

Multiple Myeloma:
Beneficial Effects of Acute Infections
or Immunotherapy (Bacterial Vaccines)

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TABLE OF CONTENTS

INTRODUCTION	3
TABLE 1. CONCURRENT INFECTION, INFLAMMATION OR FEVER: 4 CASES	12
Detailed Histories of these cases	14
TABLE 2. IMMUNOTHERAPY: 14 CASES	24
Detailed Histories of these cases	31
DISCUSSION	63
BIBLIOGRAPHY (71 REFERENCES)	64

INTRODUCTION

Multiple myeloma is a malignant tumor which arises from cells normally present in bone marrow. It is characterized by multiple foci and occurs chiefly in males between the ages of 40 and 60, the peak incidence being about 55 years. It is twice as frequent in males as in females. Occasionally it may present itself as a solitary lesion, but practically all cases will develop multiple lesions if adequately followed.

In 1928 Geschicter and Copeland were the first to review all the published cases of multiple myeloma and together with 13 cases personally observed this comprised 425 cases. (30) A more recent review (1960) is that of Osgood who made a statistical study of 600 cases including 33 personally observed (57). In 1963 Best et al reported on a group of 185 cases seen chiefly since 1956 (6) and Korst et al summarized the results in 170 cases treated by the Midwest Cooperative Chemotherapy Group. (38)

Although a rare disease, cases of multiple myeloma have been reported in the United States, Canada, all parts of Europe, the U.S.S.R., South America and Australia. It does not seem to occur more frequently in any particular social class nor in any special region or climate. Incidence is highest between the ages of 40 to 70, but cases have occurred as early as age 16 or as late as age 78.

Diagnosis:

Multiple myeloma is essentially a malignant tumor of the red bone marrow, with multiple involvement of ribs, sternum, clavicles and spine. About 40 per cent of the patients also have involvement of the skull or extremities about the shoulder or pelvic girdle.

The cells develop from the primitive cells of the hematopoietic system. The most frequent type is plasmacytoma, the erythrocytoma being the least frequent. The abnormal plasma cells are almost always found in the sternal marrow even in patients with apparently solitary myeloma. Metastases are found in the lymph nodes, spleen, liver and other viscera, very rarely in the lungs. Some observers believe it is essentially a primary tumor which metastasizes to other bones. There are two main types of the solitary lesion: a) the osteolytic which is sharply demarcated with little expansion, occurring usually in a vertebra or shaft of a long bone; this type may be differentiated from metastatic cancer or other osteolytic bone tumors; b) the giant cell type, which is multilocular and osteolytic, with sharp demarcation and occasional expansion. This type must be differentiated from

INTRODUCTION

giant cell tumors and fibrocystic bone disease. These tumors vary in size from a pin point to an orange but are generally 0.5 to 1.5. cm. in diameter. (29) Often many small lytic areas expand and coalesce to form larger lytic punched out areas.

Onset is usually insidious, with malaise, weight loss, anemia, gradually failing health, abnormal bleeding or renal symptoms. Pain is the first dominant symptom. This is vague, wandering, "rheumatic type". At times it may develop suddenly, especially when associated with a pathologic fracture. Pathologic fracture of a rib is acknowledged to be pathognomic for plasma cell myeloma. In 70 per cent of the cases pain occurs in the lumbar or sacral regions and it often radiates down the legs, is aggravated by motion or pressure. Such sudden sharp exacerbations, often brought on by the strain of lifting or an unexplained fall, first calls the patient's attention to the severity of his illness. In the final stages of the disease the suffering is most agonizing and complicating root pains, paresthesias and neuralgia occur.

Tumor formation may be the initial symptom. X-rays may reveal minimal decalcification of bone in the early stages, and no characteristic findings to permit differentiation from osteomyelitis or from primary or metastatic bone tumor. A single focus may be present for many months, or rapid development of multiple bone lesions may ensue, which may or may not be symptomatic. In typical, and especially in advanced cases, there are multiple punched out, discrete, circular, radiolucent areas of bone destruction in the skull, ribs, pelvis, spine or other bones. Some patients die with few or no bone lesions demonstrable by x-ray. (29)

Blood calcium may be normal but in 20-50 per cent of the cases it is elevated. Inorganic phosphorus is rarely decreased but may be elevated in the terminal stage. Alkaline phosphatase is seldom increased, acid phosphatase is normal. Hemoglobin, rbc, wbc and differential blood counts are often normal, but anemia tends to develop as the disease advances.

Impairment of renal function is a frequent and serious complication and is seen particularly in those patients who excrete Bence Jones protein in the urine. This abnormal protein readily passes the glomerular membrane and precipitates giant casts all through the tubular system. The ensuing tubular blockade must be one of the main causes of renal insufficiency, but reabsorption by the renal epithelium of large globules of protein may be another reason for tubular damage. The uremia caused by the "myeloma kidney" is hardly ever accompanied by hypertension. (67)

Fahey et al (1963) found that antibody responses to antigen administration was impaired in all their multiple myeloma patients, and this was related significantly to their susceptibility to infection. Impaired antibody response and low levels of

INTRODUCTION

normal gammaglobulin components indicate that reduction of normal plasma cell function is a prominent feature in multiple myeloma. (21)

The final step in assuring a correct diagnosis is the microscopic examination of tissue removed from a lytic area or by aspiration or incisional biopsy, or by sternal marrow studies when bone lesions are inaccessible. Occasionally myeloma cells enter the blood in sufficient numbers to give a leukemic picture: plasma cell leukemia.

In summary, the principal features of this disease are multiple involvement of skeletal trunk, pathologic fracture of a rib or vertebra, characteristic backache and signs of early paraplegia, Bence Jones protein in urine (may be present in only 50% of cases), otherwise unexplained anemia, chronic nephritis, azotemia, low blood pressure, increased susceptibility to infection.

Treatment and Prognosis:

Many methods of treatment have been used for multiple myeloma, but thus far none seems to have been truly effective in preventing an ultimately fatal outcome.

There is evidence that these lesions are somewhat radiosensitive and therefore radiation has been used for over half a century on most of these patients for treatment of symptomatic lesions as they occur. (29) It remains a most useful palliative agent. Following radiation, pathologic fractures may rarely heal.

Snapper used stilbamidine and pentamidine in treating these lesions. (67a) Higinbotham preferred urethane to other chemotherapeutic agents and stated he had three or four cases who survived five to ten years on urethane. It was the only drug to his knowledge that will reverse a positive Bence Jones proteinuria and at least it gives early and prompt relief of pain. Of course, like all other drugs, it is not a cure. (10)

Among those who have used melphalan (also known as sarcolysin or phenylalanine mustard (PAM)) in multiple myeloma, Brook et al noted that most patients responding to treatment showed the first signs of improvement by the 123rd day, or after receiving a total dosage of 5.0 mg/kg. (9) They felt that the effectiveness of melphalan in multiple myeloma appears to be most promising from the results of their series and previous reports, but that the ultimate evaluation will depend on an effect on survival. This agent causes peculiar dystrophic processes in the myeloma cells, starting with disintegration and loss of nuclear substance into the protoplasm and beyond the cell boundary and ending in focal osteosclerosis. Under treatment pathological fractures may heal, and the bone marrow picture may eventually become normal. Bergsagel (5) was convinced that this agent seemed to be the most effective presently available for the treatment of multiple

INTRODUCTION

myeloma. The improvement in survival was gratifying, but only 50% of the patients showed subjective response or symptomatic improvement with this therapy. In their series of 64 patients there was evidence of skeletal healing in five after 10-18 months' follow up, and there appeared to be a significantly improved survival rate. Many of the patients who responded were symptom free four years after beginning treatment.(5)

Alexanian et al reported on a series of 183 patients receiving melphalan, of whom 43% demonstrated an objective response.(3) Ten percent responded to a combination of melphalan and prednisone, 35% to intermittent melphalan and 19% to daily melphalan therapy. Symptoms decreased in all the responding patients. Median survival for patients treated with melphalan-prednisone was about six months longer than for those treated by melphalan alone. They concluded that their results support the use of intermittent courses of concurrent large doses of melphalan and prednisone in these patients.

Vélez-García and Maldonado (69) recently reported on a series of 38 cases of multiple myeloma and concluded that melphalan is the chemotherapeutic agent of choice which together with other alkylating agents such as cyclophosphamide remain the most desirable chemotherapeutic agents in this disease. An assortment of other supportive measures such as early ambulation, fluorides, systemic calcium and a comprehensive management can help yield a longer survival in these patients.

Pain in multiple myeloma is the most disturbing characteristic of the disease and its rapid alleviation, without use of narcotic analgesics is a main aim of therapy. Most of their patients improved remarkably within 10 days of beginning melphalan therapy.

As a part of a large screening program Costa et al administered vinblastine to 17 multiple myeloma patients. No significant activity against the disease was demonstrated. (17)

Dawson reported on the effects of cyclophosphamide in a 38 year old man with multiple myeloma, in which pain ceased, and submandibular masses and abnormal proteins disappeared, with opacification of all bone deposits. The remission lasted 17 months after treatment ceased. Another course caused an equally good remission lasting 11 months. This patient also received local irradiation of the pelvic and vertebral deposits. Later melphalan was begun, but stopped after a short time due to side effects. Death from rapidly progressive disease occurred 62 months after the first course of cyclophosphamide. They believed this to be the first case of sclerotic repair of osteolytic myelomatous bone lesions on two occasions following chemotherapy. (20)

INTRODUCTION

Korst et al used cyclophosphamide for up to 60 days on 170 patients. Complete regression occurred in 1 percent, moderate in 6% and mild in 18%. Responses to treatment were often delayed for several months. There was a good correlation between serum protein changes and clinical improvement. The bone marrow improved in some patients, but radiologically demonstrative improvement was rare. The mean survival time of the cyclophosphamide treated patients was 32 months as compared to 9.5 months in untreated patients.

Albert-Ludwigs et al (38) in a statistical study of 69 patients treated at the Freiburg University Clinic from 1947-1960, noted that prognosis was poorest in the sixth decade of life and there was no sex difference in life expectancy. The mean duration of the disease prior to first treatment was 9.1 months. Prolongation of survival time by treatment with ionizing radiation, urethane, cytostatic agents and corticosteroids seems likely but could be confirmed only for the alkylating agents. Irradiation did not prolong the survival time and showed no advantage over non-specific supportive measures.

It is of interest that in this series the survival time increased with an increase in the duration of the disease prior to initiation of treatment.

Osgood made a statistical study of the effects of various types of therapy being used in recent years, including urethane, P³², and the corticosteroids. He stated that the results "strongly suggest that none of the therapeutic methods now in use is different from any other in their effects on survival time and it may be that they are not different from what would be found in a series of patients treated by supportive methods only." (57)

This suggestion may deserve further consideration, for several authors reporting rare cases of long term survival of multiple myeloma have noted that these often seemed to occur in patients who received no treatment until late in the course of their disease or who were untreated. For example, Bayrd reported four unusually long survivors who lived from four to 13½ years. (4) The longest survivor (who was still living) had received no treatment at all. Davison and Balser reported that one of their 12 cases, who survived 16 years, had no treatment for seven years after onset of rib pain. (20) Feinleib & McMahon noted that patients who had symptoms for more than a year prior to diagnosis had a longer survival period. They also found that the median duration of survival of Jewish women was more than twice as long as non-Jewish women with this disease. (22)

Zinneman noted that his series of 64 patients with multiple myeloma showed a marked tendency to recurrent bouts of bacterial pneumonia. Ten of his myeloma patients were challenged with polysaccharides of pneumococci, *Brucella abortus* or typhoid-paratyphoid vaccine. Their serum antibody response was poor. There was evidence to suggest that the antibody response occurred in inverse ratio to the amount of globulins. (71)

INTRODUCTION

These findings suggest that immunological or epidemiological factors may play a role in the response of these patients to this disease.

Thus it would seem that with the exception of the alkylating agents none of the accepted methods of treatment appear to have been able to alter the uniformly unfavorable prognosis in multiple myeloma. The average duration of life from onset of symptoms in most published series is 18 to 24 months (22, 29, 30, 57).

However, a survey of cases of multiple myeloma who received bacterial toxin therapy alone or combined with radiation or other agents, has recently been made in connection with end result studies of other types of malignant tumors treated by this method (24-28, 49, 51, 52, 58, 59) or who developed concurrent infections. (53) Cases included for this study (with one exception, Case 8) had microscopic confirmation of the diagnosis; the first 12 received at least ten or more injections of the mixed toxins of *Streptococcus pyogenes* and *Serratia marcescens*, known as Coley toxins, the last two received a preparation of *Lactobacillus acidophilus Bulgaricus*, known as AB.

Three of the four infection cases survived 9, 4½ and 4 years after onset of symptoms. The fourth was still alive when reported in 1959. (58) The average survival period of the 12 Coley toxin treated cases was four years and three months, which is well over twice the usual survival period expected in such cases. Eight of these patients lived from four to ten years. One survived only five months (Case 9), a boy of 16 in which the diagnosis was originally regarded as generalized Ewing's sarcoma. He received injections for 3 ½ weeks combined with radiation for widespread skeletal involvement, without apparent benefit. Since multiple myeloma is so rarely seen under the age of 30, this case is atypical. The two cases receiving AB are discussed below.

That the duration of toxin therapy may be an important factor in treating this disease is suggested by many of these cases, for example: Case 1, treated by Thomas (68). This patient is the only one to have been treated solely by toxin therapy (following laminectomy and partial curettage). The initial rather brief course of toxins produced a prompt regression and remission of symptoms. When these recurred the toxins were resumed and continued for two years. This patient made a complete recovery. He died five years after onset of acute lobar pneumonia. Postmortem examination revealed no further evidence of multiple myeloma.

In some of the toxin treated cases the injections were not begun until the condition was grave, with paralysis, severe weight loss, and widespread involvement (Cases 2, 3, 8). That remissions could be produced in these cases is significant. Pain relief following toxins was noted in almost every case.

INTRODUCTION

Radiation was also administered in ten of these toxin treated cases (all but Case 1 and 12). There is evidence to suggest that in the cases where toxins were given before as well as during or after the irradiation they may have protected the patient against the deleterious effects of the radiation, as has now been proven to occur in animals (1, 10). For example, Case 8 received injections prior to being given whole body irradiation in the Heublein unit, and they were resumed shortly thereafter. He recovered, married and appeared to be symptom-free for the next four years. No other patient receiving whole body irradiation without toxins for other neoplasms appears to have survived for more than a few weeks or months.

Therefore, in treating future cases it may be advisable to give toxin therapy prior to rather than after irradiation.

The four infection cases are quite dissimilar. The possible effect of the infections in Garland's case is rather difficult to evaluate for the most severe of the infections developed during the prodromal period of the multiple myeloma. However, this patient survived nine years, which is far longer than any other in Garland's long experience with such cases. (29) In two of the other infection cases a truly dramatic clinical remission lasting nearly two years occurred, in Barling's, following facial erysipelas, but this was not accompanied by hematologic remission. However, in London's unusual case (Case 3), there was complete clinical and hematological remission following serum hepatitis, and Bence Jones protein also disappeared from the urine. This remission also lasted about two years.

Warren, in an early report on artificial fever therapy alone or combined with deep x-ray therapy, in 32 hopeless cases of malignant tumors, noted that in one case of multiple myeloma a remission lasting 11 months occurred, recalcification of the lesions had begun and the patient was still alive when reported in 1935. (69)

The only other cases of multiple myeloma to receive any form of immunotherapy were recently treated in Bulgaria by Dr. Ivan Bogdanov with an oral preparation of *Bacillus acidophilus bulgaricus* which he has purified after a decade of experiments involving 2000 fractions tested initially on approximately 60,000 tumor-bearing mice. The first case was in an agonal state when his preparation (AB) was begun, having been in uremic coma for a week. He had a complete clinical remission under this treatment alone lasting 17 months and then died from a very severe influenza infection. In the other case AB was begun after x-ray and cyclophosphamide had proved ineffective in controlling pain, and had produced severe leukopenia and the patient was bedridden, his general condition serious. A complete clinical remission occurred. The patient was a Czechoslovakian physician. He returned home in complete clinical remission and began to work again, and to drive his car. He finally died in March 1973, 44 months after onset, about twice the expected survival period.

INTRODUCTION

It is hoped that these results, and those obtained earlier with Coley toxins, may stimulate other investigators to utilize various types of microbial products or other agents which may stimulate the immunological defenses in multiple myeloma patients. With greater knowledge regarding cancer immunology and further study of the optimum technique of administration, as well as better preparations, and how best to use them in combination with radiation or chemotherapy, it should be possible to improve the results obtained in the past, and thus offer greater hope for these patients, not only of prolonged survival, but of more effective and complete control of the disease, achieved with little or no serious toxic side effects.

