensive process to return to work too soon, since further injuries may thus occur to the affected area. This patient had several falls which were severe, and these may have stimulated the growth rate of the tumor, which was regressing, causing the recurrence in late June 1931. The history suggests tht in these advanced cases where the disease has caused extensive destruction of bone, it is wise to place the limb in a plaster spica *at the beginning of treatment*, to prevent fractures or shortening of the limb during regeneration of normal bone. The tumor which developed in 1945 appears to have been an osteogenic sarcoma arising in the heavily irradiated pelvic bones, causing death from extensive pulmonary metastases (3; 10; 42; 43; 61).

REFERENCES: 7; 11; 37; 39; 40; 54; 68.

**CASE 21:** Highly vascular giant cell tumor of the proximal end of the tibia, confirmed by microscopic examination by Dr. A. E. Halstead, as well as by one of the leading pathologists of Chicago and Dr. R. Le Count of the Department of Pathology at Rush Medical College, who reported: "Myeloid or giant-celled sarcoma, originating from bone . . . very hemorrhagic. There is not only free hemorrhage into sarcomatous tissue, but large blood spaces are very numerous. I should judge this to be from a very rapidly growing tumor. Its malignancy is unquestioned." (81)

**PREVIOUS HISTORY:** Male, age 7. In July 1894, the child fell and sustained a contusion of the knee. The attending lameness was moderate. The great tenderness was located at the proximal end of the tibia. A fixed dressing was used for some weeks, after which the lameness disappeared, and the patient seemed cured. He again fell, resulting in lameness in the same locality. A plaster of Paris dressing was used until several days prior to December 28, 1894, when some tenderness was again observed. By this time, the patient was limping and a swelling existed at the proximal end of the tibia, in front and on each side in close relation with the epiphyseal line. The swelling was moderately diffuse and very tender, particularly in one spot, with less marked soreness in other parts. The periosteum seemed to be involved; the range of flexion was slightly diminished and extension was weak. When the ligamentum patellae was put upon the stretch by muscular action, pain resulted at the site of the swelling. The condition was regarded as periostitis. Application of actual cautery to the skin, with light plaster of Paris dressing was recommended. The patient was advised to remain in bed a month, with a window cut in the cast for observation. On March 25, 1895 the patient again came under observation. He had been up and about previous to this date. There had been no fever at any time.



**SURGERY:** An exploratory operation on March 28, 1895 showed that the bone was somewhat expanded and its cortical structure was in places as thin as parchment. There were openings here and there, through which a probe readily passed into the medullary cavity, which was much enlarged and filled with a material closely resembling liver in color and consistency, covered here and there with material analogous to old caco-plastic lymph. This was free from odor. There was no evidence of decomposition, and there was absence of temperature. The material was curetted, leaving a cavity 11.5 cm. long and the width of the bone. The cavity was packed with iodoform gauze and, except for two or more stitches in the upper and lower ends, the wound was left open. The leg was dressed in the usual way and a light plaster of Paris splint applied as a precaution. At this time Dr. John E. Owens stated: "Several questions now presented themselves to me—(1) whether I should amputate the leg and then use mixed toxins to prevent, if possible, a recurrence of the disease; or (2) to begin at once with the toxins with the view of eradicating the disease, and thus saving both the leg and the patient's life. So much had been accomplished in the inoperable cases of sarcoma by the method under consideration, it occurred to me that by the use of the toxins this operable case might be brought to a successful issue, in other words, that both leg and life might be saved." (81)

**TOXIN THERAPY (Buxton VI):** Injections of Coley toxins were begun on April 10, 1895, the initial dose being  $\frac{1}{2}$  minim. During the next 13 days, 8 were given subcutaneously, the dose being increased to 2 minims. By April 23, 1895, a mass of granulation tissue had sprung out from the sides of the cavity in the bone. Injections were made into this tissue without pain, from April 23 to May 24, 1895: 31 injections in 34 days, in doses of 1 to 3 minims. Around June 1, 1895 the leg became swollen, and temperature, restlessness and pain supervened. Drainage was established, and the cavity packed with iodoform gauze, after which the patient was much improved. From June 2 to July 10, 1895 (38 days), 24 injections were made in doses of 1 to 7 minims. On June 12, the outer side of the leg was selected for the injections, local anesthesia being employed. The total duration of toxin therapy was three months.

In discussing the reactions caused by the treatment, Owens stated: "On April 10, after  $\frac{1}{2}$  minim, first dose, there was elevation of temperature, increased frequency of pulse, some headache, chilly sensation. On the 11th marked efflorescence was observed on the right side of the leg, less on the other; glands at saphenous opening were somewhat enlarged and slightly tender; patient comfortable and with good appetite; efflorescence extended from puncture made by hypodermic syringe . . . April 18, local irritation much diminished; increased frequency of urination. April 21, local reaction diffused, covering almost the whole circumference of the leg and extending longitudinally five inches. Swelling of soft parts quite apparent. April 23, a mass of granulation tissue had now grown out of the sides of the cavity in the bone, and into this many of the injections were

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painlessly used. Drowsiness, thirst, nausea, vomiting and headache were common reaction symptoms. April 27, considerable discharge from the wound was observed, but no pus at any time. Chill lasting 20 minutes followed injection; temperature reached 100.8°F. during the morning; fell to normal in the afternoon. Patient out for two hours in wheel chair. At the beginning of the chill. . . and following other doses not causing a chill, frequency of urination was a noticeable symptom. The urine on these occasions and for a few hours afterward was quite offensive. May 4, outdoors all morning. May 7, feels nauseated, complains of his cheeks aching. The latter was not an uncommon symptom. May 9, pallor, yawning, nausea; pulse 130, temperature 102.8°, went out in wheel chair part of the afternoon. May 12, maximum temperature 101.8°F.; pain in leg, which was slightly swollen and red at site of wound; severe chill; did not sleep or regain his natural brightness until bedtime. May 13, wound (which) had been previously packed with iodoform gauze . . . had so much filled in that the packing was no longer necessary . . . " (81)(It is probably that healing would have been more rapid had no packing been used at any time).

"Owing to local disturbance above referred to, the injections were omitted from May 27th to June 2nd. June 3rd the toxins were renewed. Maximum temperature . . . 105°F.; severe chill, pain in head and cheeks; skin somewhat hot; a little delirium; slept two or three hours; awoke free from delirium. Local anaesthesia employed, as injections were now used under the skin. June 11, very little reaction; maximum temperature 99.2°F., but patient felt cool and skin was moist. . . From June 12th to 18th, reaction slight. June 18 maximum temperature 100°F., pulse 112, felt a little chilly; skin cool and moist; more than half the circumference of the leg reddened. June 24 wounds made by operation perfectly healed. Some times healing went on rapidly, and at other times very slowly. Injections of toxins into the mass of granulations did not seem to spoil the granulations or to retard the healing. June 23, maximum temperature 103.6°F., pulse 128; dizzy, headache, yawning, chilliness, drowsiness, faintness, vomiting, restlessness; better in the evening; called for food" (81). Patient had been walking with the aid of crutches. Little or no reaction from June 25 until July 10, after which date the toxins were discontinued. Owens allowed the patient to return home as from the favorable condition of the leg he believed that "recovery had practically taken place." However, he informed the parents that the boy should be kept under observation so that toxins could be resumed, should symptoms of recurrence develop. The patient was therefore examined a few times between July 10 and November 16, 1895, when Owens found the scar somewhat elevated, moderately tense and shiny, and the part beneath the scar somewhat elastic on pressure. He was unable to determine whether these indicated a return of the sarcoma, or whether it was a result of the various contusions which the leg and the part referred to had received while at play. Owens stated: "Patient was noted for his activity, on which he exercised little or no restraint out of doors, and the limb had consequently been injured a number of times." The parents were advised to



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resume the toxins for a month as a precautionary measure, but this advice was not taken at this time.

**SUMMARY OF TOXIN THERAPY:** 63 injections in 91 days, maximum dose 7 minims; maximum temperature 105°F. (on only one occasion, after injections had been suspended for five days); maximum pulse 132. Owens stated: "It will be observed that the chief symptoms that supervene after an injection of the mixed toxins are those which usher in an attack of erysipelas, such as malaise, nausea, and sometimes frequency of pulse and chill." He added: "Under the use of the toxins, the patient's general health had very much improved. His sleep, which at first was very much disturbed, was all that could be desired, unless, as occasionally happened, the reaction symptoms were prolonged to the early hours of the night."

**CLINICAL COURSE:** The patient recovered completely. He was examined from time to time and was reported in good health when last traced 18 years later. Dr. Wm.B. Coley stated in 1936 that he believed this was the first example of giant cell tumor of a long bone successfully treated conservatively. At the time this patient was treated and for many years thereafter, amputation was the method universally employed for giant cell tumors as well as for malignant tumors of bone.

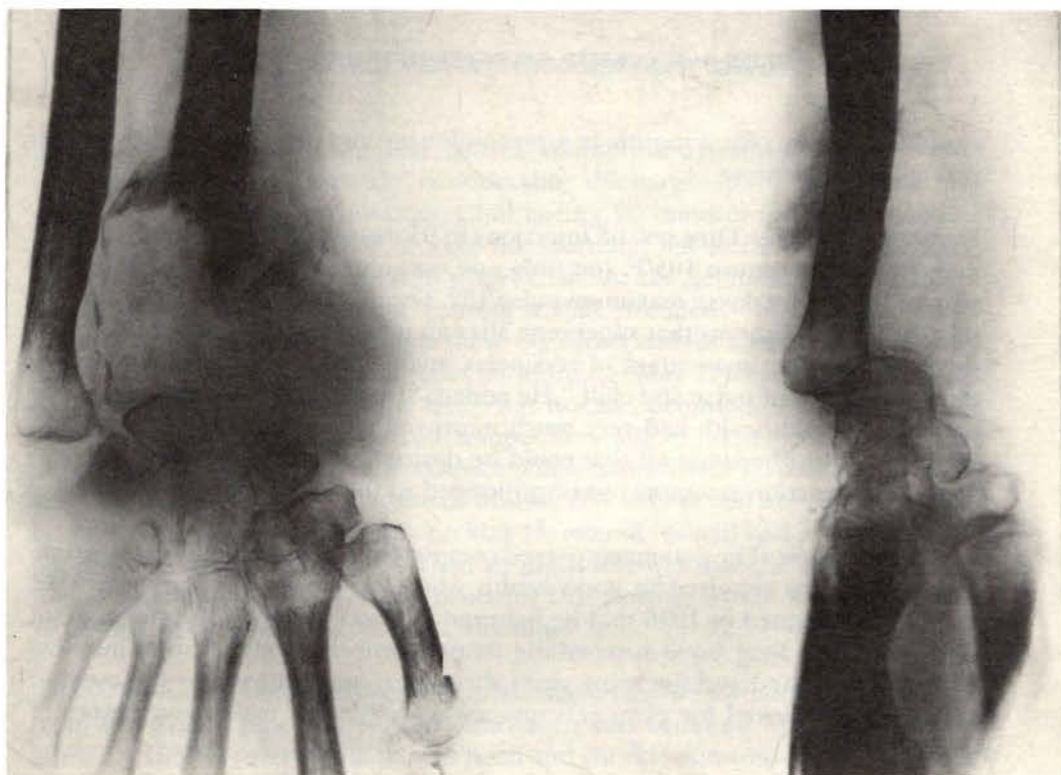
**REFERENCES:** 22; 39; 81.

