THE TREATMENT OF SARCOMA OF THE LONG BONES*

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During the past decade and a half, there has been an increasing interest in the subject of bone sarcoma, as manifested by the numerous papers and monographs that have been published both here and in Europe. Four books on the subject have appeared within the last four years, two of them by French authors, and one, the admirable work of Geschickter and Copeland, is based upon a study of a large number of cases observed at the clinic of Doctor Bloodgood at Johns Hopkins Hospital. Yet, in spite of this growing interest and voluminous writing, the treatment of bone sarcoma, especially of sarcoma of the long bones, remains in a most chaotic, unsettled state. The surgeon who, today, has to deal with a sarcoma of a long bone, even though he is acquainted with the literature on the subject, finds it most difficult to decide upon the method of treatment to be employed.

In 1921, at a symposium on bone sarcoma held during the Philadelphia meeting of the American College of Surgeons, Besley, of Chicago, stated that of twenty cases of bone sarcoma that he had treated by amputation, all that he had been able to trace, regardless of the histological type, had died; and that he had performed his last amputation for bone sarcoma. Six years later, a distinguished professor of pathology in New York who had made an extensive study of malignant tumors told me that if he personally were afflicted with a bone sarcoma, regardless of the histological type, even giant-cell tumor, he should have an immediate amputation performed.

Bone sarcoma is such a comparatively rare disease that the average surgeon sees no more than one or two cases, perhaps not even that many, in a year; and the average large city hospital admits not more than four or five cases annually. In the opinion of Forschell there are never more than twenty cases of sarcoma of the long bones in all Sweden at any given time.

It might be supposed that a study of the large amount of material collected by the Bone Sarcoma Registry of the American College of Surgeons would help one to select the best method of treatment; and yet after reading Kolodny's[1] critical review of this material, one must admit that he has gained little of practical value, and that Kolodny leaves one almost as pessimistic as did Butlin more than a generation ago. To quote Kolodny: "In bone sarcoma as in other malignant tumors the question of the therapy is still awaiting its answer. It is a strange fact that with our knowledge of minute details of the histopathology of bone tumors the progress along the practical therapeutic road is almost in the same stage that it was in some fifty years ago. As a rule malignant bone tumors are fatal and we know of no therapeutic method to prevent death from this disease."

* Observed in the Bone Sarcoma Department of the Memorial Hospital and the Hospital for Ruptured and Crippled of New York.

Crile,[2] in his recent paper on the Treatment of Malignancy, based on an experience in 7,390 cases of malignancy, discusses the treatment of malignant tumors of bones in a few lines, as follows:

> Exclusive of carcinoma of the jaw, we have seen 161 cases of malignant disease of bone. It is still uncertain whether a primary malignancy of bone should be treated by X-ray or by surgery, but two things are certain: First, if an operation is performed, it should be preceded and followed by X-ray radiation; and second, if the condition is in a limb, amputation should immediately follow radiation, provided the condition is not inoperable. As for metastatic tumors, palliative treatment by the X-ray is the only therapeutic measure. Radium is contra-indicated as it would destroy the periosteum, and necrosis would follow.
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> The data which are being accumulated by the Registry of Bone Sarcoma of the American College of Surgeons may finally lead to a decision as to the relative merits of surgery and of radiation in the treatment of malignant diseases of bone.

In other words, the material of the Cleveland Clinic furnishes no help in trying to decide on the best method of treating sarcoma of the long bones.

Turning to the foreign literature, we find that Nové-Josserand and Tavernier,[3] in their book on Malignant Tumors of Bones, state that they are not impressed with the results obtained by radiation; that this method is rarely employed in a systematic manner, and that, so far, it has usually been limited to inoperable cases after failure of surgical treatment. In a later paper, however, one of these authors (Tavernier[4]) reaches a more favorable conclusion as to the value of irradiation in the treatment of osteogenic sarcoma. He states: "All the osteosarcomas that I have treated by surgical methods, even the most radical, have died of metastases after varying periods not exceeding five months. Only one has survived the period of five years, and in this case the diagnosis was doubtful; I myself considered it a benign tumor at the time of operation, although on histological examination it presented features of a spindle-cell sarcoma; the prolonged survival after resection makes me doubtful of the diagnosis. In view of these disastrous results I have tried radio-therapy in ten cases: three have remained well for three years, one for one year, three are recent cases, and three proved failures."

In the most recent book written on Tumors of Bones, Sabrazes, Jeanneney and Mathey-Cornat[5] express the opinion that every patient afflicted with osteogenic sarcoma succumbs to the disease within a few months to two or two and one-half years, and that a mutilating operation is but very rarely followed by a longer survival. As regards the treatment of osteogenic sarcoma by irradiation, they believe the present statistics are too incomplete to justify any conclusions. Contrary to the opinion expressed by Tavernier, these authors state: "While certain osteogenic sarcoma which we ourselves have treated by irradiation have shown temporary amelioration for a month or two, they have thereafter become rapidly worse, the disease recurring and becoming generalized."

A study of the end-results obtained at Johns Hopkins Hospital, cited in the recent book of Geschickter and Copeland,[6] shows that the writers I

have quoted are unduly pessimistic. I believe that a study of the end-results obtained at the Memorial Hospital and the Hospital for Ruptured and Crippled will prove even more convincing, and will help to eradicate the present attitude of hopelessness as regards the prognosis in malignant tumors of the long bones.

Classification.—Before deciding on any method of treatment of sarcoma of the long bones it is important to determine (1) whether we are dealing with a malignant tumor or a benign tumor; and (2) if malignant, what type of tumor it is.

While the ideal classification of bone sarcoma has not yet been reached, that of the Bone Sarcoma Registry of the American College of Surgeons is, perhaps, the best available. For practical purposes, however, it is too complicated and divides the main group of bone sarcomas into too many different types. All the surgeon needs to know is (1) whether the tumor in question is a periosteal or a central sarcoma; (2) whether it is an osteogenic sarcoma or an endothelial myeloma, and (3) if a central sarcoma, whether it is a benign giant-cell tumor, a central malignant sarcoma, a multiple myeloma or a metastatic carcinoma. All the other histological sub-divisions are of little importance in deciding upon the method of treatment in a given case. The idea so widely prevalent that the large variety of neoplasms based upon histological distinctions represent an equally large number of separate diseases or entities is no longer tenable, at least, not in bone sarcoma. Berg,[7] in his fellowship thesis, showed that by injecting the dried virus of the filterable fowl endothelioma tumor into the tibia of Rhode Island Red chicks it was possible to produce five different types of bone sarcoma, including endothelioma, corresponding almost exactly with the different types found in man. If it is possible, as Berg's work has proved, to produce in animals all these different varieties of bone sarcoma by a single extrinsic agent, we can no longer regard these different varieties as different diseases but as different manifestations of a single disease produced by a single agent. This does not necessarily mean that the same method of treatment should be used in these various types of tumors. We have found by experience that certain types of bone tumors (endothelial myeloma and giant cell) are highly sensitive to both irradiation and Coley's toxins, while, on the other hand, others, such as the osteogenic sarcoma with marked new bone formation, are very highly resistant to both. Hence it is important to know before we begin treatment just what type of tumor is present. We know that the tubercle bacillus does not give rise to lesions that are always typical, but that it causes a great variety of clinical manifestations, and that no one method of treatment is suitable for all of them.

While in the majority of cases we are able to make a correct diagnosis from the clinical and röntgenological evidence alone, there is a considerable number, probably from 20 to 25 per cent., in which a correct diagnosis is impossible without the aid of a histological examination. This brings up the question of indications and contra-indications of biopsy.

Biopsy.—The question of performing a biopsy in bone sarcoma for the purpose of establishing the diagnosis is one that is still unsettled. Some advocate a biopsy in every case as part of the treatment, while others, including Ewing, would omit the biopsy altogether or limit it to a very small number of cases. In my opinion the dangers and disadvantages associated with a biopsy have been greatly over-emphasized. The two most frequently mentioned are: (1) Dissemination of the tumor, by means of which some of the cells enter the circulation and cause metastases, and (2) failure of the biopsy wound to heal, resulting in infection, possibly necessitating an amputation.

If the biopsy is performed by the surgeon who is to have the final treatment of the case, one who employs the best operative technic, the danger of infection is extremely slight; furthermore, the possibility of generalization occurring by reason of the biopsy, in my opinion is also very slight, hardly sufficient to offer any serious objection to the operation. Dr. Francis Carter Wood, in his experiments on animal tumors, has shown that the danger of metastasis is not increased by the biopsy; and my experience with human beings supports this view.

