Ancient History

There is little doubt that cancerous limbs were well recognized by ancient societies and their physicians although little was known about the nature of the lesions, particularly in the early years of our civilization. The Egyptians reported cancerous growths on various parts of the body in the Ebers papyrus believed to have been written around 1500 BC (1,2). The manuscript recommended cauterization of benign lesions but warned of the cruel nature of fungating or ulcerating tumors. It was pointed out that those tumors that involved peripheral parts of the body sometimes required amputations or resections and it is likely that some of these procedures were done for cancerous limbs (3). In fact, studies of the bones of Egyptian mummies have shown lesions consistent with benign and malignant tumors of bone and cartilage, myeloma and metastatic carcinoma (4,5).

The early concepts of the causes of cancer were dominated by the views of two individuals, Hippocrates and Galen. According to John Hunter, Hippocrates recognized various forms of cancer and attributed them to the pervasiveness of black bile, one of four humoral elements he postulated to be responsible for all disease (6) (figure 1). It was his view that cancer was a systemic disease related to this humoral abnormality rather than a localized process. He coined the word karkinos for the hard lump seen in places such as the breast, likening cancer to a crab because of its way of growth (7). Clarissimus Galen wrote a treatise on abnormal swellings in 192 AD (8,9,10) (figure 2). He adhered and advanced the humoral theory and listed an array of abnormal swellings including karkinoi and karkinoma in many sites, further enlarging the description of the hard nodules originally defined as cancer by Hippocrates (10) (figure 3). He also is believed to have introduced the word sarcoma for lesions clearly arising in the soft tissues (figure 4). The writings of these two great scientists provided the world before and shortly after the birth of Christ with views as to the nature of cancerous growth and equally importantly, the need for concern regarding outcome and effective treatment for these lesions. It was not until the 16th and 17th centuries however that the black bile humoral theory was rejected, mainly on the basis of the observations of morbid anatomists such as Vesalius (11) who postulated that cancer grew at one site and then spread via lymphatics or blood stream to other areas of the body.
Two early references to cancer affecting the extremities are included in the canonical literature. The first of these was most extraordinary and consisted of a miracle performed by Saints Cosmas and Damian in the sixth century AD (12,13). The saints were twin physicians born in the third century AD in the town of Egea in Cilicia in Asia Minor. They traveled widely in Greece, Turkey and Rome, treating ailments of all sorts and refusing payment for their services. They somehow angered the emperor Diocletian and they and their three brothers were beheaded and buried in a grave in Egea in the year 287 AD. They returned however in the 5th century to a Basilica in the Roman Forum, which now bears their name, where Deacon Justinian, a faithful church retainer with a cancerous limb was so exhausted by his pain that he fell asleep during his prayers. There came to him in a dream, the twin physicians who after amputating the limb of a Moor who had died that morning replaced the diseased part with the obtained allograft implant (figure 5). The procedure, known as the Miracle of the Black Leg was reportedly successful and because of that, the twins were subsequently canonized, receiving their sainthood in approximately the year 550 AD. Of note is the fact that the occasion and drama associated with the procedure was so extraordinary that it captured the imagination of first the painter Fra Angelico and then many other artists; and literally hundreds of some of the most extraordinary paintings depicting the procedure can now be found in many of the world museums (13).

A second miracle occurred in the case of Saint Peregrine Laziosi who lived in the 14th century (14). After an initial rebellious and anti-religious youth, the Virgin Mary came to Peregrine in a vision asking him to mend his ways. He responded by becoming a devout Catholic and subsequently a priest. In his later years, he developed a cancer of the foot and leg, which caused him great pain. The surgeons advised him to have an amputation but on the night prior to the procedure after praying to God, he fell asleep and awoke without a trace of the tumorous process. For this miracle as well as for his life of great giving, he was canonized in 1726 (Figure 6).