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TABLE 1: MULTIPLE MYELOMA WITH CONCURRENT INFECTION, INFLAMMATION OR FEVER: 4 CASES

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease Date of Onset	Treatment Prior to Infection	Treatment Concurrent to Infection	Treatment Subsequent to Infection	Infection, Fever or Inflammation and Effects	End Results; Period of Survival After Onset
1. Garland 1948 (29; 55)	M 61	multiple myeloma, myeloblastic type; T8 vertebra, left 8th rib, pelvis, rt. femur; flaccid paralysis both legs, bladder difficulties; onset early July 1939; 1941 T7 and T9 vertebrae involved; urine negative for Bence Jones protein; by 1947 many new radiolucencies in skull, ribs, spine, pelvis and proximal femora	none	none	fall 1939 rib biopsied; 3 cycles x-ray to posterior thorax (3800 r); June 1941 (2100 r); October 1941 (600 r); plaster cast to lower thorax and abdomen for 2 mos.	May 1, 1939: lobar pneumonia, pleural effusion, lung abscess, fever to 103°F. (occurred 2 mos. prior to clinical evidence of myeloma); 2nd pneumonia July 1942; 3rd caused death 1948	gradually improved, large rib lesion partially regenerated; able to walk, returned 18 mos. later, stiffness of lt. foot, back pain; again improved, gained 4 lbs. in 4 mos.; remission, felt well, able to work as night watchman; spine and rib lesions partly recalcified, many new lesions apparent in skeletal films but he continued to look and feel well; death May 2, 1948 of 3rd pneumonia, almost 9 years after onset
2. Irwin 1949 (35; 55)	F 62	terminal multiple myeloma involving entire skeleton; bedridden; pathological fractures of several vertebrae; severe pain for many mos., appeared to be dying (onset October 1945)	x-ray; stilbamadine; no apparent benefit	none	spinal brace	severe facial erysipelas lasting a wk., fever to 103°F.; "improved out of all recognition", pain free, able to be up, appetite increased; general condition, morale very good; blood chemistry and x-ray appearance of bones unchanged	remission lasted 22 mos.; symptoms then recurred, severe pain, death March 20, 1950, almost 4½ years after onset

3. London 1955 (41; 55)	F 39	multiple myeloma; no Bence Jones protein present (onset February 1949); severe anorexia, anemia, increasing weakness, 16 lb. wt. loss, nosebleeds for 1 mo.	liver injections, iron tablets; sternal puncture; ACTH for 25 days (50-100 mg. daily); 4500 cc whole blood, no apparent benefit; urethane 3 mg. daily for 4 mos.	aureomycin for 2 wks. during hepatitis; 6500 cc yellow fluid removed by abdominal paracentesis	mercurial diuretics, several more paracenteses	herpes zoster; serum hepatitis; fever 100°-103° F.; ascites developed a wk. later and further herpes zoster; moribund for 5 days, icteric index to 84; after 4 wks. fever ceased, pt. no longer stuporous, blood count improved; spectacular, complete remission of all symptoms gained 25 lbs. picture of radiant health, returned to work, felt completely well, monthly blood count normal, also sternal marrow	remission lasted 22 mos., symptoms then recurred, sternal marrow positive, rapid downhill course, death 2 mos. later, March 31, 1953, over 4 yrs. after onset
4. Osuntokun 1969 (55; 58)	M 50	multiple myeloma with osteoporosis, osteosclerosis, presenting as neuromyopathy; onset, June 1937	none	October 1967 biopsy of lymph node in groin; melphalan, anti-tubercular drugs	none	discharging sinus in scrotum healed early October 1967 following diarrhea, fever lasting 2 wks.; caseating tubercular granulomata of groin with lymphadenopathy in both groins	<i>marked improvement, 20 lb. weight gain, able to walk alone; osteosclerosis of spine remained unchanged; March 1970, still ambulant, 3 yrs. after onset; lost to follow-up thereafter (Nigeria)</i>

SERIES A, INFECTION, INFLAMMATION OR FEVER, DETAILED HISTORIES

CASE 1: Multiple myeloma (myeloblastic type) confirmed by microscopic examination following biopsy of the rib lesion at the San Francisco General Hospital in San Francisco, California.

PREVIOUS HISTORY: J.P., male, aged 61. The family and previous personal history were not recorded.

INFECTION: On May 1, 1939 he developed chills, fever and chest pains which continued for two weeks when he was admitted to the medical service of the San Francisco General Hospital. Physical examination revealed dyspnea, generalized chest pains, dullness over the right upper lobe anteriorly and posteriorly and a temperature of 103.6°F. X-ray showed consolidation of the lower portion of the right upper lobe, presumably lobar pneumonia. Blood cultures finally showed an unidentified gram-negative rod. The blood Wasserman was negative. The hemoglobin was 80%, red cells 4,000,000, white cells 16,000. The urine showed albumin (unspecified type). The course was complicated by a pleural effusion and a lung abscess. On July 13, 1939 the patient was discharged as improved.

CLINICAL COURSE: Beginning about July 1, 1939 the patient began to have abdominal pain and postprandial distention which continued. About September 1, 1939 he developed a feeling of numbness over the abdomen and legs and stiffness of the legs. On September 25, 1939 he was unable to walk and had bladder difficulties. He was readmitted on September 30, 1939. The positive neurological findings were flaccid paralysis of both legs, except for slight ability to flex the thighs on the trunk and slight knee and ankle jerks equal and hyperactive; ankle clonus on the right; positive bilateral Babinski sign; cremasteric abdominal reflexes absent; absence of pain sense to the eighth thoracic vertebra; distention of the bladder; palpable spinal kyphos with crepitation in the region of the seventh and eighth thoracic vertebrae. The urine was negative for Bence Jones protein; the blood Wasserman was negative; RBC 4,700,000; WBC 8,100; hemoglobin 85%. A lumbar puncture revealed an initial pressure of 140 mm. water; jugular compression produced pain in legs, but no rise in pressure. X-ray examination in October 1939 revealed a destructive lesion with compression of the body of T8 and a large expansile lesion in the adjacent posterior third of the left eighth rib. The skull was negative, the pelvis and right femur showed several small areas of increased density. The patient was placed in a posterior shell cast.

SURGERY: On October 21, 1939 a rib biopsy was performed by Dr. Halter; grossly the lesions appeared to be a sarcoma or a myeloma. Considerable bleeding was encountered during the procedure.

SERIES A, INFECTION CASES, DETAILED HISTORIES

RADIATION: On October 25, 1939 deep x-ray therapy was begun and 1900 r was given to the anterior and 1900 r to the posterior thorax over a circular field 20 cm. in diameter, centered over T8. By November 12, 1939 the patient was able to wiggle the toes of both feet, slightly dorsiflex the feet, flex his right knee, abduct the right leg on the hip, and move both legs slightly in extension from a flexed position.

CLINICAL COURSE: He gradually improved, but x-ray examinations in November and December 1939 showed apparent progression of the left eighth rib lesion and development of new areas of rib destruction elsewhere. The spine showed no change. The patient was discharged on January 3, 1940. He was lost to follow-up and presumed dead, but on June 30, 1941 he walked in, complaining of stiffness in the left foot and back pain. Films showed further compression of T8. The margins of T7 and T9 were now involved. The large lesion in the left rib showed partial regeneration.

FURTHER RADIATION: A second course of x-ray therapy was then given to the posterior thorax, centered over T8 (2100 r in air in ten days).

CLINICAL COURSE: By August 1941 the patient was walking and looking better. He gained four pounds by October 1941. During late October he hurt his back trying to lift a man. X-ray examination revealed some molding of T12, but no change in T8.

FURTHER RADIATION: The posterior thorax was given 600 r of x-ray therapy in three days.

CLINICAL COURSE: On November 14, 1941 a plaster cast was applied to the lower thorax and abdomen. The urine was still negative for Bence Jones protein. By January 12, 1942 the pain had practically disappeared and the patient was anxious to have the cast removed. This was done and films of the spine showed more compression of T12 than was apparent on October 30, 1941. There was some recalcification of the body of T8, and of the left eighth rib. The patient was discharged and followed at frequent intervals in the out-patient department. In March 1942 he remarked: "If I were just a little stronger I would get a job in the ship yards." In May 1942 he was seen again and was doing well. He had hurt his chest two weeks earlier jumping over a creek.

FURTHER INFECTION: He continued to do well except for another attack of pneumonia in July 1942.

CLINICAL COURSE: In February and June 1943 films of the cervical spine were negative; the thoracic spine showed no significant change. He was seen again on March 8, 1944. He felt well. No further therapy was considered necessary. He

SERIES A, INFECTION CASES, DETAILED HISTORIES

continued to do well, and worked as a night watchman. Laboratory examination in January 1947 revealed hemoglobin 82%, RBC 4,200,000 WBC 8000. The urine was still negative for Bence Jones protein. However, films of the skull, spine, ribs, pelvis and upper femora showed many new radiolucencies. The spine and rib lesions were partly recalcified. The patient was again seen in November 1947, looking and feeling well. He ultimately died at home on May 2, 1948 of left lobar pneumonia. This was almost nine years after onset.

COMMENT: Note that this patient had a severe pneumonia, pleural effusion and lung abscess at the time of onset of his multiple myeloma, and a second attack of pneumonia three years later. Since it is now known that bacterial endotoxins activate the reticulo-endothelial and hematopoietic systems, this man's initial severe pneumonia, lung abscess and pleurisy may have helped increase his natural resistance to the neoplasm which was then just about to produce symptoms. The second pneumonia, three years later, may have done likewise.

REFERENCES: 29; 55.

CASE 2: Advanced multiple myeloma, affecting all the bones, confirmed by microscopic examination of the bone marrow (following sternal puncture), the blood chemistry and the x-ray examinations.

PREVIOUS HISTORY: Mrs. A.M.J., female, age 62, housewife. The family history was negative for cancer, tuberculosis or allergies. The patient had always enjoyed quite good health until the summer of 1945. She had had no serious illnesses, accidents or operations. Onset, during October 1945, she first began to have backache. The condition was not diagnosed as multiple myeloma until April 1947, 18 months after the first symptoms of pain in the back, and during this entire period she continued to have backache. The only bones involved at this time were apparently the vertebrae, and there were pathological fractures with a good deal of bone destruction.

RADIATION: In 1947 she was given deep x-ray therapy. The treatment was given at 200 kilovolts using a thoreus filter, a focal skin distance of 40 cms. giving a total dose of 3250 r to the fifth and sixth dorsal vertebrae and a tumor dose of 3250 r to the tumor of the sacrum. The other lesions were too widespread to treat efficiently with radiotherapy. Dr. B. Barling, F.R.C.P., London, England, reported that "she felt generally better for this for a short time but the pain persisted, especially in the left shoulder." She was also given stilbamadine, but Barling felt that neither this nor the x-ray therapy "had any noticeable effect on the disease. During the early part of 1948 her condition was steadily deteriorating and she appeared to be dying." (55)

SERIES A, INFECTION CASES, DETAILED HISTORIES

CONCURRENT INFECTION: He stated: "On March 12, 1948 she developed erysipelas of the face and from then onwards improved out of all recognition. With a spinal brace we were able to get her up for a short period of time. The erysipelas was severe, but was confined to her face and head and lasted six or seven days. The fever went to 103°F. and lasted five or six days. Following this infection she became free from pain. . . ." (for the first time in 2½ years). (55) It is of interest to note that the blood chemistry showed no appreciable changes and the x-ray appearance of the affected bones remained unaltered during this period of marked clinical improvement.

CLINICAL COURSE: The patient was then allowed to go home, but after a few weeks she found that the pain in her back was becoming more severe. She was readmitted to St. James Hospital and it was suggested that Coley toxins be given. However, it was never actually used. Barling reported in August 1949 that the patient felt generally better although she was still unable to get up. Her appetite increased and in "every way her appearance improved beyond all recognition." On January 23, 1950 he wrote: "Her general condition and morale are very good and ever since the attack of erysipelas she has been more or less free from pain." (55) This was 22 months after the erysipelas developed, at which time she had been in an agonal state apparently. She died on March 20, 1950, over four years after onset of backache. Barling stated that the cause of death was generalized myelomatosis, and that during the last two or three months of her life her bone pains were more severe.

REFERENCES: 35; 55

CASE 3: Multiple myeloma, confirmed by microscopic examination of sternal marrow and blood examinations.

PREVIOUS HISTORY: F.H., female, aged 39. There had been one normal pregnancy in 1936, preceded by a single spontaneous abortion. In 1945 she developed epigastric pain. Gallbladder and stomach x-rays were found to be normal. Onset, in February 1949 she began to notice the gradual appearance of yellow pigmentation of the skin of the eyelids and axillae. In July 1949 there was increasing weakness and she was examined by a physician who found she was anemic. This did not respond to liver injections and iron tablets. During the next eight months the weakness became more marked and was associated with a 10 pound weight loss, anorexia and a severe paroxysmal cough productive of mucoid sputum. Nosebleeds occurred daily for one month, but no other hemorrhagic tendency was noted. The patient was first seen by Dr. Rose E. London on February 25, 1950. Physical examination at this time revealed a chronically ill white woman with a diffuse yellowish discoloration of the skin in both axillary areas, and wide orange-yellow pigmented bands encircling the nasal half of the eyelids. The

SERIES A, INFECTION CASES, DETAILED HISTORIES

unaffected skin and mucous membranes were pale, and there was oozing of blood from a "small erosion of the nasal septum." The remainder of the examination was normal except for a mass in the abdomen, deep in the right upper quadrant, which moved with respiration and appeared to be the right kidney. During the next month very complete laboratory studies were done at Mt. Sinai Hospital, Miami Beach, Florida: Blood count: rbc. 3,080,000; hemoglobin 8.5 gm.; wbc. 17,900 with a differential count of 47% polymorphonuclear leukocytes, 51% lymphocytes, 1% myelocytes and 1% monocytes. The smear showed marked rouleaux-formation. Platelets were 60,000 per cm. The hematocrit was 20 mm. Bleeding time was normal, clotting time was prolonged. Urinalysis was normal, and no Bence Jones protein was detected. Sternal marrow showed plasma cells, 74%; lymphocytes 25%; polymorphonuclears, 6%; bands, 10%; metamyelocytes, 6%; myelocytes 2%. The plasma cells showed great variability in form, ranging from immature to adult type. X-rays of the long bones, chest, skull and kidneys were normal, except for slight demineralization of the pubic bones.

STEROID, TRANSFUSION AND CHEMOTHERAPY: Upon establishment of the diagnosis of multiple myeloma the patient was sent to another hospital to receive ACTH. The diagnosis was confirmed and 2 plus albuminuria was noted for the first time and the blood urea nitrogen was 21 mg. %. The patient received ACTH for 25 days, in doses of 50 to 100 mg. daily, in addition to 4,500 cc. whole blood without benefit. In June 1950 urethane was begun and she received 3 mg. daily for four months. During this time she lost an additional six pounds and complained of severe anorexia, repeated vomiting, nocturnal diarrhea, pain and numbness in the right leg and weakness of both hands.

CONCURRENT INFECTION: An acute attack of herpes zoster occurred but cleared in several weeks.

CLINICAL COURSE: Repeated transfusions were necessary and it was obvious that the patient was deteriorating despite therapy.

CONCURRENT ACUTE SERUM HEPATITIS: On September 8, 1950 she was readmitted to Mt. Sinai Hospital because of the onset of itching and yellow discoloration of the skin, more frequent vomiting and right upper quadrant pain. Urethane was discontinued. She was acutely ill with marked jaundice and an enlarged, tender liver. The icteric index was 600; total cholesterol 250 mg. per 100 cc. with cholesterol esters of 93 mg. %; cephalin flocculation was 4 plus and the prothrombin time was 21 seconds (control 14 seconds). Temperature fluctuations between 100° and 103°F. occurred daily, jaundice increased and the patient became alternately drowsy or hyperirritable. Aureomycin was given in 250 mg. doses every four hours for two weeks.

CONCURRENT ASCITES AND INFLAMMATION AND FEVER: On the seventh day ascites first appeared, the icteric index increased to 84, and a painful eruption of herpes

SERIES A, INFECTION CASES, DETAILED HISTORIES

zoster rapidly involved the left side of the neck and ear. The patient became increasingly dyspneic, cyanotic and stuporous. The ascitic fluid accumulated rapidly together with edema of the legs, necessitating abdominal paracentesis with removal of 6,500 cc. of yellow fluid. After five days in this moribund condition the patient began to improve. Over the ensuing four weeks the icteric index dropped, fever disappeared and the patient became alert. The liver increased in size and tenderness. At this time it was noted that the red blood cells had increased to 4,700,000 with 15 gm. hemoglobin; the total protein was 8.88 gm. with albumin 1.59 and globulin 7.29 gm.

