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Irradiation therapy of bone neo-plasma

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IRRADIATION THERAPY of BONE NEOPLASMS

Floyd W. Schow

Senior Thesis presented to the University
of Nebraska College of Medicine, 1937

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INTRODUCTION

One of the innumerable prerequisites, and, at present, most alarming to the author, for graduation from the University of Nebraska College of Medicine is the writing of a Senior Thesis; thus, the only plausible reason for this paper.

In considering irradiation therapy of bone neoplasms one is first confronted with the problem of classification, which will be the first division. The etiology and incidence of bone tumors as a whole is perhaps the second division. The subject matter then divides itself into the consideration of irradiation therapy in each of the separate headings of the classification (see page two). Each in turn will be taken up as presented there.

CLASSIFICATION of BONE NEOPLASMS

Before 1920, because of the rarity of bone neoplasms, few men had observed enough cases to gather sufficient data to set forth more than the crudest classification of this disease. About the best they could do was to divide them into two main groups, i.e., benign and malignant. However, at about this time a Boston physician, Codman, who was taking care of a patient with a primary bone tumor became particularly interested in this disease. In order to gain more information, he wrote to numerous friends asking them to send him their observations in similar cases. This correspondence gradually became more extensive and eventually evolved into the Registry of Bone Sarcoma. Through the Registry sufficient cases and data were collected to establish a more or less satisfactory classification of bone tumors. (34)

The classification as set forth by the Registry is as follows:

1. Metastatic tumors primary in other tissues than bone.
2. Periosteal fibrosarcoma.
3. Osteogenic tumors, (a) benign, (b) malignant.
4. Inflammatory conditions.
5. Benign Giant Cell tumors.
6. Angiomata, (a) benign, (b) malignant.
7. Ewing's tumor.
8. Myeloma.

The above classification has been used by such men as Codman, Ewing, Kolodney and others who have made remarkable

contributions towards the comprehension of this subject. Of course, these men do not agree in entirety with the above classification. However, to discuss, these conflicts would be to diverge from the purpose of this paper. I, therefore, refer you to the well written papers presented by these authors. (14, 35, 34, 52, and others).

ETIOLOGY and INCIDENCE of BONE NEOPLASMS

Neoplastic lesions of bone are indeed quite rare. Kolodney (52) states that their occurrence is one in one thousand population. In 123,285 hospital admittances, Moore (69) found 96 cases of primary bone tumors. He reports, also, 277 cases of metastatic malignancy occurring in 5, 883 cases of carcinoma.

Tumors of bone, as new-growths in other tissues still baffle the man who attempts to explain their etiology. Such factors as age, sex, heredity, embryonic arrests, irritation or trauma, constitutional predisposition and so forth, have all been advanced but fail to withstand critical analysis.

Kolodney (52) emphasized trauma as frequently being linked with primary bone neoplasms. He brought out the fact that young growing cells when they reach the stage of physiological maturity cease to develop further. This he terms "growth restraint." However the mature cells do not lose their growth abilities, the latter having merely changed from kinetic to potential. Trauma with subsequent necessity for repair or regeneration temporarily lifts this growth restraint. He states that in some instances, in the presence of predisposing factors which are not understood, trauma may lead to a complete loss of growth restraint in the traumatized region. However, we must remember that even though bone tumors frequently seemingly follow a history of trauma, trauma actually is rarely followed by a new growth.

METASTATIC TUMORS of BONE; PRIMARY in
OTHER TISSUES THAN BONE

The effect of irradiation upon metastatic lesions of bone primary in other tissues was first demonstrated by Pfahler and Parry (Rose, 83) in 1916. At this time they reported a case with bone destruction from metastatic carcinoma, which showed regression of tumor, bone regeneration and a corresponding clinical improvement following the use of radiation therapy. This apparently introduced roentgen and radium rays as therapeutic measures in the treatment of secondary carcinoma of bone. Since then, remarkable advance has been made as is evidenced by the numerous studies of various authors now found in the literature.

The site of the primary carcinoma is most frequently the breast, then the prostate, and less commonly the lung, uterus and cervix, thyroid, urinary tract, and gastro-intestinal tract. (63, 75, 42, 89). Pfahler (75) and Herendeen (42) believe that of all metastatic carcinoma to bone, which the radiologist is called upon to treat, those of the breast are by far more frequent. Lenz and Freid (58) found in 165 cases of carcinoma of the breast with metastases that in 85 cases (or 55 per cent) the skeletal system was involved. Leddy and Desjardins (56): "In 573 inoperable cases of carcinoma of the breast, osseous metastasis was second only to metastasis to the infraclavicular node." In the 330 cases with skeletal metastasis (table A) that I obtained from the literature 261 (79.9 per cent) were

TABLE A

Tabulation of Results of Roentgen-Ray Therapy in 330 Cases of Metastatic Carcinoma to Bone, Appearing in the Literature

(78, 57, 56, 75, 73, 82, 33, 58, 59)

Primary Carcinoma		Results of Therapy on Symptoms					
		No Relief	Complete Relief	Partial Relief	Not Known	Total	Percent
Breast	Case	64	144	32	21	261	
	Percent	24.5	55	12.5	8		79.9
Prostate	Case	23	7	27	5	62	
	Percent	37.1	11.3	43.5	8.1		19
Thyroid	Case		2			2	
	Percent		100				0.6
Hyperne- phroma	Case		1	2	2	5	
	Percent		20	40	40		1.5
Totals	Case	87	154	61	28	330	
	Percent	26.2	46.9	18.5	8.5		

from primary lesions of the breast.

The second most common carcinoma which metastasizes to bones is probably that of the prostate. Bumpus, quoted by (57), has found it in 30 per cent of his cases, while Kaufmann observed metastases to bone in 16 of 22 cases. On 330 cases with skeletal metastasis (table A) I found 62 (19 per cent) in which the primary lesion was located in the prostate.

Metastases to bone from carcinoma of the thyroid, lung, uterus and cervix, urinary tract, and gastro-intestinal tract are no doubt decidedly less frequent. Ginsburg (39) remarks: "In 1892 in a report of 50 cases of carcinoma of the thyroid at the Vienna Pathological Institute from 1882-1892, Hinterstoistner found metastases to bone in 20 per cent. In 1902 Ehrhardt, at Kocher's Clinic, in 238 cases of thyroid tumor, found skeletal metastases in 66." I found in 330 cases with skeletal metastases (table A) that the primary lesion was located in the thyroid in only 2 cases (0.6 per cent) and in the kidney in 5 cases (1.5 per cent).