**CASE 36:** Extensive giant cell tumor of the distal left radius involving the ulna. No exploratory operation was made, as the x-ray and clinical diagnoses were so positive. (For photographs, see Fig. 1-6).

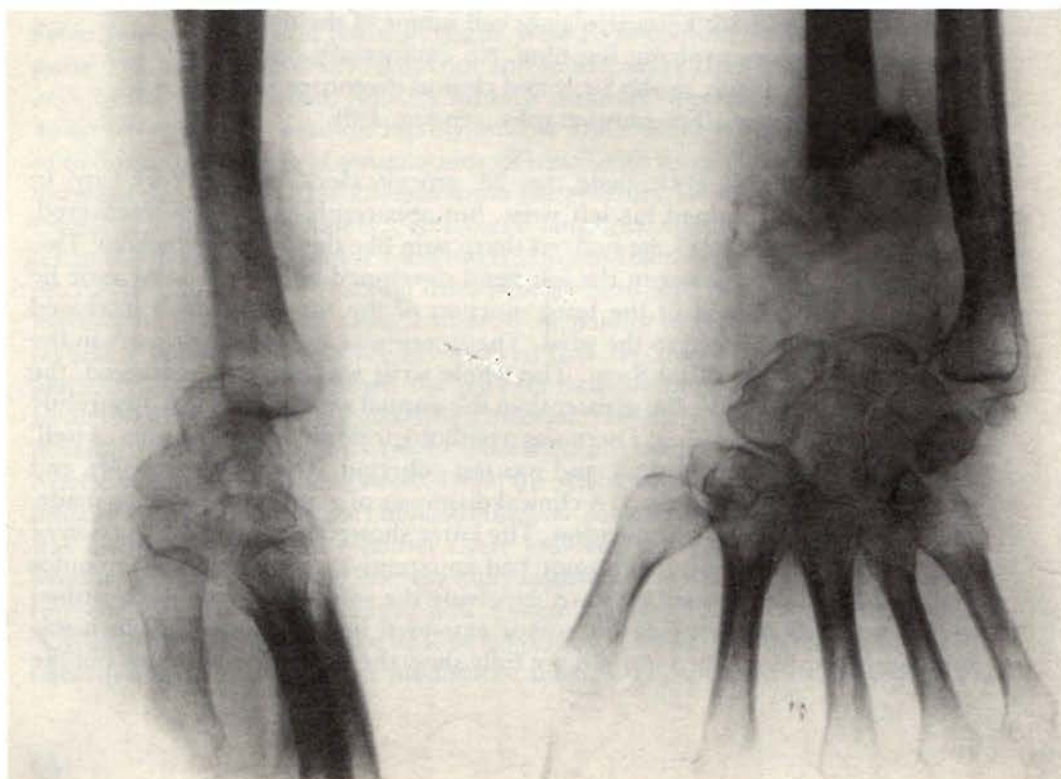
**PREVIOUS HISTORY:** L. D'G., male, age 28, grocery clerk, of New York City. In 1909 the patient sprained his left wrist, but apparently completely recovered. Onset, in November 1917, he noticed sharp pain like the prick of a needle. Two months later loss of power in the left hand developed and at the same time he noticed an enlargement of the lower portion of the forearm, which increased steadily, extending down to the wrist. The tumor was apparently primary in the radius, involving the distal 8 cm. The whole wrist was markedly enlarged, the circumference being 6½ cm. greater than the normal wrist. There was apparently some thickening of the ulna. There was a pathological fracture of the ulna as well. The overlying skin was normal, and was not adherent. The tumor was soft, and semi-fluctuating in consistency. A clinical diagnosis of giant cell tumor was made, and confirmed by x-ray examination. The latter showed complete destruction of over 5 cm. of the radius. The tumor had apparently broken through the outer shell of bone and extended outward, involving the soft parts which were pushed to one side. On the left side the tumor extended beyond the ulna, which was apparently involved. The x-ray did not fully show the damage to the ulna, but the



**SERIES A, CASE 36.**

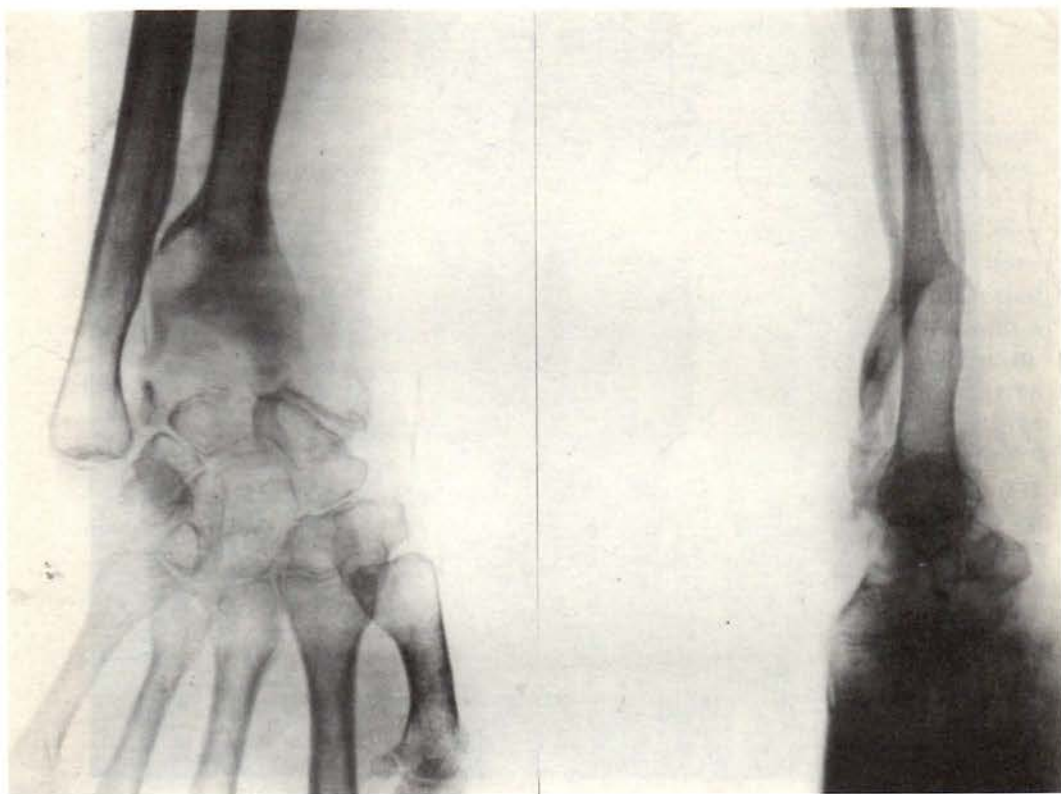


**FIGURE 1. JUNE 1, 1918, 5 WEEKS AFTER TOXINS WERE BEGUN.**

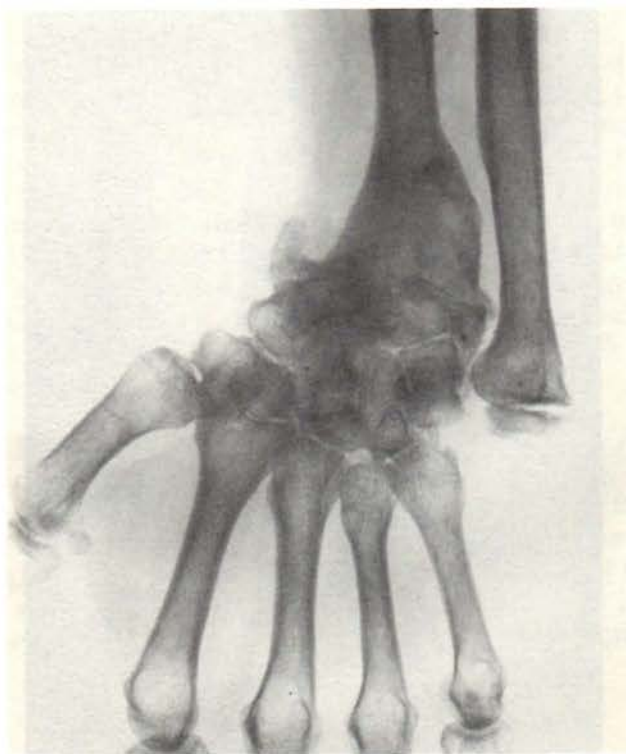


**FIGURE 2. 2 WEEKS LATER.**

**SERIES A, CASE 36.**



**FIGURE 3. JANUARY 31, 1919, 9 MONTHS AFTER TOXINS WERE BEGUN.**

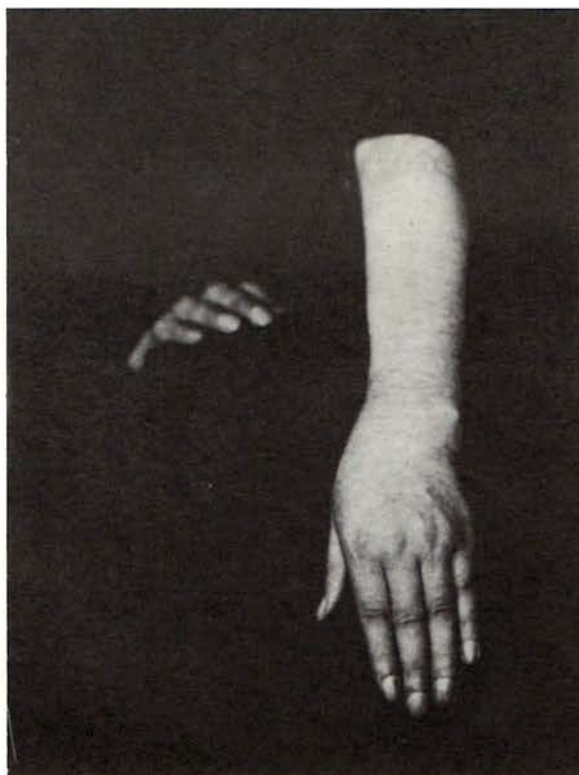


**FIGURE 4. NOVEMBER 1928 (NO OTHER THERAPY).**

**SERIES A, CASE 36.**



**FIGURE 5. MAY 4, 1918, 9 DAYS AFTER FIRST INJECTION.**



**FIGURE 6. NOVEMBER 1928, 11 YEARS AFTER ONSET.**



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clinical examination showed almost complete pathological fracture. Amputation had been advised, and the patient was willing to sacrifice the arm if necessary.