As to the exact value of the biopsy, after it has been performed, there is also much difference of opinion. Pfahler and Parry[8] believe that when the expert radiologist is in doubt, the pathologist is also often in doubt; and if the microscopical slides are sent to several equally expert pathologists, the opinions are apt to differ. Furthermore, he quotes Ewing as saying that the röntgenograms are of equal or greater importance than the microscopical section.* Kolodny often finds that with a good clinical history and röntgenograms, one can be as sure of a diagnosis as from seeing the patient, the lesion, the gross specimen and numerous sections, and adds, "Not infrequently a röntgenogram is more decisive than a number of microscopic sections." This opinion has been expressed by many of the leading pathologists as well as Ewing.

My personal opinion is that when trying to make a diagnosis of bone sarcoma, especially in the early stages of the disease, we should not trust to the röntgenogram alone unless the clinical evidence strongly supports it. It is most important that a correct diagnosis be made as early as possible if the treatment is going to be of any avail. While it is often possible in the later stages of the disease to make a positive diagnosis of osteogenic sarcoma from the röntgenogram alone, this is not true in the early stages. Therefore, in trying to make a diagnosis in the early stages, one should take advantage of all that is to be gained from a careful study of the clinical history, the physical examination and the röntgenogram. In a limited number of cases it will be necessary to make, in addition, a histological study of the gross specimen and microscopical sections removed at biopsy.

Two years ago† the opinion was published in the lay press that all that

* I believe that Ewing has usually qualified his statement by "sometimes."

† In connection with the Bone Sarcoma symposium at Baltimore, Md.

was needed to make a correct diagnosis of bone sarcoma was for the family physician to send a film of a suspected tumor to a radiologist and get his diagnosis by return mail. This idea gives a very erroneous impression of the many difficulties associated with the early diagnosis of bone sarcoma. The impracticable side of this plan is well illustrated by the following statement of Bloodgood:[9]

"A surgical colleague tells me that he has submitted the X-ray of a bone to sixteen consultants and got sixteen opinions. Another informs me that he submitted his case to eight authorities; all agreed on amputation without biopsy, and after amputation the lesion proved to be osteomyelitis of the Garre non-suppurative type."

It is only by a careful weighing of all the evidence including the clinical, röntgenological and pathological, that one is able to reach a correct diagnosis in many of the more difficult cases; and in a certain and fortunately very limited number of cases the most experienced observer will find it impossible to do so with the aids mentioned.

Frozen-section Diagnosis.—Many writers, including Bloodgood and Lewis, advocate making a diagnosis from frozen sections obtained at the biopsy; if the condition proves to be malignant, an amputation is at once performed; if the condition proves to be a benign giant-cell tumor, conservative treatment is employed. Personally, I do not believe that such an important matter as the amputation of a limb should be determined from a microscopical examination of frozen sections of a bone tumor. In many instances the specimen contains so much bone and cartilage that it is impossible to make sections without decalcification. In other cases in which the specimen contains soft tissue only, I find it frequently impossible to tell whether we are dealing with a benign condition or a malignant one. Therefore, I have given up trying to make a definite diagnosis from frozen sections. I believe it is perfectly safe to wait for the paraffin sections; I have seen no harm result from this delay.

A clinical history of rapid tumor growth accompanied by severe pain, even with a doubtful röntgenogram or no röntgenogram at all, may furnish sufficient grounds for an amputation. I have performed an amputation in a considerable number of cases of bone sarcoma without a biopsy, upon clinical and X-ray evidence alone, and in each case the condition has proved to be malignant.

Surgical Treatment.—The treatment of sarcoma of the long bones by amputation dates back to the time when this condition was first recognized as a malignant process, although classified under a great variety of names.

Unfortunately, in the earlier years, and, in fact, until recently, amputation was not performed until the disease had progressed so far that there was little or no hope of saving the patient's life by any method of treatment.

Not until 1920 did we begin to see marked improvement in the results of amputation alone for sarcoma of the long bones. In 1922, Meyerding[10] reported a series of 100 cases treated by amputation; in many, prophylactic-toxin treatment was given, and in some this was supplemented by röntgen

therapy. At the time of the report, 50 per cent. of the patients were living, 16 per cent. over five years.

In May, 1923, at a symposium on Bone Sarcoma by the Association of Surgeons of Great Britain and Ireland, in London, Gask reported a series of fifty-seven cases of sarcoma of the long bones, exclusive of giant-cell tumors, admitted to St. Thomas's Hospital from 1901 to 1921. Out of forty-six cases in which amputation was performed, twelve were alive three years later, and seven more than five years later; one of these died of metastasis to the skull more than six years after amputation.

I believe the improvement in prognosis during the last decade is undoubtedly due to our ability to make an earlier diagnosis by reason of a more correct interpretation of the early röntgenograms and an early adoption of surgical measures (amputation). In our own series the prognosis has improved as a result of combining the systemic treatment with the toxins of erysipelas and *Bacillus prodigiosus* with surgical operation or irradiation.

Disarticulation.—I have performed hip-joint disarticulation for sarcoma in seventeen cases without mortality but with only two permanent recoveries. In one case the recovery was due not to the amputation alone but to the prophylactic-toxin treatment as well.

This patient, a young girl, was operated upon by Dr. William T. Bull, in 1893, for a periosteal fibrosarcoma of the metatarsal bone; an amputation above the ankle was performed. One and a half years later the disease recurred in the stump, and a metastatic tumor the size of a child's head appeared in the popliteal space. Under Coley's toxins the disease showed marked regression; but one year later it began to increase in size and I performed a hip-joint amputation. Within a short time extensive metastases developed in the gluteal region and the condition became quite inoperable. Under prolonged toxin treatment the disease steadily regressed until it had entirely disappeared. The patient is well at the present time, thirty-eight years since the treatment was first begun. In a second case of amputation at the hip by Dr. Stuart McGuire (1917), for round-cell sarcoma (endothelial myeloma) in a boy aged three and one-half years, the patient was referred to me for treatment of extensive, inoperable metastases to the skull (June, 1919); under toxin- and radium-treatment the tumors disappeared and the patient is in fine health today, thirteen years later.

During recent years I have performed very few disarticulations and these only in cases in which the disease occupied the middle and upper third of the femur. In nearly all the cases in which the disease occurred in the lower half of the femur I have found is possible to amputate below the trochanter leaving a sufficient stump to permit the use of an artificial leg. I believe if prophylactic-toxin treatment is given after such an amputaion one will get practically as many permanent recoveries as if a disarticulation had been performed.

In performing an amputation without disarticulation, it is important that this should be done at a point at least four or five inches beyond the apparent extension of the tumor as shown by palpation and röntgen-ray. In a very large number of cases in which we have amputated below the trochanter for periosteal sarcoma of the lower portion of the femur, there has been a re-

currence in the stump in only four cases. In two cases of osteogenic sarcoma of the upper end of the humerus very satisfactory results were obtained by resection and irradiation; both patients are well over ten years.

My first successful result with the toxins in sarcoma of the long bones occurred in 1897, in a young man twenty-seven years of age with an extensive periosteal spindle-cell sarcoma of the tibia, in which the diagnosis had been confirmed by Dr. John Caven, Professor of Pathology of the University of Toronto. Many who had seen the patient before he came to me had advised an amputation. I decided to try the toxins alone.

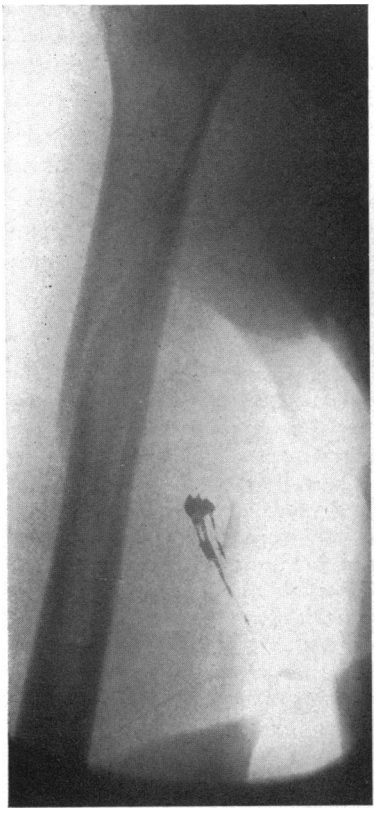

FIG. 1.

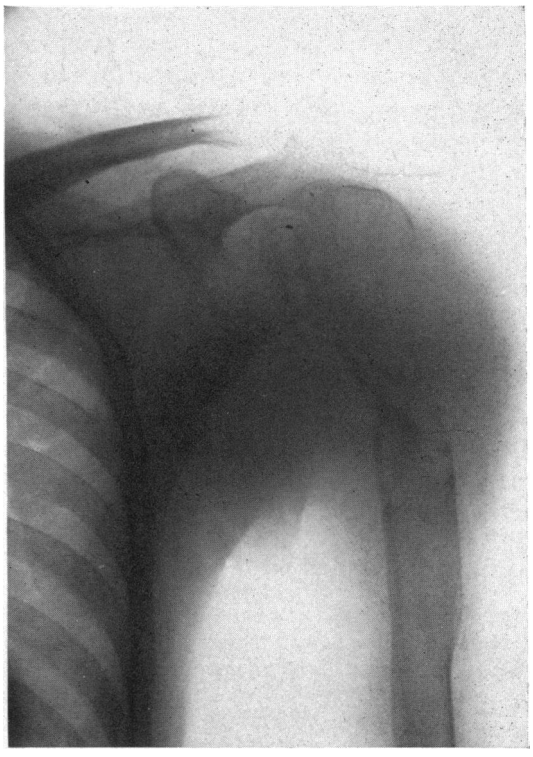

FIG. 2.