The bones most frequently involved are the spine, pelvis, femur, ribs, and humerus. Leddy and Desjardins (56) found spinal and pelvic metastases by far more common. Peden (53) believes that metastasis below the knee or elbow are extremely rare. Pfahler (74) has found metastasis (in order of frequency) from breast to spine, pelvis, femur, skull, ribs, humerus, and sternum; from prostate to pelvis, spine, and ribs; from thyroid

to spine and sternum; from hypernephroma to pelvis, spine, femur, humerus, ribs, feet, skull, and sternum; and from ovary and uterus to pelvis and spine.

As has been emphasized by numerous writers, metastatic carcinoma of bone is merely one manifestation of a generalized carcinomatosis. Therefore, in treating these lesions we cannot hope for cures. The best that can be expected is for amelioration of symptoms and prolongation of life. (73, 12) Pfahler (74) states: "The local lesion can be cured with brilliant results, however the generalized metastasis allows progress of the disease in other tissues or localities."

The success of irradiation in the treatment of secondary carcinoma of bone depends primarily upon the sensitiveness of the malignant cells to irradiation. The metastatic cells from the breast are generally accepted as being the most sensitive, while those from the thyroid are second and from the prostate, third. Metastasis from the urinary tract, uterus and cervix, and the gastro-intestinal tract are distinctly the least sensitive. (47, 54, 74). Herendeen (42) in speaking of secondary carcinoma from breast to bone states: "It may be said that in general the response of these tumors as compared with the response of other carcinomatous metastasis to bones, as indicated by relief from pain and evidence of attempt at repair, is more prompt and indicates a sensitivity seldom demonstrated in carcinomatous metastasis from other glands." He says also that prostatic metastasis to bone respond to irradiation with only relief from

pain, while the response of similar lesions from primary tumors of bladder, uterus, and gastro-intestinal tract is indeed disappointing. In table A we find in 261 skeletal metastasis from the breast that 55 percent obtained complete relief, 12.5 per cent partial relief, 24.5 per cent no relief, and 8 per cent results not known; in 62 cases from the prostate 11.3 per cent complete relief, 43.5 per cent partial relief, 37.1 per cent no relief and 8.1 per cent results not known; in 2 cases from the thyroid both had complete relief; and in 5 cases from hypernephroma 1 had complete relief, 2 partial relief, and in 2 cases the results were not known.

Lenz and Freid (58) in using roentgen rays and radium in treating secondary carcinomatous lesions from the breast have observed: "They caused diminution and at times marked temporary regression of the clinical and roentgenographic signs of skeletal metastasis. Clinical improvement started 24 to 48 hours after the first treatment and lasted a few weeks to years." Roemer (82) says: "The patients are made quite comfortable and are able to perform their household duties, and life can be prolonged for several years." Peden (73) remarks: "The patient with bone metastasis from carcinoma of the breast may not by x-ray therapy have her life prolonged, but she certainly is relieved of suffering and made more comfortable than without x-ray." Pfahler (5) concludes: "Only local curative results and a prolongation of life from one to four years can be expected. The healing is indicated by a recalcification of the

affected part. Involvement of other parts of the body must be continually expected."

The opinions appearing in the literature are agreed that irradiation of prostatic carcinomatous metastasis to the skeleton, though not as effective as with similar lesions from the breast, is still definitely of value. Leddy and Gianturco (57) have observed that a beneficial effect from roentgen treatment is obtained in about one-half the cases of pain from metastasis in cases of carcinoma of the prostate gland.

Skeletal metastasis from the thyroid gland respond in a manner comparable to those of the breast when subjected to irradiation. (74, 32, and others)

In metastasis from other glands to bone it is generally agreed that the results are quite disappointing. Herendeen (42): "The hypernephroma appears to be one of the most resistant to radiation of all carcinomatous metastasis to bones. These tumors are highly vascular and this may be a factor in their radioresistance." He also claims that the skeletal metastasis from primary carcinoma of the bladder, mouth, tongue, eye, and cervix respond very poorly to irradiation with little if any relief from symptoms, thus suggesting radioresistance rather than sensitivity.

Rose (83) in speaking of metastatic carcinoma to bone aptly remarks: "I have satisfied myself that, although this treatment does not cure, it prolongs life, relieves the sufferers of their pain to a surprising extent and often makes them able to enjoy

life and participate in activities of their home or even their business to such an extent that they feel the x-ray treatment has put them back on their feet again."

Irradiation accomplishes its results by destruction of the carcinomatous cells. These neoplastic cells are more sensitive to roentgen rays than are the osteoblasts of the bone. Therefore, by giving such dosages of x-ray as will destroy the malignant cells and not the bone forming cells we can stop the progress of and even kill the former and thereby allow the latter to repair the damaged bone. (74, 75, 63, and 57). Pfahler (75) remarks: "If we had primary carcinoma of bone, our most brilliant results would occur here; but the generalized carcinomatosis is responsible for our failure in metastatic carcinoma to bone."

Dresser (33) from 1929 to 1934 has treated 50 cases of carcinoma of the breast with skeletal metastasis to bone by irradiation of the ovaries. His results were quite satisfactory especially in those patients who had not yet reached the menopause. He found in this group that 30 per cent obtained complete symptomatic relief with bone regeneration which lasted from several months to two to three years, and that 43 per cent showed temporary symptomatic relief. The results in the patients who had passed the menopause were not so encouraging, 43 per cent experiencing only slight relief. His technique of administration of irradiation consisted in: "200 K.V., 50 cm. distance, 0.5 mm. Cu filter, 600 'r' measured in air, and given

in front and back of pelvis respectively through a 15 cm. by 15 cm. portal. This dosage will produce a cessation of menses in the average women 35 or older. In younger or more obese women the depth dose should be increased, preferably by increasing the skin distance from 50 cm. to 80 cm. The treatment is generally given in daily doses of 300 'r' each. Menses should cease in two months."