CLINICAL COURSE: The patient was discharged on October 15, 1950. She required several more paracenteses and frequent mercurial diuretics for ascites. By the end of November 1950 marked improvement was apparent, peripheral edema and ascites had completely disappeared and the red blood count remained around 4,500,000 per cm. with 17 gm. hemoglobin. The albuminuria disappeared and the total protein dropped to 6.4 gm. *For the following two years the patient showed a spectacular and complete remission of all symptoms, gained 25 pounds in weight and was the picture of radiant health. She was able to return to work and felt completely well. Her monthly blood count, urine and total blood protein remained within normal limits, the red blood count never falling below 4,200,000 per cm. with 14 gm. hemoglobin. A sternal marrow aspiration differential on July 3, 1952 was normal with 3% plasma cells of adult type.*

On December 11, 1952 slightly more than two years following the disappearance of signs and symptoms of multiple myeloma, the patient presented herself with recurrence of her disease. There was pain, numbness, burning and weakness of both hands. There was slight pallor of the skin and mucous membranes. The pigmentation of the eyes and axillae and an erythematous appearance of the palmar surface of the hands. There was diminution in sensation in both hands from the metacarpo-phalangeal joints to the finger tips. The blood count revealed 2,960,000 rbc, 11.9 gm. hemoglobin, 9,500 wbc. The differential showed 32% polymorphonuclears, 34% band cells, 25% lymphocytes, 1% monocytes, 4% basophils; 2% promyelocytes. The total protein was 15.6 gm. globulin. The patient was readmitted to Mt. Sinai Hospital. Sternal marrow aspiration revealed sheets of myeloma cells varying in morphology from immature to mature, and comprising 90% of the marrow cells. X-rays of the long bones and skull were negative. The patient failed rapidly during the next two months with disability and excruciating pain of both hands, requiring narcotics for relief.

ANTIBIOTICS AND CHEMOTHERAPY: A severe paroxysmal cough reappeared which failed to respond to antibiotics. Because of intractable vomiting following oral urethane, this drug was given intravenously over a 10 day period beginning March 17, 1953. The patient tolerated the medication well. Two days after her discharge she developed severe pain and tenderness of the right shoulder and the upper arm was swollen and slightly mottled. During the next 24 hours she became feverish and disoriented (temperature 104°F., pulse 120, respiration 42). Chest

SERIES A, INFECTION CASES, DETAILED HISTORIES

x-rays were normal. The blood count showed 2,940,000 rbc, hemoglobin 8.43; wbc. 8,750. The patient died on March 31, 1953, over four years after onset. Post mortem examination showed multiple myeloma with involvement of the ribs, sternum, vertebrae, lungs, liver, spleen and kidney; portal cirrhosis, nephrosis; pulmonary fibrosis and cor pulmonale.

In reporting this case London stated: "The picture of multiple myeloma as presented by this patient was of a rapidly progressive disease of approximately eight months duration in which the clinical course, the pleomorphic appearance of plasma cells and the profound changes in the blood forbode an early termination. The poor prognosis was confirmed by the failure to respond to adequate therapy with adrenocorticotrophic hormone and urethane. The onset of a serious liver involvement with jaundice and ascites rapidly led to a moribund state. Following a week of hepatic coma there was an unexpected reversal of the clinical condition with complete recovery not only from the liver disease, but also from the symptoms and signs of multiple myeloma. *For two years the patient felt completely well and a monthly hematologic and total protein studies revealed no abnormalities. Even the bone marrow at the end of 21 months was normal.*

"Two features of this remission should be emphasized: (1) its length and (2) its completeness. In general the prognosis of multiple myeloma from the onset of symptoms to death is between 18 and 24 months. . . . The completeness of the recovery is the second spectacular feature. In the 51 cases reviewed by Meacham, urethane gave relief of bone pain and variable subjective improvement, but no alteration of the anemia or serum globulin. In our case the clinical status was completely normal, as were the peripheral blood, bone marrow and the total protein of the blood." (41)

In guessing at the cause of this unusual remission London considered that the marked derangement of metabolic processes produced by severe hepatocellular damage had a prolonged suppressive effect upon the myeloma cell and added: "It has been noted that acute infections occasionally alter the course of chronic infections or malignancies. . . . Certainly in our case there was fundamental derangement of all metabolic processes. The fact that severe liver derangement was followed by remission appeared to be more than coincidental."

REFERENCE: 41

CASE 4: Multiple myeloma, confirmed by bone marrow aspiration and blood examinations.

PREVIOUS HISTORY: A.O., male aged 50. Onset in June 1967 he developed numbness, sensation of pins and needles and progressive weakness in the lower limbs with difficulty in walking.

SERIES A, INFECTION CASES, DETAILED HISTORIES

CONCURRENT TUBERCULOSIS, DIARRHEA AND FEVER: In August 1967 he noticed a discharging sinus in his scrotum. In early October he developed diarrhea and fever lasting two weeks. The sinus in his scrotum healed just prior to admission in October 1967. Examination revealed no disturbance in sphincteric function, but the patient had low back pain and was unable to walk due to this pain and weakness. He was emaciated with marked pallor of the mucosa. There were a few palpable glands in the groins and the right axilla. The scrotum showed a healed scar. There was marked tenderness over the lower fourth of the right metacarpal bone; symmetrical weakness and wasting of the small muscles of the hands and the distal part of both forearms; a fine tremor of the outstretched hands, bilateral foot drop, with marked wasting of the muscles of the anterior tibial compartments and the quadriceps femora; no fasciculations were seen; no sensory loss was demonstrable; knee and ankle jerks were absent; the plantar reflexes were extensor; the peripheral nerves were not palpably enlarged. No palpable abnormality was found in the chest, cardiovascular system, liver, kidneys or spleen. Blood count showed hemoglobin 7.4%, w.b.c. 4,700 with a normal differential. The urine contained Bence Jones protein. X-ray examinations showed diffuse multiple infiltrates in both lung fields. The vertebral column and pelvis showed osteoporosis with new bone formation around the 4th and 5th lumbar vertebrae (osteosclerotic bridging). There was a general decrease in bone density of the hands with a rounded lucency at the base of the fourth metacarpal. Plain radiographs of the skull showed no abnormality. Bone marrow aspiration showed hypocellular marrow fragments and the appearance was consistent with multiple myeloma. Culture of the bone marrow for mycobacterium tuberculosis grew no organism after six weeks. Electromyography findings were suggestive of a neuropathy.

SURGERY: A biopsy from the right quadriceps muscle showed a histological picture consistent with neuromyopathy. A biopsy of one of the lymph nodes in the groin showed caseating granulomata consistent with tuberculosis. A biopsy of the rectal mucosa showed no evidence of amyloidosis. The diagnosis of multiple myeloma, associated with neuromyopathy, osteoporosis with some osteoblastic reaction, and concurrent tuberculous adenopathy was made.

CHEMOTHERAPY: The patient was given melphalan (2 mg. initially for two weeks, then 4 mg. daily for four weeks, and then 2 mg. daily twice weekly). He also received streptomycin for three months and isonicotinic hydrazide and para-amino salicylic acid for 18 months.

CLINICAL COURSE: His condition improved remarkably. The pain in the low back and right wrist gradually subsided. The low grade fever he ran before treatment returned to normal. He gained 20 pounds in weight in six weeks. The erythrocyte sedimentation rate fell to 40 mm/1st hour (Westergren) in six weeks. (It had been 135 mm/1st hour on admission) He still had considerable osteoporosis on discharge, but was able to walk on his own. The osteosclerosis of the spine remained

SERIES A, INFECTION CASES, DETAILED HISTORIES

unchanged. The patient was last seen in March 1970, still ambulant, although he had lost a good deal of weight. This was two and a half years after onset. He was lost to follow-up thereafter.

REFERENCES: 55; 58

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TABLE 2: MULTIPLE MYELOMA TREATED BY IMMUNOTHERAPY: COLEY TOXINS, 12 CASES; AB, 2 CASES

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease Date of Onset	Treatment Prior to Immunotherapy	Concurrent Treatment	Subsequent Treatment	Type of Toxins Technique Reactions, Effects	End Results; Period of Survival
1. Thomas 1901 (11, 12, 13, 15, 68)	M 39	multiple myeloma proximal dorsal spine involving rib, with compression of cord, retention of urine, uncertain gait, Bence Jones protein in urine; onset, August 1900, severe pain, girdle sensation	explored December 20, 1900; incomplete curettage followed by complete paraplegia, retention of urine; mass in rib enlarged	none	none	Coley toxins (Buxton VI), January 1901, every 3rd day; marked reactions at first; gradual regression, no pain, ate, slept, walked well, felt fine; toxins stopped; recurrence, very severe pain (due to pathologic fracture of rib?) toxins resumed, continued 2 years, growth regressed completely, rib regenerated	complete recovery, NED until sudden death April 1906, acute lobar pneumonia, over 5½ years after onset, autopsy revealed no evidence of multiple myeloma
2. W.B. Coley 1927 (12, 13, 14, 34, 46)	F 45	plasma cell myeloma involving proximal 1/3 lt. femur, pathologic fracture; numbness, "pins and needles" toes of lt. foot, difficulty in walking (onset April 1919, 6 mos. after fall) complete loss of power lt. leg, partial in rt. leg suggesting spinal involvement; 25 lb. weight loss	treated for rheumatism, exploratory operation May 1921; spica applied	1 radium pack (8924 mch) to femur 2 mos. after toxins begun	none	Coley toxins (Parke Davis XII) July 18, 1921, tried for moral effect, daily at first 51 i.m. in 5 mos., 9 chills, 3 marked reactions (103°-106°F.); x-ray evidence of improvement in 3 wks., general condition improved steadily, bone regenerated, gained 20 lbs., gradually recovered strength	in excellent condition - asymptomatic until July 1923; "attack of unconsciousness", cause unknown; disease reactivated in ribs, brain that autumn; refused further treatment; death December 1923, over 3½ years after onset

3. W.B. Coley 1931 (13, 14, 15)	M 56	terminal multiple myeloma involving spine, several ribs, vocal cord, complete paraplegia 56 lb. weight loss, paralysis of 1 vocal cord, trophic ulcers gluteal region, lt. foot; very weak, frequent vomiting, coughing spells; onset 1922, vague pains radiating down legs	x-ray caused considerable relief; May 1924 laminectomy, incomplete removal; x-ray relieved paralysis, pain but not incontinence of bladder and rectum; further x-ray spring 1928 for recurrence of pain, paralysis, no effect	few x-ray treatments during 1st mo. of toxins; x-ray (3) before and during 2nd course toxin injections; final x-ray late 1932, not effective	none	Coley toxins (Parke Davis XIII) September 1928; 17 i.m. in next 27 days; almost immediate continuous improvement, very much stronger in 6 wks.; ulcers healed, vomiting ceased, nutrition improved, gained weight, voice nearly normal, no toxins given in October 1928; sudden pain r.u.q. October 22, 1928, doughy mass in gall bladder region, clay colored stools, slight jaundice; injections resumed about November 1, 1928, given i.m. for 3 mos.; complete recovery; final course of toxins late 1932, no apparent benefit	in good health 4 yrs.; late in 1932 disease reactivated; death January 1933, 10 yrs. after onset
4. W.B. Coley 1929 (8; 46)	M 48	multiple myeloma lt. humerus and scapula; onset sudden sharp pain (strain at work) June 28, 1929	"electric treatments", November 1929; x-ray (2); radium (50,000 mch) to humerus	radium pack (8000 mch) December 17, 1929; arm immobilized in spica (did not prevent pathologic fracture)	interscapulo-thoracic amputation January 29, 1930	Coley toxins (Parke Davis XIII) November 20, 1929; wound suppurated February 8, 1930; 2nd course toxins 13 days p.o., 9 i.v. in 20 days (only 2 reactions of 103° F.), wound healed well;	patient became manic-depressive, committed to State Hospital October 1930; disease reactivated summer 1931, generalized fractures in 3 ribs, death November 26, 1931 almost 2½ years after onset

TABLE 2: MULTIPLE MYELOMA TREATED BY IMMUNOTHERAPY (con'd.)

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease Date of Onset	Treatment Prior to Immunotherapy	Concurrent Treatment	Subsequent Treatment	Type of Toxins Technique Reactions, Effects	End Results; Period of Survival
5. McFee 1936 (14; 42; 55)	M 44	multiple myeloma lt. femur (10 cm.) pathologic fracture; onset August 1929 (urine generally negative for Bence Jones bodies until November 1934)	curettage, cautery October 15, 1929; fracture during convalescence	none	Thomas splint for 2nd pathologic fracture March 1930; x-ray 3300, 2 in next 3½ mos.; x-ray 1932 to spine, pain ceased, lesion healed	Coley toxins (Parke Davis XIII) January 11, 1929 given by Bloodgood: 20 i.m. in 21 days; pain ceased almost at once, regeneration of bone soon evident; toxins stopped after severe reaction at patient's request; returned to work, restaurant manager; well 2 yrs.	disease reactivated October 1932 in L3 vertebra; well 2 more yrs. after x-ray to spine; then rt. fibula involved though appeared clinically well; November 1934 progressive anemia, disease generalized, death November 29, 1936, 7 yrs. after onset
6. W.B. Coley 1930 (8; 14; 34)	M 15	multiple myeloma bony pelvis, vertebrae (D11, possibly L2 and L3); ribs, distal rt. tibia, possibly fibula, (epilepsy since birth); onset early 1930 after fall on ice, anemic, urine positive for Bence Jones protein	incisional biopsy rt. ilium March 1930	x-ray begun 10 days after toxins; transfusion (500 cc)	none	Coley toxins (Parke Davis XIII) March 26, 1930 i.m. and i.v. for 3 wks.; 1 more injection May 1, 1930, marked reaction	very severe anemia (1,270,000 r.b.c.), death May 5, 1930, 5 mos. after onset
7. W.B. Coley 1930 (14, 34)	M 31	multiple myeloma lt. 6th rib, skull; broke several ribs with severe hemorrhage in accident prior to onset fall 1929; fainted, fell, pathologic rib fracture January 1930, intense pain	incisional biopsy	radium pack (10,000 mch each to skull, rib)	radium to chest late April 1931 caused radiation sickness; morphine for severe pain that summer; returned to work; x-ray to hip, chest, skull, fall 1931, given weekends so he could work	Coley toxins (Parke Davis XIII) March 31, 1930, 8 i.m., 3 i.v. in 11 days; mild reactions (maximum 101.2°F.) injections continued at home, duration and reactions not recorded; disease arrested, rib regenerated somewhat	disease then progressed, by April 1931 involved 3 ribs, proximal femora, iliac bone, ischium; down hill course, stopped working late January 1932, death February 17, 1932, 27 mos. after onset

8. W.B. Coley & Fitzsimons 1938 (14; 23; 46; 55)	M 39	multiple myeloma involving ribs, spine, skull, pelvis, femora; anemia, large amount albumin in urine; 30 lb. wt. loss; (onset May 1932, contracted severe cold, severe pains over entire body; cold cleared, lumbar pains persisted)	x-ray (10) September 1932, some temporary improvement; severe chest pain 10 days later; 1 more x-ray; apparently improved somewhat but lost 30 lbs. in 5 mos.	whole body x-ray (30%) erythema dose in Heublein unit	transfusion (600 cc)	Coley toxins (Parke Davis XIII) October 1, 1932 begun by Lambert given i.m., no reactions; referred to W.B. Coley; injections every 24-48 hrs., i.m., then i.v. (latter gave reactions 102°-105° F.); toxins resumed immediately after x-ray, given i.v.	complete clinical recovery, in best of health, married, returned to Ireland; well 4 yrs. then fell from bicycle, fracturing rt. femur; x-rays showed widespread skeletal disease; much Bence Jones protein in urine, but general health appeared excellent; bedridden due to fracture, cold abscesses, profuse discharge, extreme cachexia; death in 3 mos. over 6 yrs. after onset
9. W.B. Coley (14; 34; 46)	M 61	multiple myeloma lumbar, dorsal vertebrae, skull (onset early 1934, dull lumbosacral pain increasing in severity, diagnosed as lumbago, then as Ewing's sarcoma at Mayo Clinic); patient a urologist	physiotherapy; x-ray to spine, 1800 r at Mayo Clinic; further x-ray at Memorial Hospital to spine, 500 r, and to skull, 1400 r	spinal brace applied, further x-ray, 400 r to rt. and to lt. skull, 600 r to lumbar, 400 r to dorsal spine	morphine September 1934	Coley toxins (Parke Davis XIII) February 8, 1934; 8 i.m. in 13 days, little reaction except once (103.2°F.); complete pain relief in 3 wks.; 7 more injections toxins after x-ray, 1 very severe reaction; concurrent influenza; felt very well by May 1934, gained wt., blood improved	disease reactivated by September 1934, progressed very rapidly in ribs, especially adjacent to sternum; death September 19, 1934, 9 mos. after onset

TABLE 2: MULTIPLE MYELOMA TREATED BY IMMUNOTHERAPY (con'd.)