FIG. 1.—Spiral fracture of the shaft of the humerus (May, 1923), showing no evidence of a pathological condition at the time of injury.

FIG. 2.—Same case as shown in FIG. 1, this film having been made one year later showing a very extensive endothelial myeloma of the humerus at the site of the fracture. The condition was inoperable at the time of the author's first observation. The case was treated with toxins for two and a half years in addition to two radium-pack treatments. Good recovery was made, the patient being well eight and a half years later, with a useful arm.

Under two months' treatment, the tumor had almost entirely disappeared and the bone cavity had healed by healthy granulations. Just as he was about to be discharged, he contracted a severe attack of erysipelas which started at the site of an old sinus from a previous operation and extended over the entire leg and thigh. The patient made a complete recovery and was discharged from the hospital three weeks later. When last traced, thirty-two years later, he was still in excellent condition with a perfectly useful limb.

I had continued to use conservative treatment (a brief course of Coley's toxins) before amputation in all cases of periosteal sarcoma. However, since 1920, I have come to realize that the osteogenic type, especially that associated with new bone formation, is highly resistant to toxins as well as to irradiation, and that immediate amputation followed by prophylactic toxin treatment offers the greatest hope of benefit.

After amputation or resection for osteogenic sarcoma, Fraser[13] believes in exposing the skeletal outline, the lungs and the mediastinum, to intensive X-rays, concentrated if possible within twenty-four hours, using 250,000 volts and giving a 70 per cent. (sarcoma) dose. He states that this has been responsible, in two cases in which resection was performed, for the prolongation of life. He also maintains that Coley's toxins are of value in preventing or delaying metastases. He feels that the latter, in conjunction with resection, offers a field of possibilities as great if not greater than that of amputation.

Irradiation.—During the past ten years there has been an increasing tendency to refer all cases of bone sarcoma to the radiologist for treatment. The reason for this is obvious: Up to 1920 the results of amputation in malignant periosteal sarcoma were so bad that the surgeon, and, even more, the patient, were ready and willing to turn to any other method of treatment that offered any reasonable hope, especially if such method avoided the sacrifice of the limb. While irradiation was employed soon after the discovery of the röntgen-ray, it was not until the introduction of the high-voltage machine and the acquisition of large amounts of radium that the treatment of bone sarcoma by irradiation was carried out on a large scale.

The impression has been given by some writers, *i.e.,* Evans and Leucutia,[14] that I am definitely opposed to irradiation for bone sarcoma. On the contrary, I was the first to employ X-rays in the treatment of bone sarcoma (in 1902 at the Memorial Hospital) and during the past fifteen years I have made an earnest effort to determine its value in the different types of bone sarcoma. Between 1915 and 1928, practically all the service cases, including those of giant-cell tumor, at the Memorial Hospital were treated by primary irradiation. Having a large amount of radium at our disposal, at first four grams, and later eight grams, a considerable number of cases were treated with the radium pack; this was sometimes supplemented by bare tubes of radon or gold seeds inserted into the tumor. The majority of cases, however, were treated with röntgen-rays by Doctors Herendeen and Duffy. It was hoped that in the event of failure to control the disease by irradiation, a later amputation after prolonged irradiation might yield better results than would an early amputation without pre-operative irradiation. Unfortunately, this hope proved unfounded. In 1928, a careful review of the results obtained in more than 140 cases of primary operable malignant sarcoma of the long bones treated by irradiation showed only four patients alive and well beyond the five-year period. Hence, we have abandoned irradiation as the primary method of treatment for osteogenic sarcoma, and have substituted immediate amputation followed by a course of prophylactic treatment with Coley's toxins.

At the International Cancer Congress in London, 1928, Ewing,[15] who

had long been a strong advocate of primary irradiation for bone sarcoma of all types, gave his views as follows: "When the signs point to a true osteogenic sarcoma of medullary and sub-periosteal, sclerosing, or telangiectatic type, the best treatment is probably immediate amputation, preceded if necessary by a biopsy at the same time. With these cases, radiation seems to have accomplished very little."

On the other hand, we find Pfahler and Parry,[16] in 1931, advocating irradiation for osteogenic sarcoma. However, their report of fifty-seven cases contains only six cases of sarcoma of the long bones well for a period of five years or more; four of these six cases were treated by amputation in addition to irradiation, and one by excision. The only one treated without surgery had no microscopical confirmation of the diagnosis. Therefore, the results in this series were not obtained by irradiation alone but by irradiation *plus surgery*. Had irradiation been continued for a longer period of time, as in the Memorial Hospital series and as is advocated by Holfelder, I am certain that the results reported by Pfahler and Parry would have been much less favorable. In the Memorial Hospital series, primary irradiation was given for a much longer period than one month, and amputation was performed only after failure to control the disease by irradiation; the number of five-year recoveries is exceedingly small, much smaller than in the group treated by primary amputation and prophylactic-toxin treatment.

Holfelder,[17] the Director of the Röntgen Institute of the Surgical University Clinical, Frankfort, whose statistics are frequently quoted, especially by Pfahler, reports twenty-five cases of bone sarcoma treated with deep röntgen therapy during the years 1920–1921 and 1925–1926 (up to June 30). Sixteen of these cases were traced upwards of three years, and the remaining nine for more than two years. Of the sixteen cases, six are stated to have been clinically cured; three of these were under observation for more than five years. In only three of these six cases was the diagnosis verified by histological examination. In six other cases improvement was noted which lasted over a period of from one to two years. Ten patients died of the disease. Of the nine cases that were traced for upwards of two years, seven remained clinically cured at the time of the report; in six of these the diagnosis was confirmed by histological examination. It is important to note that nearly one-third of these cases were giant-cell tumors.

While Holfelder deems the number of cases reported and the period of observation insufficient to justify more definite conclusions as regards end-results, he believes they do warrant the conclusion that the clinical results of röntgen treatment of bone sarcoma, if properly conducted, will certainly not be worse than the best results obtained with radical operative procedures. He states that inasmuch as röntgen treatment of bone sarcomas completely avoids the serious mutilation of radical operation, he feels it a duty, even at this early date, to advocate conservative röntgen therapy for all types of bone sarcoma, in preference to any of the mutilating operations. He goes

still farther than Pfahler and Parry in advocating prolonged irradiation, rather than amputation after a short period of irradiation.

However, I believe Holfelder's series of cases is far too limited in number, and the period of observation too short to influence one in substituting irradiation for amputation in the treatment of osteogenic sarcoma of the long bones.

According to Forssell,[18] radiological treatment alone should not as yet be advised for operable cases of osteogenic sarcoma of the long bones. While pre-operative and post-operative irradiation should be used with conservative operation—this combined method has doubled the proportion of cures at the Radiumhemmet—he doubts whether irradiation prior to or after amputation is of any use. Yet "it may be worth while considering the possibility that a healing process initiated by radiation may in some cases bring about an increased resistance against tumor formation." He urges that tumor treatment, both surgical and radiological, be centralized in the largest hospitals, since special technic and training are so necessary. He estimated that in all the hospitals in Sweden only twenty malignant tumors of the long bones are admitted each year, hence the necessity of concentrating the material.

Undoubtedly, a very large number of osteogenic sarcomas have been treated in this country by primary irradiation during the past ten years, and the statistics of the Bone Sarcoma Registry of the American College of Surgeons should show a considerable number of five-year recoveries, had the method proved successful. As a matter of fact, however, the Registry shows only two cases of osteogenic sarcoma (one of the long bones) cured by irradiation alone; and in one of these cases the diagnosis was based on the clinical and röntgenological evidence alone, and in Doctor Ewing's opinion was by no means positive; he believed the condition simulated a myositis ossificans.

Preliminary Irradiation.—While Bloodgood believes that a brief trial of preliminary irradiation before biopsy entails no risk, personally I have seen several cases in which I believe harm has resulted from irradiating a long bone sarcoma for even a short period of time, *i.e.,* less than one month.

In spite of the improved results from early amputation, the fact remains that at the present time a very large number (in my opinion, the majority) of osteogenic sarcomas are being treated by primary irradiation as the method of choice—and this is true of some of the foremost hospitals of the country.