**TOXIN THERAPY (*Tracy XI*):** Before resorting to amputation, Dr. Wm.B. Coley tried conservative treatment. Beginning April 25, 1918, intramuscular injections were used with the exception of a single dose of  $\frac{1}{8}$  minim which was injected directly into the tumor. The latter was followed by a marked reaction, with a temperature of 104°F., nausea, vomiting, and marked herpes labialis. The intramuscular injections did not produce any marked chill or severe febrile reaction until the dose had been increased to six minims. During the first two or three weeks, very little improvement was evident, and in the early part of June when Coley was out of town for a week, his associate, Dr. Joseph Hoguet, came very near to amputating the arm, believing that there was little or no hope of saving it by conservative treatment. Coley had intended to use radium as well as toxins in this case, but when he returned on June 10, 1918, there was considerable improvement, so he decided not to use the radium, and the toxin injections were kept up regularly every other day, in doses sufficient to produce a febrile reaction of 102° to 104°F. By the end of June, the swelling had nearly disappeared, and by the end of July it had entirely disappeared. The arm was kept in splints during the early part of the treatment and later, after the tumor had regressed, it was kept in plaster of Paris cast with the hand in an abducted position, to avoid deformity while the new bone was forming. The patient was discharged from the hospital and the injections were continued two or three times a week until the end of January 1919, a duration of nine months.

**CLINICAL COURSE:** Frequent roentgenological examinations were made of the wrist, and these showed gradual increase in new bone taking the place of the 8 cm. of the radius and portions of the ulna which had been completely destroyed by the tumor. The patient wore a short palmar splint for six months. The new bone which had replaced the lower end of the radius did not become entirely solid until the spring of 1919. However, the patient was able to use the arm from January 1919, doing his regular work as a grocer with normal function and little deformity. He was presented by Coley at the Clinical Congress of Surgeons, October 23, 1919. Further x-rays were taken in 1929 and revealed normal bone. The patient remained in perfect health in September 1942, 25 years after onset. Attempts to trace him since have failed.

**COMMENT:** This case indicates that an excellent result may be obtained by toxin therapy alone in giant cell tumor. Note that no improvement was evident until after three weeks' treatment. This is believed to be due to the fact that injections were made intramuscularly (with one exception). It is now known that this technique does not produce as rapid regression as when more of the injections are given in or near the tumor, combined with some intravenous injections. In presenting this case at a Bone Tumor Clinic at Memorial Hospital in September

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1927, Coley stated: "It is worthy of note that this excellent result was obtained with a very short period of disability and without the disadvantages associated with biopsy or the complicated operation of bone grafting advocated by Bloodgood and other surgeons." (34)

REFERENCES: 7; 11; 28; 29; 34; 38.

**CASE 42:** Inoperable recurrent malignant giant cell tumor of the ilium, confirmed by microscopic examinations by Dr. James Ewing, who reported: "It is chiefly of small spindle-cells in which lie many giant cells of the epulis type. There are numerous areas of hemorrhage, and the giant cells are most numerous in these areas. The structure is that of a tumor of moderate malignancy. Its position may render it more serious than if it were in a superficial position." (68)

**PREVIOUS HISTORY:** Mrs. F., female, aged 30. The family history was non-contributory. In February 1908 the patient had a severe fall on the ice striking the left buttock and ilium. Onset, two months later, in April 1908 a tumor developed at the same site.

**SURGERY:** An operation was performed in Chicago by Dr. Andrew J. McCosh at Presbyterian Hospital, and microscopic diagnosis of "giant cell sarcoma" was made.

**RADIATION** X-ray therapy was given post operatively but the tumor recurred and became inoperable. Radium treatment was begun in June 1909 by Dr. Robert Abbe of New York, and continued in large doses during 1910 by Dr. Wickham of Paris. A sinus had persisted since the first operation in 1908, occasionally becoming blocked, causing septic temperature.

**SURGERY:** Openings were made into the tumor and tubes inserted in different places.

**FURTHER RADIATION:** The tendency to toxemia seemed to be greatly aggravated after the application of a large amount of radium (250 mg. used ten hours at one time; "the largest amount which had ever been used on any individual"). The pain, which had been constant from the beginning, became very severe and often excruciating.

**SUPPURATION:** About February 1, 1911, a large swelling formed in the outer aspect of the ilium above the trochanter, extending to the crest and occupying the whole dorsal surface. This finally broke into the old sinuses, and between a pint and



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quart of purulent material escaped. In the latter part of April 1911, when first seen by Dr. William B. Coley, the patient was markedly anemic and considerably emaciated, confined to bed all the time, requiring large doses of morphine to control the pain. Physical examination showed a large swelling in the whole outer aspect of the ilium above the trochanter and extending to the anterior posterior spine. There were three sinuses not far from the sacroiliac synchondrosis. The proximal one was kept open by a rubber catheter 15 cm. deep and packed with gauze. The leg was flexed to an angle of 160°, and could not be fully extended.

**TOXIN THERAPY (*Tracy XI*):** Injections were begun by Coley on May 2, 1911, the initial dose being 0.5 minim, which was gradually increased to 3 minims in three weeks. The patient proved very susceptible to the toxins. At the time treatment was begun she had been running a temperature of 101°F. This dropped to normal within 24 hours and remained so for several weeks, except during the febrile reactions following the toxins. Very soon improvement was noted in both the local and general condition, which continued without interruption. During July the improvement was very striking, and by August 2, 1911, only one sinus was discharging (very small quantity). The tumor was decreasing in size and the general condition of the patient was improved to such an extent that she was able to motor 30 miles. She gained 2½ pounds in weight during the last two weeks of July. The tumor became more and more fluctuating, breaking down more rapidly than it was possible for the necrotic material to escape through the sinus, and early in September there were signs of toxemia from absorption.

**SURGERY:** Coley therefore made a large incision and curetted out about a pint of necrotic material. Only a very little of it was sufficiently organized to permit of microscopical examination, which was made by Ewing (see above). The hemorrhage at operation was very severe and a large cavity the size of two fists was packed with gauze. The patient made a very rapid recovery, and her general condition improved markedly. She gained 20 pounds in weight. The toxins were discontinued early in September for over three months.

**FURTHER TOXIN THERAPY:** Injections were resumed the latter part of December 1911, as it was not thought that the tumor had been entirely absorbed.

**SURGERY:** At the end of January the sinuses again became blocked, and again absorption symptoms set in, which required another operation. The sinuses were enlarged under ether, and considerable necrotic material evacuated with some trabeculae, and free drainage was established. After careful microscopic examination, Ewing reported the material to be "entirely necrotic". A more severe attack of toxemia occurred in April 1912, requiring a third operation to establish drainage. Evidently not only the external part of the ilium was involved but a large part of the sacrum, making it difficult to get good drainage. The general condition of the patient was very greatly affected by the attacks of toxemia, and pain was so



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severe that it required large doses of morphine to control it. Her condition became so desperate that no hope of recovery was entertained. Finally, in June 1912, she began to show slight improvement, and in August improvement became very rapid. The sinuses gradually healed, pain disappeared, and she began to increase in weight. Improvement continued steadily. She gained 30 pounds in weight and in November 1912, no tumor could be found on most careful examination.

**CLINICAL COURSE:** Coley examined her January 10, 1914 and found her in excellent health. No trace of the tumor could be found, the enlarged lymph nodes had disappeared, and she had regained her erect posture and former weight. The patient remained well five years, and then died of symptoms of what was considered as "probable intraabdominal and pelvic metastases." This was approximately 11 years after onset. It is now believed that death may have been due to an osteogenic sarcoma arising in the heavily irradiated pelvic region five years previously.(3; 10; 42; 45; 61.)

**COMMENT:** This case indicates first: the danger of delaying toxin therapy in cases of malignant tumors in this region until the disease is very extensive because the problem of drainage of necrotic tumor may be difficult in this area. A second important point is the effect of heavy preliminary radiation in this case: it not only did not arrest the disease, but it lowered the patient's vitality so that she could not stand aggressive toxin treatment. Also, such heavy radiation produced fibrosis and impairs the vascular and lymphatic channels, thus greatly interfering with the destruction of the tumor by toxins and of absorption of necrotic tumor tissue and regeneration of normal tissues. It is now apparent that if recurrence of metastases develop the injections should be resumed at once, so that the disease may be permanently controlled. Compare this case with the cases of extensive giant cell tumor of the spine or sacrum successfully treated and traced 35 to 64 years later (Table 1, Cases 40, 41, 42). In those three patients the toxins were given more steadily and aggressively and in two of them no radiation was used.

**REFERENCES:** 22; 32; 68.

**CASE 43:** Inoperable giant cell tumor of the sacrum, with paralysis of the right leg, confirmed by microscopic examinations at Lenox Hill Hospital and by Dr. James Ewing at Memorial Hospital, as well as by x-ray examinations at Lenox Hill Hospital and the Hospital for Special Surgery.