In treating the skeletal metastasis it is much better to use high than low voltage technique for as pointed out by Pfahler (74) the over-lying tissues absorb less rays with high than with low voltage. The usual procedure is to use from 200 to 240 K.V., 4-5 ma., skin distance of 50 cm. to 80 cm., filter 0.75 mm. Cu plus 1 mm. Al and delivered through as many portals of entry as available; to the pelvis four fields are recommended, an anterior, posterior, and two lateral fields; and to the spines bilateral fields with the rays converging upon the spines. Most authors use from 80 per cent to a full erythema skin dose delivered at one setting or at daily intervals so regulated as to obtain a full depth dose which is to be maintained. Pfahler (74) suggests the following procedure: "Deliver gradually an erythema dose into affected (by daily doses) tissues within a week to ten days, and then maintain saturation for another week to ten days. After this a 50 per cent dose delivered into the part in two doses at an interval of one month will probably give best results." (32, 80, 56, 57, 89, 75, 82).

The patient who has a primary carcinoma especially in the

breast, prostate and thyroid should be carefully watched and x-ray plates taken to determine whether there are skeletal metastasis. This is especially true where there is a history of pain which is apparently located in the bones. As has been emphasized by various authors (80, 12, 73, and others), the earlier roentgen ray therapy is commenced in such skeletal lesions the more striking will be the end results.

Malignant Invasion of Bone.

Tyler (92) presents three cases with malignant bone invasion which have apparently been greatly helped through the use of radiation therapy.

Case 1: Male, age 41, with erosion of mandible from left angle to incision region by a squamous cell carcinoma. It was treated by high frequency electrical current (coagulation of diseased mandible) and heavily filtered radium. Patient well four years after treatment.

Case 2: Male, age 45, with cancer of floor of mouth and gums involving the mandible. It was treated with radium and high voltage x-ray using tolerance dosage over a period of three months. At the present time the mandible is completely gone from first molar to last molar, but the floor of the mouth is covered by normal closed mucous membrane and the tongue is unchanged in shape. There has been no recurrence in nine years.

Case 3: Male, age 41, with a squamous cell carcinoma of the inner left cheek involving the left mandible, left floor of mouth and left anterior pillar of pharynx. Patient was treated

by high frequency electrical current and removal of coagulated tissue followed by heavily filtered radium. At present time the mandibular border is now depressed from the left angle to the right cuspid. The floor of the mouth and inner side of the cheek are covered by normal mucosa. The left side of the tongue is fixed to the floor of the mouth with exception of 0.75 cm. at the tip. The patient can talk but has difficulty in forming words involving the use of letters as p, t, and b. The patient is well with no evidence of recurrence for more than four years.

Larkin (55) in speaking of epitheliomata (of either the basal or squamous cell type) says: "Lesions in which the cartilage or bone are involved have not been cured or healed by us without employing surgical measures. Inhibition of growth, prolongation of life, and promotion of comfort are accomplished, but in no case has healing occurred from radiation alone." Of his seven cases with bone and cartilage involvement and treated by screened irradiation, all cases were living with the disease.

It appears that even with this inadequate number of cases irradiation is definitely indicated as an adjuvant to surgical procedures in the treatment of carcinomatous lesions (especially epitheliomata) which have invaded bone.

PERIOSTEAL FIBROSARCOMA

These tumors are apparently exceedingly rare. In the literature I found reference specifically to only four cases which were mentioned briefly by Coley (19). Kolodney (52), though he did not give percentages did emphasize the rarity of these neoplasms.

The periosteal fibrosarcoma arises from the outer fascicular layers of the periostium and possibly the adjacent fascia and tendinous insertions. It does not invade the adjacent cortex, but may by pressure erode the surface. They contain no osteoid tissue being composed principally, as the name implies, of fibrous and sarcomatous tissues. (52 and 34) Moore (69) in speaking of these neoplasms says that they are less distinctive in their radiological manifestations than are the osteogenic group. He believes that their spread and metastasis are apparently the same as sarcoma arising in the soft tissues and wholly independent of bone.

In treating these tumors Pfahler (74 and 75) recommends the use of irradiation to be followed probably by amputation. In discussing therapy Coley (19) says: "The periosteal fibrosarcoma which is characterized by little bone involvement we have found most responsive to treatment. Three patients are well three years and one is well two years. We used irradiation alone in one and toxins and irradiation in three." Kolodney (52) concludes: "The periosteal fibrosarcoma of the cases registered bear out the fact that this tumor is of decidedly better prognosis

than the osteogenic sarcoma.

From this one might assume that these tumors, though rare, do have a much better prognostic outlook than the osteogenic sarcoma. Further, they are apparently relatively radiosensitive and should thus be treated, no doubt, by the use of full tolerance roentgen-ray therapy followed possibly by surgical removal or amputation.

OSTEOGENIC TUMORS

The term osteogenic as set forth by the Registry was intended to apply to those tumors derived from the ancestors of the mature bone cells, which are osteoblasts. These cells, however, may not be producing bone, for this is only a potential characteristic. Accordingly, the predominating cellular element may be, depending upon the degree of differentiation, mucoid, cartilaginous, spindle cell, and so on, or a combination of two or more of the above. The malignant character of these tumors may also be as varied as the cell type. Some are definitely benign while others are highly malignant. Ranging between these two extremes we find them showing varying degrees of benignity and malignancy. For practical purposes the group as a whole may be divided into three main divisions: (1) benign osteogenic tumors, (2) borderline osteogenic tumors, and (3) malignant osteogenic tumors (osteogenic sarcoma). (52)

The Benign Osteogenic Tumors

This group includes the exostoses, osteomas, chondromas, fibromas, myxomas, fibrochondromas, fibromyxochondromas, etc. The class as a whole is composed of tumors which are benign from the onset and tend to remain so. As long as the benign character persists, they are non-sensitive to radiation. Under these circumstances treatment is entirely a surgical problem. (32, 2, 11, 47)

The Borderline Group of Osteogenic Tumors

Desjardins and Popp (32) and others have emphasized the fact that under certain circumstances, especially repeated surgical treatment of recurrences, the benign osteogenic tumors tend to undergo malignant degeneration. This, as emphasized by Evans and Leucutia (34) is especially true of the chondroma and myxoma. In speaking of the chondroma they say: "They may remain quiescent for years until trauma suddenly produces a change for the worse. At this time the cartilaginous matrix becomes richer in blood supply, the benign cell element gradually undergoes malignant degeneration, and often distinctly sarcomatous changes result. The course from this moment on is not unlike that of osteogenic sarcoma. Generalized metastasis, as a rule, forms the closing chapter." They further state that in treating this lesion a sharp line must be drawn between the two stages. They aptly remark: "As long as the process maintains its benign character and remains localized to one focus, irradiation is of little benefit and radical surgical intervention is the treatment of choice, but as soon as the lesion becomes generalized and signs of malignant degeneration appear, irradiation, in the form of deep x-ray becomes of great value. This manifold behavior of the chondroma to irradiation is easily explained by the histological changes occurring within the tumor. Since cartilage is highly resistant to x-ray, the response to irradiation would be nil. As soon as the cartilage shows malignant degeneration, a typical cell element will make it's appearance, and as these elements,

as a rule, are more or less radiosensitive, irradiation will result in their destruction, with ultimate clinical arrests of the process, lasting for a period of many years."