Earliest Identifications of Bone Tumors

The earliest views of bone tumors in historical data were that they were simply cancers of the limbs rather than neoplasms arising from connective tissue. It should be noted that histologic evaluation of tumors depended on the microscope which was not in common use for that purpose until the mid 19th century and of perhaps greater importance was the fact that Wilhelm Conrad Roentgen did not introduce X-ray imaging until 1895 (15) (Figure 7). Recognition of tumors of bone...
and soft tissue and their histologic definition and origin were at best rudimentary early in the 19th century. It was therefore not until the latter part of that century that imaging allowed sophisticated recognition of tumorous processes in the bones and histology allowed speculation as to cellular origin of the tumor.

The first description of a tumor arising within connective tissue probably was that of Abernathy in 1803 who described a neoplasm of the limb probably of soft tissue origin (4). He is alleged to have re-introduced the term sarcoma from the Greek term for tumors of soft tissue, suggesting that tumors of connective tissue may have substantially different cellular origins.

It was shortly thereafter that Baron Guillaume Dupuytren further defined the entity of osteosarcoma (describing it as an aggressive lesion arising from bony elements) and alluded to its malignancy and ability to metastasize (16). However, it was not until 1845 that histologic evidence of a lesion arising in bone was presented and documented as containing cells which seemed bony in origin. In that year Hermann Lebert described a case of giant cell tumor of bone (17), the cells of which resembled bone cells, particularly the osteoclasts seen in normal tissues. Subsequently, Rudolf Virchow (18,19) (figure 8) and Sir James Paget (20) showed convincing histological evidence that the giant cell tumor had some of the same cellular elements that existed in bone and was almost surely bony in origin. The investigators further showed that the giant cell tumor could and did locally destroy the bone of origin (18,19). In his exceptional three volume work published from 1863 to 1867, Rudolf Ludwig Karl Virchow, considered by many to be the father of modern pathology, described many entities and published the Virchow Archives, still in use today.

Figure 8: Rudolf, Ludwig Karl Virchow (1821-1902) was the father of modern pathology. He described many entities and published the Virchow Archives, still in use today.

Perhaps the first real identification of the nature of bone tumors was the report of Samuel Gross, a Professor of Surgery in Philadelphia who in 1879 published a paper in the American Journal of Medical Science based on a study of 165 cases (25). His article stated that 70 could be histologically identified as giant cell tumors, 45 were probably parosteal osteosarcomas and 28 were central sarcomas. Of that last group, 16 were considered to be forming a matrix (probably osteosarcoma or chondrosarcoma) and 12 consisted of small round cells (probably in retrospect, Ewing’s sarcomas). He also noted that these tumors frequently metastasized to the lung and much less commonly to lymph nodes. Because of the nature of these lesions and their aggressive character, he recommended amputation as the treatment of choice.

At approximately the same time, a number of studies defined the tumor population which are considered hematopoietic in origin. In 1848 Dalrymple in an article in the Dublin Quarterly, described the entity of myeloma (26) and in the same year Henry Bence-Jones described the characteristics of the urinary protein in these patients that bears his name and is believed to be diagnostic for that disease (27). Similarly several authors described bone lesions with a greenish color which became known as chloromas; and which were established as having a relationship and indeed being diagnostic of leukemia (26).

TUMOR RECOGNITION AND BIOLOGICAL BEHAVIOR

The next 35 year period was a time of development of an understanding of connective tissue tumors, based not only on the discoveries of the nature and characteristics of these lesions; but also by establishing some concept of their biological behavior. It was the period when the great pathologists of the 20th century contributed to our knowledge and established an order to the prior chaos. The contributors of this era included Paget, von-Recklinghausen, Erdheim, Bloodgood, Jaffe, Ewing, Coley, Geschickter, Copeland, Phemister, Schmorl, Codman, Fischer, Albright, Lichtenstein, Schajowicz, Enzinger, Dahlin and many more. It should be noted that these individuals not only defined and graded the tumor populations, but also-