Treatment of Osteogenic Sarcoma.—In view of the fact that osteogenic sarcoma is highly resistant to both irradiation and Coley's toxins, I believe an amputation should be performed as soon as a positive diagnosis has been made. I do not approve of preliminary irradiation. Within one week of the operation the patient should receive prophylactic treatment with the mixed toxins of erysipelas and *Bacillus prodigiosus.* (Coley.) This treatment can be carried out at home later on by the local physician. The initial dose should be small, not over one-half minim, and gradually increased to the point of producing a moderate reaction, a temperature of 101° or 102°. The injections should be kept up, with occasional intervals of rest, for at least six months; they need not greatly interfere with the patient's routine of life. I believe that the prophylactic toxin-treatment more than doubles the number of five-year recoveries obtained by early amputation alone.

There is a certain type of osteogenic sarcoma now classified as periosteal fibrosarcoma which involves the periosteum alone or the muscular attachments of the periosteum, in which there is little or no bone involvement. This is more benign than the ordinary osteogenic sarcoma. In this type one is justified in trying to save the limb by conservative treatment (local irradiation and systemic toxins). We have under observation at present four cases in which the disease has been held apparently under complete control for three years. In addition there are a few cases of osteogenic sarcoma of the osteolytic type, highly cellular, with little or no new bone production, that have been cured by toxins alone or in conjunction with irradiation.

However, these apparent permanent recoveries under considerative treatment are limited to a certain rare type of osteogenic sarcoma. As a general rule, I believe that early amputation followed by a course of prophylactic treatment with Coley's toxins should be the method of choice in the treatment of osteogenic sarcoma of the long bones.

Endothelial Myeloma or Ewing's Sarcoma.—This type of tumor has been found to be much more amenable to treatment with toxins and radium than has the osteogenic type. It is a type with very definite clinical, röntgenographical and histological characteristics, different from those found in osteogenic sarcoma. As Ewing[19] pointed out, it originates chiefly in the shaft of the long bones, and occurs mostly in children or young adults. The röntgenogram, together with the clinical history and physical signs, is usually sufficient to establish the diagnosis; but in the small group in which it is impossible to make a correct diagnosis, I believe one is justified in performing a biopsy. We have used the aspiration method of biopsy in this type with some success.

Treatment.—Surgery alone has given very poor results: only one case in twenty-two reported by Howard and Crile[20] was alive three years after amputation. I have never seen a case cured by amputation alone.

Some remarkable recoveries under toxins and irradiation combined are reported in my paper on Endothelial Myeloma, already referred to (1931). While a very considerable number of cases have been treated by primary irradiation alone (twenty-five cases in our own series), so far there has been only one five-year cure, but, unfortunately, in this case there was no microscopical examination to verify the diagnosis.

We are able to report but a very few cases treated by amputation after prolonged irradiation for the reason that while one is congratulating himself on the rapid diminution or complete disappearance of the primary tumor, metastases frequently develop, and it is then too late to amputate. We have, however, ten cases in which amputation was performed after prolonged irradiation. This group contains one five-year cure; no patient survived amputation much longer than one year. A review of the earlier statistics of Gross, and of the later statistics of Meyerding and others, shows but few cures from amputation alone in that group previously classified as small round-cell sarcoma but now known as endothelial myeloma or Ewing's sar-

coma. While we have been able to treat successfully a considerable number of cases of endothelial myeloma that were beyond amputation, and in some of which metastases had already developed, we must admit that we have not infrequently failed to control the disease even when the treatment (toxins and irradiation) was begun at an early stage. Thus it is difficult to decide on the best method of procedure in an early operable case of endothelial myeloma of a long bone. If we amputate at once, following this with prolonged prophylactic-toxin treatment, we may expect a permanent cure in about 50 per cent. of the cases. If we try to control the disease by local irradiation combined with systemic toxin treatment, we shall probably get a successful result in at least 30 per cent. of the cases. A certain number,

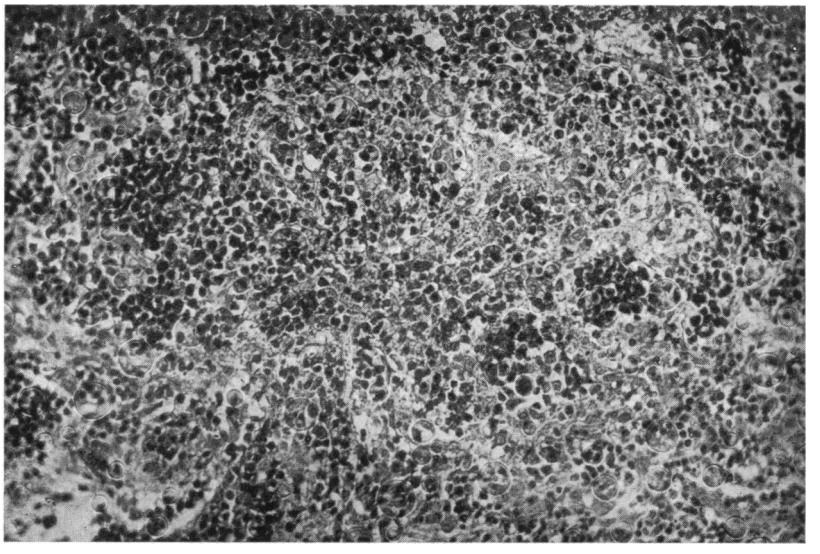

FIG. 3.—Microphotograph.

however, will develop metastases while undergoing treatment and even while the local condition is showing marked improvement; then amputation cannot be considered. In view of the complexity of the question of treatment, it is well when dealing with an adult patient to explain the matter as fully as possible and to let him have some voice in the decision.

A careful analysis of the end-results of different methods of treatment would seem to warrant the conclusion that while endothelial myeloma is the most malignant of all types of bone tumor, one is justified in trying systemic treatment with the toxins of erysipelas and *Bacillus prodigiosus* (Coley) combined with local irradiation, preferably the radium pack, for a limited period before resorting to amputation. If no marked improvement is noticed at the end of six or eight weeks, amputation or resection should be performed, followed by prolonged prophylactic-toxin treatment. Further delay without evidence of improvement may result in the development of metastases, with the loss of all hope of saving the life of the patient.

The most significant fact brought out by our statistics is the comparatively large number of inoperable cases that have recovered and remained well for five years or more. Fifteen cases of inoperable long-bone sarcoma were well more than five years; nine were treated by toxins, and six by toxins and radiation.

Multiple Myeloma.—This type of tumor has long been regarded as uniformly fatal, so much so that but scant reference to the subject of treatment is made in any of the literature. Geschickter and Copeland,[25] in their report of thirteen cases observed at Johns Hopkins, pass over the subject of treatment with the following brief statement:

> With no proved case reported as cured it is evident that palliative symptomatic treatment only is available. Nursing care to avoid unnecessary pain on motion and pathologic fracture is important. When fractures occur, the ordinary methods of treatment by fixation may be given, as pain is thus minimized and healing often accomplished. Morphine for pain, liver diet and tonics for anæmia and inhalations for respiratory complications are helpful.

According to Ewing,[27] these cases invariably have a fatal termination. Meyerding[26] believes treatment is of little avail. He states: "Radiotherapy may produce temporary benefit; surgical treatment is of no value except as a diagnostic aid, and transfusions are of transient value."

In a recent paper on the subject, covering fifteen cases of multiple myeloma, I reported a case in which the disease involved the spine and ribs; there was partial paraplegia; the diagnosis had been confirmed by microscopical examination. Under Coley's toxins alone this patient made a complete recovery and remained well for five years, when he died of lobar pneumonia. In another case in which the disease involved the spine and ribs and was accompanied by complete paraplegia and loss of fifty pounds in weight, and in which irradiation had been tried without success, the patient made a good recovery under Coley's toxins. One year later, he was able to walk about with the aid of a cane, he had regained most of his lost weight, and röntgenograms of the skeletal bones showed no evidence of the disease. He was still in good health when traced, more than three years after the beginning of treatment; but I have learned recently that he has a recurrence.

Inasmuch as these tumors are radiosensitive and as most of the bones are involved, the Heublein unit established at the Memorial Hospital a year ago would seem to be the best method of administering the treatment. By this method the patient receives continuous irradiation all day, with the exception of short intervals for meals and medical visits, over a period of many days or until the desired erythemic dose has been received, depending on the indications in a given case. The usual period is from two to three weeks. One patient with multiple myeloma was treated in the Heublein unit of the Memorial Hospital about six months ago with very marked improvement. The Heublein method of irradiation, combined with systemic treatment with Coley's[28] toxins, seems far superior to any other for such a temporary condition.

In view of the results obtained in our series, I have come to the conclusion that the prognosis in multiple myeloma is by no means as hopeless as is universally believed. In a number of cases the disease has been held in check for a considerable period of time by Coley's toxins alone and by irradiation alone; it is apparently susceptible to both agents; therefore I believe a combination of systemic toxins and local irradiation is the method of choice in the treatment of multiple myeloma; and no case should be given up as hopeless until this combined treatment has been given a thorough trial.