Bloodgood (11) is of the opinion that there have been no cases of myxoma which have been cured by surgery alone. He states that in all cases recurrences following surgical attack have occurred within several months to a year. Evans and Leucutia (34) report one case of myxoma which they cured by the use of curettage and cautery followed by a thorough course of roentgen-ray therapy.

As long as these benign osteogenic tumors, the chondroma and myxoma, maintain their non-malignant character, as evidenced by clinical course and growth of the neoplasm, the treatment is surgical. However, as soon as the picture changes for the worse, that is, malignant degeneration occurs, then irradiation, in the form of deep x-ray therapy, becomes essential as an adjuvant to surgery.

The Osteogenic Sarcoma (Malignant Osteogenic Tumors)

Many attempts have been made to subdivide osteogenic sarcoma by classifying them according to preponderance of cell type, i.e., spindle cell, giant cell, chondromatous, etc., or anatomically as periosteal, subperiosteal, medullary, etc.

(69, 34, 52, 35, 14 and others) However, as pointed out by Kolodney (52) such a classification has little, if any, clinical significance for regardless of predominating cellular type or

of anatomical variation the prognostic outlook and therapeutic application is little different. To attempt to use such a terminology as is suggested above would only make the paper more confusing. This group in general will be spoken of, therefore, as a whole rather than to use such subdivisions.

The osteogenic sarcomas are highly malignant. Moore (69) observes: "Osteogenic sarcoma spreads rapidly into blood vessels and spaces which may form along areolar tissues, and for distances which cannot be suspected." He also brings out the fact that they tend to metastasize early through the blood stream. Kolodney (52) points out that these tumors not infrequently spread up and down the medullary canal for considerable distances. Barnes (1) remarks: "Pulmonary and pleural metastasis occur with striking frequency in the bone malignancies, particularly in the osteogenic group." The individual who develops one of these new-growths, therefore, has a definitely bad prognosis. Tumors which grow rapidly, metastasize early, and are highly invasive are difficult to control with any type of therapy.

It is generally conceded that of the primary malignant bone tumors the osteogenic sarcomata are decidedly the least sensitive to irradiation. The group as a whole responds rather poorly. There seems to be some difference of radiosensitivity within the group itself, depending apparently to some extent upon the predominating cellular element. Those tumors which are made up largely of cartilaginous tissue seem to be the more sensitive, while the myxomatous type seem to be most

resistant. Another factor which appears to have some bearing upon sensitivity is the anatomical location. It has been observed that the periosteal group are seemingly more resistant than the medullary group. (1, 40, 2, 24, 88, 55, 13).

By the use of heavy thorough irradiation it is possible in most cases to obtain regression of the tumor and relief from symptoms. However, the results are, except in rare instances, only temporary. Sooner or later, in the majority of the cases, the neoplasms again become active, and the final chapter consists of metastasis and death. (43, 30). It has been pointed out by Bartlett (2) and others that apparently a large percentage of reported cases are not true osteogenic sarcoma. Bartlett (2) has shown that in the accepted cases of the Registry the cases well five or more years were predominately composed of chondromatous tissue and were, therefore, not true osteogenic sarcoma.

Desjardins (30) and Herendeen (43) as well as others have separated the chondrosarcoma from the osteogenic group. Desjardins has observed: "By sufficient intense irradiation chondrosarcoma can be made to retrogress perceptibly and sometimes to a considerable degree for a limited period of time (weeks or months) but, as osteogenic sarcoma, complete and permanent disappearance of such a neoplasm is a rare occurrence."

Bloodgood (8) states that prior to 1913 there were no verified cures of sarcoma of the long bones treated by amputation or any other method. In 1913 two cases which he operated became

five year cures in 1918. He further points out that in 1920 less than four percent of the cases showed five year cures, and in 1932 twenty-five percent. He attributes this improved prognostic outlook to earlier diagnosis resulting from education of the public to the value of x-ray pictures with pain, swelling, tenderness, loss of function, or injury to the skeletal structure. Barnes (10) aptly expresses it: "At this time early diagnosis is important, for too many bone tumors are treated by massage, bakes, high frequency current, baths, etc."

There is considerable dispute among various authors as regards the method of treating these bone tumors. There are three main types of therapy: (1) surgical intervention, (2) irradiation of involved region, and (3) the systemic use of a toxin prepared by Coley. Some years ago Coley observed a spontaneous cure of a malignancy in a patient who developed erysipelas. Following this he worked out an erysipelas and prodigiosus toxin which when injected subcutaneously has apparently produced some rather striking results in his and a few other hands. (20, 22, 21). Besides the above three forms of therapy we find all possible combinations of them being used.

Neill (71), Moore (69), Evans and Leucutia (34), Palmer (72), and others favor early radical surgery and possibly post-operative irradiation. Opposed to this we find Brooks (13) and others who feel that the radical removal of tumors by surgery is hardly justifiable, and recommend the palliative use

TABLE B

Tabulation of Results of Therapy in 522 Cases of Osteogenic Sarcoma Appearing in the Literature.