Of critical importance to this system was the use of the microscope in the definition of tumors. Despite earlier discovery of optics and the lens and the microscope, the technology was not applied to the body tissues and more specifically tumors until the middle of the 19th century (3). The first positive identification of tumorous tissues was attributed to Hermann Lebert who published an illustrated atlas entitled Physiologie Pathologique in 1845 which not only contained pictures of the histologic structures of tumors but some of these were in color (17). In the same year, the Scottish clinician and anatomist John Hughes Bennett described microscopic differences between benign and malignant cells (21). In 1853, Donaldson reported on the microscopic characteristics of cancer (22) and in the following year, Lionel Beale a Professor at King’s College wrote a treatise The Microscope in its Application to Practical Medicine in which he proposed some histologic markers which distinguished normal from cancerous tissue (23). All of these techniques were very useful but were only available on examination of the histologic section of a specimen submitted to a pathologist. It was not until 1891 that surgeons and pathologists collaborated in providing a diagnosis of malignant disease on a rapidly performed frozen section (24).
described the histological and in some cases the radiologic characteristics of a variety of neoplastic and non-neoplastic disorders. Several of these contributors stand out. Earnest A. Codman (1896-1940) was a general surgeon who worked at the Massachusetts General Hospital, who was interested and quite knowledgeable about bone disease and more specifically tumors (figure 9). In 1920 in an effort to further define the field of orthopaedic oncology, he along with James Ewing and Joseph Bloodgood established a Bone Tumor Registry (28,29,30). Codman became fascinated with the shoulder and published a book on that subject in 1934 in which he not only described the anatomical structure and particularly the rotator cuff, but also described and defined the entity of chondroblastoma (known since as Codman’s tumor) (31).

James Ewing (1866-1943) was a pathologist who worked in Pittsburgh and developed an osteomyelitis of the femur from which he was never cured (32) (Figure 10). He became fascinated with the microscope and with bone disease based in part on his illness and became a pathologist in New York City around the turn of the century. He was the first Chief of Pathology at Cornell University and was not only Chief of Pathology at Sloan-Kettering Hospital but served as Director of that Hospital for a number of years. He described the tumor that bears his name in 1921 calling it diffuse endothelioma of bone, indicating the highly malignant nature of the lesion (32).

Henry L. Jaffe (1896-1979) (Figure 11) and his colleague Louis Lichtenstein (1906-1977) were perhaps the most prolific contributors to our knowledge of bone tumors. Jaffe was born in New York City and became Chief of Pathology at the Hospital for Joint Diseases, a position he held from 1928 to 1965. He was an excellent educator, an astute clinical scientist and an ardent collector. Based in large measure on his well catalogued and massive collection of tumor material he beautifully enhanced the description of some already known entities and described some new ones. He and in some cases his colleague Louis Lichtenstein added substantially to our knowledge of the pathology of giant cell tumor (33) and chondroblastoma (34) but also initially described the entities of osteoid osteoma (35), pigmented villonodular synovitis (36), osteblastoma (37), aneurysmal bone cyst (38) and eosinophilic granuloma (39).

Joseph Bloodgood (1867-1935) was a student of Halsted and gained renown as a tumor surgeon at Johns Hopkins Hospital where he subsequently became Director of Surgical Pathology. In 1912 he became fascinated with the entity of giant cell tumor, partly because most patients survived, despite the malignant appearance of the lesion (40).

William B. Coley (1862-1936) was one of the early treating physicians at the Memorial Hospital in New York and defined the natural history of osteosarcoma and the effect of radiation on high grade cancers of bone (41). He was impressed with the amazing remission of a patient with wide spread malignant disease which appeared to coincide with the development of erysipelas. He introduced Coley’s toxins, a sterilized bacterial solution, which appeared to act on the patient’s immune system to help ameliorate neoplastic disease (42). This is considered by some to be the first example of adjuvant therapy for cancer.

Charles Geschickter and Murray Copeland published a book in 1936 which established the state of the science and specifically the pathology at the time for bone tumors (43) and subsequently identified the entity known as parosteal osteosarcoma and indicated its less malignant nature than the centrally placed lesions (44). Several years later George Pack and Irving Ariel did the same for soft tissue tumors but with special emphasis on surgical management (45). Several authors defined the development of a peculiarly virulent bone sarcoma in patients with Paget’s disease (46,47). In 1888, Friedrich von Recklinghausen defined neurofibromatosis of soft tissue (48).