Giant-cell Tumors.—Curiously enough, there still remain the same doubt and uncertainty that existed seventy years ago, as to the true nature of the so-called benign giant-cell tumor. The theory that these tumors are always benign and never metastasize dates back to the first half of the nineteenth century (Lebert,[31] Paget[30] and Nélaton[32]). Virchow[33] (1862), however, contended that giant-cell tumors are sometimes malignant and give rise to metastases, and his opinion was strongly endorsed by Gross,[34] (1874). Some twenty-two years ago the whole question was revived by Bloodgood,[35] and it was largely due to his somewhat dogmatic and frequently reiterated statement that giant-cell tumors are always benign and never metastasize, that surgeons were led to abandon amputation as the primary method of treating giant-cell tumors, and to attempt to save the limb by curettage or irradiation. Irrespective of whether we agree with Bloodgood's views or not, we *must* admit that his teachings have had an important influence towards a more conservative treatment of these tumors, and that many limbs have been saved thereby. The view of the benignity of giant-cell tumors gradually gained adherents, and by 1924 it might be stated that the majority of pathologists all over the world had adopted it. In my[36] paper on the Prognosis in Giant-cell Sarcoma of the Long Bones, based on a study of fifty cases personally observed, I stated:

> There is only one explanation of these cases which still leaves it possible for one to entertain the theory that giant-cell tumors are always benign; and that is to assume that all of the cases here reported, in which metastases developed ending in death, were cases of mistaken diagnosis. As a matter of fact, however, in the author's personal series of cases, the diagnosis of benign giant-cell sarcoma was made not only by competent pathologists, but in many cases by the very pathologists who had made a most careful study of bone tumors; so that if men of such wide experience are unable to differentiate the benign from the malignant type until death from metastases occurs, how much less likely is it that pathologists of ordinary experience will be able to make such differentiation.

Since the publication of that paper I have had an opportunity of studying forty-eight additional cases, making a total of ninety-eight cases of giant-cell tumor of the long bones observed at the Memorial Hospital and the Hospital for Ruptured and Crippled. In no less than fourteen cases the condition proved to be malignant; in four of these cases the early diagnosis of giant-cell sarcoma rested on clinical and röntgenological evidence alone; later, after prolonged irradiation, the diagnosis was confirmed by microscopical examination.

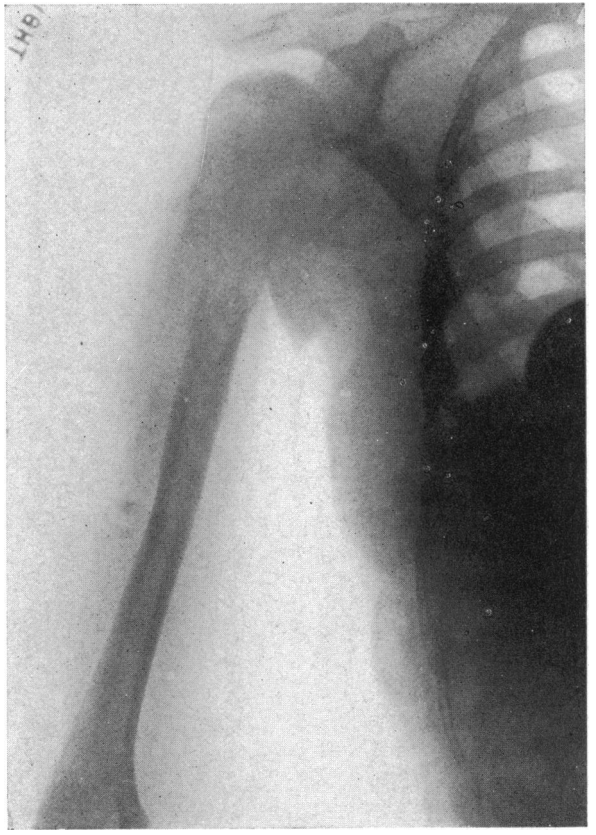

FIG. 4.

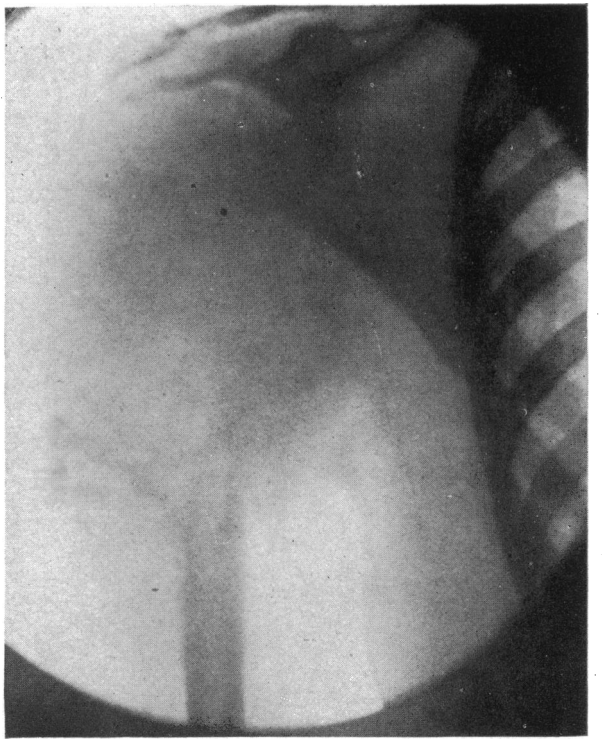

FIG. 5.

FIG. 4.—May, 1923. Giant-cell sarcoma of humerus. Toxins and radiation after exploratory operation. Patient well nine years later. Bone Sarcoma Registry at first classified this case as a malignant osteogenic sarcoma; later revised diagnosis.
FIG. 5.—Same case six months later.

A number of other surgeons have published cases of giant-cell tumor associated with metastases: Behring[37] collected 384 cases of sarcoma of the long bones operated upon in the leading hospitals of Sweden during the years 1901 to 1926. The diagnosis was verified histologically in all but two cases of a series of 246. Of this group, twenty-seven were classified as giant-cell sarcoma. All were operated upon more or less radically. In all of these cases the diagnosis of giant-cell sarcoma was made histologically by pathologists of large experience in the study of bone tumors. However, no less than

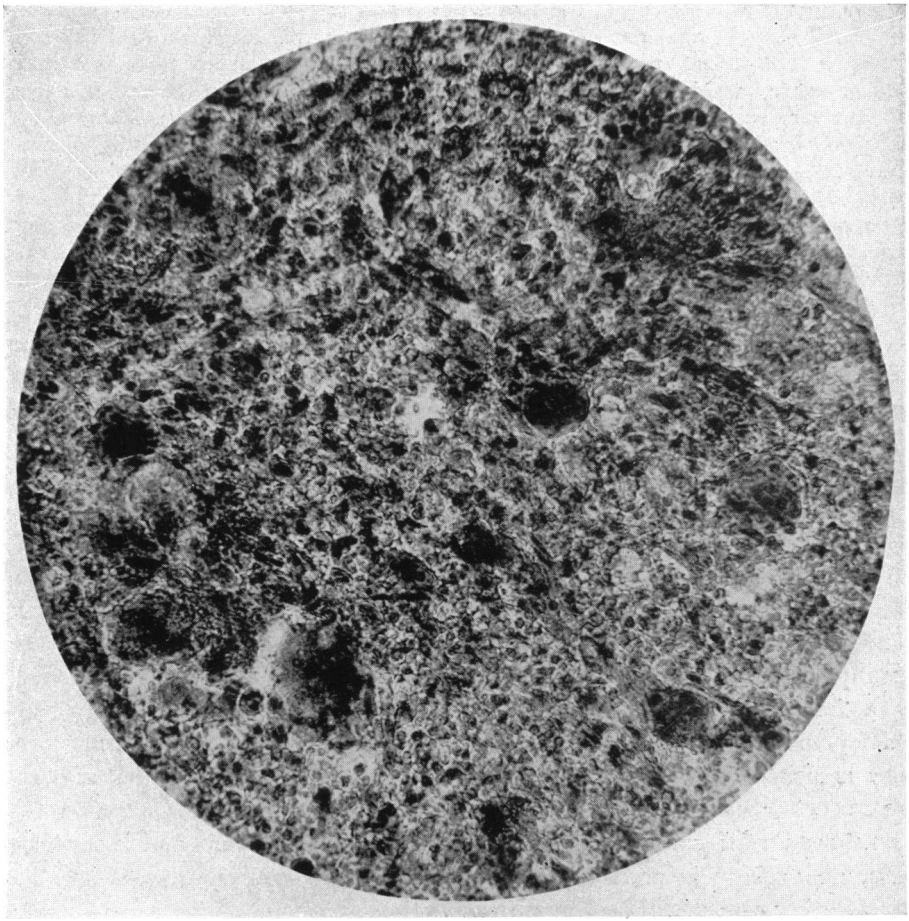

FIG. 6.—Microphotograph of same case as FIG. 4.

six of the twenty-seven patients died of metastases. Behring feels that the question of whether giant-cell tumors are always benign must be left open for the present.