(68, 11, 24, 19, 17, 77, 70, 49, 2, 36, 92, 61, 86, 51, 4, 67, 28)

Therapy Used		No Re-sults	Symptomatic Relief Only	Years Patients Survived						Total	Per Cent	
				0-1	1-2	2-3	3-4	4-5	over 5			
Surgery Alone	Case Percent						4 18.1		18 81.9	22		3.5
Radiation Alone	Case Percent	7 16.2	6 13.9	7 16.2	6 13.9	6 13.9	3 6.9	2 4.6	6 13.9	43		8.2
Toxins Alone	Case Percent						13 6.5.		7 3.5	20		3.8
Surgery & Radiation	Case Percent	13 8		43 25.6	29 17.2	18 10.7	17 10.1	3 1.7	45	168		32.1
Surgery & Toxins	Case Percent						16 44.4		20 55.6	36		7
Radiation & Toxins	Case Percent			1 10					9 90	10		1.9
Surgery, Radiation, & Toxins.	Case Percent								10 10	10		1.9
Totals	Case Percent	20 3.8	6 1.1	51 9.8	35 6.7	24 4.8	53 10.1	5 9.7	115 22.2	309		60

Of the remaining 213 cases, all treated by surgery, irradiation; 204 cases did not survive three years, one was well eight years but not followed, and eight were not traced.

of x-ray where it is possible to make the patient as comfortable without subjecting him to the mutilating procedure of amputation. Others who favor irradiation alone or as an adjuvant to surgery are (11, 6, 7, 48, 74, 41, and numerous others). Coley (17 to 23) is the strongest advocate of the use of toxins and recommends their use in combination with surgery. He states: "I believe that an amputation as soon as diagnosis has been made, followed by prolonged treatment with Coley's toxin is the method of choice. This method has given a higher percentage of cures than amputation alone, or amputation followed by radiation." Pfahler and Parry remark: "Preliminary irradiation of the tumor area and irradiation of the pulmonary area followed by amputation, has given us the best results to date, but based upon Hofelder's results it would seem that we have not waited long enough for the full beneficial effect of the irradiation." Bloodgood (9) has aptly concluded: "The treatment will depend upon the point of view of the one responsible, the choice being between x-ray or radium radiation and exploration, with further diagnosis by gross frozen sections, followed by resection or amputation."

In the 522 cases of osteogenic sarcoma which I found in the literature (table B) surgery alone was the method of choice in 22 cases (3.5 percent), radiation alone in 43 cases (8.2 percent), toxins alone in 20 cases (3.8 percent), surgery and radiation in 381 cases (73.1 percent), surgery and toxins in 36 cases (7 percent), radiation and toxins in 10 cases (1.9 percent), and surgery, radiation and toxins in 10 cases (1.9 percent). Surgery alone or

supplemented by some other method of therapy was used in a total of 449 cases (86 percent). The cases which received toxins as a supplement to surgery were largely those treated by Coley (17 to 23). Irradiation was used as a supplement to surgery in 391(87 percent) of the 449 cases. If this data has any significance, we cannot help but conclude that surgery with irradiation is the method of choice.

The percentages of cures and relief from symptoms as set forth in table B are not very reliable when considering the group of osteogenic sarcoma as a whole, for the 522 cases represented there are largely those cases in which the results of therapy have been more or less satisfactory. As a rule, authors do not report their unsatisfactory results.

There are two schools of thought with regard to the use of irradiation as a supplement to surgery. In one school, Herendeen (42) and others, preoperative irradiation is advocated. The opinion here is that irradiation so used brings about a retrogression of the tumor growth and tends to limit it by encapsulation. Besides irradiating the tumor area they also feel that the lung fields, the most common site of metastasis, should, even though apparently negative radiographically, be irradiated. Such preoperative irradiation of the lung fields may destroy small foci which later on would be much more difficult to control. Meyerding (66), Simmons (88), Knerr (50) and others are opposed to preoperative irradiation, for they feel that the added delay only enhances the possibilities of metastasis and for this reason feel that

early diagnosis, prompt radical surgery and heavy thorough post-operative irradiation are the method of choice.

It seems to the author that the logical thing to do is to start some form of therapy whether it be toxins, irradiation or surgery as soon as a diagnosis of a possible bone tumor is made. Naturally if there is any question as to the character of the neoplasm the more conservative procedure should be followed. However, every attempt should be made to arrive at an early exact diagnosis. When this early diagnosis is that of osteogenic sarcoma immediate radical surgery followed by a thorough course of irradiation of tumor area and lung fields appears to be the most sensible course.

In those far advanced cases of osteogenic sarcoma not amenable to surgical attack because of the extent of the new-growth, irradiation as has been pointed out by Simmons(88), Moore (69), Coley (19) and others is of definite value as a palliative measure to make the remaining weeks or months of the patient's life more endurable.

In using irradiation therapy for the treatment of osteogenic sarcoma one can use either radium or high voltage x-ray. However, because of the expensiveness of the former and the large quantities needed few have been able to use it. Coley (22) has used it in a number of cases and recommends the following:

"Radium pack containing large doses--2,000 millicuries of $4\frac{1}{2}$ to 5 hours, i.e., a total of 9,000 to 10,000 millicuries at a

distance of 6 cm. or from 15,000 to 20,000 millicuries applied at a distance of 10 cm. In the long bone cases the treatment is given over three aspects so that the total dosage often reaches as high as 30,000 to 60,000 millicuries."

High voltage x-ray, because of availability and that it is equally as satisfactory as radium, is more commonly used. Rapid saturation to the point of tolerance with subsequent maintenance doses is generally recommended. As pointed out by Desjardins (29) with these tumors we must take drastic steps and have less regard for surrounding soft tissue structures if we are to attain the best results. It is usual to use from 200 K. V. to 220 K. V., a 1 mm. to 2 mm. Cu filter, 45 cm. to 50 cm. skin distance, and the radiation being given through as many portals of entry as are available. The fractional method is to be used with doses being given once and even twice daily. (49, 54, 29, 74, and others).

INFLAMMATORY CONDITIONS

These are mentioned here only because of the fact that they are important from the standpoint of differential diagnosis.

Inflammatory conditions such as osteitis fibrosa cystica, myositis ossificans, osteoperiostitis (traumatic, syphilitic and infectious), simple bone cysts, and Paget's disease may clinically simulate a bone neoplasm and must be differentiated from them before therapy can be instituted. (34, 49, 52, 15, 2, and others.)

Marland (62) has also emphasized the fact that malignant sarcomatous degeneration has, especially in Von Recklinghausen's disease and Paget's disease, rarely occurred. Under such circumstances irradiation, as in other osteogenic sarcoma, would be indicated.

Merritt (64), Fohle and Paul (81), Costlow (26), and others reported cures in osteitis fibrosa cystica following the use of roentgen-ray therapy of the involved area. Merritt's cases were treated by x-ray therapy of the parathyroid and they showed good results.