**MANAGEMENT OF BONE AND SOFT TISSUE TUMORS**

The management of malignant bone and soft tissue tumors was until the middle of the 20th century and somewhat beyond a very discouraging area. Benign tumors were managed well with little major problem aside from a high local recurrence rate for such tumors as giant cell tumor or osteoblastoma. The malignant tumors such as Ewing’s tumor or osteosarcoma or high grade soft tissue tumors had...
very high local recurrence, metastasis and death rates. High grade chondrosarcoma had a lower rate of metastasis but those lesions about the pelvis did poorly. The great changes that occurred in the last thirty years arose principally because of the use of chemotherapeutic agents, radiation oncologic treatments and improved imaging technology.

Shortly after Roentgen discovered the X-ray as an imaging technique in 1895, radiation was considered a potential treating agent for cancer. The Curie's provided a radioactive source of considerable strength in 1898 (49). Shortly thereafter, in 1900 Kienbock reported some experiments with rats who were radiated who underwent an unmistakable series of effects; and it was then agreed that radiation might well be of value in the management of patients (50). Armed with this information, the treating radiologists became concerned about sources of radiation, the amount of radiant energy delivered to the patient and the dosage required to treat disease (51). It should be noted however that in 1933, Emil Grubbe of Chicago reported that he had treated a patient with breast cancer in 1896 and also noted the occurrence of dermatitis (in his own hands) (52). He also was allegedly the first to use lead shields to reduce the amount of radiation to unaffected anatomical parts.(52). Radium or Crooke's tubes and subsequently radon seeds were initially the sources of the radiation but devices to shield and focus the beam became an essential part of the system (51,53,54). The first treatment of a sarcoma with radiation was reported by Coley in 1905 and soon thereafter with better equipment the radiation technology became an essential part of oncologic management of patients with bone and soft tissue tumors (41).

In terms of chemotherapy, the earliest approaches were those of Coley (Coley's toxins) (42) and Sullivan with L-phenylalanine mustard (55) but neither were considered successful. It was not until 1954 that Sidney Farber reported successful treatment of several children with Wilm's tumors with actinomycin D (56), which began the period of discovery for chemotherapeutic agents. In 1973, Norman Jaffe and coworkers introduced high-dose methotrexate with leucovorin rescue for the treatment osteosarcoma (57,58) (figure 12). At almost the same time, Cortes and Holland and others reported the effect of adriamycin or doxorubicin on osteosarcoma and found that they could bring the survival rate to greater than 40% (59,60). Cis-platinum was introduced in 1979 by Baum and shortly thereafter, Marti introduced ifosfamide, thus establishing the four principal players in the chemotherapeutic regimen for this and other malignant connective tissue neoplasms (3). In the 1970's Rosen introduced the concept of neoadjuvant therapy, which allowed the treating physicians to assess the impact of the drugs chosen on the tumor prior to resective surgery, and thus allow possible changes in protocol (61). This brought the curve up further and also made limb-sparing resective surgery considerably safer. These drugs and the neoadjuvant approach have shifted the curve for all the high grade tumors such that the average long term survival rate for osteosarcoma and other tumors is as much as 70% or 80%. We owe a debt to the intrepid pioneers in this important field who have provided us these adjuvants which offer the patients a much greater chance at local control and prolonged disease free survival.

ORTHOPAEDIC MANAGEMENT OF PATIENTS WITH SARCOMAS

Until the 1940's, tumor management was difficult at best and at least for high grade tumors the patients usually had amputations performed (mostly for osteosarcoma or chondrosarcoma) or received radiation (principally for Ewing's sarcoma, lymphoma, myeloma or metastatic carcinoma). Reconstruictive surgery had little place in their care and limb-sparing surgery was a very rare event. Local resection could be performed but often failed because the surgeon had limited ability to know the extent of the lesion or to provide a wide enough margin to prevent recurrence. The success of local resection depended on the site of the tumor, the proximity of adjacent neural or vascular structures and whether sufficient skin or soft tissue could be maintained to avoid problems with wound closure. Such surgery was made more difficult by the fact that without modern imaging techniques, planning was difficult and without frozen sections at the time of definitive surgery, the assessment of the proximity of the tumor to the surgical margin was often inaccurate.