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease Date of Onset	Treatment Prior to Immunotherapy	Concurrent Treatment	Subsequent Treatment	Type of Toxins Technique Reactions, Effects	End Results; Period of Survival
10. Memorial Hospital (46)	M 42	multiple myeloma frontal bone, lt. parietal, D7 and D8 vertebrae, lt. mid humerus, 4th rib adjacent to sternum, apparent primary; (onset spring 1940 following pneumonia, pleurisy, empyema, pleurotomy; had had severe headaches all his life; after onset they were more frequent and severe)	growth excised from lt. anterior rib November 1941	June 22-July 1942 liver extract every 2nd day; x-ray to 5 affected areas in skull, vertebrae, humerus (1500 r each)	spinal brace applied; further x-ray September 1942 (800 r to D8 vertebra, 1200 r to L4 vertebra); sulfadiazine for pneumonia; November 1943, transfusion; December 1943, x-ray to chest (1800r)	March 1942 acute streptococcal pharyngitis, bronchopneumonia; ethmoid sinusitis, otitis media, mastoiditis (Strep. hemolyticus); Coley toxins (Parke Davis XIII) June 14, 1942, 22 in 30 days, at first moderate reactions, then 7 marked reactions, (104°-105.4°F.) marked subjective improvement, back pain disappeared but D7 vertebrae partially collapsed; marked palliation; all bony lesions healed by October 1942, in excellent health, no longer anemic, gained weight, able to work; bronchopneumonia; urine positive for Bence Jones protein	disease progressed, December 1943 patient weakened, speech affected due to involvement of brain, skull, alveolar process, death April 10, 1944, 4 yrs. after onset

11. B.L. Coley (46)	M 47	multiple myeloma rt. 6th rib, pathologic fracture (fell November, 1946; shortly after developed sharp pain under scapula after severe sneeze; patient had overworked during World War II)	rib resected, lesion size of lemon present	penicillin (1,500,000 units)	penicillin for 10 mos. at monthly intervals, total 10,000,000 units; March 1948 x-ray to skull (2400 r); complete regression, asymptomatic; pathologic fracture 7th rib summer 1948, x-ray to asymptomatic lesion L3 October 1949, also to shoulder for pain; urethane, violent emesis, continued 1950	Coley toxins (Parke Davis XIII) January 15, 1947; 12 i.v. in 13 days, reactions averaged 102°-103°F. (maximum 104°F., minimum 101.4°F.), did well, returned to work, played golf, asymptomatic; x-rays negative until March 1948 then lesion seen in skull above mastoid	disease progressed lesions to lower jaw, pubic bones; intestinal flu, severe cold early 1950, another October 1950; (2 more ribs fractured during coughing); another u.r.i. May 1951, pain worse; death February 2, 1952 5 1/4 yrs. after onset
12. Fowler (55)	F 61	multiple myeloma involving lt. 7th rib and lt. mandible, rt. humerus, rt. femur, onset pain in rib about January 1961	injections of procaine to rib region; incomplete excision of mandibular region January 1962	none	put on 1000 calorie diet 1966 for obesity; morphine for pain terminally	Coley toxins (Johnson XV), February 14, 1962, 65 i.v. in 19 mos., reactions 100°-104°F.; did well for a yr. then developed lesion in mouth, deglutition very difficult, appeared terminal, brisk bleeding from tumor in cheek; growths gradually regressed, regained lost weight (very obese), normal activities until January 1966, pathologic fracture lt. humerus, it healed, toxins resumed briefly	progressive bone lesions in various areas; recurrence of buccal tumor, 2nd pathologic fracture humerus shortly before death, January 12, 1967, over 5 yrs. after onset

TABLE 2: MULTIPLE MYELOMA TREATED BY IMMUNOTHERAPY

Author Date Published (References)	Sex Age	Histologic Diagnosis Extent of Disease Date of Onset	Treatment Prior to Immunotherapy	Concurrent Treatment	Subsequent Treatment	Type of Toxins Technique Reactions, Effects	End Results; Period of Survival
13. Bogdanov (55)	M 47	multiple myeloma involving entire skeleton (onset May 1968); at first diagnosed as nephritis, unbearable pain in all bones, condition gradually deteriorated, severe cachexia, extreme weakness, could not raise hands, then stuporous, in uremic coma for 1 wk., moribund	biopsy	none	none	Bacillus acidophilus Bulgaricus (AB) August 12, 1968, given orally 3 times daily before meals, regained consciousness during 1st wk., general condition, appetite improved, spontaneous pain diminished; recovered his voice in 15 days, pain free, drugs no longer required; improvement continued: after 1 yr. of treatment, symptom-free, able to walk without help, using cane; able to look after himself when discharged; complete clinical remission	early in January 1970 death from very severe influenza (did not receive medical aid in distant village where he lived), this was over 18 mos. after onset
14. Bogdanov (55)	M 42	multiple myeloma vertebrae T4, T8, and L3 (onset about July 1969); extremely severe girdle pains prevented any movement, even deep breathing; bedridden	x-ray to spine; Endoxan, causing severe leukopenia (1500) but no pain-relief	none	Endoxan resumed after 9 wks. of AB condition very soon deteriorated wbc 2500; pain in lt. hand; Endoxan stopped September 8, 1970	Bacillus acidophilus Bulgaricus (AB) June 16, 1970; appetite, general condition, blood picture gradually improved, pain ceased; normal condition in 9 wks.; oral AB resumed in larger doses September 18, 1970 continued steadily for at least 18 mos.; patient more active, 3 diffusely osteoporotic vertebrae recalcified	clinical and hematological remission continued; returned to Czechoslovakia in full clinical remission; began to work (was a physician), drove his car, etc.; died March 1973, 44 mos after onset

**SERIES B: PLASMA CELL MYELOMA TREATED BY
IMMUNOTHERAPY: COLEY TOXINS, 12 CASES; LACTOBACILLUS
BULGARICUS (AB), 2 CASES: DETAILED HISTORIES**

CASE 1: Multiple myeloma, primary in the spine with compression of the cord (for full histological report see 68, p. 368).

PREVIOUS HISTORY: Male, aged 39, married, a lawyer. The family history was negative. The patient had diphtheria at ten, and an ulcerated throat at 15. He married at 37. At this time he had an attack of urticaria. He had never had syphilis, rheumatism or any antecedent local trauma. Onset, August 15, 1900 he was attacked by a severe pain between the shoulders, which confined him to bed for four or five days. After this time a certain amount of pain persisted in the back. About October 1st he noticed a slight uncertainty in the use of his legs. The feet were numb and there was a girdle sensation in the abdomen. Once, on stooping to pick up something, he fell to the floor. He also noticed some difficulty in retaining his urine, after the desire to micturate came on, and there was some difficulty in starting the stream. He also had a slight lessening of sexual desire, but no loss of power. No dizziness, no headache. Pain in the back, between the shoulders, was aggravated on motion, diminished with rest. Examination, October 18, 1900, showed nothing abnormal in his gait, but some swaying on standing with his eyes closed. No ataxia or incoordination in the movement of arms or legs, though the patient said it was diminished in the legs. All reflexes in the arms were normal and equal; also the knee-jerks were normal, reinforcible and not increased. There was no ankle-clonus and no front-tap contraction. The plantar reflex was absent on both sides, as were the cremasteric, abdominal and epigastric reflexes. Sensation to touch and pain was diminished below the level of the eighth dorsal vertebra and the eighth rib. Pupils were normal to light and accommodation. There was no tenderness of the spine, to pressure or percussion. There was a slight general kyphotic curve of the spine, more marked in the upper dorsal region, and the movements of the spine were fairly free. No muscular spasm could be made out and there was no pain in the back or pressure upon the head. A diagnosis of pressure upon the spinal cord, probably from a tumor in the upper dorsal region was made, and a plaster of Paris jacket, massage and vigorous antisyphilitic treatment advised. The patient was seen again on November 16, 1900, a month later. The gait had become slightly ataxic. There was slight disturbance of the sense of position of the toes, slight weakness of the legs, ankle-clonus of both feet, sensation of pain and temperature much diminished, and that of touch diminished to the level of the fourth rib, and the fourth dorsal spine in the back. There was no tenderness of the spine to percussion or pressure. Motion, which before had been painful, was free and painless at this time. The patient said uncertainty of gait had increased and difficulty in controlling the bladder continued, although girdle sensation had gone. On December 17, 1900 he was seen

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

again, in consultation with Dr. P.C. Knapp. The gait was slightly spastic-ataxic, Romberg's symptom was present, there was incoordination of the legs, marked general paresis of the legs, most marked on flexing the thigh on the trunk. The sense of pain and temperature were absent and that of touch diminished below the level of the sixth dorsal vertebra. The pupils reacted sluggishly to light, and the left was slightly larger than the right. There was a slight swelling on the left fifth rib, which had been noticed before, but no tenderness on pressure. Bence-Jones bodies were present in the urine.

SURGERY: An operation was performed December 20, 1900, by Dr. J.C. Munro. The first, second, third and fourth dorsal laminae were removed. The lamina of the fourth on the left side was thin and bluish, with the cortex destroyed over a small area on the upper posterior surface. The medulla of the spinous process and of the lamina was full of soft reddish-brown material, and was found extending through the head of the rib, which was not eroded, to the left side of the vertebral body, where the bone was loose and rough, easily bleeding, and evidently infiltrated with new growth. Probably some of the same growth lay anterior to the lamina, pressing upon the dura, but without infiltrating it. The dura looked healthy and was not tense. As much of the growth as possible was curetted out, and bleeding controlled by gauze packing. After the operation the patient developed complete paraplegia with retention of urine, but this gradually improved, and the wound healed well. The lump on the rib became larger after he left the hospital. The patient was referred to Dr. John Henks Thomas, of Boston, by Dr. Hunting, of Quincy, Massachusetts.

TOXIN THERAPY (*Buxton VI*): Injections of Coley toxins were begun by Thomas in January 1901 and were made every third day. At first, four minims caused a sharp febrile reaction, but by March 14, 1901 only a slight increase in the pain in the tumor of the rib was noticed. This had meanwhile decreased in size. Occasionally it had been painful and tender but by March 14, 1901 it was quite small. Upon examination Hunting got a distinct crepitus, as if from a broken rib. At this time the patient walked well with no pain in the legs, he ate and slept well and felt absolutely fine. He had already returned to his professional work.

CLINICAL COURSE: Late in April, while pulling a toy wagon, the patient suddenly felt a pain in the left lower chest so severe that he had to be helped home. After this he had much pain on both sides of the chest at the level of the eleventh rib, running round the body when he moved, no pain when quiet. By May 18, 1901 there was a well-marked swelling on the left seventh rib, which was not tender, though it had been so. On the left sixth rib there was tenderness and slight swelling at the juncture of the cartilage and the bone. Another swelling, not tender, was present on the left eleventh rib; there was tenderness to percussion at the tenth dorsal spine, and pain passing around the trunk on pressing the head. The spine was held rigid, and the patient moved with great difficulty, supporting

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

himself until erect, when he was able to stand without support. Strength in the legs was good, with no muscular spasm. There was no disturbance or pain anywhere. All reflexes were normal and equal.

FURTHER TOXIN THERAPY: Injections were resumed and this time were continued for over two years, the growth regressing completely. The treatment did not interfere with the patient's continuing his law practice.

CLINICAL COURSE: He made a complete recovery and remained well and free from recurrence. In April 1906, he died of acute lobar pneumonia, over five years after toxin therapy was begun. There was no return of the multiple myeloma at the time of his death, according to the autopsy.

COMMENT: It was found that only 12 cases of this type of tumor were ever treated by Coley toxins and in most of these, the toxin therapy was given during or following heavy radiation. Coley felt that the effects produced in the above case and that of Mr. A. (Case 3) and Mrs. C. (Case 2) justified advocating the toxins in every case of multiple myeloma. This case suggests that if toxin therapy is administered for a considerable period without preliminary radiation or chemotherapy that a permanent result may be obtained. It appears necessary to prolong the treatment in this type of tumor in order to prevent reactivation of the disease.

Few cases of any type of bone tumor which developed recurrence or metastases were given a second intensive and prolonged course of toxin therapy. However, where this was done, some permanent results were obtained, as in the above case or in other types reported more recently. (49)

REFERENCES: 11, Case 54; 12; 13; 15; 54; 68.

CASE 2: Inoperable plasma cell myeloma, involving the proximal third of the left femur, confirmed by microscopic examination by Dr. James Ewing of Memorial Hospital, as well as Mandlebaum of Mt. Sinai Hospital, who reported: "a tumor originating in the bone marrow and chiefly made up of plasma cells." (Ewing's original diagnosis in 1921 had been endothelioma, but this was changed when the case was reviewed in 1930.)

PREVIOUS HISTORY: Mrs. L.A.C, female, aged 45. The family history was negative for cancer or tuberculosis. The patient had "pleural pneumonia" 24 years previously. She had several miscarriages following the birth of one living child. Five years prior to onset she had peritonitis following one of these miscarriages.

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

Otherwise, her previous health had been good. In the autumn of 1918 she fell, striking her hip on the sharp edge of a piece of furniture. Onset, in April 1919, she began to notice a "pins and needles sensation and numbness" in the four lesser toes. Following this the ankle became weak, causing difficulty in walking. In September 1920 she began to use a cane, owing to weakness of the knee. During this period she was treated for rheumatism. In February 1921 she fell while walking in the street, and was taken to Neurological Institute.

SURGERY: A lymph node was dissected from the inguinal region and one from the neck, but these showed no pathology.

CLINICAL COURSE: X-ray examination at the Hospital for Joint Diseases, then revealed a tumor of the femur. X-rays taken at Memorial Hospital on March 26 and April 5, 1921, by Dr. Ralph Herendeen, were suggestive of osteomyelitis rather than a bone tumor. No treatment was given. In April 1921 she came under the care of Drs. Howard Lilienthal and H. Neuhof, of Mt. Sinai Hospital.

SURGERY: An exploratory operation in May 1921 revealed a tumor involving the upper portion of the femur. A pathological fracture had occurred with complete loss of power in the left leg and partial loss in the right, pointing to possible involvement of the spine. A spica was applied ten days after the operation. The condition was regarded as hopeless and the patient was referred to the House of Calvary, a home for incurable cancer patients.

CLINICAL COURSE: Dr. William B. Coley first saw the patient at the urgent request of her husband in July 1921. He also gave a hopeless prognosis, but for the moral effect upon the patient it was decided to try the toxins. She was transferred by ambulance to Memorial Hospital on July 18, 1921. She had been unable to walk for five months. There was numbness in both legs, and marked weakness of the muscles, but no areas of anesthesia. The general condition was poor, and she had lost 25 pounds in weight. A Buck's extension and side splints were applied to the thigh. Physical and x-ray examinations at this time showed a tumor about 18 cm. in length, involving the upper third of the femur, with pathologic fracture. Marked increase in the destructive process was noted since the pictures taken in March and April 1921.

TOXIN THERAPY (*Tracy XI*): Injections were begun by W.B. Coley on July 18, 1921, the initial dose being 0.5 minim. They were given daily, occasionally every other day, during the first three weeks, gradually increasing the dosage to 16 minims. There was very little febrile reaction (99°-100°F.) until the ninth injection, when the temperature reached 101.8°F. At the end of two weeks a roentgenogram showed marked local improvement with no further extension of the disease and also beginning regeneration of bone. Improvement in the general condition was also noted and continued without interruption. On August 15, 1921, the patient

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

had a severe reaction: following a dose of 18 minims the temperature sank to 96°F. then rose rapidly to 106°F., and did not go below 100°F. until the following day. No injections were given during the next six days, and then the dose was reduced to 8 minims, which caused a febrile reaction of 103.2°F. From August 15 to September 15, 1921, only seven injections were given (less than two a week). By this time union of the pathological fracture was sufficiently firm to justify removal of the Buck's extension, and the leg was put into a plaster cast.

RADIATION: On September 10, 1921, one radium pack was applied over the incision on the left femur (2,231 mc. at 6 cm. distance for four hours, totalling 8,924 mch.).

FURTHER TOXIN THERAPY: During the first ten days following radiation five more injections were given, the febrile reactions being 99°-100°F. On September 23, 1921, another severe reaction was produced following a dose of 8 minims: 104°F. and a chill lasting 40 minutes. Three more injections of 5 minims each were given, the dose being maintained at 5 or 6 minims. There was only one slight chill and the febrile reactions averaged 99° to 100°F. By November 1, there was further marked clinical improvement. During October, November and December the x-ray examinations continued to show further marked regeneration of bone, and they were negative for metastases. About December 5, 1921, the cast was removed and a Thomas splint applied, as the bony union had progressed and appeared to be fairly firm. The patient gained about 20 pounds in weight during the first 4½ months of toxin therapy; she felt well and she had a good appetite. Dr. Eugene Leddy, the resident surgeon, stated: "No evidence of fracture in thigh. Patient has been out of bed. Could not walk because of atrophy of both legs from disuse (she had been bedridden for nine months); general condition excellent." Gradually muscular power returned in the legs. This patient received a total of 51 injections in 140 days (about five months), with nine chills and three severe reactions of 103°-106°F.