THE BENIGN GIANT CELL TUMOR

The term Benign Giant Cell Tumor has been accepted by the Registry to represent this group formerly called Giant Cell Sarcoma. There is some conflict of opinion in the literature as to whether these tumors are benign or malignant. Goforth (40) believes that it depends upon the predominating cell type. He points out that some of the tumors contain a high percentage of mature adult cells while others are composed largely of immature more active young cell elements. The former, he believes, are always benign, while the latter may show tendencies to become malignant. This tendency to malignant degeneration is pointed out by other authors. (87, 60, 93, 16, 47, and others). Ewing (35 and 37) and Stone and Ewing (91) have pointed out the fact that malignant degeneration usually occurs following repeated surgical attack for recurrences. Ewing is of the opinion that the tumors are essentially benign, but that by repeated irritation and trauma the cellular elements might undergo malignant degeneration. This follows Kolodney's theory of trauma (see etiology of bone tumors page 4) and is also emphasized by others who feel the tumors are essentially benign (65, 90, 14, and others). I am inclined, from my reading, to agree with the latter viewpoint.

The benign giant cell tumors respond to irradiation in a manner which is characteristic of none of the other bone tumors. Shortly after being exposed to roentgen-rays these tumors respond

with marked swelling and increased pain, tenderness and redness which often leads the novice to feel that the condition is becoming worse. This has in certain circumstances been the factor back of unnecessary amputation. Apparently the larger the dose of roentgen-rays the more marked is this reaction. Herendeen (42 and 43) and Pfahler (74) state that by the use of small carefully regulated dosages of radiation they have been able to avoid this soft tissue reaction in all of their cases. However, if the use of irradiation is properly continued, in four to six weeks the reaction gradually subsides with a corresponding disappearance of symptoms and definite growth restraint. Ossification can then be demonstrated by x-ray and progresses to complete dense calcification of the whole tumor mass. In these neoplasms the age of the patient is a definite factor with respect to response, for the younger the patient the more sensitive are these new-growths. As compared with bone neoplasms as a whole, the benign giant cell tumor is less sensitive to irradiation than the endothelioma of Ewing or the multiple myeloma and more sensitive than the chondrosarcoma of the osteogenic group. (37, 74, 54, 46, 76, 42, 43, and others).

Again, as in the osteogenic group, there is considerable disagreement as to which method of therapy is to be used. Radiation has been favored by some, curettage and cautery by others and toxins by still others.

Pfahler (76) was apparently the first individual to treat

the benign giant cell tumors with irradiation. In 1906 he started treatment of a case which was reported in 1907 and was still well in 1932. As pointed out by Coley (18), Herendeen (42), through his work has proved definitely that giant cell tumors can be cured by radiation. Coley, however, feels that, as yet, there have not been sufficient cases, so treated, to determine whether irradiation or curettage is the better method. He also feels that the patient treated by irradiation is subjected to a longer period of disability and thus an added expense as compared to the patient treated surgically. Herendeen (45 and 46) does not agree with this. He states: "A more rapid ossification is brought about with a more rapid restoration of function than when surgical procedure is the method of choice." He points out that by the use of a walking Thomas splint he is able to keep his patients ambulatory and thus there has been no real period of disability from the time treatments were started.

Another argument Coley presents is that without biopsy one is unable to determine whether the tumor is benign or malignant. However, as has previously been stated, those cases showing malignant degeneration are more frequently those which have had repeated surgical attack. Furthermore, Herendeen (30) states that the roentgenograph can usually be relied upon to establish the diagnosis, and, Pfahler and Parry (76) are of the opinion that if an expert radiologist is in doubt, so, also, will be the pathologist.

In favor of roentgen-ray therapy Herendeen (45) further

points out that recurrences occur in about 25 percent of those cases subjected to surgery, that the probability of infection is increased by surgery, that because of infection or recurrences amputation may be necessary, and that the functional results following surgery are frequently unsatisfactory because of varying degrees of ankylosis. Pfahler and Parry (76) agree with this and further add that by breaking through the well encapsulated tumor in doing the surgery one prepares, by setting free cells and fragments of tissue, the way for metastasis.

Herendeen, Pfahler and Parry and others have pointed out that x-ray therapy when used following surgery is less effective than if surgery has been used. For this reason they feel that x-ray is deserving of a fair trial before surgery is used.

Again Coley (18) is the advocate of the use of toxins which in his hands have produced some apparently satisfactory results. He remarks: "It is possible to cure benign giant cell sarcoma and even far advanced borderline cases (giant and spindle cell sarcoma) by the injecting of the mixed toxins of erysipelas and prodigiosus without other treatment. Furthermore it is possible to cure those cases by a combination of toxins and radiation or toxins and curettage."

Bartlett (51) is convinced: "We know now that giant cell tumor is curable probably in all instances by x-ray or radium. These agents, while they may not cause any appreciable shrinkage in the size of the tumor mass, do bring about an ossification and limit the further spread of the disease." Moore (69) feels

TABLE C

Tabulation of Results of Therapy in 114 Cases of Benign Giant Cell Tumor Appearing in the Literature.

(11, 18, 76, 49, 79)

Therapy Used		No Results	Symptomatic Relief	Years Patients Survived							Total	Per-cent
				0-1	1-2	2-3	3-4	4-5	over 5			
Surgery Alone	Case	1		7	3	3			4	18		
	Percent	5.5		3.9	16.6				22.2		16	
Toxin Alone	Case	2			1		1		2	6		
	Percent	33.3			16.6		16.6		33.3		5.2	
Radiation Alone	Case			4	3	4	3	3	13	30		
	Percent			13.3	10	13.3	10	10	43.3		26.2	
Radiation & Toxin	Case					1				1		
	Percent					100					0.87	
Surgery & Toxin	Case	1		1		1	1	1	7	12		
	Percent	8.3		8.3		8.3	8.3	8.3	58.3		10.5	
Surgery & Radiation	Case	1	1	9	6	1	4	2	16	40		
	Percent	2.5	2.5	22.5	15	2.5	10	5	40		35	
Radiation, Toxin & Surgery	Case				1	1			5	7		
	Percent				14.2	14.2			71.4		4.8	
Totals	Case	5	1	21	14	11	9	6	47	114		
	Percent	4.4	0.87	19.3	12.3	9.8	7.9	5.2	41.2			

that radiation should be the first method of choice. Simmons (88) is of the opinion that irradiation should be tried first, for as he states: "If it is unsuccessful, amputation or operation can follow later." Desjardins and Popp (32) also advocate irradiation as do others (79, 59 and 38).