**PREVIOUS HISTORY:** Miss L.T., female, age 32, Russian born actress. The family history was negative for malignancy or tuberculosis. The patient had diphtheria in 1917, pneumonia in 1918, but no other serious illnesses. Her general health

had always been good. She was obese, weighing about 200 pounds in 1924, and for this reason she was given x-ray treatments over the ovaries. Thereafter she did not menstruate again. She also dieted and took thyroid but her weight remained around 185 pounds in 1926. About 2½ years prior to onset she fell downstairs back-stage, sustaining a very serious injury to her lower back, in the region of the sacrum. She was unable to walk for six months and thereafter the condition was not entirely normal, and if she walked much there was pain. Onset, in the latter part of April 1928, while recovering from a cold, she suddenly felt acute pain in the right leg. This persisted and in June she was taken to Mt. Sinai Hospital where the condition was diagnosed as sciatica. An epidural injection was given after which the patient stated that the pain was almost unbearable, causing loss of appetite, weight, sleep, etc. The whole right limb became paralyzed and she could not walk at all. After six days at Mt. Sinai Hospital the patient left against the advice of her physicians and returned home, where she remained in bed for ten weeks. During this period massage and passive exercise were tried without improvement. Late in July 1928 a roentgenological examination was made at Mt. Sinai Hospital, at which time the patient was told that she had a "slight inflammation of the vertebrae in the lower spine, that nothing further could be done." Another physician was consulted in late August who suggested diathermy. This was administered for seven weeks and the patient felt a little better but she still was unable to walk and had very severe pain. She then went to Lenox Hill Hospital where the condition was regarded as a neoplasm of the sacrum. Roentgenological examination at this time revealed a lesion of the right sacro-iliac joint, a purely destructive process the size of a hen's egg, involving the lateral process of the sacrum, in which no bony structure could be made out. The growth extended from the spinous processes of the sacrum to the articular margin on the right. There was no evidence of metastases.

**SURGERY:** An exploratory operation was performed at Lenox Hill Hospital on October 12, 1928 through an 8 cm. incision. The posterior aspect of the sacrum was very thin, like a paper shell, and was easily punched in with forceps, revealing pink firm tumor tissue within. Several pieces were curetted for biopsy, and the wound was sutured in layers. The specimen consisted of several hemorrhagic friable pieces of tissue. Sections showed giant cell tumor of the epulis type. The giant cells were large and very numerous and contained many small round nuclei. In localized areas there was a predominance of small chromatic cells of round, oval and spindle form. The tumor was rich in capillary blood vessels and showed many small hemorrhages.

**TOXIN THERAPY (Parke Davis XIII):** Injections were begun on October 15, 1928, at Lenox Hill Hospital and the initial dose was 0.02 cc. Eleven injections were given subcutaneously in the next 15 days, the dose being increased gradually to 0.2 cc. Reactions occurred following all but four of the injections, the maximum being 106°F. There were five chills, some of which were very severe. Roentgeno-



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logical examination of the sacrum on November 3, 1928 showed what appeared to be some filling of the involved area, especially noticeable at the superior margin where the line of bone destruction was not so distinct as previously.

**X-RAY THERAPY:** The patient was given two cycles of x-ray treatments, the first being from October 16 to 23, the second from December 18 to 24, 1928. These consisted of five treatments to the right sacrum anteriorly, posteriorly and laterally, and seven treatments to the right pelvis, anteriorly, posteriorly and laterally. There was severe radiation sickness with nausea and complete lack of appetite lasting several weeks. The patient stated that she "subsisted on small quantities of caviar, and little else for some time".

**CLINICAL COURSE:** X-ray examination on December 21, 1928, showed no further regeneration of bone, the area of bone destruction being fully as large as at the previous examination, eight weeks before. The patient was discharged from Lenox Hill Hospital on January 7, 1929, and the prognosis was regarded as hopeless. She had lost over 100 pounds since onset. She was told of Dr. William B. Coley and was advised to consult him with a view to having further toxin therapy. She was therefore admitted to the Hospital for Special Surgery the same day. Examination revealed a swelling in the sacral region, noticeable on the right side and gradually subsiding to normal on the left. There was tenderness on pressure over the lower back and buttocks and along the course of the right sciatic nerve. X-ray examination by Dr. R.M. Lewis on January 8, 1929 was reported as follows: "Anterior, posterior and lateral views of the dorsal spine show a quite pronounced productive type of arthritis and calcareous deposits at the margins of the vertebral bodies. The diaphragm is somewhat high, especially at the right. There are shadows in both lung roots, in the left root almost suggesting a mass. Anterior, posterior and lateral views of the spine show an extensive destructive process in the right side of the sacrum. There is no evidence of bone production or repair. The sacro-iliac joint is apparently not destroyed. The appearance suggest a malignant growth which may be either primary or secondary. A giant cell tumor also has to be considered as a possibility."

**SECOND COURSE OF TOXIN THERAPY (*Parke Davis XIII*):** Injections were resumed by Coley on January 7, 1929, the initial dose being one minim, given into the buttocks. The first five were given intramuscularly in the gluteal region, in doses of from 1 to 3 minims, causing febrile reactions of 99.1°-103.2°F. and local swelling (rather painful indurations). Thereafter, the intravenous route was used, beginning with a dose of 1/60 minim, which caused a febrile reaction of 104°F.

**RADIATION:** During the week of January 15 to 21, 1929, injections were suspended and four radium pack treatments were administered at Memorial Hospital, totalling 30,000 mch.



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**FURTHER TOXIN THERAPY:** Injections were resumed on January 21, and were continued steadily until March 4, 1920. During this period of six weeks, 19 intravenous and five intramuscular injections were given. Marked febrile reactions resulted following almost every injection, also severe chills and diaphoresis. The patient stated that the injections were usually made at 5:30 P.M., the chill occurred within 15 to 20 minutes, then the fever and profuse sweating. By one or two in the morning the entire reaction had subsided and she would sleep the remainder of the night. During the chills hot water bags and blankets were used. Injections were given every other day on an average. When the toxins were begun the patient was unable to walk and the pain was excruciating. About three weeks after Coley began to administer the toxins, the patient stated that the pain began to ameliorate and gradually subsided. Two weeks later she began to walk on crutches. An x-ray examination on February 5, 1929, was reported as follows: "No change in the diseased process can be determined. There appears to be neither any increase in the area of destruction nor any new bone formation." On March 3, 1929, the report was "no appreciable change". During the three months that the patient was at the Hospital for Special Surgery under toxin therapy she gained approximately 50 pounds of the weight she had lost since onset.

**CLINICAL COURSE:** As she had been hospitalized a good part of the previous nine months, the patient was allowed to go home on March 4, 1929. She improved rapidly during the next few weeks and it was decided that no further injections would be necessary. She was able to walk with a cane and was seen frequently at Coley's office. Further x-ray examinations were made at the Hospital for Special Surgery by Lewis, recording the progress of the case as follows: April 4, 1929: "Comparison of the present films of the sacrum with the films taken during the past three months show a regeneration of bone at the margin of the cystic process. There has evidently been some repair." May 1, 1929: "Views of the sacrum suggest there is increased calcification of the periphery of the eroded area." June 26, 1929: "Views of the sacrum show the condition to be essentially the same as at the last examination . . . The margins of the areas of destruction appear sclerosed and sharply defined." The patient made a complete recovery and when examined periodically by Coley during the next few years, appeared in excellent health. She was able to walk without the slightest difficulty, performed her own housework, and stated that she could run, dance and bend without the slightest pain or any disability. She resumed her work as an actress. Further x-ray examinations were reported as follows: March 3, 1931: "There has evidently been a deposition of new bone in the diseased area in the right side of the sacrum". May 2, 1932: "There has evidently been extensive repair . . . The cystic appearance and the bulging of the cortex as shown in the lateral views and the long duration of the condition with the extensive repair indicate that the disease was probably a giant cell tumor". January 9, 1935: "The cystic area in the right side of the sacrum appears to have almost completely filled in and there is a densely calcified periphery. There is no suggestion of any active condition." The patient remained

in excellent health when examined by Dr. Walker E. Swift at Memorial Hospital on December 13, 1944. The latter reported: "No swelling over sacrum. No mass felt. Slight tenderness in region of healed scar. Slight superficial telangiectasis." Interim report: patient had been in excellent health since 1930, with the exception of a nervous breakdown in 1939-40, when she had a severe neural dermatitis which cleared up following 16 sulphur baths taken in California. Her weight on December 14, 1944 was 137½ pounds, a gain of over 40 pounds from the weight at the beginning of Coley's treatment." She remained in good health, actively engaged in her profession until about 1960. She retired to live in Florida. In September 1961 she had a severe coronary thrombosis for which she was hospitalized for several weeks. Her weight declined to 120 pounds in 1962. Death occurred on May 27, 1963, due to chronic cholecystitis, diabetes mellitus, and arteriosclerotic heart disease. This was 35 years after onset of the giant cell tumor of the sacrum.

COMMENT: In 1927 Coley stated that he had observed 17 cases of sarcoma (or giant cell tumor) of the spine or sacrum, in all of which the disease had reached the inoperable stage at the time of his first observation. In addition, two other cases of sarcoma of the spine had been treated with the Coley toxins by other surgeons under his direction, making a total of 19 cases in all. This series included 10 females and 9 males. The locality of the tumor was as follows: 2 cervical, 7 dorsal, 7 lumbar, and 3 sacral. A microscopic examination was made in all but two of the cases, and the following classifications given: 9 giant cell, 4 spindle cell, 2 mixed cell, and 2 round cell. The age of the patients ranged from 10 to 60 years. Nine, or 47% of the 19 cases remained alive and well from 3 to 24 years; one patient died of a recurrence at the end of six years. In the nine cases in which recovery took place the toxins alone were used. (33)

(Coley then gave brief case histories of seven of these cases, of which we have been able to obtain detailed histories in all but Cases V and VI.)

Coley stated that he believed that "the result obtained in Dr. Lilienthal's case (33, p. 616) showed the importance of not abandoning all hope even in the seemingly quite desperate cases . . . Cases treated with the mixed toxins differ from those treated by radiation or even surgery, in that in the former group, once the tumor has entirely disappeared a recurrence seldom takes place and the patient usually remains permanently well. In proof of this he cited the results of a recent follow-up of 93 cases of inoperable sarcoma treated with the toxins alone, reported to him before the Johns Hopkins Medical Society in 1896 as follows: 16 cases remained alive and well from 8 to 33 years, and 12 from 10 to 33 years. Coley stated that when we consider how very few cases of malignant tumor, either sarcoma or carcinoma, there are on record in which the patients have been found to be alive and well ten years after treatment, the results obtained in the series quoted become extremely important. Coley called attention to the report of



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Gibson in the Annals of Surgery for August 1926, covering 437 cases of all types of malignant disease operated upon at the New York Hospital, in which only 64 were found to be living and without recurrence, and only 13 had reached the five-year limit . . . ."