Korchow,[38] of the State Institute of Radiology and Cancer Research, Leningrad, has made a study of fifteen cases of giant-cell tumors of bones observed during one year. It is interesting to note that in eleven cases trauma seemed to be an important etiological fact. While thirteen cases ran a benign course, two proved malignant. Eleven were treated by X-rays and four by operation. One was cured, two improved, nine unaffected, two became worse, and one died (but not as a result of the tumor). The author concludes that these tumors start as osteitis fibrosa but owing to trauma and other unfavorable factors the osteitis develops into a tumor which may become malignant. He

advocates biopsy for diagnosis and treatment. In most cases he believes that surgical treatment should be conservative (curettage, resection). According to Korchow, irradiation does not give very satisfactory results and is only specially indicated when operation is difficult or impracticable on account of the site of the tumor.

Simmons[39] states, in his review of the giant-cell tumors of bone collected by the Bone Sarcoma Registry prior to 1925 (116 in number), that he has seen four cases of giant-cell tumor in which death occurred from metastases; two were registered prior to 1925 and two since that date. Simmons adds that he knows of several other unpublished cases observed at other clinics, and that Codman also has seen several other cases.

These statistics and others would seem to force one to the conclusion that while the majority of giant-cell tumors are benign or only locally malignant, there is a very definite number which, while clinically and microscopically benign in the earlier stages, do later take on malignant characteristics and cause death by metastases. These cases, I believe, furnish conclusive proof that the view held by Virchow and Gross is more nearly correct than that of Nélaton. This does not mean that we as practical surgeons should move the clock backwards and again treat giant-cell tumors of the long bones by amputation as formerly. Experience has taught us that amputation as a primary method of treatment should seldom, if ever, be employed. Practically all these cases should be treated by conservative measures. I have not performed a primary amputation for a benign giant-cell tumor of a long bone for thirty years.

Treatment of Giant-cell Tumors.—The main objections to the surgical treatment of giant-cell tumors have been especially emphasized by Ewing and Herendeen. They are: First, the danger of serious hæmorrhages in the larger and more vascular giant-cell tumors; and second, the danger of infection either at the time of operation or later, due to failure to obtain primary union of the biopsy wound. It is asserted that if the larger cavities are packed with gauze they are apt to become infected sooner or later, while if an unhealed sinus persists, re-infection may occur, and amputation may become necessary.

Such is the picture often drawn illustrating the dangers of surgical treatment. There is no doubt that these dangers do exist and have been associated with the surgical treatment of giant-cell tumors in the past. The matter of chief practical importance is: are they seen frequently or but rarely, and are they associated with some failure in surgical technic? The critics of this treatment apparently think they are very common sequelæ. As a matter of fact, however, if curettage is performed with sufficient care and thoroughness, no packing is necessary; the wound can be entirely closed, and in nearly every case it will heal by primary union.

A careful analysis of more than 200 cases treated surgically at Johns Hopkins (100 by curettage) gives no support to the theory that infections with their attendant dangers are of frequent occurrence. In the entire series they were extremely rare and there were no deaths.

On the other hand, the bad results of irradiation in the treatment of giant-cell tumors are almost never mentioned, and from a study of the literature one might infer that they never occur. If we analyze the cases treated by this method at the Memorial Hospital, we find a considerable number of bad results that are quite as serious, if not more so, than those connected

with surgical treatment. Among them may be mentioned that of pathological fracture. This not infrequently follows prolonged irradiation, especially in sarcoma of the femur. Of twenty cases of giant-cell tumor of the femur treated by irradiation at the Memorial Hospital, six developed a pathological fracture.

Then there is the danger of a late osteomyelitis developing after an apparent cure by irradiation. This has been observed in two cases under my own obsevration; in both an amputation was necessary. In addition there is the risk of radium burns which still occur occasionally even in the hands of experienced radiologists.

My chief objection to regarding irradiation as the method of choice in

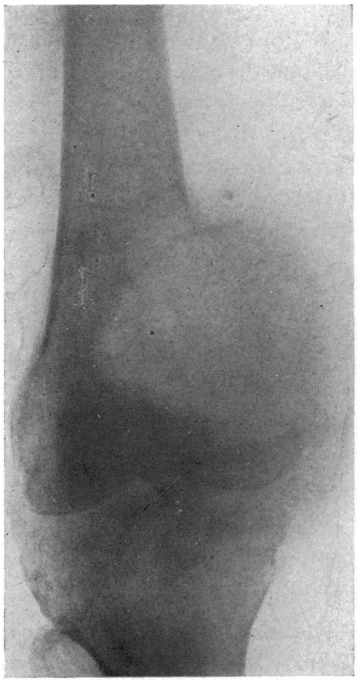

FIG. 7.

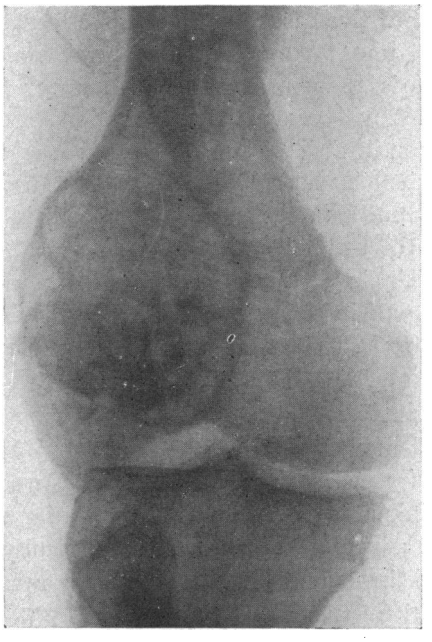

FIG. 8.

FIG. 7.—Giant-cell medullary sarcoma of lower end of femur, knee-joint, and upper end of tibia. Treated with toxins and radium. Limb saved. Patient well eight years later when she died of hæmorrhages from childbirth.
FIG. 8.—Same case as FIG. 7, showing how Nature has reformed the destroyed condyle. Five years after treatment.

the treatment of giant-cell tumors of the long bones are: (1) The long period of disability, and (2) the impossibility of making a correct diagnosis of benign giant-cell tumor in at least one out of five cases from the clinical and röntgenological evidence alone.

Another advocate of irradiation for giant-cell tumors is Regaud,[40] but a glance at his statistics shows that of the fourteen cases reported, twelve occurred in the jaw (in these he had nearly 100 per cent. recoveries); one in the cervical spine, and only one in a long bone. This, unfortunately, was

treated primarily by resection and later by irradiation for a recurrence, so that Regaud's statistics offer practically no evidence of the value of irradiation in the treatment of giant-cell tumors of the long bones.

The prognosis in this group of tumors has been found to vary greatly with the particular bone affected, being graver when the disease is located in the lower end of the femur and the upper end of the tibia than when the radius, ulna or fibula is involved.

While our results at the Memorial Hospital have proven beyond a doubt that it is possible to cure a giant-cell tumor of a long bone, even of the femur or tibia, by irradiation, I do not think we have as yet proven this method to be superior to all others. There is still a grave objection to treating a supposed giant-cell tumor of a long bone by primary irradiation without a biopsy —as advocated by Ewing and Herendeen—for the reason that in at least one out of five cases it is impossible to make a correct diagnosis of benign giant-cell tumor from the clinical and röntgenological evidence alone. In other words, if we proceed in this manner we shall find that one out of every five cases will prove to be a malignant osteogenic sarcoma. By the time the error in diagnosis is discovered it is usually too late to save the life of the patient by amputation. Furthermore, the period of time required for this treatment in the majority of cases is too long to justify a general adoption of the method.

A simple biopsy should never be performed in a case of giant-cell tumor or one in which the clinical and röntgenological evidence points strongly towards a giant-cell tumor. If a giant-cell tumor, particularly of the long bones, is cut into at all, a thorough curettage down to healthy bone should be performed, the wound swabbed out with chloride of zinc or carbolic acid, and, if possible, closed without drainage. If this is done, then we have not performed a biopsy but have employed the surgical treatment, which, in my opinion, is the method of choice for giant-cell tumors. A simple biopsy is not advocated because of the difficulty of obtaining primary wound-healing, and the danger of sinus formation and infection owing to the high vascularity of these tumors.

During the last two years at the Memorial Hospital, in many cases of giant-cell tumor in which the bony shell* has been penetrated, we have found it possible to make an accurate diagnosis by the aspiration biopsy of Martin and Ellis[41] or[42] the Hoffman-punch biopsy. If a diagnosis can be made by the aspiration method without an incision, then my principal objection to the use of primary irradiation in the treatment of giant-cell tumors will have been overcome.