An analysis of table C will show that of the 114 cases represented there those treated by radiation received as good, if not better, results than by any of the other methods. Of all the cases which received irradiation alone or supplemented by some other form of therapy (78 cases) only one case which also received surgery was not benefited, while in those cases not receiving radiation (36 cases) four were not helped by the therapy. This together with the other facts shown in the table as well as the discussion which has gone before point definitely to irradiation as the method of choice in the treatment of the benign giant cell tumor.

In treating these neoplasms by the use of roentgen-ray radiation moderate dosages are recommended. Herendeen (42) states: "Not only may heavy doses be followed by severe, unnecessary reactions or pathological fractures, but, more important, bone regeneration may be retarded." Desjardins (29) aptly concludes: "Giant cell tumors require only small doses of rays of medium wave length. It is easy to over treat such a tumor and receive inferior results; whereas, if not over treated, excellent results may be obtained." Others are of

the same opinion (54, 88, 76, and others).

Herendeen recommends the following technique: "140 K. V., 4 ma., 4 mm. Al filter, a 10-12 inch target skin distance, and, depending on the case, 6 to 12 minute exposure. We have given on the average of from 8-10 treatments, a series consists of three exposures through different portals. An interval of six weeks to two months is allowed to elapse before these treatments are repeated." Other men agree in general with this though most of them have used a somewhat higher voltage, (200 K. V.). (54, 32, 74, 47 and others).

THE ANGIOMATA of BONE

As pointed out by Kolodney (52) the angiomata of bone are exceedingly rare. Codman (14) has also emphasized the fact that these tumors are seldom, if ever, seen. Kolodney in speaking of the angiomata says: "The term angiosarcoma given by Kolerzek, originally was intended for the so-called peritheliomata, tumors originating from the vessel wall and not from the endothelial lining of the vessels. Later this term found its way to tumors with a clear endothelial origin, which are better called angio-endothelioma." Kolodney, because of the rarity of these hemangiomas in bone, feels that they are not well enough understood to justify a separate heading and has, therefore, placed them under the heading of "Unclassified Tumors." To this group he has also added the periosteal fibrosarcoma which, he feels also, because of their rarity, do not deserve a separate heading. These hemangiomas consist of two groups, those which are benign and those which are malignant. (14, 52, 77, 74, and others).

Hemangiomata of bone are apparently moderately radiosensitive, and react to irradiation as do similar neoplasms of other tissues. Occasionally certain of these tumors show a mixed cellular element of angioma and endothelioma character. Under this circumstance the resultant tumor is less sensitive to radiation than would be a tumor composed wholly of either. (32 and 66). Desjardins and Popp (32) observe: "Repeated irradiation is often, if not usually, followed by gradual regression and improvement until healing occurs. Repeated and continued doses of 75 percent to 80 percent

erythema dose repeated every three to four weeks as long as the patient's condition continues to improve are recommended. The tumors disappear relatively slowly. Failure is due usually to a failure to recognize the tumor, because treatment is not repeated or continued long enough, or because excessive doses are employed."

Pfahler and Parry (77), Kolodney (52), and others recommend that the benign type of hemangioma be treated by surgical removal, while the malignant angioma of bone, they feel, is best treated by irradiation.

EWING'S TUMOR

Keating (49) states that these new-growths are one-fourth as common as the osteogenic sarcoma (the largest group of the primary bone tumors). As pointed out by Cofield (15) the neoplastic cells originate from the endothelium of the blood vessels and lymph channels. The lesion is localized at the start to one of the long bones, though it usually occupies the entire shaft. It is distinctly invasive of surrounding soft tissue and apparently always gives rise to metastasis, but neither is quite as marked as with the osteogenic sarcoma. From the start the disease simulates, by its clinical picture, (rarely occurring after 20, temperature, leucocytosis, and pain) osteomyelitis and offers an interesting diagnostic problem because of this. (14, 53, 25, 35, 52, and others).

Ewing's Tumor responds so characteristically to roentgen or radium-rays that as brought out by Desjardins and Popp (32), Kress (54) and others, it is almost diagnostic. The local lesion, when exposed to irradiation yields in a very short time with disappearance of symptoms, retrogression of tumor mass, and shortly later beginning ossification which progresses to complete calcification. If this local lesion were the whole picture, the use of x-ray therapy would produce our most brilliant results. However, metastases almost invariably take place through apparently both the lymph channels and blood vessels. These metastases, principally to the lungs and other bones but also other tissues, appear within a month to several years. They

respond to radiation therapy almost as readily as do the primary lesions, but by this time the disease is so generalized that only temporary amelioration of symptoms can be hoped for even with therapy carried to the very limits of tolerance. The final chapter is thus, almost invariably, death from the metastatic lesions. (88, 11, 54, 42, 31, 84, and others).

In the treatment of these new-growths we again find the therapeutic application of radiation, surgery, toxins, and combinations of the three. Moore (69) feels that there is definite indication that the disease may be systemic in character and feels that for this reason radiation, in view of the sensitivity of Ewing's Tumor, is the method of choice. Some writers believe that the almost invariable occurrence of metastases makes radiation the only logical therapeutic step. (1, 74, 53, and others)

Others, particularly Evans and Leucutia (34) are convinced that the disease when it is just developing is a localized rather than a systemic disease. For this reason these authors advocate early amputation followed by an extensive course of radiation. Conner (25) concludes: "The prognosis with a combination of surgery and irradiation, is not always death. Patients have lived for five years or longer, one sixteen years, after amputation, and many who have been treated by a combination of surgery, radiation, and toxins, are living over three years after the onset. The prognosis seems to be distinctly better than that of osteogenic sarcoma and other myelomata, and for this reason it is urged that these be considered special cases, in which, by

TABLE D

Tabulation of Results of Therapy in 232 Cases of Ewing's Sarcoma
Appearing in the Literature.