In conclusion, Coley stated that "in the last ten years so much attention had been given to radium and roentgen ray treatment of malignant tumors that the value of toxin therapy had been lost sight of, or relegated to the back-ground. He stated that if treatment by radiation could produce better results than those obtained by the older method, then there was no cause whatever for reviving the latter. He wishes to call attention to the fact, however, that a careful comparative study of the end results obtained by the use of the various methods showed that neither x-ray nor radium had been able to produce anything like the number of actual cures in inoperable sarcoma that had been obtained by the use of toxins. (33)

REFERENCES: 11; 33; 40; 54; 58; 68.

**CASE 47:** Extensive inoperable giant cell tumor of the inferior maxilla, confirmed by microscopic examination at Madison General Hospital, Madison, Wisconsin, following biopsy.

**PREVIOUS HISTORY:** C.F.B., male, aged 18, of Oshkosh, Wisconsin. The family history was negative for venereal disease, tuberculosis, diabetes, hay fever or allergy. There was no history of malignancy in the patient's mother's family, but on the father's side there was one case of cancer of the bladder and one of cancer of the throat. The patient had had diphtheria at 15 months, followed by a serious heart condition. At the age of three he developed a small growth on his left side at the level of the umbilicus. (This patient had Recklinghausen's disease, but this was not recognized until many years later.) This increased in size rather rapidly, but due to the heart condition the doctors did not consider operation advisable. (It was finally removed in 1930.) He attained his full growth, 5 feet 11½ inches, at the age of 14. Onset, in late January 1928 a growth appeared on the lower jaw. There was no antecedent injury, infection or dental work, and the lower teeth appeared to be in good condition. Dr. Burton Clark of Oshkosh was consulted. He had two of the lower teeth extracted to see if they were causing the trouble. They proved to be in perfect condition. He then removed a specimen of the bone tumor for microscopic examination.

**RADIATION:** One radium treatment was applied to the gum for 24 hours (50 mg.) early in February 1928. This caused a severe burn which took four months to heal, and the resulting pain was so severe that morphine was necessary, for many weeks, as well as rectal feeding. During this period the patient lost a considerable



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amount of weight. His normal weight had been 150 pounds and he went down to 70 pounds and was in very poor condition. During the period following radiation the lower teeth began to fall out. Dr. Boyd Williams of Minneapolis was consulted in March 1928. At this time the growth was so far advanced that the lower part of the patient's face was frightfully deformed due to the enlargement of the lower jaw. Williams suggested toxin therapy be administered at home by the family physician.

**TOXIN THERAPY** (*Parke Davis XIII*): Injections were begun on March 27, 1929, by Dr. H.E. Johnston of Oshkosh. They were made daily or every other day until May 28, 1929. In this two month period 29 injections were given intramuscularly in ascending doses, starting with  $\frac{1}{4}$  minim, the site being the back and the gluteal region. The maximum dose was about 10 minims. The reactions were severe. The growth began to break down under treatment and small pieces of necrotic tumor tissue occasionally sloughed away.

**CLINICAL COURSE:** Six weeks after the toxins were stopped, the patient felt well enough to go swimming. By July 26, 1928, the tumor had just about disappeared, but the tissues still looked somewhat angry and red over the maxilla inside the mouth. The growth regressed completely, leaving the jaw flat on the affected side. A sinus remained inside the mouth for about a year, which was sore and had a bad odor. The patient's general condition improved rapidly. At the end of a year only four lower teeth remained, due to the radiation necrosis. A partial plate was made which facilitated eating. There was no recurrence of the tumor of the jaw. The growth on the left side at the level of the umbilicus was finally removed surgically on June 20, 1930, the pathological report being neurofibroma. This appears to have been the first recognition that this patient had Recklinghausen's disease. Multiple small nodules developed over the torso, and about 15 of these were removed surgically during the next 14 years.

The patient was married and three normal, healthy children were born between 1942 and 1949. Early in 1944 he sustained an injury to the right knee joint. In April a swelling developed at the distal end of the femur. This was removed surgically by Dr. Marvin A. Steen of Oshkosh on June 28, 1944. Sections revealed "well-formed osseous caseous trabeculae. A few trabecular spaces contained a scanty, cellular, spongy, myxomatous fibrous tissue. The fibrous tissue in places was infiltrated with lymphocytes and plasma cells. There was no evidence of a malignant neoplasm in the sections. No definite diagnosis was made, but the condition was considered as possibly on an inflammatory basis." (It now appears that this was another manifestation of osteitis fibrosa cystica or Recklinghausen's disease.) The patient made a satisfactory recovery following the operation. Steen reported on November 28, 1944: "The patient's weight is normal, and at present there does not appear to be any abnormalities except the area of excessive pigmentation which extends over the entire chest and abdomen anteri-

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only and posteriorly. There are also multiple small nodules over the torso and I excised one of them at surgery on the bone tumor . . . and pathological report was neurofibroma." (11) On April 10, 1946, the patient wrote that he still had pains in his left limb, usually a dull ache, but occasionally very sharp. These were not localized, but covered an area from the knee to the hip. (Bone pain is a characteristic of Recklinghausen's disease.) X-rays taken in March 1946 showed the bone cavity resulting from the operation was filling in very nicely, and there was no evidence of recurrence. The patient reported on October 29, 1950, that he was in "excellent health, having had a thorough physical examination a few months previously." He reported that his three children were all in fine health. His health continued to be excellent until November 1952, when he developed "coronary insufficiency". After resting a month in bed, he was allowed to work for half a day for about three months, thereafter resuming a normal schedule. His weight in 1946 was 146 pounds and from 1950 to 1953 it was about 180 pounds. Thereafter it was maintained at about 168 pounds, just three pounds more than it had been in 1927. In the spring of 1959 he woke up one morning unable to breathe. An emergency tracheotomy was required. In June 1959 a thoracotomy revealed an extensive neurofibroma in the trachea which was excised. His trunk was still covered with the café au lait lesions (none on head). Following this operation he had intractable pain in the region of the thoracotomy, and he refused to allow the tracheotomy to be closed although the airway was normal. Despite nerve transection, pain continued requiring analgesics. During the winter of 1966 he suffered from general pulmonary congestion and a short period of failure. A myelogram in 1960 showed a congenital meningocele of the sacrum. The severe intercostal pain continued despite nerve blocks and requiring considerable analgesic medication. It was better in 1971 but recurred in 1972. He continued to insist on retaining the tracheotomy tube despite adequate airway (it was inserted in 1959). Death occurred on December 29, 1972, of complications following surgery for a duodenal ulcer. This was almost 47 years after onset of the giant cell tumor.

REFERENCES: 11; 40

## **SERIES B: FAILURES TREATED BY IMMUNOTHERAPY, 10 CASES**

Table 2 contains the 10 cases of giant cell tumor unsuccessfully treated by Coley toxins (at least 10 injections). Three other cases were excluded as they had only five to nine injections. Such a brief course is not considered sufficient to have any effect.

Nine of these cases were malignant giant cell tumors. In only two were the toxins given for the primary lesion. In the other eight the disease was inoperable (some were enormous, three were recurrent as well); lung metastases were present in one case.

Analysis of these failures indicates four of the most significant factors affecting prognosis unfavorably, that is: (a) the danger of administering large amounts of radiation, especially when given prior to toxin therapy (case 5); (b) the importance of giving the toxin injections for about three to four months, rather than for less than three weeks (case 10); (c) the importance of assuming that if pain recurs either locally or at a distant site, it should be regarded as evidence of reactivation of the disease and injections should be resumed at once and given aggressively and persistently in order to produce a permanent result (case 10); and (d) the danger of a malignant bone tumor arising in heavily irradiated bone many years later, especially if radiation is given prior to toxin therapy (case 5).





TABLE 2, SERIES B: GIANT CELL TUMOR UNSUCCESSFULLY TREATED BY TOXIN THERAPY  
COMBINED WITH SURGERY AND/OR RADIATION: 10 CASES

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate and Final Result Period of Survival
FEMUR: 5 cases						
1. W.B. Coley (15; 30; 32; 34)	F 16 (E.R.)	malignant giant cell tumor distal lt. femur; onset about February 1, 1906, pain inside lt. knee when walking; rapid increase in size of swelling, lameness	explored April 6, 1906: tumor very vascular, hemorrhage, required gauze packing	amputation 10 cm. below trochanter, 3½ mos. after onset, May 18, 1906, causing "good deal of shock"	Coley toxins (Buxton VI) April 9, 1906, small doses i.m.; injections resumed 3 wks. after amputation 32 i.m. in 5 mos. in stump and other thigh	at first decided improvement, very soon no effect, rapid increase in size; gained up to 2 lbs. a wk. during summer (14 lbs. in 4 mos.) appeared in perfect health; 3 yrs. later metastases in pelvic bones and lungs, caused death 1909, 3 yrs. after onset
2. W.B. Coley (21; 40)	F 29 (E.A.)	recurrent malignant giant cell tumor arising in myositis ossificans; 1905 thrown from carriage in runaway accident; severe trauma to distal outer lt. thigh; 2 yrs later slight asymptomatic enlargement of bone noted; very slight increase in size; February 1909, Chicago surgeon diagnosed it as bone sarcoma, advised immediate amputation (severe psychic trauma to patient); May 1909 immediate amputation again advised by another surgeon; Coley consulted, diagnosed as myositis ossificans originating from trauma; by March 1912 general condition greatly deteriorated	explored July 7, 1909 diagnosis confirmed; in perfect health normal activities 1909 to early 1912, when enlargement increased considerably; January 8, 1912 again explored, nearly 8 oz. bony material removed; again reported as myositis ossificans but with many cellular areas (giant cells); by March 20, 1912 recurrence; incisional biopsy revealed giant cell tumor	amputation April 22, 1912	Coley Toxins (Tracy XI) in minute doses for 3 wks. prior to amputation	no apparent effect from brief toxin therapy; poor recovery after amputation; general condition considered too poor to resume toxins, metastases to dorsal and lumbar vertebrae, very severe sciatic pain; death 7 yrs. after injury 15 mos. after onset