It should be clearly evident that amputation was the method of choice for malignant bone or soft tissue tumors unless the lesions were small or remarkably accessible (figure 13). Mott in 1828 reported on having performed a resection of the clavicle for osteosarcoma (62) and Langenbeck reported on a complete scapular resection for a cartilage tumor in...
Morris partially resected a forearm for a giant cell tumor successfully and reported the procedure in 1876 (64) and Hinds introduced scraping for palliative treatment of myeloma in 1895 (65). Amputations could be modified such as with the turnabout procedure as designed by Van Nes and applied to the management of sarcomas by Kotz and Salzer (67). Another similar approach for tumors of the upper end of the femur was the turnup-plasty advocated by Sauerbruch in 1922 (68). Despite problems with surgical complications, Pringle reported on a two interpelvic abdominal resections in 1916 (69).

In more recent times, with the neoadjuvant and adjuvant radiation and chemotherapy and improved surgical technology, orthopaedists have developed a series of systems for surgical eradication of the lesions and replacement with autograft, allograft, plastic materials and metallic implants. These systems are in many cases quite successful in maintaining a functional limb and have greatly decreased the disability of the affected patients and allowed the patient to maintain a functional limb.

It should be apparent however that none of these specialized surgical procedures could have been done earlier. Orthopaedic management of patients with bone and soft tissue tumors has advanced considerably since the early part of the 20th century and have established new and exciting parameters in treatment of these difficult and unpredictable lesions. There are several reasons for these advances:

1. For both benign and malignant lesions, the knowledge of the nature of the lesion has made behavior more predictable and allowed the surgeons and caretakers greater leeway in planning the patient’s therapy.

2. Vastly improved imaging technology using radiographs, bone scans, computerized tomography and magnetic resonance imaging have allowed the surgeons to define with greater certainty the anatomical position of the tumor and what would be necessary to remove it.

3. A staging technique for bone and soft tissue tumors has advanced our ability to predict outcome and define the goals of treatment; and another system has been introduced to evaluate end results.

4. Clearer assessment of biopsy technology has made it possible to know in advance what the tumor’s behavior is likely to be.

5. The use of neoadjuvant chemotherapy and radiation has made marginal or wide surgery safer than in the past and allows better and far less disabling limb-sparing surgery.

6. The ability to effectively treat lung metastases with chemotherapy and resective surgery, thus enhancing the patient’s chance at survival.

7. Modern technology for construction of custom or modular prostheses has made it possible to replace joints and adjacent bony parts.

8. Allograft banks have allowed a supply of good bony segments with attachment sites for ligaments and tendons and improved selection and harvest technology have made grafts biologically safer and more successful.

**SUMMARY AND DISCUSSION**

Perhaps there is no area within the specialty of Orthopaedics where there has been such a spectacular achievement in dealing with potentially life threatening disease. In early days, virtually everyone with high grade sarcomas succumbed and if they had a surgical solution to their problem, it was an amputation. Over the decades that followed these dreadful early days, the pathologists contributed knowledge about the tumors and identified their features and the radiologists their cardinal findings on radiological imaging. The medical oncologists provided drugs in adjuvant and neoadjuvant protocols and the radiation oncologists offered better and better means of safely radiating the lesional area, both of which vastly enhanced the patient’s survival rate. The orthopaedist provided a means of staging the patient and developing a protocol for assessing the patient’s degree of disease and stage and at least in part predicting the outcome. In addition based on the modern technology of surgery and the information gained as a result of the staging studies, the treating team has developed protocols for the resection of the bone and soft tissue tumors which are safe and cause the least damage to adjacent muscular, vascular and neurological structures. Finally the orthopaedists and their engineering and tissue banking colleagues have developed methods of safely and functionally replacing a part of the skeleton after resection of the tumors. No greater success or achievement has been recorded in tumor treatment.
References

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