(16, 61, 25, 78, 74, 27, 31, 49)

Therapy Used		Symptomatic Relief	Years Patient Survived							Total	Per- cent
			0-1	1-2	2-3	3-4	4-5	over 5			
Surgery Alone	Case	8	6			2			4	20	
	Percent	40	30			10			20		8.6
Radiation Alone	Case	5	6	4	2	1	2	1		21	
	Percent	22.8	28.2	18.8	9.4	4.7	9.4	4.7			9
Toxin Alone	Case							8		8	
	Percent							100			3.4
Surgery & Radiation	Case	12	5	2	1	2	1	5		28	
	Percent	42	17.5	7	3.5	7	3.5	17.5			12
Surgery & Toxin	Case						1	8		9	
	Percent						11.1	88.9			3.8
Radiation & Toxin	Case	1						8		9	
	Percent	11.1						89.9			3.8
Surgery Toxin & Radiation	Case	1	3	2		2				8	
	Percent	12.5	37.5	2.5		2.5					3.4
Totals	Case	27	20	8	3	7	4	34		103	
	Percent	11.6	8.6	3.4	1.3	3	1.7	14.2			

Of the remaining 129 cases: 128 were listed only as surviving less than 5 years of which 20 were treated by surgery alone, 55 by irradiation alone, 3 by toxin alone, 10 by surgery and irradiation 8 by surgery and toxin, and 32 by toxin and radiation. In the remaining case no treatment was given. The patient survived only a short time.

energetic measures, a permanent cure may be possible." (37)

Coley (22) again is the strongest advocate for the use of toxins, but in this disease he also emphasizes the value of irradiation. He states: "The method of choice is local irradiation combined with the systemic action of mixed toxins, reserving amputation for only those cases such as failed to show marked improvement under this treatment." Meyerding (66) observes: "Early radio-therapy before metastasis has occurred, may result in permanent cure. Opinions as to the merits of treatment recently appears to favor amputation, irradiation, and toxins."

Table D which represents 232 cases of Ewing's Tumor which were collected from the literature agrees fairly well with the opinions set forth above. Of the 232 cases 40 (17.2 percent) were treated by surgery alone and only four cases survived the five year period, 76 (32.7 percent) received irradiation alone and only one case survived the five year period, 11 (4.7 percent) received toxin alone and of these eight were reported as surviving the five year period, 38 (16.3 percent) received surgery and irradiation and five cases were credited as surviving the five year period, 17 (7.2 percent) received surgery and toxin and eight of these survived the five year period, 41 (17.6 percent) received radiation and toxins and eight survived the five years, 8 (3.4 percent) treated by surgery, toxins, and irradiation showed none who survived the five years. The cases treated with toxins seem to show a higher percentage of five year cures.

However, it must be remembered that these cases were largely treated by Coley (16) and further the total cases receiving toxin alone or with some other form of therapy were only 77 or 33.1 percent of the total 232 cases. Only eight of the 77 were treated by toxins alone.

In giving the roentgen-ray irradiation the high voltage technic (same as suggested for osteogenic sarcoma), delivered through as many portals of entry as are available, and with the rays converging upon the center of the tumor, is the usual procedure. The patient should receive radiation to point of tolerance, and over a long period of time. (61, 42, 74, and others). Desjardins and Popp (32) suggest: "Success of the treatment depends upon a large total dosage concentration upon the tumor. This may be accomplished by (1) cross firing using multiple ports with careful calculation so that the maximum intensity of irradiation is at center of the tumor. Each field may be exposed to a moderate erythema dose on successive days (500 to 550 'r' measured in air) or small doses to all fields for from fifteen to twenty days. Important in using several fields that the beams of rays converge on center of tumor, and as fields increase in number respective doses to each field must be decreased to avoid tissue destruction from over radiation. If the initial course is given in one week to ten days, it should be repeated two or three times at intervals of three to six or eight weeks depending on quality of rays employed, number of ports, response of tumor and condition of patient. If treatment is given in small

daily increments continued for twenty to forty days, or when the total dose of rays directed towards the tumor is large, do not repeat treatment or wait two to six months."

MYELOMA

The multiple myeloma according to Evans and Leucutia (54) are very rare. They have observed only one case, and point out that only nine typical and five atypical cases appear in the Registry over a period of five years (1923-1928).

The disease is characterized by the simultaneous appearance of nodules of varying size in the marrow cavity of both the long and flat bones. The neoplastic cells are derived from the myelocytic series and may, therefore, be myelocytes, lymphocytes, or erythrocytes. The disease is generalized from the onset and tends to develop insidiously, so that by the time it is recognized it is most commonly far advanced. The disease tends to metastasize to the regional and more distant lymph glands and is also distinctly invasive of surrounding tissue. (52, 15, and others).

The cells of the myelocytic series are quite sensitive to roentgen and radium rays and therefore, respond readily to radiation therapy. The myelomata are generally considered as being slightly less sensitive than the endothelioma of Ewing and more sensitive than the benign giant cell tumor. However, because of the generalized involvement from the onset and also the insidious development, the disease can be only temporarily controlled by the use of radiation therapy. The disseminated character of the disease is a definite contraindication to surgery. Mixed toxins would appear to be of some value, though I found no mention of their use in the literature. (32, 1, 74, 47, 66, and 34).

The prognosis is definitely bad. Pfahler (74) in discussing radiation therapy states: "Darbois and Davigneow reported a case in which temporary healing has lasted sixteen months, and Regaud reported eight cases, one of which had local healing for twenty-one months, but all died of the generalized disease in the osseous system."

In treating this disease it is generally customary to use the high voltage technic as suggested under metastatic carcinoma to bone. (32, 74, and others).

CONCLUSIONS

1. Irradiation therapy is of definite value in metastatic carcinoma of bone, primary in other tissues, as a palliative measure for amelioration of symptoms and prolongation of life from one to four or five years.

Irradiation therapy is indicated as an adjuvant to surgery in malignant invasion of bone (especially with epitheliomata).

2. In the treatment of periosteal fibrosarcoma irradiation is useful in conjunction with surgery.

3. The benign osteogenic tumors are radioresistant and should be treated by surgery.

The borderline group of osteogenic tumors are relatively radiosensitive and should receive irradiation together with surgery.

The malignant osteogenic tumors (osteogenic sarcoma) should receive surgery and irradiation therapy and probably the mixed toxins of Coley.

4. Paget's disease and von Recklinghausen's disease have been cured by the use of roentgen-ray therapy.

5. Irradiation therapy is the method of choice in the treatment of the benign giant cell tumors.

6. The benign hemangioma are relatively radioresistant and are, therefore, a surgical problem.

The malignant hemangioma should receive roentgen-ray therapy and surgery.

7. Ewing's Tumor (endothelioma) is very sensitive to x-ray and apparently responds to Coley's toxin. The treatment of choice is irradiation and possibly toxins to be followed if necessary by surgery (cures are rare).

8. Irradiation therapy is useful as a palliative measure in producing definite amelioration of symptoms and slightly increasing life of patients who have multiple myeloma.

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