3. Winter (32; 68)	M. 14 (A.G.)	inoperable very extensive malignant giant cell tumor distal femur 50 cm. in circumference, metastases to iliac nodes; onset after injury early January 1908	treated as tuberculosis 1st 4 mos. 1908, then explored; completely inoperable; very rapid increase in size after surgery	none	Coley toxins (Parke Davis XII) early May 1908 for a month, mostly locally	large purple veins nearly disappeared, tumor stationary, general condition good during toxin therapy; rapid increase after injections were stopped; "growth became almost as large as the patient;" death about 9 mos. after onset
4. W.B. Coley (32; 68)	M. 35 (C.P.R.)	malignant giant cell tumor distal femur with pulmonary metastases; fell May 1917 dislocating knee, hospitalized in cast 6 wks.; by July 1918 tumor 26 cm. long, leg 14 cm. larger than normal limb, motion almost lost; distal femur almost totally destroyed	none	radium, July 23-29, 1918 & November 1918, about 80,000 mch.	Coley toxins (Tracy XI) July 17, 1918: 6 i.m. in 6 days prior to radium; total of 46 in 5½ mos. mostly i.m.; little or no reaction except from few given into tumor (102°-103.2°F.)	January 1919, extensive metastases rt. lung (flat to percussion); June 1919 large portions rt. thigh sloughed due to radiation necrosis; death July 5, 1919 over 2 yrs. after onset



TABLE 2, SERIES B: GIANT CELL TUMOR UNSUCCESSFULLY TREATED BY TOXIN THERAPY  
COMBINED WITH SURGERY AND/OR RADIATION (con'd)

Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate and Final Result Period of Survival
5. B.L. Coley (7; 68)	M. 25 (A.H.)	huge inoperable aggressive giant cell tumor involving neck, intertrochanteric region & shaft rt. femur, 23 cm. long with eventual transformation into fibrosarcoma; onset Spring 1930, pain in rt. hip, very lame, weak, crutches needed to walk; 30 lb. wt. loss	treated as arthritis for 4 mos. Alpine lamp; February 1931 tonsillectomy; May 1931 aspiration biopsy; May 8, 9, 12, 1931 x-ray to hip (2,300 r); straight spica cast; further x-ray June 8, 16, 1931, (765 r each)	traction July 1931; x-ray August 28-September 2, 1931 (2295 r); 4th cycle x-ray January 1932; plastic surgery for large radiation ulcer (3 stage); ultra violet radiation; maggots applied to necrotic areas twice; February 1934 radium pack for recurrence; zinc chloride paste, further ultra violet radiation	Coley toxins (P.D. XIII) July 2, 1931, after 2nd cycle of x-ray; daily i.m. then i.t. for 21 days; febrile for a wk. after last injection (99°-100° F.); few more injections September 1931 & February 1933; 3 attacks erysipelas in areas treated by ultra violet radiation; osteomyelitis of ilium with suppuration after radium	pale anemic wasted appearance summer 1931; hospitalized 6½ mos.; discharged pain-free in short spica November 24, 1931; 2 mos. later tumor smaller, leg 6 cm. shorter; could walk with cane (walking spica as brace); by April 1932 deep radiation ulcer 10 cm. long; hospitalized 7 mos. for plastic surgery, pathologic fracture; gained 14 lbs; fracture began to heal, part of flap sloughed; pinch grafts didn't take; gained 36 lbs between April 1932 & January 1934; recurrence on abdomen (where flap had been taken); pain several severe hemorrhages from ulcerated area; recurrence slowly regressed after 3rd erysipelas & suppuration, finally healed June 1937, pain-free; patient feared if he tried to ambulate disease would reactivate, Coley urged him to try; within 3 mos. large tumor present, pain severe, hemorrhages from large fungating mass; rapid downhill course, death December 4, 1939, 9½ yrs. after onset; autopsy showed malignant fibrosarcoma of femur, acetabulum & pubes (in irradiated bones)

# HUMERUS: 2 Cases

6. W.B. Coley & Bellis (20; 24; 30; 32; 68)	M. 10 (H.L.B.)	enormous malignant giant cell tumor proximal 1/3 lt. humerus extending to mid-clavicle & scapula; January 1910, onset slight pain in shoulder, elbow, wrist; 3 wks. later fell off haystack, striking lt. shoulder on ice; complete disability due to pathologic fracture; marked increased in size next 3 wks., veins enlarged	treated as rheumatism after injury, arm in splints; March 17, 1910, shoulder joint amputation (no prior biopsy)	none	Coley toxins (Tracy XI) begun as soon as wound had healed, twice a wk. for 5 mos.	good recovery from surgery; in excellent health for 6 mos. after last toxin injection; May 1911 slight cough, lassitude, general malaise, then dyspnea & symptoms of extensive lung metastases; death August 20, 1911, 19 mos. after onset
7. Mason (23; 30; 40; 68)	F. 14 (R.F.)	malignant giant cell tumor rt. proximal humerus; no prior trauma; onset June 1911, intermittent pain in rt. forearm; early August 1911, swelling in proximal humerus, rapid growth	x-ray (dose not recorded); shoulder joint amputation, August 23, 1911	none	Coley toxins (Tracy XI) September 6, 1911, 2 wks. after surgery: 4 i.m. in pectoral region, no reaction; resumed a wk. later brief course, only 2 adequate reactions (102.6°-103°F.)	recurrence apparent by mid-September 1911; no apparent effect from toxins; very large recurrence present by mid-October 1911, signs of septic absorption, pulmonary metastases, death, October 28, 1911 4½ mos. after onset
8. Harmer (53; 66)	M 34 (J.A.)	inoperable recurrent giant cell tumor lt. ilium, sacrum & spine 4 cm. in diameter; date of onset not recorded	operated elsewhere for primary; recurred promptly	x-ray for 2 wks. during toxin therapy; no effect	Coley toxins (P.D. XII) March 31, 1913; for 13 wks. moderate reactions	no appreciable effect growth increased to bleeding ulcerated mass size of football; death August 20, 1913

TABLE 2, SERIES B: GIANT CELL TUMOR UNSUCCESSFULLY TREATED BY TOXIN THERAPY  
COMBINED WITH SURGERY AND/OR RADIATION (con'd)

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Physician or Hospital (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Immunotherapy	Prior Therapy	Subsequent Therapy	Immunotherapy Site, Duration Reactions Elicited	Immediate and Final Result Period of Survival
9. B.L. Coley (68)	M 34 (A.S.)	inoperable malignant giant cell tumor lt. ilium involving pubis & ischium for considerable distance above acetabulum; femoral head displaced inward; onset after tonsillectomy, August 1930, limp, pain in lt. hip, much weight loss, general condition poor	December 11, 1930 incisional biopsy, x-ray (6); no effect; February 27, 1931, Coley gave further x-ray to anterior lt. pelvis; March 3, 1931 radium pack; no response to radiation; March 6, 1931, biopsy; March 20, 1931, further radium; limb in traction to improve position of femoral head	April 21-23, 1931, x-ray (6885 r); May 5, 6, 1931 x-ray (1474 r)	Coley toxins (P.D. XIII) March 6, 1931: 12 in 31 days, 1st 3 i.m. (no chills, little or no febrile reactions); 9 i.v. (reactions averaged 102°-102.8°F., maximum 103.6°F.; chills 8 times)	no apparent benefit; tumor extended beyond mid line up to umbilicus by April 25, 1931; disease progressed; death September 15, 1931, about 13 mos. after onset



Patella, 1 case:

10. B.L. Coley (68)	F 47 (H.A.)	malignant giant cell tumor lt. patella; onset Spring 1938; (patient fell on knee 4 times last one April 1940); by May 1940 patella 3 times normal size, with surrounding soft tissue swelling; chest films showed nodular density lt. hilar region	February 1939 x-ray taken, arthritis reported; after last fall cast applied; May 13, 1940 lt. patella removed surgically; 2 wks. later cast applied	physiotherapy for sciatica early 1943; adhesive strapping, sodium salicylates; May 19-26, 1943 x-ray to spine (1600 r), caused great deal of nausea, little pain relief; entire lt. leg acutely tender along sciatic nerve; June 18, 1943 lt. thoracentesis; dry tap	Coley toxins (P.D. XIII) May 30, 1940 (old bottle); 17 in 19 days 9 i.m. little or no reaction; 8 i.v.; marked reaction (105.4°F.) rest moderate; beginning summer 1941 3 episodes uterine abscess with discharge of pus & blood in about 6 mos.; took sitz baths	very satisfactory result, symptom free, no limp; during summer 1942 pain in gluteal region, around hips; menses ceased December 1942 (menopause); then sciatic pain rt. leg, also much discomfort low back & gluteal regions; took defense job; back pains subsided but acute lt. sciatica continued; by mid-May 1943 extreme pain lumbar spine, lt. hip & leg due to metastases L4 vertebra; in bed most of time, pulmonary metastases upper lt. lobe, caused cough; slight intermittent fever July 1943; appeared stronger in August; disease then progressed, pitting edema legs, death November 1, 1943, 5½ years after onset
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TABLE 3, SERIES C, GIANT CELL TUMOR OF BONE WITH POSTOPERATIVE INFECTION OR FEVER: 4 CASES

Physician (References)	Sex Age (Initials)	Site, Extent, Duration of Disease Prior to Infection	Prior Therapy	Subsequent Therapy	Type, Extent and Duration of Infection and/or Fever	Immediate & Final Result; Years Traced After Onset
I. W.B. Coley (11; 40; 68)	M 25 (I.R.)	recurrent giant cell tumor distal rt. femur; onset March 1920 shortly after being kicked in knee by a bull; recurrence June 1924	exploratory operation August 1920; limb immobilized in cast; 5 wks. later radium packs; 4 courses in 8 mos. totalling 151,154 mch. (calculated as tumor dose 4400 r); pathological fracture following fall January 1923 (bone extremely brittle due to radiation); took 7-8 wks. to heal; gangrene of heel from pressure of splint, healed in 5 mos; diathermy 1924 caused large burn (8 cm) on inner distal thigh (healed in 7 mos.)	4 cm. radiation ulcer excised, skin grafted April 1949; underlying tissues avascular & fibrotic; pinch grafts May 4, 1949	severe erysipelas infection in region of burn spread to groin, lasting 3 wks., fever 104°-105°F.; 2nd erysipelas infection April 1949; fever 101°F., diffuse pseudocellulitis lymphangitis & node in rt. groin; pyocyanous infection	burn finally healed after the erysipelas infection; recurrence apparently regressed, no further evidence disease; almost complete regeneration of bone; irradiated skin in reasonably good condition, general health excellent; motion limited to 15° flexion from full extension; walked without limp by 1944 weighed 237 lbs; 4 cm. radiation ulcer over exterior condyle of femur excised, skin grafted 1949; continued to work until 1954 in good health except for arthritis; 1974: developed bronchogenic carcinoma, which metastasized, causing death July 19, 1974, 54 yrs. after onset