In many cases, however, it has been found necessary to introduce a large needle into a number of areas; and it is quite conceivable that in a highly vascular tumor some of the cells set free by the aspiration might enter the

*If the bony shell has not been destroyed it is impossible to use the aspiration biopsy method.

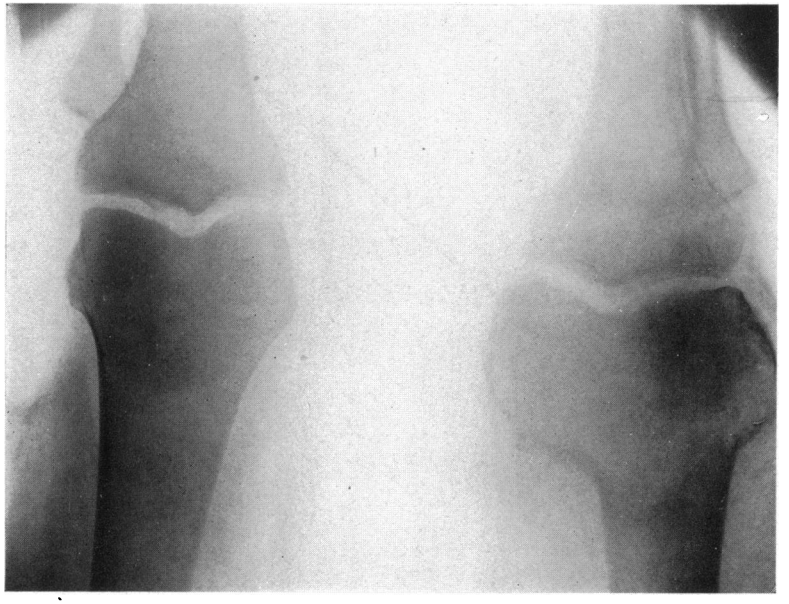

FIG. 9.

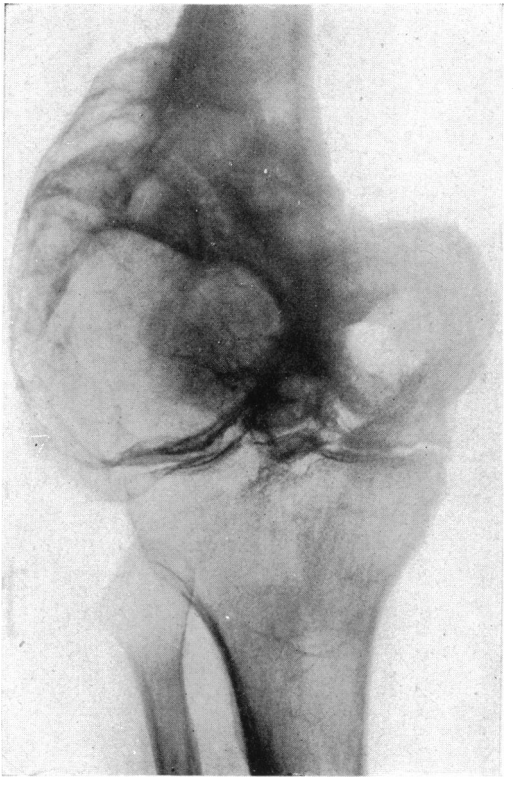

FIG. 10.

FIG. 9.—Giant- and spindle-cell sarcoma of femur with extensive involvement of entire knee-joint. Exploratory incision; toxins. Patient well fourteen years later. Picture shows Nature's attempt to form new condyle.
FIG. 10.—Another view of same case as FIG. 9.

circulation and be carried to other parts of the body, thus giving rise to metastases. I am not at all sure but that this risk might be as great if not greater than any associated with a biopsy of the ordinary type. In one case, a large, highly vascular tumor of the ilium, the patient died suddenly of embolism on the day after an aspiration biopsy. It is possible that it was in no way connected with the biopsy.

If, on the other hand, the case is treated primarily by surgery combined with toxins or toxins and irradiation, the entire tumor will have been removed by curettage and the surgeon will have the benefit not only of a clinical, röntgenological and macroscopical examination, but of a careful histological examination as well. If the tumor proves to be a malignant central sarcoma,

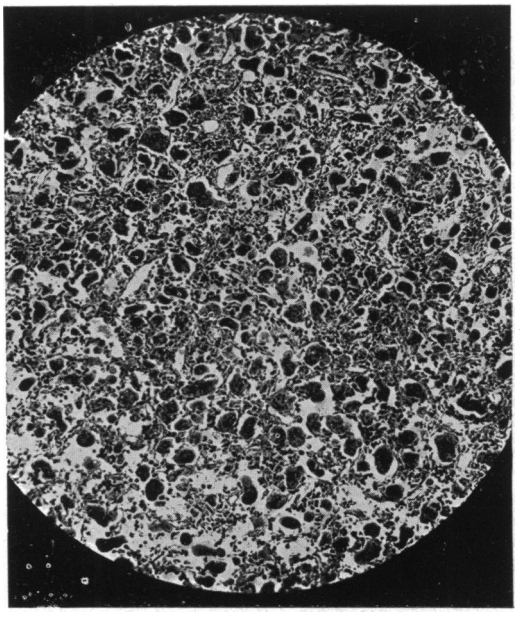

FIG. 11.

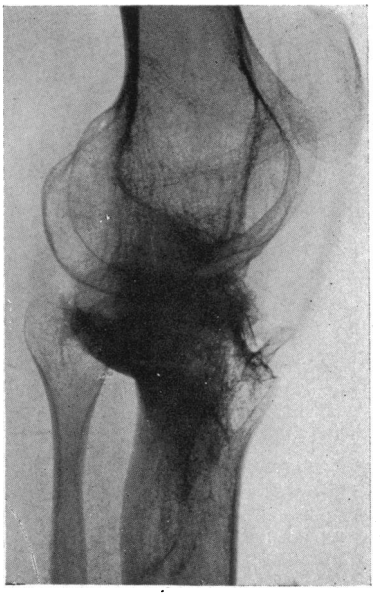

FIG. 12.

FIG. 11.—Malignant giant-cell sarcoma of mid-dorsal region. Microscopical diagnosis: round-cell sarcoma with many atypical giant cells. (Dr. Harlow Brooks.) Complete paralysis of bladder, rectum and lower extremities. Under four months' toxin treatment, patient made a complete recovery and is well thirty years later.

FIG. 12.—Giant- and spindle-cell sarcoma of tibia with destruction of upper four inches, treated by curettage, toxins and radium. Limb saved; patient well eighteen years later. Picture shows replacement of new bone five years later. Well seventeen years later.

immediate amputation should be performed followed by a course of prophylactic-toxin treatment. This method offers a much greater chance of saving the life of the patient. If the tumor proves to be a benign giant-cell sarcoma, the curettage and toxin treatment will, in my opinion, effect a complete recovery in the great majority of cases and in a shorter period of time than is required by irradiation.

Summary of Results.—In view of Bloodgood's repeated statement that the Johns Hopkins series prior to 1913 contains no case of bone sarcoma that has remained well for a period of five years, following any method of

treatment, I should like to call attention to the fact that our earlier series treated prior to 1913 contains nineteen cases of bone sarcoma of verified diagnosis that have remained well for from five to thirty-eight years. Nine of these cases were classified as endothelioma or small round-cell sarcoma, and ten as osteogenic sarcoma.

To this group we might add one other case of malignant giant-cell tumor of the spine associated with complete paraplegia and loss of fifty pounds in weight, treated in 1902 with Coley's toxins alone. (Fig. 13.) This patient was in excellent health with perfect function when I last examined him in July, 1932, thirty years after treatment.

In my[48] paper of 1913 I gave a tabulated report of 125 cases of sarcoma successfully treated with the toxins by other men. In this group were thirty cases of bone sarcoma that had remained well for five years or more; sixteen were inoperable sarcomas of the flat bones (diagnosis confirmed microscopically in eleven cases) and fourteen sarcomas of the long bones: six osteogenic sarcoma, five endothelioma, one giant-cell tumor, and no microscopical examination in two cases.

Results in 168 Cases of Primary Operable Osteogenic Sarcoma of the Long Bones Treated by Irradiation

Method	Cases
Röntgen-ray	84
Röntgen-ray and radium	10
Radium (element pack in 30 cases)	35
Irradiation and Coley's toxins	39
	168

Of the eighty-four cases treated by röntgen-ray, the only five-year cures occurred in two cases in which amputation was performed after irradiation, and in one case treated by resection followed by irradiation.

Of the ten cases treated by röntgen-ray and radium, five-year cures occurred in two cases in which amputation was performed after irradiation.

Of the thirty-five cases treated by radium alone, the only five-year cure occurred in one case in which amputation was performed after irradiation, and in one case treated by resection and irradiation.