CLINICAL COURSE: She was transferred to the Hospital for Special Surgery on December 28, 1921, where she remained until July 22, 1922. X-ray examination on January 22, 1922, showed well-marked regeneration of bone at the site of the fracture with firm union. By March 22, the patient was able to get about on crutches and her general condition continued to improve steadily. In March 1923 she was presented before the New York Surgical Society in excellent condition. In July 1923 she had an "attack of unconsciousness," the cause of which was not known. During the autumn of 1923 there was evidence of renewed activity of the disease. Metastases developed in the ribs and brain. The patient refused further treatment of any kind. Death occurred in December 1923, over 3½ years after onset.

In reporting this case in 1931, Coley stated: "The result of treatment was most striking, but I believe I erred in stopping the toxins too soon. They were

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

stopped at the end of five months, whereas in the Boston case (see above, Case 1) they were kept up for nearly two years." (13)

REFERENCES: 8, Case 414; 12, Case 58 in text, case 19 in Table; 13; 14; 34; 46.

CASE 3: Terminal multiple myeloma, involving the spine, several ribs, and vocal cord with complete paraplegia. Confirmed by roentgenological and microscopic examinations by Drs. Maurange, Sicard, Babin-ski, and Casteau of Paris, France, and by Dr. James H. McWhorter, pathologist of the Hospital for Special Surgery, New York.

PREVIOUS HISTORY: L.L.A., male, age 56, of Denver, Colorado. Onset, during the years 1922 and 1923 the patient complained of vague pains radiating down the legs.

RADIATION: He received high voltage x-ray therapy in September 1923, with considerable relief.

SURGERY: In May 1924 he was operated upon by DeMartel, of Paris, France. Laminectomy revealed a semi-cylindrical tumor pressing on the cord, and nearly encircling it. It was removed as thoroughly as possible.

FURTHER RADIATION: Post-operative x-ray therapy was used with relief of paralysis and pain, although control of the bladder and rectum was not regained.

CLINICAL COURSE: In the spring of 1928 the symptoms returned and roentgenograms revealed a destructive lesion involving several ribs, the spine and the chest.

FURTHER RADIATION: X-ray therapy was resumed but had no effect.

CLINICAL COURSE: He then consulted Dr. Claude Régaud of Paris, who advised against further radiation and suggested toxin therapy under Dr. William B. Coley. On his return to America in May 1928 he was feeling so miserable that he proceeded directly to his home in Denver, Colorado, without stopping off in New York. Coley was not consulted until August 1928, by which time the patient had developed complete paraplegia with paralysis of one vocal cord, and had lost 56 pounds in weight. He also had trophic ulcers in both gluteal regions and on the left foot. At the time the toxins were begun the patient was so weak that he could not move himself in bed, and his appetite was very poor. There was frequent vomiting and coughing spells. Coley told the family physician, Dr. Thompson Anderson, that in view of the patient's condition, he did not believe that much could be expected from the use of the toxins.

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

TOXIN THERAPY (*Parke Davis XIII*): Injections were begun by Anderson, under Coley's direction, on September 3, 1928, the initial dose being 0.25 minim which was increased daily by 0.5 minim. On September 9, 1928 (the sixth injection) the first febrile reaction was produced, following a dose of 3 minims. During September, 17 injections were given, all in the pectoral muscles. Almost immediate improvement took place, which was continuous. On October 21, 1928, Anderson wrote: "The patient's general appearance is very greatly improved. His color is good. He is very much stronger, can get out of bed unassisted and has fairly good control now of the lower extremities. His trophic ulcers have healed, with the exception of one over the left gluteal muscle, which is much smaller and healing satisfactorily. His appetite is good. He is no longer bothered with vomiting. His voice is practically normal, and the throat specialist reports that the left vocal cord is 50 per cent better and he thinks it will shortly be in normal condition. The patient's nutrition is obviously improved. The skin, which was dry, scaly and dead, is moist and pink, and he has gained some weight. Physical examination of the chest shows decided lessening of the dullness, particularly in the left infraclavicular region, and the last x-ray film, made after three weeks of the treatment, shows a decided lessening of density in this same region. He is cheerful, and states that he feels greatly improved in every way. . . . Now he can rest on his back indefinitely without discomfort. . . . I feel that we have definite evidence that the toxins have been of benefit to him. Both of the consultants agree."

CONCURRENT RADIATION: X-ray therapy was also given during this month. Anderson reported: "While these have always helped him temporarily . . . he always shows some reaction shortly after the x-ray treatments, for which reason we never administer toxins on those days. After we had reached a dose which brought on a (febrile) reaction I was impressed with the apparent fact that the same dosage as we progressed seemed to produce a greater reaction. One striking illustration of this occurred during the last week of treatment. On the 25th of September he was given 6½ minims at 2:45 P.M. and at 3:30 P.M. had a marked reaction which caused no apprehension, but which seemed more severe than we were warranted in subjecting him to. On the 26th, 27th, and 28th he received no toxins, but on the 27th had an x-ray treatment. On the 29th, not wishing so marked a reaction as on the 25th, I gave 5 minims with a much more severe reaction than he had from 6½ on the 25th, and one which lasted very much longer. In fact the nurse called me at the onset of the rigor, and I went at once and stayed with him until 10 P.M." (This detailed observation of the effects noted when radiation is given during toxin therapy of multiple myeloma is of interest. Other cases of malignancy so treated also indicated that apparently smaller doses are tolerated when radiation is administered concomitantly). Recent as well as older studies indicate that bacterial toxins may potentiate the tumor destructive effects of subsequent radiation therapy (20, 24, 26, 49) while protecting the normal tissues from deleterious radiation injury (1, 10, 49).

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

The patient received no injections of toxins between September 30 and the end of October 1928. About October 25th he very suddenly developed some pain in the upper right quadrant of the abdomen, and in 24 hours there was a doughy mass distinctly palpable in this area. At this time he began to pass clay-colored stools, with bile in the urine and a slight jaundice. These symptoms were apparently due to a metastatic mass in the gall bladder region causing pressure on the common duct. An x-ray treatment was immediately given over this region, and in 48 hours the gall bladder was apparently emptying again. Bile disappeared from the urine, appeared in the stools, the jaundice cleared up and he was quite comfortable. He received two subsequent x-ray treatments over this region.

FURTHER TOXIN THERAPY: Immediately after the first x-ray treatment over the gall bladder, the injections were resumed. The patient had quite a severe reaction from a dose of 0.5 minim, with a hard chill, cyanosis, and some cardiac and respiratory disturbance. For a day or two following this reaction there was quite a disturbance in the renal output, with considerable albumin and some casts in the urine. From that time on the dose was increased by only 1/16 minim so as to establish a dose which would give a good febrile reaction without too prolonged chills or depression. Anderson found that during November and December 1928 the patient could not tolerate more than 13/16 minim. Injections were given at two to four day intervals, according to the reaction and the general condition of the patient, as well as the renal function. There was some recurrence of the growth in the gall bladder region, but by December 3, 1928, the gall bladder again began to empty. Toxin therapy was continued through January 1929.

CLINICAL COURSE: The patient was examined by Coley in New York in September 1929, at which time he was walking with the aid of only one cane, and scarcely any limp. Coley advised a further course of toxin therapy, but the patient felt so well that he did not see any necessity to continue treatment. He remained in good health until the latter part of 1932, more than four years after the toxins were begun. His symptoms then returned.

FURTHER TOXIN THERAPY AND CONCOMITANT RADIATION: In spite of further toxins and x-ray therapy, the disease then progressed, causing death in January 1933, 10 years after onset.

COMMENT: This case suggests the need for more sustained therapy, especially in multiple myeloma patients who have already had irradiation (the initial course of toxins consisted of only 17 injections). Note that in this case only small doses were tolerated, even by the intramuscular route. However, it is remarkable that a complete remission was produced by toxins and x-ray therapy lasting four years, even though the patient was terminal when the toxins were begun.

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

REFERENCES: 13; 14; 15.

CASE 4: Plasma cell myeloma of the left humerus and left scapula, confirmed by microscopic and x-ray examinations at Memorial Hospital and by the Bone Sarcoma Registry Committee, including Dr. Fred W. Stewart, who reported on the amputated specimen: "The upper middle third of the humerus is occupied by a cystic tumor 7 cm. in length, very slightly expanding the shaft, walled in by thin fragmented particles of bone filled with bits of grayish tissue and dark red blood. There is a pathological fracture. Gross diagnosis: benign cyst with possibly fragments of giant cell tumor in wall. Microscopic: plasma cell myeloma." (It is possible that the preliminary radiation and toxin therapy may have contributed to the benign gross appearance of this tumor).

PREVIOUS HISTORY: J.A.C., male, age 48, of Middletown, New Jersey. The family history was negative for cancer and tuberculosis. The patient had had a tonsillectomy in 1915, an appendectomy in 1919, catarrh for years and frequent headaches, but no other illnesses of importance. On June 28, 1929, he was carrying a 250 pound bag of salt on his shoulder. When he let the bag drop he felt a sudden sharp pain. Thereafter he had trouble with his left shoulder, but he was able to continue working. There was pain in the middle third of the left humerus. Ten days after the injury, the pain was so severe that he quit work. The area began to swell slightly. On July 17, 1929, while swimming, he had severe pain in the arm and called a physician. At this time the arm swelled rapidly to twice its normal size. The only therapy given was "electric treatments". In about two weeks the swelling subsided considerably. About November 1, 1929, the patient noticed a small nodule on the left scapula. Examination on admission to Memorial Hospital, November 9, 1929, revealed a large male in good general condition. A fusiform painful swelling was present at the juncture of the upper and middle thirds of the left arm. The overlying skin was slightly reddened. The arm was abnormally mobile as if there might be a pathologic fracture. Apparently there was none at this time, however. Along the axillary border of the left scapula there was a hard, fixed rounded mass about the size of an olive. X-ray examination on admission showed a large area of bone destruction in the middle third of the shaft of the left humerus, which was apparently medullary in origin. There was no evidence of pulmonary metastases.

RADIATION AND CONCURRENT TOXIN THERAPY (*Parke Davis XIII*): Two high voltage x-ray treatments were given on November 12 and 13, 1929 (14 minutes each).

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

The patient also received six radium pack treatments at 6 cm. distance totalling 32,000 mch. over the anterior aspects of the left humerus between November 11 and 17, 1929, and one more on December 17, (8,000 mch.) making a total of 40,000 mch. of radium. Injections were begun on November 20, 1929, one week after the first x-ray treatment. The first eight doses of 0.5 to 7 minims were given intramuscularly. Thereafter 10 intravenous injections were given in doses of 1/60 to 1/4 minim. The intramuscular injections caused only one moderate reaction (102.6°F.) with a slight chill. Moderate febrile reactions and marked chills occurred following several of the intravenous injections (average 101.6° to 102.6° - only once 103°F.), the chills lasting 15 to 20 minutes. On November 29, 1929, the arm was put in a spiral spica splint extending to the wrist, to prevent what seemed to be an imminent pathological fracture of the humerus. X-ray examinations on December 12 and 18, 1929, showed no evidence of change. The cast was removed on December 18, 1929, because of discomfort. On December 26, 1929, a large shoulder spica extending to the hand was applied. Despite these precautions a pathologic fracture occurred through the thinned out cortex. An aspiration biopsy was made at this time and no tumor cells were found.

CLINICAL COURSE: Another x-ray examination made on January 25, 1930, by Dr. Ralph Herendeen, did not reveal any marked change, although the upper and lower limits of the tumor appeared to be somewhat more clean cut in outline. The growth involved the middle third of the humeral shaft and appeared to be growing slowly, dilating the medullary portion of the bone and thinning the cortex, through which numerous fracture lines were apparent. Herendeen added: "It is somewhat trabeculated above; it lacks the features of carcinoma metastasis, but metastasis from hypernephroma occasionally produces a similar appearance. The findings are more suggestive of a primary process, relatively benign. It lacks the features of osteogenic sarcoma or Ewing's sarcoma although a slowly growing angio-endothelioma might conceivably produce this appearance. We can conceive of a bone cyst lined with giant cells producing these changes, and this is placed first on the list of probabilities." (46)

SURGERY: Because the x-ray findings showed no evidence of improvement, Coley performed a shoulder joint disarticulation on January 29, 1930. The x-ray diagnosis of bone cyst was not supported by the microscopic findings, which showed it to be plasma cell myeloma. No evidence of metastases was found in chest films nor any bone changes in the skeletal films. The post-operative course was uneventful except that on February 2, 1930, when allowed out of bed, he had pain in the left foot and ankle. His general condition was excellent.

WOUND INFECTION: On February 8, about two ounces of purulent discharge were evacuated from a pus collection about 2 by 2 cm. from the medial angle of the incision.

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

POSTOPERATIVE TOXIN THERAPY (*Parke Davis XIII*): Injections were begun on February 11, 1930, 13 days after the operation. Nine intravenous injections were given in the next 20 days in doses of 1/60 to 1/14 minim. Only two marked reactions occurred from doses of 1/16 minim (103°F., with chills lasting 10 to 25 minutes). By February 25, 1930, the wound was well healed, except for the lower angle which was almost healed, and there was no evidence of disease.

CLINICAL COURSE: The patient was discharged on March 5, 1930, by which time the wound was entirely healed and he had no complaints. He remained in excellent condition, with good color, and gained weight. An x-ray of the chest taken 12 weeks after his discharge showed no evidence of pulmonary metastasis. The patient did not return to the Out-Patient Department thereafter. In May 1930 the case was thrown out by the Workmen's Compensation Board because he had not reported the accident at the time it occurred. He was given clothing, etc., by the Memorial Hospital Social Service Department in June 1930 and referred to the Welfare Society in Red Bank, New Jersey. He had not yet obtained work. In October 1930 he was admitted to the New Jersey State Hospital for the Insane and acting Medical Director, Dr. Robert G. Stone, sent the following report:

"History of definite depression, well over four months' duration. Considerable trouble with his wife over financial matters. Quite a suggestive history of paranoid ideas toward his wife also developed after a law suit in which he was unable to gain compensation for the loss of his arm. At staff he admits worry and depression. In very good touch, however. Diagnosis: manic depressive insanity, depressed type with some indefinite paranoid trends. Dental condition to be attended. Remaining tonsil stump has been removed."

There was no evidence of a return of the plasma cell myeloma during the next nine months. Stone reported on June 5, 1931: "Patient remains mildly depressed and is not yet in condition to be released from this hospital." However, within a few weeks he began to fail physically. He complained of a great deal of pain in his shoulders and thoracic region. A thorough x-ray examination was made in early August 1931. This revealed numerous small "moth-eaten" areas scattered over both clavicles, and the upper four ribs, especially marked in the left third rib; this same type of rarefaction was also seen scattered through both scapulae and the right humerus, being especially marked in the head and the lower third of the shaft. These areas were confined almost entirely to the medullary and subcortical regions except in the first and third left ribs, where the entire thickness of the cortex was also involved. There appeared to be a pathologic fracture of the first, second and third left ribs. There was considerable increase in fibrosis and some widening of the mediastinum, with some mottling along the right lower mediastinal border. The cardiac shadows extended 2.5 cm. to the right of the normal limits. The remainder of the skeleton was negative. No treatment was given. The disease progressed and became generalized, causing death on November 26, 1931, almost 2½ years after onset.

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

COMMENT: The first course of toxins given during irradiation consisted of only 18 injections in 61 days. The second course of toxins was not begun until 13 days following disarticulation and consisted of nine small doses which elicited only two satisfactory febrile reactions. Note also the concurrent psychiatric problem in this case.

REFERENCES: 8; 46.

CASE 5: Multiple myeloma primary in the proximal left femur, confirmed by microscopic examinations by Drs. Bloodgood, Geschicter and Cohn. At first this was regarded as a solitary plasma cell myeloma; later multiple lesions developed, with Bence-Jones bodies in the urine. (For microphoto see 42).

PREVIOUS HISTORY: C.I.S., male, age 44, married. The family history was negative for malignancy. Onset, on August 6, 1929, the patient first felt a slight pain in the upper left femoral region which affected him only when he was on his feet and physically active. In the early part of September, while doing strenuous work, he was seized with a sharp pain in the same region, so severe that he had to sit down. Following this he was treated symptomatically for a time but did not improve. A roentgenological examination made several days later revealed a tumor in the upper left femur (42, Fig. 3A). He was seen by Dr. Joseph C. Bloodgood of Baltimore, Maryland, early in October 1929. Examination at this time showed a growth involving the proximal fifth of the shaft of the left femur, 10 cm. in length. There was no expansion of the cortical bone, the bony shell being intact. All other examinations were negative, including Bence-Jones bodies in the urine.

SURGERY: On October 15, 1929 Bloodgood operated under spinal anesthesia, revealing an extensive central lesion. The tumor, described as a very bloody, spongy mass, was curetted and cauterized (thermal and chemical: 50% zinc chloride). It proved to be a plasma cell myeloma. During convalescence there was very little new bone formation and the patient suffered a pathologic fracture.

