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Multiple myeloma

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INTRODUCTION

It is the purpose of this paper to acquaint the reader with the highlights of multiple myeloma as have been gleaned from a review of the available outstanding articles on the topic which have appeared in the medical literature. As many of the important articles on the subject have appeared in the German and Italian publications and could not be included in this paper, the following discussion is in no wise a complete review of all the literature on the subject; those articles written in the English language being the only ones reviewed.

It may be stated here that much of the statistical data presented in the ensuing pages has been made available through the outstanding work in completely reviewing all the literature on the subject by Charles F. Geschickter,M.D. and Murray M. Copeland,M.D. in 1928. Grateful acknowledgment is made to these authors for the material made available through their excellent publication.

The subject to be dealt with, as the name implies, is a disease which produces extensive involvement of the skeleton. This disease goes even farther in that widespread systemic manifestations of the condition are not infrequently encountered. The question of a fitting and adequate definition is not one easily solved, however, in

the literature the definition which seemingly is most highly regarded and certainly most frequently used is that propounded by Ewing in 1919. It is that definition which will be used in this paper to introduce to the reader the subject of multiple myeloma.

"Multiple myeloma is a specific malignant tumor of bone marrow, arising probably from a single cell type and characterized chiefly by: multiple foci of origin; a uniform and specific structure, composed of plasma cells or their derivatives; rare metastases; albumosuria; and a fatal termination."

Ewing states further that this orthodox definition is, however, subject to extensive modifications. This fact will be noted by the reader in the subsequent context.

HISTORY

According to Morse(1920) this disease was first termed multiple myeloma by v.Rustizky in the German literature in the year 1873. In any historical review of the literature, however, the reader is usually taken back to a publication written by MacIntyre in 1850. This report is a lengthy one written regarding a case of a male individual aged 45, who suffered from what was then termed "mollities and fragilitas ossium". Although this condition had been diagnosed in cases previous to that time, in the case which came under the observation of MacIntyre, a peculiar protein was encountered in the urine of the patient, which urine was submitted to Henry Bence Jones for examination and analysis. It was regarding the peculiar protein in the urine of this same patient that Henry Bence Jones wrote his lengthy report concerning the substance which has since come to bear his name.

As has been stated above, and as Geschickter and Copeland(1936) point out, v.Rustizky first named the condition multiple myeloma after reporting on the histologic nature of the growth. Geschickter and Copeland further state that in the work of Kahler(1889), also published in the German literature, was a connection between multiple myeloma and the presence of Bence-Jones bodies in the urine first described.

Case reports in the literature up to the year 1890 were very limited in number. Following the work of Kahler, however, reports began to appear more frequently. Anders and Boston, writing in 1903, state that prior to their publication some 21 cases had appeared in the literature in which a diagnosis of myelomata was made at autopsy.

Cases became much more frequently diagnosed and reported in the early part of the twentieth century and by the time Geschickter and Copeland set about to review the literature in 1928, they were able to review some 425 cases.

ETIOLOGY AND INCIDENCE

Multiple myeloma is in general considered a disease of the latter decades of life. According to Geschickter and Copeland(1928), 80 per cent of all cases occur between the ages of 40 and 70 years. Compilation of statistics cited by these writers was made from a rather complete study of all cases reported in the literature from 1848 until 1928 when their review appeared. Their study included 13 cases studies by them in practice, and the total number of cases reviewed gave them access to some 425 cases on which to base their statistics regarding the incidence of the disease. This is by far the most complete review of the literature on the subject, and the only near-accurate account of incidence. According to this compilation the disease has a predilection for the male sex, occurring in this sex in 70 per cent of the cases reviewed. Regarding its age incidence, Geschickter and Copeland's statistics show that the peak of incidence is at 55 years. These writers state that in this respect the disease closely follows other malignant diseases, coinciding almost exactly with the age incidence of a series of over 300 cases of metastatic carcinomatous skeletal tumors studied in the surgical pathological laboratory of Johns Hopkins Hospital.