In other words, of 129 cases of osteogenic sarcoma treated by irradiation, there were no five-year cures obtained without amputation or resection. The percentage five-year cures in this group was 5.42 or seven cases.

Of the thirty-nine cases treated by irradiation and Coley's toxins, there were two five-year cures obtained without amputation, and two with amputation. Three other cases in which the limb was saved have remained well from two to four and one-half years. One of the five-year cures without amputation was a very extensive tumor of the humerus treated with irradiation and toxins over a period of one year. While the Bone Sarcoma Registry committee at first classified it as an osteogenic sarcoma, five years later they revised their diagnosis to that of giant-cell tumor. Excluding this case we have three five-year cures in a group of thirty-nine cases (7.9 per cent.).

Of the total number of 168 cases of operable osteogenic sarcoma of the long bones treated by primary irradiation, nine, or 6.4 per cent., were well for five years or more.*

While the results obtained by irradiation and Coley's toxins (7.9 per cent. five-year cures) are a little better than those obtained by irradiation without toxins (5.42 per cent. five-year cures) they are no better if as good as the results obtained by early amputation alone without pre-operative irradiation. This proves that osteogenic sarcoma is highly resistant to both irradiation and toxins and that we are no longer justified in substituting either for early amputation. The only two cases in the entire series of 168 operable osteogenic sarcoma in which the limb was saved were two in which the toxins were used in conjunction with irradiation.

Results in 72 Cases of Endothelial Myeloma of the Long Bones

Treatment	Cases	Five-year Recoveries
Amputation alone	2	0, or 0 per cent.
Coley's toxins	9	6, or 66.66 per cent.
Coley's toxins plus amputation or resection	14	9, or 64.3 per cent.
Irradiation	25	1, or 4 per cent.
Toxins and irradiation	22	6, or 27.27 per cent.
Totals	72	22, or 30.55 per cent.

NOTE.—Of forty-five cases in which the toxins were used either alone or in conjunction with surgery or irradiation, twenty-one, or 46.6 per cent., have remained well for five years.

Results in 217 Cases of Malignant Tumor of the Long Bones in which Amputation Was Employed

Treatment	Cases	Five-year Recoveries
Amputation alone	15	0
Amputation and Coley's toxins	81	24, or 29.6 per cent.
Amputation after prolonged irradiation without toxins	98	5, or 5.1 per cent.
Amputation after prolonged irradiation with Coley's toxins	23	2, or 8.7 per cent.

Of the latter two five-year recoveries, one was a periosteal fibrosarcoma of the tibia.

Femur Cases.—In making a comparative study of early and late statistics, it will be found that the most notable improvement in results are in sarcoma of the femur. While Butlin was able to find only one three-year recovery in a group of sixty-eight cases of sarcoma of the femur treated by disarticulation or amputation below the trochanter, our series of over 100 cases of sarcoma of the femur shows twenty-one five-year recoveries (twelve osteogenic and eleven endothelial myeloma). Of the eleven endothelial myelomas, no less than seven were inoperable and three had extensive metastases at the beginning of treatment; the limb was saved in seven cases. The treatment employed in these cases was as follows:

* In 10 of these cases the X-ray treatment had been carried out at other hospitals before the patients came under my observation.

	Five-year Recoveries	Per Cent.
Amputation alone in 10 cases	0	0
Amputation followed by Coley's toxins in 42 cases	12	28.57
Amputation after prolonged irradiation in 48 cases	3	6.3
Toxins and irradiation	3	
Toxins alone	3	
Total	21	

As to giant-cell tumors of the femur, our results at the Memorial Hospital would seem to lend some support to the view of Phemister (quoted by Pfahler) that these cases should not be treated primarily by irradiation. We have seventeen cases of giant-cell tumor of the femur that were treated by primary irradiation; nine went on to amputation, and four died. Two other cases, after amputation, proved to be malignant osteogenic sarcomas, but these are too recent to mention the end-result.

Results in 98 Cases of Giant-cell Tumor of the Long Bones

	Cases
Treated by Coley's toxins, with or without surgery	21
Proved to be malignant osteogenic sarcoma	2
Primary amputation (one by another surgeon)	2
Secondary amputation	5
Well five years or more	12
Dead (osteogenic sarcoma)	2
Treated by toxins and irradiation	16
Proved to be malignant osteogenic sarcoma	2
Amputation	9
Well five years or more	9
Dead	2
Treated by irradiation without biopsy or operation	31
Proved to be malignant osteogenic sarcoma	6
Amputation	8
Well five years or more	11
Dead	5
Died of another cause	1
Treated by irradiation after biopsy or curettage	17
Proved to be malignant osteogenic sarcoma	2
Later amputation	7
Well five years or more	6
Dead	4
Treated by surgery alone	13
Proved to be malignant osteogenic sarcoma	2
Primary amputation (two by other men)	4
Resection	3
Secondary amputation	3
Well five years or more	2
Dead	2

It should be noted that in the thirty-one cases of benign giant-cell tumor treated by irradiation without a biopsy, six proved to be malignant osteogenic

sarcoma; all dead. In the entire group of ninety-eight cases there were fifteen deaths.

Five-year Recoveries.—Of a total of 261 cases of malignant sarcoma of the long bones, exclusive of giant-cell tumors, treated prior to November, 1927, or five years ago, fifty-four, or 20.7 per cent. have remained well for five years or more. Twenty-two were classified as endothelial myeloma, and twenty-two as osteogenic sarcoma. Coley's toxins were used in forty-four of these five-year recoveries. Fifteen cases were either inoperable when the treatment was begun or became inoperable during the course of treatment.

Limb saved.—Of these fifty-four five-year recoveries, the limb was saved in twenty-one cases (twelve endothelial myeloma and nine osteogenic sarcoma). In all but two cases the diagnosis was confirmed by microscopical examination, but in these two there was a rapidly growing, extensive tumor of the femur involving the upper half of the shaft, beyond hip-joint amputation. One patient recovered under toxins alone and was well ten years later when last traced, and the other had toxins and one radium-pack treatment, and is well fifteen and one-half years later.

Conclusions.—I believe that a study of the results obtained in this series of 360 cases of malignant operable sarcoma (exclusive of 98 giant-cell tumors and nearly 100 inoperable cases) will prove that the present pessimistic attitude regarding the prognosis is without foundation in fact. The prognosis depends largely upon an early diagnosis and a wise choice of treatment.

For osteogenic sarcoma, especially the type associated with marked new bone formation, I advise immediate amputation as soon as the diagnosis has been established. In order to lessen the chances of a recurrence, Coley's toxins should be given as a prophylactic, for a period of six months.

While endothelial myeloma is highly sensitive to both toxins and irradiation, rarely has the disease been controlled by irradiation alone. On the other hand, the toxins alone or toxins combined with irradiation have resulted in a large number of five-year recoveries even, in some instances, after the disease had reached the inoperable stage and had developed metastases. I believe that a combination of the systemic effect of Coley's toxins plus the local effect of irradiation offers the greatest hope of saving the patient's life as well as his limb in this type of tumor. Early amputation followed by prolonged toxin treatment would undoubtedly give a higher percentage of five-year recoveries, and for this reason it is well to let the patient have a voice in the final decision as to the method to be employed.

I still believe that the most efficient method of treating giant-cell tumors of the long bones is: Early and thorough curettage, swabbing out the cavity with 50 per cent. chloride of zinc or carbolic acid and alcohol, closing the wound without drainage, and then on the third or fourth post-operative day starting a short course (four weeks) of prophylactic-toxin treatment to be given in moderate doses. Primary amputation or resection should practically never be performed in this type of tumor. Our series contains many cases

in which large areas of bone-destruction were completely restored by Nature, showing that resection and bone-grafting are unnecessary.

The series of cases reported in this paper differs from all others in two important points: (1) It includes a large number of inoperable, hopeless cases that have recovered under treatment and have remained well for more than five years, and (2) it contains a large number (19) of permanent recoveries that have taken place prior to 1913. The only possible explanation of these results is, that in the majority of cases Coley's toxins either alone or in conjunction with some other method were used.

In closing I wish to express my great appreciation to the following: to Dr. James Ewing and Dr. Frederick W. Stewart, for their kindness in examining most of the microscopical sections in this series of cases; to Dr. Ralph Herendeen and Dr. James J. Duffy, for their skilful treatment of the cases in which irradiation was employed; and to Dr. Bradley L. Coley, who has been associated with me for the past ten years in the Department of Bone Sarcoma at the Memorial Hospital and the Hospital for Ruptured and Crippled and who has performed the majority of amputations during this period.

Bone sarcoma is a field in which a careful weighing of all evidence, the clinical, the röntgenological and the histological, is required. In other words, in order to arrive at a correct diagnosis, especially in the early stages of the disease, a close coöperation on the part of the surgeon, the röntgenologist and the pathologist is most essential.

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