TOXIN THERAPY (*Parke Davis XIII*): Beginning January 11, 1930, Bloodgood administered 20 intramuscular injections of toxins in doses of .2 to .8 cc daily for three weeks. Pain ceased almost immediately after the toxins were begun and the formation of new bone was observed soon afterward. The injections were then stopped because the patient had a severe "convulsion" following an injection, and refused further treatment. (14) Cohn stated that the only reaction occurring during the earlier part of toxin therapy was "bad dreams at night, approaching nightmare." (55)

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

CLINICAL COURSE: On February 28, 1930, 4½ months after operation, the patient was permitted to leave the hospital on crutches. He was thought to have fairly good union at that time and returned to New York on March 1, 1930. The next morning, while getting out of bed, there was a sharp, sudden "snap" in the upper left thigh with excruciating pain. He remained in bed and made no further attempt to move the leg. The patient was seen by Dr. William MacFee at this time. Examination revealed external rotation, and about 4 cm. shortening of the left leg. There was a long scar over the lateral surface of the upper shaft of the femur, with two sinuses discharging thin, seropurulent material. At this time there was considerable external bowing of the femur. The patient appeared to be in great pain and there was marked tenderness. A Thomas splint was applied, and moderate traction maintained by the use of moleskin adhesive straps. A roentgenogram taken at St. Luke's Hospital on March 10, 1930, showed that a second pathological fracture had occurred through what appeared to be a new growth just below the lesser trochanter.

X-RAY THERAPY: Eleven deep x-ray treatments were given between March 11 and June 30, 1930. Relatively small doses (300 r) were administered at weekly intervals. At the end of this period roentgenologic examinations of the fracture showed union of the fragments. He was fitted with a caliper-type brace and allowed to get about on crutches, being discharged on July 7, 1930, about four months after admission. X-ray therapy was repeated at intervals.

CLINICAL COURSE: The patient was able to return to his regular occupation as manager of a restaurant. No further foci of disease were noted until October 1932, over two years later. At that time he complained of pain in the lumbar region and x-rays showed some destruction of the body of the third lumbar vertebra (42, Fig. 2A).

FURTHER RADIATION: Under deep x-ray therapy the pain disappeared and the lesion apparently healed.

CLINICAL COURSE: A roentgenologic study of the patient's skeleton made in October 1934 (42, Fig. 2B and Fig. 3C) revealed no suspicious areas except a rarefaction of the head of the right fibula. The patient appeared to be clinically free from disease on September 13, 1934. MacFee reported:

"The urine generally has been free of Bence-Jones protein. In November 1934, however, the patient complained of thirst and polyuria, and a urine examination made at that time revealed a large amount of the Bence-Jones protein. The patient now has firm union with about 6 cm. of shortening. He was able to discard his brace and now, three years after the fracture, walks, usually with a cane, but sometimes without it. He has shown, however, a progressive anemia of the secondary type, the last count being: r.b.c., 1,700,000; hemoglobin 31%; w.b.c. 6,000; polymorphonuclear leukocytes, 64%; large monocytes, 36%."

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

Ultimately multiple bone lesions developed, a typical case of multiple myeloma. Death occurred on November 29, 1936, seven years after onset, autopsy showed involvement of practically all the bones of the body. (55)

REFERENCES: 14; 42; 55.

CASE 6: Multiple myeloma, involving the whole pelvis; confirmed by microscopic examination by Dr. Fred W. Stewart of the Bone Sarcoma Registry Committee. (This case was first regarded as Ewing's sarcoma.)

PREVIOUS HISTORY: J.F., male, age 15, of New York City. The family history appeared to be negative. The child had had convulsions from birth (*petit mal*). He had a tonsillectomy and adenoidectomy in 1928. In January 1920, while running across an icy road he fell on his right knee. There was no pain or discomfort thereafter until several days later when the leg "went into a tremor with twitching of the muscles of the right thigh and pain in the groin". The pain gradually increased and on two occasions the boy vomited following severe pain. The family physician was consulted and he advised hospital treatment. The boy was admitted to the Jersey City Hospital on February 7, 1930. He had pain in the left lower quadrant and right hip and pain when walking. When examined there was abdominal muscle spasm, tenderness over McBurney's point and pain in the right hip on sudden motion. The temperature was 102°F., but the boy was not acutely ill. The blood count showed w.b.c. 17,000; r.b.c. 3,400,000. The urine was entirely negative. X-ray examination on February 8 showed no pathology, but on February 31, 1930, films showed a rarefaction about the main portion of the ilium containing the acetabulum; the whole pelvis was distorted. The rarefaction was considered as possibly due to osteomyelitis. Further x-rays showed extension of the disease, and on April 7 chest films suggested considerable infiltration of the left apex and some thickening of the left hilus suggestive of metastases.

SURGERY: On March 22, 1930, an incisional biopsy was performed, material being taken from the right ilium with rongeurs.

TOXIN THERAPY (*Parke Davis XIII*): Injections were begun on March 26, 1930, the initial dose being .02 cc, which was increased daily by .01 cc for eight days. On April 9 an intravenous injection was given (1/80 m.), alternating thereafter with a .10 cc dose by the intramuscular route. These were continued until April 20, the doses being slightly increased: maximum .12 cc intramuscularly, 1/50 m. intravenously.

RADIATION: On April 5, 1930, an x-ray treatment was given (200 K.V.; 4 mil-

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

liamps, 1½ hours; 50 cm.) to the anterior surface of the ilium. Another was given on April 21, 1930, for one hour, to the posterior surface of the ilium.

CLINICAL COURSE: On April 22, 1930, a transfusion of 500 cc. of whole blood was given, and the patient was referred to Dr. Wm. B. Coley and was admitted to the Hospital for Special Surgery. Examination there revealed a fairly well nourished and well developed white male of 16, with a pale, pasty complexion, appearing chronically ill. The abdomen was moderately distended, of doughy consistency, and the musculature of poor quality. The right leg was swollen and edematous, and the boy could not move it because of pain in the knee and hip. A provisional diagnosis of "neoplasm of the right pelvis" was made. A film taken that day showed "a malignant disease which is purely destructive, which has entirely destroyed the right acetabulum and most of the ischium as far down as the tuberosity and most of the right pubic bone, also involving the ilium to a level higher than the anterior superior spine and as far back as the sacroiliac joint. The femoral head and the proximal portion of the neck are considerably eroded." Chest films showed no evidence of lung metastases or evidence of involvement of the bones. The x-ray findings were consistent with the pathologic diagnosis of Ewing's sarcoma of bone. Two days later, further views of the skeleton showed the following destructive lesions: the body of the 11th dorsal vertebra was almost completely destroyed and collapsed down to half its normal vertical diameter, its articulating ribs being displaced laterally, and there was probably erosion of the head of the right, and probably the left, rib. There was involvement of the head of the eighth left rib and of the right rib near its angle. There appeared to be slight involvement of the bodies of the second and third lumbar vertebrae anteriorly (not certain). There was involvement of the distal right tibial diaphysis and epiphysis on their lateral aspects, and possibly of the fibula (same level). There was thickening of the tibial cortex along both crests. Urinalysis on April 24, 1930 was positive for Bence-Jones protein.

FURTHER TOXIN THERAPY: One more injection was given on May 1, 1930, this time using the intravenous route (dose 1/100 minim). This caused a febrile reaction of 105°F. and a chill lasting 45 minutes. A blood count taken after this injection showed hemoglobin 30%, 2,000,000 r.b.c. (a drop of 500,000 in the six days since his admission). Another blood count taken May 5 showed 1,270,000 r.b.c., hemoglobin 20%.

CLINICAL COURSE: The patient was discharged in extremely serious condition on May 5, 1930 at the parents' request, and died that day, five months after onset.

COMMENT: This case is of interest because it came under observation very shortly after onset, before the diagnosis of multiple myeloma could be made. Compare the result with the cases in which heavy radiation was not given prior to toxin therapy (or at all).

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

REFERENCES: 8, No. 1244; 14; 34.

CASE 7: Multiple myeloma of the left sixth rib and skull confirmed by microscopic examination by Dr. Bernhard Steinberg of the Toledo Clinic, Toledo, Ohio and Dr. John E. McWhorter, pathologist at the Hospital for Special Surgery; also by Drs. James Ewing and Fred W. Stewart of Memorial Hospital. The urine was negative for Bence Jones protein.

PREVIOUS HISTORY: R.G., male, aged 31, of Akron, Ohio. The family history was negative for cancer, tuberculosis or diabetes. The patient had had measles and scarlet fever as a child, but no surgery. He had been in an accident (date not given) in which he broke several ribs, with severe hemorrhage. He had always been in good health until onset in the fall of 1929 when he suffered from "heart burn" and a feeling of heaviness in the chest. This was relieved somewhat by bicarbonate of soda. On January 14, 1930 he had an attack of dizziness in which he fell, apparently sustaining a fracture of a rib. He was examined at the Toledo Clinic just after he recovered consciousness. He was suffering rather intense pain over the entire left chest and upper abdomen. X-ray therapy revealed a mass in the region of the sixth rib which elicited bony crepitus to the level of the heart. X-rays of the ribs were taken and showed destruction of the sixth rib, apparently due to some type of tumor. Because of the possibility of it being a multiple myeloma, skeletal x-rays were taken which revealed an area of bone destruction about 3 cm. in diameter in the parietal region, and density throughout the left chest. The chest was strapped. It was thought that the patient had sustained a pathologic fracture of the rib in falling. His pulse rate had gone up, he was dyspneic and the blood pressure had dropped to 80/50.

SURGERY: A few days later an incisional biopsy was performed by Dr. W.E. Neill of the Toledo Clinic. He found the rib covered with a thickened periosteum. The rib proper was destroyed and replaced with very vascular tissue which cut easily with a knife. The microscopic report was plasma cell myeloma. The patient was discharged on January 26, 1930 and referred to Dr. William B. Coley by Dr. Carl H. Bayha, of the Toledo Clinic. Examination on admission to the Hospital for Special Surgery on March 31, 1930 showed a scar over the left lateral lower chest which was surrounded by an area of dullness to percussion. No rales were heard, no changes in breath or voice sounds.

TOXIN THERAPY (*Parke Davis XIII*) COMBINED WITH RADIATION: Injections were begun on March 31, 1930 and 11 were given in 11 days. Eight of these were given intramuscularly in doses of 0.5 to 6 minims causing little or no real reactions (averaging 99°F. to 100.2°F., minimum 98°F., maximum 101°F.). Three injections were given intravenously in doses of 1/80 to 1/70 minim. These caused febrile

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

reactions of 101.2°F. or 100.6°F. Slight chills occurred on two occasions. The radium pack was applied on April 6, 1930 over the right temporal region (10,000 mch.) and over the left fifth and sixth ribs (10,000 mch.). Chest films taken on April 9, 1930 showed pleural exudates at the left base and along the lateral chest wall. There was considerable rarefaction of the sixth posterior rib just lateral to its angle and doubtful areas at about the same level on the fourth and fifth ribs below this. The patient was discharged improved on April 11, 1930. The injections were continued at home by the family physician (exact duration not recorded).

CLINICAL COURSE: The disease was arrested as indicated by x-ray examinations taken on September 3, 1930. By January 6, 1931, Lewis reported that the pleural changes had diminished considerably and that the lesion in the sixth rib showed changes suggesting further regeneration of the resected area. By April 24, 1931, chest films showed that the pleural condition had healed, and the ribs showed regeneration with a peculiar cystic looking bone, also a diffuse clouding about the upper left lung root indicating "an inflammatory condition of some sort, possibly malignant growth as a basis." The eighth rib posteriorly had a cystic appearance in the scapular line but these were considered as possibly due to superimposed shadows. The left seventh and eighth ribs showed destructive changes. The pelvis showed rounded areas of bone destruction in the proximal shaft on one side and less definite areas of bone destruction in the proximal femoral shaft on the opposite side, with extensive destruction of the adjacent iliac bone above the upper margin of the acetabulum. There was a rounded area of destruction in the tuberosity of the opposite ischium. Films of the skull showed no changes. Views of the knees showed much swelling of the soft tissues and destruction of the joint capsule with exudate but no definite bony changes were detected.

FURTHER RADIATION: Radium pack treatments were given over the chest under the direction of Drs. William B. and B.L. Coley in New York in late April 1931. After the patient's return to Ohio, a delayed radiation sickness occurred. The patient's morale sank very low.

CLINICAL COURSE: That summer during a dreadful seige of pain "he took refuge in morphine." This caused pernicious vomiting and dehydration. His wife stated that he "sank so low that we gave up all hope of his recovery. He came out of that miraculously and felt perfectly well again . . . stopping the drug altogether." Glucose injections were given and within two weeks he was improved and able to return to work.

FURTHER X-RAY THERAPY: Between October 1, 1931 and Christmas 1931, x-ray therapy was given to the hip, the chest and the skull over the right eye. These treatments were given each week-end so that the patient could continue to work during the week.

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

CLINICAL COURSE: From Christmas on he grew weaker and less able to work all day. His wife stated: "No food would stay down for long. He drank carbonated water and just about lived on soda." About January 20, 1932 he had to stop working. A few weeks later there was edema of the ankles and dyspnea. Finally there was edema of the entire body (his normal weight was 136 pounds and he weighed 150). Death occurred on February 17, 1932 of acute dyspnea, 27 months after onset.

REFERENCES: 14; 34; 55.

CASE 8: Multiple myeloma involving the ribs, spine, skull, pelvis and femora, confirmed by complete physical and x-ray examinations of all the skeletal bones, and by urinalysis, which revealed Bence Jones bodies.

PREVIOUS HISTORY: P.J. McC., male, age 39, prison guard, born in Ireland, of New York City. The family history was non-contributory. In 1927 the patient fell from a height, sustaining two fractures of the left foot and one fracture of the right foot. A year later he contracted a facial erysipelas, the attack lasting two days. Onset, in May 1932 he developed a severe cold and suffered severe pains all over the body. The cold cleared up but the pains in the small of the back continued. The patient was anemic at the time. On going swimming he became "stiff all over". The house physician in the penal institution in which he was employed made a diagnosis of kidney disease, in view of the large quantities of albumin in the urine. The patient improved somewhat, but the stiffness and pain in the back persisted, and he was unable to bend forward. In the latter part of September 1932 he was admitted to Bellevue Hospital. Roentgenograms were taken of the skeletal system, and a diagnosis of multiple myeloma was made.

RADIATION: The patient remained at Bellevue for four weeks and received ten x-ray treatments, with some improvement in the condition. He then returned home. Ten days later he experienced severe pain in the right side of the chest and between the shoulders. He was readmitted to Bellevue, remaining ten days, during which time he had one more x-ray treatment, and again improved somewhat. He had lost about 30 pounds in weight in the five months since onset.

TOXIN THERAPY (*Parke Davis XIII*): Injections were begun about October 1, 1932, by Lambert at Bellevue Hospital. They were given intramuscularly and did not produce the desired reaction. On November 14, 1932, the patient was transferred to Memorial Hospital under the care of Dr. William B. Coley. Injections were resumed and given daily or every other day. X-rays taken on November 18 were characteristic of multiple myeloma, showing numerous punched-out areas throughout the ribs and spine. During the first ten days the toxins were given intramuscularly, thereafter mostly intravenously. The maximum febrile reaction

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

from intramuscular injections was 102°F., the average being 99° or 100°F., whereas the average reaction following intravenous therapy was 104°F., the maximum being 105°F. All the intravenous injections produced chills, some of which were severe, lasting 45 minutes. From November 14, 1932 to January 9, 1933, the patient received 21 injections of toxins, seven of which were intravenous. On December 2, 1932, the injections were suspended for a week, as he had a spontaneous elevation of temperature to 102°F. and malaise, anorexia and headache. During the following week he also complained of earache. The injections were again suspended on December 13, 1932 for two weeks. At this time he had no further pain and no areas of tenderness over the ribs, vertebrae or long bones. His appetite was fair, but there was a tendency toward constipation.

FURTHER RADIATION: On December 14, 1932, he was placed in the Heublein unit, where he remained for 13 days, receiving 30% of an erythema dose (250 hours) of whole body radiation.

FURTHER TOXIN THERAPY: Injections were resumed on December 28, 1932. Following one intravenous injection there was considerable herpes labialis.

CLINICAL COURSE: On January 15, 1933, the patient had severe epistaxis. Three days later he received a transfusion of 600 cc. of blood. On January 19 his hemoglobin was 65%, the r.b.c. 3,200,000; w.b.c. 1800. At this time the patient received a compensation award from the State Industrial Board and he decided to return home to Ireland immediately. He was therefore discharged on January 28, 1933, with a note from Coley to Sir Arthur Ball in Dublin, describing his condition. X-ray examinations made at St. Patrick Dun's Hospital, Dublin, on March 23, 1933, were reported as follows: "Good movement of the diaphragm on each side. Mediastinum clear. No visible deposits in thorax or ribs. Throughout the pelvis there are areas of rarefaction, and a similar condition is present in the upper ends of both femora. Skull and leg bones negative." Another examination on May 16, 1933, was reported thus: "There appears to be some addition in the rarefaction generally." No further treatment of any kind was given after the patient left Memorial Hospital in January 1933. On December 20, 1933, he wrote to Coley: "Have had a remarkably speedy recovery and am now enjoying the best of health. I have had no occasion to see my doctor since March 1." (8) A similar report was sent to Coley on January 14, 1935. The patient subsequently married.