2. B.L. Coley & W.B. Coley (11; 68)	F 18 (J.McC.)	recurrent malignant giant cell tumor whole proximal humerus, shoulder 1½ times normal size; had adolescent type goiter; onset June 1929 after influenza; provisional diagnosis: osteogenic sarcoma; recurrence April 1932 below clavicle following influenza; specimen reported as malignant osteogenic sarcoma; (patient exhausted after prolonged menses)	radium packs (50,000 mch.) July 25-August 9, 1929; pain increased, function markedly reduced; August 14, 1929, shoulder joint disarticulation; scapulectomy for recurrence in glenoid fossa	bed rest for t.b.; 1949 neuroma around 3 nerve trunks of brachial plexus excised; basal cell carcinomas cauterized 1952	Coley Toxins (Parke Davis XIII) August 5, 1929; 4 i.v., moderate reactions; 1932 developed pulmonary tuberculosis (6th case in her family)	recovered from t.b. no further recurrence or metastases; in excellent health, working full time as college professor, able to drive car; 1949, neuroma brachial plexus; 1952, 5 basal cell carcinomas in irradiated skin; in very good health to 1958, thereafter had recurring thrombophlebitis; 1967, benign endometrial polyps, excised; 1970, pulmonary emboli, diabetes, lt. vocal cord paralyzed for 6 mos; alive & well working full time 1975, 46½ years after onset
3. W.B. Coley (11; 68)	M 30 (R.R.)	giant cell tumor proximal rt. fibula 20 cm. long, affected limb 6½ cm. larger; onset April 1916	family physician aspirated the tumor; April 18, 1918 complete resection of fibula; fulguration of wound for 10 minutes	immediate amputation under chloroform	2 days after surgery fever 104°F., 4 hrs. later 107.8°F., patient comatose, delirious; foot cyanotic, cold, beginning gangrene in wound	excellent recovery from amputation no further evidence of disease; died "old age" 1972, 56 years after onset
4. B.L. Coley (7, #2079; 68)	F 26 (M.B.)	rather cellular giant cell tumor involving entire proximal lt. fibula extending to soft tissues; patient obese (230 lbs.), underdeveloped breasts, small nipples, endocrine imbalance; onset after fall downstairs February 18, 1936, unable to get out of bed, severe pain, swelling	exploratory operation March 24, 1936; cortex completely destroyed, periosteum intact tissue removed by expressing it, wound packed to control bleeding; February 15, 1936 thorough curettage by Coley, proximal fibula entirely destroyed, growth extended into soft tissues, contents spongy, yellowish not usual color of giant cell tumor	wound opened considerable grey discharge; February 27, 1937, fibula resected, perineal nerve resected	fever 101-103°F. after curettage; infection in mid-calf in hair follicle August 1936; lymphangitis, cellulitis further furunculosis; fever 103.6° chill after resection; 101.4° -103.2° for 3 days, wound infection	weight increased to 241 lbs.; wound completely healed, full range of motion, symptom free by early October 1936; late October occasional pain in proximal fibula, by February 25, 1937 recurrence apparent (12 x 10 cm.) involved perineal nerve; complete recovery, joined gym club, danced despite foot drop; married; alive & well April 1950; 14 yrs. after onset; lost to follow up thereafter





## BIBLIOGRAPHY

1. Ainsworth, E.J. & Forbes, P.D.: The effect of *Pseudomonas pyrogen* on survival of irradiated mice. *Radiation Research* 14: 767-774. 1961. (Also personal communications.)
2. Albany Hospital Records.
3. Arlen, M., Higinbotham, N.L., Huvos, A.G., Marcove, R.C., Miller, T. & Shah, J.C.: Radiation-induced sarcoma of bone. *Cancer* 28: 1087-1099. 1971.
4. Barss, H.deB.: Coley's mixed toxins in the treatment of sarcomata, with a report of four cases of osteosarcoma treated by this method. *J. Mich. State Med. Soc.* 15: 497-505. 1916.
5. Berger, F.M.: The effect of endotoxin on resistance to infection and disease. *Advances Pharmacol.* 5: 19-46. 1967.
6. Bloodgood, J.C.: The conservative treatment of giant cell sarcoma. *Ann. Surg.* 56: 210-239. 1912.
7. Bone Sarcoma Registry Records, now with the Armed Forces Institute of Pathology.
8. Buinauskas, P., McDonald, G.O. & Cole, W.H.: Role of operative stress in the resistance of the experimental animal to inoculated tumor cells. *Ann. Surg.* 148: 642-645. 1958.
9. Bureaus of Vital Statistics, state or municipal: Death Records.
10. Cahan, W.G., Woodard, H.Q., Higinbotham, N.L., Stewart, F.W. and Coley, B.L.: Sarcoma arising in irradiated bone; report of 11 cases. *Cancer* 1: 3-29. 1948.
11. Cancer Research Institute Records: Personal communications from patients, their physicians, relatives or hospitals where they were treated.
12. Cohen, D.M., Dahlin, D.C. & MacCarty, C.S.: Vertebral giant-cell tumor and variants. *Cancer* 17(4): 461-472. 1964.
13. Coley, W.B.: Amputation of the hip-joint for sarcoma, with a report of seven cases without mortality. *Trans. South. Surg. & Gyn. Assn.* 16: 77-96. 1903.
14. Coley, W.B.: Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and *Bacillus prodigiosus*. *Amer.J.Med.Sc.* 131: 375-430. 1906.
15. Coley, W.B.: Sarcoma of the long bones; the diagnosis, treatment and prognosis with a report of sixty-nine cases. *Ann. Surg.* 45: 321-368. 1907.
16. Coley, W.B. & Gibney, V.P.: Round cell sarcoma of dorsal spine. *Ann. Surg.* 47: 819-822. 1908.
17. Coley, W.B.: The treatment of sarcoma with mixed toxins of erysipelas and *Bacillus prodigiosus*. *Boston Med. & Surg. J.* 158: 175-182. 1908.

18. Coley, W.B.: The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of erysipelas streptococcus and *Bacillus prodigiosus*). *Proc. Royal Soc. Med., Surg. Sect.* 3: #3, 1-48. 1909-1910.
19. Coley, W.B.: A plea for more conservative treatment of sarcoma of the long bones. *J.A.M.A.* 54: 333-343. 1910.
20. Coley, W.B.: Le traitement conservateur du sarcome des os longs. Extrait des *Comptes Rendus du 24<sup>e</sup> Congrès de l'Association Française de Chirurgie*. 1911. Paris.
21. Coley, W.B.: Myositis ossificans traumatica; a report of three cases illustrating the difficulties of diagnosis from sarcoma. *Ann. Surg.* 57: 305-337. 1913.
22. Coley, W.B.: The treatment of malignant inoperable tumors with the mixed toxins of erysipelas and *Bacillus prodigiosus*, with a brief report of 80 cases successfully treated with the toxins from 1893-1914. Brussels, M. Weissenbruch, 1914.
23. Coley, W.B.: Some problems in the early diagnosis of sarcoma of the long bones. *Ann. Surg.* 60: 103-108; 537-566. 1914.
24. Coley, W.B.: Cure of sarcoma of the dorsal and lumbar vertebrae under the treatment with the mixed toxins. *Ann. Surg.* 60: 772-774. 1914.
25. Coley, W.B.: Central sarcoma of the lower end of the femur with extensive involvement of the knee joint successfully treated with the mixed toxins of erysipelas and *Bacillus prodigiosus*. *Ann. Surg.* 65: 370-372. 1917.
26. Coley, W.B.: Conservative treatment of sarcoma of the long bones. *Ann. Surg.* 65: 375. 1917.
27. Coley, W.B.: Very large inoperable sarcoma of the upper portion of the femur, following a recent fracture; disappearance under combined toxins and radium treatment. *Ann. Surg.* 69: 553-554. 1919.
28. Coley, W.B.: Further observations on the conservative treatment of sarcoma of the long bones. *Trans. Amer. Surg. Assn.* 37: 273-336. 1919.
29. Coley, W.B.: Central sarcoma of the radius, clinical and x-ray diagnosis, inoperable without sacrifice of the arm. *Ann. Surg.* 69: 551-553. 1919.
30. Coley, W.B.: Prognosis in giant-cell sarcoma of the long bones based upon the end results in a series of 50 cases. *Ann. Surg.* 79: 321-357; 561-595. 1924. (Also in *Trans. South. Surg. & Gyn. Assn.* 36: 127-197. 1924.)
31. Coley, W.B. and Coley, B.L.: End results in 169 operable cases of periosteal osteogenic sarcoma and endothelioma, including a small group of malignant central sarcoma. *Trans. Amer. Surg. Assn.* 43: 857-949. 1925.



32. Coley, W.B. and Coley, B.L.: Primary malignant tumors of the long bones; end results in one hundred and seventy operable cases. *Arch. Surg.* 13: 779-836. 1926; 14: 63-141. 1927.
33. Coley, W.B.: Discussion of case presented by Dr. H. Lilienthal (N. Y. Surg. Soc.) *Ann. Surg.* 85: 615-621. 1927.
34. Coley, W.B.: Prognosis and treatment of giant-cell sarcoma, based on a further study of end results in sixty-nine cases. *Ann. Surg.* 86: 641-665. 1927.
35. Coley, W.B.: Sarcoma of the long bones; clinical lecture on end results. *Am. J. Surg.* 4: 223-231. 1928.
36. Coley, W.B.: Sarcoma of the long bones. Clinical lecture on end results. Exhibition of patients illustrating end results of treatment. *Surg. Clin. North America* 9: 583-618. 1929.
37. Coley, W.B.: Malignant changes in so-called benign giant-cell tumors. *Am. J. Surg.* 28: 768-820. 1935.
38. Coley, W.B.: Endothelioma, or Ewing's tumor. *Amer. J. Surg.* 27: 7-18. 1935.
39. Coley, W.B.: Diagnosis and treatment of bone sarcoma. *Glasgow M.J.* 126: 49-86; 128-164. 1936.
40. Coley, W.B.: Office Records.
41. Copeland, M.M.: Primary malignant tumors of bone. Evaluation of current diagnosis and treatment. *Cancer* 20: 738-746. 1967.
42. Cruz, M., Coley, B.L. & Stewart, F.W.: Post-radiation bone sarcoma; report of 11 cases. *Cancer* 10: 72-88. 1957.
43. Dahlin, D.C.: Hazard of radiation therapy for giant cell tumor of bone. 7<sup>e</sup> Congrès Soc. Internat. de Chir. Orthopédique et de Traumatologie. Barcelona. 1957. (pp. 710-713)
44. Dahlin, D.C., Cuppo, R.E. & Johnson, E.W., Jr.: Giant cell tumor; a study of 195 cases. *Cancer* 25: 1061-1070. 1970.
45. Ewing, James: Neoplastic Diseases. A Treatise on Tumors, 4th Edition. Philadelphia and London. W.B. Saunders Co. 1940. (p. 147; 318)
46. Fowler, G.A.: Testicular cancer treated by bacterial toxin therapy as a means of enhancing host resistance. End results in 63 determinate cases with microscopic confirmation of diagnosis. 20 operable (86% success), 26 inoperable (35% success), 17 terminal (6% success). Monograph #7, New York Cancer Research Institute, New York, N. Y. 1968.\*

\* In 1973 the name of the Institute was changed to Cancer Research Institute, Inc.