In reporting this case in 1937, Dr. J.J. Fitzsimons stated that a few months after his return to Ireland in 1933, the patient's condition had improved sufficiently to allow him to take up a position as gate checker, in which capacity he continued working until March 25, 1937, when he fell from a bicycle, following which he was unable to use the right leg. Two days later he was seen by Fitzsimons at Richmond Hospital, Dublin. X-ray examination showed a pathologic fracture of the proximal third of the shaft of the right femur. Physical examination at this

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

time showed an extremely well nourished male, with a ruddy complexion. The clinical examination was negative except for some bad teeth and limitation of respiratory movement. The Wasserman reaction was negative. Radiological examination showed widespread disease of the skeleton. The skull appeared free, although the patient stated that it had been affected in 1932. The urine was "loaded with Bence Jones proteose." The blood picture was as follows: erythrocytes, 3,310,000; leukocytes, 6,400; polymorphonuclears, 48%; color index, 0.9; lymphocytes, 48%; large mononuclears, 4%; hemoglobin, 60%; anisocytosis, slight; serum calcium, 10.8 mg.; plasma phosphorus, 3.7 mg. Fitzsimons stated at this time: "The case is remarkable in the length of survival of the patient, who is in excellent health even today, apart from the terrifying condition of his skeleton." (23)

The patient was discharged from the Richmond Hospital and returned home to Leebary, County Cavan. He remained bedridden and developed what appeared to be "cold abscesses" with profuse discharge, nocturnal temperature and extreme cachexia. The condition was regarded as tuberculosis of the spine by the physician who attended the patient during the last months. Death occurred on July 21, 1938, over six years after onset. (55)

REFERENCES: 14; 23; 46; 55.

CASE 9: Multiple myeloma, involving lumbar and dorsal vertebrae and skull. Confirmed by x-ray examinations at the Mayo Clinic and at Memorial Hospital.

PREVIOUS HISTORY: W.J.W., male, 61, of Oklahoma City, Oklahoma, a urologist. The family history was negative for cancer, tuberculosis or diabetes. The patient had had no infectious diseases, no malformations, no serious injuries. He had an appendectomy in 1919, chronic prostatitis in 1933. In January 1931 he slipped and fell down some steps. This fall caused some residual soreness for which seven or eight osteopathic treatments were given. Following this he felt very well until onset, early in January 1934, when without any apparent predisposing factors dull pain occurred in the lumbosacral region. Pain and discomfort gradually increased in severity with spasm in the spinal and lumbar muscles in this region. A local physician was consulted who thought it was lumbago, and the patient was sent to Texas for treatment (baths and massage). After being there four days he went to the Mayo Clinic on January 20, 1934, where x-rays were taken and a diagnosis of Ewing's sarcoma was made.

RADIATION: Four x-ray treatments were given (approximately 1800 r) over three fields extending from the fourth thoracic to the fifth lumbar vertebra.

CLINICAL COURSE: The patient then consulted Dr. Wm. B. Coley and was admit-

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

ted to Memorial Hospital on February 5, 1934. Examination at this time revealed marked rigidity of the lumbar and lower dorsal vertebrae due to spastic spinal muscles. There were no abnormal curvatures of the spine, no gross deformity, but there was slight tenderness over the lumbosacral region. There was some involvement of the skull as seen in the x-rays taken prior to admission - "punched out areas scattered throughout most of the skull." An x-ray examination was made by Dr. Ralph Herendeen and the diagnosis was multiple myeloma.

FURTHER RADIATION: He was then given 1400 r to the skull and 500 r to the fifth lumbar vertebra.

TOXIN THERAPY (*Parke Davis XIII*): He was discharged from Memorial Hospital and transferred to the Hospital for Special Surgery on February 8, 1934, where he received eight intramuscular injections of toxins in 13 days, in doses of 0.5 to 4½ minims. Only one chill occurred after the seventh dose, and this also caused the maximum febrile reaction, 103.2°F. Most of the injections caused little or no febrile reaction, but only headache and a sense of chilliness and pain in the back. There was some relief of pain. On February 23, 1934, the patient was fitted with a Knight spinal brace. He was discharged two days later; the discharge note read: "... he suffers less pain in his back. However, his general appearance is poor and he appears to have lost some weight."

CLINICAL COURSE: He was readmitted to Memorial Hospital on February 28, 1934 at which time it was noted that the pain had disappeared and that the sensation of weakness was relieved by wearing the brace.

FURTHER RADIATION: He received 400 r each to the right and left skull, 600 r to the lumbar and 400 r to the lower dorsal spine. He was discharged on March 7, 1934, at which time there was no material change in the x-ray films, but there was less pain and less stiffness of the spine.

CLINICAL COURSE: He returned home, about March 8, 1934, feeling quite weak but somewhat better than he had prior to going to New York.

FURTHER TOXIN THERAPY: Injections were resumed by Dr. Anson L. Clark, of Oklahoma City, on March 25, 1934, the initial dose being 0.5 minim. This caused a slight chill and a very slight rise in temperature (99.4°F.). The patient felt quite badly, so did not take another injection until 48 hours later, when a dose of 1 minim caused a febrile reaction of 100.4°F. following a slight chill. The third dose (1.5 minims) was given on March 29, 1934, and caused a febrile reaction of 102.8°F., following a chill lasting an hour, also rather profuse sweating. By March 31, 1934, the patient was feeling "quite good". He reported: "While I am having quite a reaction, I don't believe the shock is as great as it was while I was in the hospital, and since my symptoms are improved, I am certainly very much en-

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

couraged." He reported on April 17, 1934, that "about an hour after the seventh dose in this series a terrific pain struck me corresponding to the lower portion of the sternum about two inches in diameter, which made it difficult to breathe, and at the same time, when it would subside, the pain became very intense over the third and fourth lumbar area. With this (injection) I had a terrific chill, and before it was relieved, it required 0.5 grain of morphine and after about half an hour the pain subsided. Since then I have felt quite weak, and I am just out today for the first time." (Inadvertently the toxins had been kept outside the refrigerator instead of inside it, and therefore the preparation may have become deteriorated, or contaminated, thus causing this severe reaction.)

CONCURRENT INFECTION: The patient then developed quite a severe attack of influenza with a very irritable cough which "knocked him out" for almost a month.

CLINICAL COURSE: He reported to Coley on May 18, 1934, ". . . At this time I am feeling very good, have gained some in weight, my blood picture is showing a slight improvement."

FURTHER TOXIN THERAPY: It is believed that another course of injections were given at this time, but no details were found as to technique.

CLINICAL COURSE: By September 1934, the disease seemed to progress very rapidly in the ribs and the greatest pain was centered in the third and fourth ribs on either side of the sternum. About September 15th, there was a spontaneous fracture, and the sternal plate was pushed outward. Thereafter large doses of morphine were absolutely necessary. Death occurred on September 19, 1934, 9½ months after onset.

COMMENT: In this case radiation was given first and only a rather small number of intramuscular injections of toxins were administered.

REFERENCES: 14; 34; 46.

CASE 10: Multiple myeloma involving the left rib anteriorly and posteriorly, the vertebral column, the skull, particularly the left frontal bone, and the bony pelvis, confirmed by roentgenological and microscopic examinations by Dr. Fred W. Stewart at Memorial Hospital. Bence Jones bodies were also found in the urine.

PREVIOUS HISTORY: K.B., male, age 42, Armenian draftsman. The family history was essentially negative. The patient had had the usual childhood diseases, also

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

a great many colds, and had always suffered from headaches ever since he could remember. He is believed to have had an attack of malaria at the age of 20, which never recurred. He had complained of a swelling of the left breast since 1939. In March 1940, he had pneumonia after which he developed pleurisy and empyema, and a left high pleurotomy was performed with drainage during 20 days. Onset, the patient was very weak after the pneumonia and he had infrequent episodes of vague discomfort and occasional shooting pains when coughing and sneezing. He consulted his local physician who made a diagnosis of tumor of the rib.

SURGERY: The growth was removed on November 9, 1941, and was reported to be Ewing's sarcoma. It was described as a soft encapsulated tumor involving the fourth rib to the left of the sternum just above the nipple. The marrow, parietal pleura, and intercostal muscles did not seem to be involved.

CLINICAL COURSE: The patient's headaches became more frequent and severe. X-rays of the skull revealed bone involvement in two areas.

CONCURRENT INFECTION: On March 12, 1942, the patient had an attack of acute streptococcal pharyngitis and bronchopneumonia. He made a good recovery with sulfadiazine. During convalescence he had a mild relapse and also an episode characterized by pain in the superciliar region. The ethmoid sinusitis was treated by a physician who diagnosed streptococcal infection and on account of partial deafness and dizziness insufflated the Eustachian tubes. The fever went up and after having sharp pain in the right ear the tympanum burst, giving issue to hemopurulent discharge. Between June 1 and 6, 1942, he was given sulfadiazine. During this time the pain stopped and the drainage became less profuse. However, the drainage continued, alternately increasing and diminishing. The patient's appetite remained normal and he did not lose weight. He had had mild dyspnea on exertion. He stated that occasionally he felt so weak that he could hardly walk, and sometimes he had to pull his leg or arm so as to initiate the movement. Physical examination on admission to Memorial Hospital, June 12, 1942, showed a poorly nourished, rather pale, Armenian male. His right external auditory canal was filled with serohemopurulent exudate; the ear drum appeared perforated. The mastoid was only slightly tender. There were a few soft non-tender nodes in the right supraclavicular triangle. The thorax showed the scar of a transverse pleurotomy in the fourth left space, and some signs of residual pleural thickening. Anteriorly the fourth rib had been resected for about 8 cm., 6 cm. to the left of the mid-line. A culture was taken of the discharge from the ear which proved to be *Streptococcus hemolyticus*. The pain in the right ear became severe during the two days following his admission, and the discharge was profuse. A diagnosis of acute mastoiditis was made.

TOXIN THERAPY (*Parke Davis XIII*): Injections were begun by the house staff on June 14, 1942, the initial dose being 0.1 minim given intramuscularly. This

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

produced a febrile reaction of 103.6°F. and profuse diaphoresis. The injections were discontinued for a week, during which time the patient's ear condition cleared up considerably, the mastoid tenderness disappeared and the discharge lessened. He was given a citrate transfusion on June 16, 1942. He also was given injections of liver extract (2 cc. intramuscularly, every second day). The toxins were resumed on June 21, 1942, and were then given daily for 13 days in doses of 1/15 to 8 minims. The reactions were moderate, averaging 101° to 102°F., until June 29, 1942, when a dose of 6 minims produced a febrile reaction of 105°F. with a chill lasting 30 minutes and profuse diaphoresis.

X-RAY THERAPY: Beginning June 22, 1942, the patient received high voltage x-ray therapy over the frontal bone, left and right, the left parietal bone, the seventh and eighth dorsal vertebrae, the middle of the left humerus; these five areas each received a total of 1500 r in three doses of 500 r each given on separate days between June 22 and July 9, 1942.

FURTHER TOXIN THERAPY: The injections were suspended again between July 4 and 7, 1942. Thereafter they were given every second day until July 19, 1942. He thus received 21 injections in a little over a month, the maximum dose being 12 minims. On six occasions the temperature rose to 104°-105.4°F.; the other reactions averaged 101° to 102°F. and chills occurred on six occasions. Most injections produced profuse sweating. Bowden reported on July 14, 1942: "There has been marked subjective improvement over the past two or three days. Patient up in chair today." By July 22, 1942 he reported: "Back pain has disappeared. Patient complains only of pain in anterior tip of seventh left rib." He was fitted for an anterior Taylor back brace as the seventh dorsal vertebra was partly collapsed. During this period of six weeks he received three blood transfusions. He was discharged on July 31, 1942.

CLINICAL COURSE: The patient was readmitted on September 22, 1942, still complaining of back pain and multiple bone pains.

FURTHER RADIATION: He was given two x-ray treatments over the eighth dorsal vertebra on September 23 and 24, 1942 (400 r each). Further radiation was given in October over the fourth lumbar vertebra, 300 r each on four occasions. Pack reported at this time: "There has been very marked palliation in this case."

CLINICAL COURSE: The patient was again seen on October 23, 1943, at which time Pack reported: "This man is in excellent health. All of the bone lesions have healed very well. He is no longer anemic. He no longer has the intermittent hyperpyrexia. He has gained some weight. He has no complaints of any kind. He is able to work and is ambulatory."

PNEUMONIA INFECTION: On November 27, 1943, the patient was admitted to St.

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

Barnabas Hospital, Newark, New Jersey, apparently suffering with bronchopneumonia. Urinalysis showed a small trace of albumin and was positive for Bence Jones protein. His hemoglobin on November 27th was 49%, the r.b.c. 2,720,000. He was given an indirect citrate transfusion of 300 cc. on that day. No pneumococci were found and the patient was discharged on December 5, 1943. The blood picture had not improved at the time of his discharge.

CLINICAL COURSE: He was readmitted to Memorial Hospital on December 8, 1943, because he had been getting weaker and had been unable to work. Four to six weeks prior to admission his speech became affected (slow enunciation and high pitch). There was also pain in the right shoulder. Examination revealed marked thickening of the alveolar process about the right upper rear molar with accentuated depression posteriorly in the gingivo-buccal area. X-ray examination showed evidence of two large areas of bone destruction in the left frontal parietal bone. Films of the chest showed evidence of a large metastatic deposit in the medial and lower portion of the right base with some irregular infiltration in the left lower lobe. The impressions given were: (1) Intracerebral myeloma, cranial origin with pressure and with aphasia; (2) Thoracic wall (?); (3) Enlarging deformity of right upper alveolar process (4) Partial right hemiplegia.

FURTHER RADIATION: The patient was given six palliative x-ray treatments (300 r each, 250 KV over the right lower chest anterior and posterior, (1200 r x 2), between December 28 and January 4, 1944. The disease was not controlled; death occurred on April 10, 1944, four years after onset.

REFERENCE: 46.

CASE 11: Multiple myeloma, confirmed by microscopic examination by Dr. Sophie Spitz of Memorial Hospital, following resection of the right sixth rib. (V6024)

PREVIOUS HISTORY: Dr. J.G., Jewish male, age 47, of Meadville, Pa. The family history was noncontributory. The patient had had rheumatic fever at the age of 14 and a nasal septum removed at the age of 16. His tonsils and adenoids had been removed, but he had had no other operations. He was married and had a son and daughter. He was a roentgenologist and during the shortage of medical personnel during World War II had taken over additional work in two other hospitals in addition to his regular schedule. In early November 1946 he fell, landing on the right side. This accident had caused no immediate difficulty, but shortly thereafter he developed sharp pain under the right scapula following a severe sneeze. The pain persisted for several minutes and an area of soreness persisted for several weeks. X-rays then revealed a pathological fracture of the sixth rib. The patient continued his work as he felt no disability nor pain, but

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

soreness persisted. He was admitted to Memorial Hospital on January 3, 1947. Examination revealed a firm, rounded, slightly tender elevation the size of a lemon, posteriorly at the level of the angle of the scapula, involving the right sixth rib. The patient was well developed and well nourished, and in good general condition. X-rays revealed an osteolytic area. The provisional diagnoses of Dr. Bradley L. Coley prior to operation were, in order of choice: 1. Fibrous dysplasia; 2. chondroma of rib; 3. solitary (?) plasma cell myeloma; 4. metastatic carcinoma, primary unknown.

SURGERY: On January 6, 1947 the sixth rib was resected by B.L. Coley. The post-operative diagnosis was fibrous dysplasia. However, microscopic examination revealed plasma cell myeloma. Sternal aspiration was negative. Urinalysis was negative for Bence Jones bodies.

TOXIN THERAPY (*Parke Davis XIII*): Between January 15 and 28, 1947, 12 intravenous injections of Coley toxins were given in doses of 1/60 to 2 1/4 minims. These caused febrile reactions averaging 102°-103°F. (minimum 101.4°, maximum 104°F.) and chills lasting 20 to 45 minutes. The patient was discharged on January 30, 1947 in good condition. He resumed his active practice as a roentgenologist.

ANTIBIOTIC THERAPY: While at Memorial Hospital he was given 1,500,000 units of penicillin. Every four weeks during the next 10 months he again took 1,000,000 units of calcium soluble penicillin in divided doses (250,000 units in 2 cc of saline every 24 hours for five days). By November 13, 1947 he had had 10,000,000 units without any unpleasant effects. The patient was convinced that this had helped him.

CLINICAL COURSE: He was examined at frequent intervals in the Bone Tumor Clinic and remained free from disease and laboratory and x-ray studies were negative until March 19, 1948, 14 months after toxin therapy, when x-ray films revealed a single area about 3 mm. in diameter in the left part of the skull above the mastoid region.

RADIATION: X-ray therapy was given over this area (2400 r, 300 x 8, 220 K.V. through a 5 x 5 cm. portal) in the occipital region. Subsequent films at intervals appeared to show improvement and no evidence of disease appeared in the film in September 1948.

CLINICAL COURSE: The patient was again seen in September 16, 1948 appearing in the best of health and symptom free except for occasional slight discomfort in the ribs posteriorly below the scapula on the left. He described an episode which had occurred that summer which was suggestive of a fracture of the 7th right rib. Films made at the time failed to disclose any fracture, but subsequent ones

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

showed it with a callus. Skeletal films at this time were completely negative and the patient's progress was regarded as most satisfactory. It remained so during the next year. He was allowed to play golf two days a week during the summer of 1949. From 1947 to 1949 Bence Jones protein urea was absent on many occasions. (After 1949 it remained 1 plus). Routine x-ray films in October 1949 revealed an osteolytic process on the lower right margin of the third lumbar vertebra.

FURTHER RADIATION: X-ray therapy was given over this area (factors not stated). There was no pain and films taken subsequently suggested regeneration. Shortly thereafter the right shoulder began bothering the patient and radiation was given over this region which stopped the pain but not the destruction of bone.

CHEMOTHERAPY: Beginning in October 1949 the patient began taking urethane and by December 5, 1949 he had taken 80 grams. During the first week he became very nauseated and one night during violent vomiting the left 9th and 10th ribs were fractured. This caused pain which for a time was quite disturbing. The only way the patient could rest was sitting up in bed or in an easy chair. He was quite miserable for six weeks. Nevertheless he continued to take urethane. The white blood cell count dropped from 7200 to 3200. The weight decreased from 184 to 178. In spite of the pain, and the nausea following four hours after chemotherapy the patient did not miss a day from his practice, working six hours a day. Urethane was continued daily until early in February, the total dose up to then being 180 grams. The maximum dose tolerated was 2 or 3 grams daily and sometimes this had to be reduced to 1 gram a day. In addition to nausea and occasional vomiting and a metallic taste, this drug caused bowel irritability and a reddish colored soft stool. Also there was itching of the skin, and if scratched a slowly healing lesion. There was increased urinary output, a tired feeling and leukopenia with loss of lymphocytes and blood platelets. The first beneficial effect noted was disappearance of pain in the right shoulder. Although the left lower jaw lesion seemed to progress, the pain was not too bad and the patient was able to chew without discomfort, with full range of motion of the joint. He stated that he had very little general pain and was on the whole very comfortable.

CONCURRENT INFECTION: In February 1950 the patient had intestinal flu followed by a severe cold which lasted a month. In spite of coughing a lot no rib gave way although there was some pain along the upper part of the incision. X-ray films, taken in March 1950 revealed that the lesion in the right scapula had new bone and the small lesions in the clavicles had disappeared. It was felt that the skull lesions were increasing very slowly. The lesion in the spine had remained stationary but small lesions had appeared in the pubic bone. There had been about a 10 pound weight loss.

FURTHER CHEMOTHERAPY: Urethane was continued thereafter alternate weeks

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

until an additional 40 grams had been taken making a total of 220 grams. X-ray films showed some of the areas of bone destruction had regenerated, particularly on the right scapula. Coley examined the patient on April 6, 1950 and suggested that he take a steady maintenance dose of 1 gram of urethane daily rather than 2 grams daily alternate weeks. During the summer of 1950 he played golf twice a week, and continued his work as a radiologist.

CONCURRENT INFECTION: In early October 1950 he caught cold, and while coughing due to this cold he cracked his 10th and 11th ribs. In three weeks he felt all right again.

FURTHER CHEMOTHERAPY: The patient continued to take urethane and by May 3, 1951 had taken 300 grams. X-rays at this time did not show much change from those taken a year before. There were possibly a few more lesions in the skull and the size of the individual lesions might have changed but this was not striking. By September 1951 he had taken 400 grams of urethane.

THIRD CONCURRENT INFECTION: In May 1951 he had another upper respiratory infection; the patient stated that the cough "raised the devil with my lower right ribs, no fractures but terribly painful."

FURTHER CHEMOTHERAPY: The patient continued to take 1 gram of urethane daily. He was readmitted to Memorial Hospital on September 24, 1951 for a general check up. He had maintained his weight at 173 pounds, and he stated that his general condition was satisfactory in all respects, but that he had had recurrent spontaneous rib fractures during the previous eight weeks. In the early part of August 1951, his hair began falling out and suddenly turned white in a two week period. He also had pain centered over the left sacro-iliac region extending down the posterior thigh. The hemoglobin had dropped to 55% in August. Two transfusions on August 20 and 24, 1951 restored it to 73% by September 24, 1951. System review was essentially negative. The patient was a well developed, well nourished white male of 51 in no distress. Several ribs were tender to pressure. At this time x-ray examination showed extensive plasma cell myeloma of all the skeletal bones. The patient was seen by Dr. Lloyd Craver in consultation and he advised continuing urethane and giving palliative x-ray therapy for the painful areas, and occasional blood transfusions as needed. In November 1951 the patient was admitted to Spencer Hospital, Meadville, Pa. and remained there until his death on February 2, 1952, five years and three months after onset.

COMMENT: Note that this patient was a radiologist and that onset occurred following about four years of exceptionally heavy work due to the war. At least three other radiologists are known to have developed multiple myeloma following prolonged professional exposure to x-ray (60).

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

REFERENCES: 46.

CASE 12: Multiple myeloma involving the left seventh rib, left mandible, right humerus and right femur, confirmed by microscopic examination following incomplete surgical removal of the mandibular lesion at Sharon Hospital, Sharon, Connecticut and by bone marrow aspiration.

PREVIOUS HISTORY: Mrs. E.S., female, aged 61, bookkeeper. Onset, about January 1961 she developed pain in the left seventh rib. This was treated with local injections of procaine after x-ray examination revealed no evidence of pathology. This pain gradually subsided. In the late October 1961 she developed a tumor in the left parotid region which slowly increased in size during the next three months. The patient was admitted to Sharon Hospital of January 28, 1962. Examination on admission revealed a moderately obese, healthy, elderly woman weighing 157 pounds, with visible swelling anterior to the tragus of the left ear. Palpation revealed a diffuse hard fixed mass apparently deep in the body of the parotid approximately 2 cm. in diameter. The preoperative impression was that it was a mixed tumor of the parotid salivary gland.

SURGERY: At operation on January 29, 1962 the tumor was found not to be in the parotid gland but deep to the left masseter muscle apparently beneath the periosteum of the ascending ramus of the left mandible. Dr. George A. Fowler partially excised the left parotid gland with complete dissection of the left facial nerve and partially excised the tumor of the left ascending ramus of the mandible.

CLINICAL COURSE: Postoperatively there was a moderately diffuse swelling of the left face with puffiness below the eye and slight weakness of the left upper and lower lips, but no other muscle weakness. Drainage was moderate and gradually diminished. Pathological report was plasmacytoma involving the left mandible and a normal left parotid gland. The urine was negative for Bence Jones protein. Serum protein partition electrophoresis revealed a marked elevation of gamma globulin to 2.8 grams %. This was repeated and this time was 3.17 grams %. Meanwhile, skeletal survey revealed a tumor of the left seventh rib, also some small areas of rarefaction in the middle third of the shaft of the right humerus with some periosteal proliferation. There was a rounded area of rarefaction in the distal third of the right femur. Further x-rays of the region of the seventh rib on the left side in the anterior axillary line revealed considerable soft tissue swelling and a destructive lesion of the seventh rib in this area. It was felt that the appearance of this lesion was that of multiple myeloma. In view of these findings and that on bone marrow aspiration, showing a large number of plasma cells, and bone marrow count of 9.2 plasmablasts, proplasmacytes and plasmacytes, the

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

actively and sit up in bed for 10 to 15 minutes without feeling any pain. After a condition was regarded as plasma cell myeloma. Because of the general poor prognosis in this neoplasm, it was felt that toxin therapy might be advisable.

TOXIN THERAPY (*Johnston XV*): Injections were begun by Dr. George A. Fowler on February 14, 1962, 16 days after surgery. The initial dose (0.25 cc of a 1:400 dilution) was given in the region of the left seventh rib in the anterior axillary line. There was no immediate reaction but generalized malaise lasting about 20 hours. The following day her temperature rose to 101.4°F. but fell to normal. The second day it rose to 100°F. but then remained normal. The second injection (same dose) was given intravenously two days later. This caused a chill and a febrile reaction of 104.2°F., nausea, vomiting and some pains in the right hip. The same dose intravenously for the third injection five days later caused no chill and no immediate reaction. However, the next day she had generalized aches and pains. Her final hospital dose was given intravenously on February 23, 1962 and caused no reaction. The operative area healed well with no visible deformity of the left face but at the time of her discharge there remained some slight weakness of the left lips which seemed to be improving. Toxin therapy was continued on an outpatient basis. A total of 65 injections were given intravenously over the next 19 months causing good chills and febrile reactions of 100°-103°F.

In March 1963 she developed a soft tissue tumor in the buccal area of the mouth. This gradually increased in size despite continued toxin therapy until the injections were stopped on August 27, 1963. At this point she could not chew and was living on liquids which she swallowed with great difficulty. The condition appeared terminal.

HEMORRHAGES: She then had repeated episodes of brisk bleeding from tumor masses in the cheek when she would accidentally bite them requiring pressure and gelfoam for control.

CLINICAL COURSE: The tumors then gradually regressed. The patient regained her lost weight, and again became active, mowing her lawn, etc. She remained clinically well, doing all her own work for over two years, but she became extremely obese. She sustained a pathological fracture of the left proximal humerus on January 17, 1966 for which she was readmitted on that day. The urine at this time was again negative for Bence Jones protein. X-ray examination revealed multiple small osteolytic areas in the shaft and distal right humerus with considerable periosteal thickening, more marked than at the last examination on March 7, 1963. There was a 2 cm. oval area of radiolucency overlying the left iliac crest, which was possibly gas in the colon or an osteolytic metastasis. The osteolytic lesion originally seen in the right femur on May 31, 1962 was less apparent and appeared to be somewhat sclerotic. There appeared to be a few small osteolytic areas in the left intertrochanteric region. A chest film again showed the soft tissue

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

density projecting somewhat inward from the left lateral chest wall, which appeared essentially unchanged from films taken March 7, 1963. The heart and mediastinum appeared within normal limits. The lungs appeared clear. There was a slight blunting of the left costophrenic angle. The patient was treated with bed rest and placed on a 1000 calorie diet because of her extreme obesity, and the weakness of her involved bones. She gradually became ambulatory. The pain in the fractured shoulder gradually subsided and she was discharged on her 19th hospital day, her weight having declined from 168 to 164 1/4 pounds. The fracture healed, but the patient continued to have progressive bone lesions in various skeletal areas. In the last few weeks of 1966 she redeveloped the buccal tumor with inability to chew and bleeding episodes. She lost weight.

FURTHER TOXIN THERAPY: Injections were resumed briefly.

CLINICAL COURSE: Early in January 1967 there was a second pathological fracture of the humerus. She was readmitted to Sharon Hospital. Death occurred five days later, on January 12, 1967, over five years after onset.

CASE 13: Multiple myeloma involving all the bones, confirmed by microscopic examination following punch biopsy and skeletal x-ray examinations.

PREVIOUS HISTORY: S.A.B., male, age 57. Onset occurred in May 1968. The patient was admitted to the Mine Hospital in Pernik, Bulgaria with a diagnosis of "chronic nephritis". His condition gradually deteriorated in the next two months with unbearable pain in all the bones requiring drugs. There was severe cachexia with disappearance of all the subcutaneous fat and the whole musculature. The patient was so weak that he could not raise his hand. Skeletal films showed "overlapping areas of multiple myeloma". A biopsy was reported as plasmacytoma. The patient became stuporous and lapsed into uremic coma for a week. Laboratory tests showed urea - 160 mg. %; hemoglobin, 44%; Wgr. 140/160. The patient appeared to be dying.

TOXIN THERAPY (*a preparation known as AB derived from Bacillus Acidophilus Bulgaricus*): On August 12, 1968 oral administration of AB was begun by Dr. Ivan Bogdanov, of Sofia, Bulgaria. During the first week of treatment he regained consciousness and his general condition and appetite improved and spontaneous bone pain diminished. After 15 days he recovered his voice and was pain free so that drugs were no longer needed for pain relief. The urea was 44 mg. %; Wgr. 34/63 mm. By October 30, 1968 the general condition had further improved. The muscles of the thorax and hands had recovered and the patient began to sit up in bed. There was no spontaneous bone pain. (Wgr. was 15/23 mm.) By the fifth month after beginning AB treatment he was in excellent general condition having almost fully recovered his muscle tone, except for the legs. He could move

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

year of treatment the patient was symptom free and able to walk about the hospital corridors without help, using a cane.

CLINICAL COURSE: After his discharge he went to live in the country where he looked after himself alone and was able to walk and lift objects off the floor, etc. without pain. This clinical remission lasted 17 months without any evidence of recurrence. Early in January 1970 the patient died from a very severe influenza because he did not receive qualified medical aid in the distant village where he lived. Death occurred over 18 months after onset.

REFERENCE: 55

CASE 14: Multiple myeloma involving three vertebrae (T4, T8, and L3), confirmed by x-ray, biochemical and histological examination.

PREVIOUS HISTORY: N.V., male, age 42, a physician. Onset occurred in the middle of 1969. By May 1970 the patient had extremely severe girdle pain and was bedridden. On May 24, 1970 he was admitted to the Neurosurgical Clinics in Isul, Bulgaria, with very severe pains in the lumbar region which prevented any movement, even deep breathing.

RADIATION AND CHEMOTHERAPY: Local x-ray therapy was given and cyclophosphamide (Endoxan) was begun. Two weeks later these had to be stopped because of the severe general condition of the patient, and the severe leukopenia (1500), which they had caused, without producing any pain relief.

TOXIN THERAPY (AB): Oral administration of AB was begun on June 16, 1970 by Dr. Ivan Bogdanov, of Sofia, Bulgaria. At first there was only an improvement in the appetite and general condition. On the 20th day the wbc was only 2000. The pains gradually subsided and at the end of 6½ weeks had entirely ceased. Treatment was continued for nine weeks, until August 20, 1970 when the blood count and general condition had fully returned to normal.

FURTHER CHEMOTHERAPY: Endoxan was then resumed. Very soon the patient's condition deteriorated. The wbc again decreased to 2500 and pain developed in the bones of the left hand. Endoxan was discontinued on September 8, 1970.

FURTHER TOXIN THERAPY: Oral administration of AB in larger doses was resumed on September 18, 1970 and continued without interruption. The general condition and appetite improved, the pain disappeared and the patient began to move actively in bed. A month later he was able to sit up without any help and without pain. In another month he was able to get up and walk with little help. X-ray examinations revealed calcification of bone had occurred in the three formerly diffusely osteoporotic vertebrae. The clinical and hematological remission con-

SERIES B: IMMUNOTHERAPY, DETAILED HISTORIES

tinued. The patient returned home to Czechoslovakia in complete clinical remission. The AB treatment was continued for at least 18 months. He was able to return to work as a physician and to drive his car, etc.

CLINICAL COURSE: No further details are available except that the patient died March 1973, 44 months after onset.

REFERENCE: 55

DISCUSSION:

These two interesting cases of Bogdanov's suggest the need for further evaluation of this material derived from cultures of *Lactobacillus acidophilus* *Bulgaricus*. This preparation is completely nontoxic and can be given orally which is an obvious advantage, especially for maintenance therapy. Bogdanov has recently produced a fraction which can be used for intravenous injections. Although clinical trials of the oral preparation are not as yet extensive, it would seem that remarkable remissions have been obtained in several other types of malignancy, lasting for over three years.

The need to obtain more stable, purified preparations of the Coley Toxins derived from *Streptococcus pyogenes* and *Serratia marcescens* is clearly recognized and the Cancer Research Institute is working on this problem.

The dramatic effects observed in the two cases who developed erysipelas infections suggest the possibility of inoculating attenuated cultures intradermally in multiple myeloma patients in order to control the extreme pain, even if the procedure provides only temporary remissions.

The apparently permanent result obtained by Thomas in the first case to receive toxin therapy due to prolonged treatment (two years), suggests the importance of sustained therapy with microbial products such as Coley Toxins, AB, BCG or yeast extracts (zymosan or glucan) in treating multiple myeloma now and in the future.

Cooperative studies will be necessary in order to arrive at definite conclusions as to the best agents to use and how to administer them most effectively. Possibly better results may be achieved if immunotherapeutic agents are used alone or if they are begun prior to immunosuppressive treatments such as radiation and chemotherapy.

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