47. Fowler, G.A.: Enhancement of natural resistance to malignant melanoma with special reference to the beneficial effects of concurrent infections and bacterial toxin therapy. Monograph #9. New York Cancer Research Institute, New York, N. Y. 1969.\*
48. Fowler, B.A.: Beneficial effects of acute bacterial infections or bacterial toxin therapy on cancer of the colon or rectum. Monograph #10. New York Cancer Research Institute, New York, N. Y. 1969.\*
49. Fowler, B.A. & Nauts, H.C.: The apparently beneficial effects of concurrent infections, inflammation or fever and of bacterial toxin therapy on neuroblastoma. Monograph #11, New York Cancer Research Institute, New York, N.Y. 1970.\*
50. Green, R.M.: The use of Coley toxins in the treatment of sarcoma. Boston M. & S. J. 165: 1-6. 1911.
51. Halpern, B.N., Prévot, A.R., Biozzi, G., Stiffel, C., Mouton, D., Morand, J.C., Bouillier, Y. & Decreusefond, C.: Stimulation de l'activité phagocytaire du système réticuloendothélial provoquée par *Corynebacterium parvum*. J. Réticulo-endothelial Soc. 1: 77-96. 1964.
52. Harmer, T.W.: Remarks upon the effects observed in the use of the mixed toxins (Coley) in certain cases of sarcoma. Boston Med. & Surg. J. 171: 253-261. 1914.
53. Harmer, T.W.: A study of the efficiency of mixed toxins (Coley) in inoperable sarcoma. A critical analysis of 134 microscopically proven cases. Boston M. & S. J. 172: 331-338; 373-377; 411-416; 440-448. 1915.
54. Hospital for Special Surgery Records.
55. Jefferson Hospital Records.
56. Kelly, M.: Corticosteroids and carcinogenesis: a clinical survey. Acta. Rheum. Scand. 5: 286-290. 1959.
57. Kelly, M.: Steroids and cancer. Lancet 1: 1375-1376. 1963.
58. Klein, G.: Immunologic surveillance against neoplasia. In: the Harvey Lectures 69: 71-102. 1975.
59. Lenox Hill Hospital Records.
60. Levin, A.S., Byers, V.S., Johnston, J.O., Hackett, A.J. & Fudenberg, H.H.: Host-tumor relationships in giant cell sarcoma of bone: measurement by quantitative immunofluorescence. Clin. Research 22: 492a. 1974.
61. Lilienthal, H.: Office Records.

\* In 1973 the name of the Institute was changed to Cancer Research Institute, Inc.

62. McLeod, J.J., Dahlin, D.C. & Ivins, J.C.: Fibrosarcoma of bone. *Am. J. Surg.* 94: 431-437. 1957.
63. Marcove, R.C., & Miller, T.R.: The treatment of primary and metastasized bone tumors by cryosurgery. *Surg.Clin.N. Amer.* 49: 421-430. 1969.
64. Marcove, R.C. & Miller, T.R.: Treatment of primary and metastatic bone tumors by cryosurgery. *J.A.M.A.* 207: 1890-1894. 1969.
65. Marcove, R.C., Leyden, J.P., Huvos, A.G. & Bullough, P.B.: Giant cell tumor treated by cryosurgery: a report of 25 cases. *J. Bone & Joint Surg.* 55A: 1633-1644. 1973. (And personal communications, 1972-1976)
66. Martin, D.S., Fugman, R.A. & Hayworth, P.: Surgery, cancer chemotherapy, host defenses and tumor size. *J. Nat. Cancer Inst.* 29: 817-834. 1962.
67. Massachusetts General Hospital Records.
68. Matagne, J.H.J.: La guérison du cancer. *Scalpel* 106: 1387-1395. 1953.
69. Memorial Hospital Records.
70. Miller, G.F. & Ketcham, A.S.: Effect of bacterial infection on tumor cell contamination of operative wounds. *Surg. Forum* 13: 98-99. 1962.
71. Miller, T.N. & Nicholson, J.T.: End results in reticulum cell sarcoma of bone treated by bacterial toxin therapy alone or combined with surgery and/or radiotherapy (47 cases) or with concurrent infections (5 cases). *Cancer* 27: 524-548. 1971.
72. Nauts, H.C., Swift, W.C. & Coley, B.L.: Treatment of malignant tumors by bacterial toxins as developed by the late William B. Coley, M.D. reviewed in the light of modern research. *Cancer Research* 6: 205-216. 1946.
73. Nauts, H.C., Fowler, G.A. & Bogatko, F.H.: A review of the influence of bacterial infection and of bacterial products (Coley toxins) on malignant tumors in man. *Acta Medica Scandinavica*, Vol. 145: Supplement 276. Stockholm, 1953.
74. Nauts, H.C. & Fowler, G.A.: End results in lymphosarcoma treated by toxin therapy alone or combined with surgery and/or radiation or with concurrent bacterial infection. Monograph #6. New York Cancer Research Institute\*, Inc., New York, N.Y. 1969.
75. Nauts, H.C.: The apparently beneficial effects of bacterial infections on host resistance to cancer: end results in 435 cases. Monograph #8. New York Cancer Research Institute, Inc., New York. 1969. 2 volumes. 800 pp. with bibliography of 969 references. (out of print)

\* Name changed in August, 1973 to Cancer Research Institute, Inc.



76. Nauts, H.C.: Host resistance to cancer. Review of the early and recent literature. Monograph #5. (2nd ed.) New York Cancer Research Institute, New York. 1970.\* (out of print)
77. Nauts, H.C.: Enhancement of natural resistance to renal cancer with special reference to the beneficial effects of concurrent infections and immunotherapy (bacterial vaccines). Monograph #12. New York Cancer Research Institute, New York. 1972.\*
78. Nauts, H.C.: Ewing's sarcoma of bone: end results following immunotherapy (bacterial toxins) combined with surgery and/or radiation. Cancer Research Institute, Monograph #14, New York. 1974.
79. Nauts, H.C.: Multiple myeloma: beneficial effects of acute infections or immunotherapy (bacterial vaccines). Cancer Research Institute Monograph #12. New York 1975.
- 79a. Nauts, H. C., Osteogenic sarcoma: end results following immunotherapy (bacterial vaccines) 165 cases, or concurrent infections, inflammation or fever, 41 cases. Cancer Research Institute, Monograph #15. 1975.
- 79b. Nauts, H.C.: Sarcoma of the soft tissues, other than lymphosarcoma, treated by toxin therapy. End Results in 186 determinate cases with microscopic confirmation of diagnosis: 49 operable, 137 inoperable. Monograph #16. Cancer Research Institute, New York, N.Y. 1975.
80. Old, L.J., & Boyse, E.A.: Prospects for immunotherapy of human cancer. *Ann. Int. Med.* 69: 393-397. 1968.
81. Owens, J.E.: The use of toxins in the treatment of sarcoma, particularly of operable cases. *Illinois State Med. Soc. Trans. (Chicago)* 218-227. 1897. (Also *New Orleans M. & S. J.* 50: 1-8. 1897.)
82. Pelner, L.: Host-tumor antagonism. IX. The reticulo-endothelial system and neoplasia. *J. Amer. Ger. Soc.* 5: 916-931. 1957.
83. Pelner, L.: Host-tumor antagonism. X. Radiation—a double-edged sword. *J. Amer. Ger. Soc.* 6: 424-436. 1958.
84. Pelner, L., Fowler, G.A. and Nauts, H.C.: Effects of concurrent infections and their toxins on the course of leukemia. *Acta Medica Scand.*, Vol. 162: Suppl. 338. 1958.
85. Phillips, T.L. & Sheline, G.A.: Bone sarcomas following irradiation therapy. *Radiology* 81: 992-996. 1963.
86. Presbyterian Hospital Records.

\* In 1973 the name of the Institute was changed to Cancer Research Institute, Inc.

87. Riddle, P.R. & Berenbaum, M.C.: Postoperative depression of lymphocyte response to phytohemagglutinin. *Lancet* *1*: 746-748. 1967.
88. Smith, W.W., Alderman, I.M. & Gillespie, R.E.: Hematopoietic recovery induced by bacterial endotoxin in irradiated mice. *Amer. J. Physiol.* *102*: 549-566. 1958.
89. Steiner, G.C.: Postradiation sarcoma of bone. *Cancer* *18*: 603-612. 1965 (case 3).
90. Stjernsward, J. & Levin, A.: Delayed hypersensitivity-induced regression of human neoplasms. *Cancer* *28*: 628-640. 1971.
91. Sweetnam, R.: Tumours of bone and their management. *Ann. Royal Coll. Surg. (Eng.)* *54*: 63-71. 1974.
92. Weiss, D.W., Bonhag, R.S. & DeOme, K.B.: Protective activity of fractions of tubercle bacilli against isologous tumours in mice. *Nature* *190*: 889-891. 1961.
93. Zweifach, B.W., Kivy-Rosenberg, E. & Nagler, A.L.: Resistance to whole body x-ray in rats made tolerant to bacterial endotoxins. *Amer. J. Physiol.* *197*: 1364-1370. 1959.