The entity is not entirely limited to the "over-forty" group, for as early as 1903 Anders and Boston reported two cases in individuals 30 and 32 years of age. These two cases were never definitely proved by microscopic study, but their clinical pictures strongly suggested the presence of this specific tumor. Williams, Evans, and Glynn(1910) also report a case in an individual of 30. Moore(1925) reports his case in an individual of but 27, and this case as well as the one reported by Williams, Evans, and Glynn was conclusively proved to be multiple myeloma by a thorough microscopic study.

A variance of opinion arises in the literature with regard to the occurrence of multiple myeloma in children. Berkheiser reported in 1924 a complete case study on two patients, a boy aged 12 and a girl aged 3. His studies on these two cases convinced him that he was dealing with multiple myeloma in both. Geschickter and Copeland in their review of Berkheiser's cases concluded that one of the cases very closely resembled Christian's disease, and the other simulated Ewing's endothelial myeloma. A case reported by Gilmore in 1925 was conceded by some authorities to be multiple myeloma while other authorities dissented. This case was in a female child 6 years old. Walkey in 1923 reported a case which occurred in a boy of 12, in which the clinical picture and course was typical

of this particular entity, and at autopsy the diagnosis of multiple myeloma was conclusively made. Harbitz gives colored plates of findings in two new-born infants in a report written in 1923. The two patients showed ascites and also foci of incompletely developed blood corpuscles, representing a type of myeloerythroblastosis. The third case reported at that time by Harbitz was in a woman 51, with multiple myeloma of the erythroblastoma type. He suggests the possibility of some connection between the cases. The actual occurrence of multiple myeloma in children is still a matter of question.

Geographically the occurrence of myeloma appears to be widespread. Cases have been reported in all parts of Europe, in Canada, in the United States, in South America and in Australia. Members of the white, black and yellow races have been included in the cases reported. Apparently all strata of society are susceptible, and no evidence of climatic or regional immunity has been noted.

Regarding the general incidence of the disease, several attempts have been toward its estimation. Geschickter and Copeland state that Symmers and Vance found but 3 cases among 4,000 autopsies at Bellevue Hospital, and the records at the Johns Hopkins Hospital show 4 cases in 9,000 cases studies at autopsy.

Geschickter and Copeland(1928) concluded that the condition occurs in about 0.03 per cent of all types of malignancy. Their conclusion was based on life insurance tables in which sarcoma in general rated seventh in frequency in the list of malignancies, or 3.5 per cent, with sarcoma of the bone one-third of this, or about 1 per cent. Among 400 cases of sarcoma of bone in the surgical pathological laboratory at the Johns Hopkins Hospital, 3 per cent were multiple myeloma.

As to the actual etiology of the condition little in the way of actual fact can be obtained from the literature. Numerous theories have been propounded, including heredity, trauma, and infection, with no actual proof that these play any definite role in the production of the entity. In several of the foreign articles reviewed by Geschickter and Copeland, some familial linking was vaguely apparent. In one of Meyerding's cases(1924), the aunt of the patient had a bone disease of some nature with which she suffered a pathologic fracture. Concerning the relation of trauma to the disease, Geschickter and Copeland(1936) state, "There is more plentiful, if not more convincing, evidence at hand with respect to trauma, so much stressed in the etiology of tumors of the bone. Although trauma as a factor in the disease was probably not sought for in a considerable portion of the cases, it precedes all other factors, and we

found it in the history of 20 per cent. When recorded in some cases, it preceded the disease by an interval sufficiently long to render its significance questionable. More frequently, the justifiable conclusion is that the trauma was superimposed on a preexisting disease state, since it was of such slight nature that in healthy persons symptoms could hardly have been produced." Wood and Lucke in 1923 cite a case in which the patient gave a history of a back injury to which he attributed the onset of the condition. They state that this has frequently been claimed and is of importance from a medico-legal standpoint as well as being a possible etiological factor. In their analysis of the reported cases in which a history of trauma was elicited, they arrive at the conclusion that in most cases the injured bone was already diseased and the trauma merely called forth definite symptoms.

Osgood(1923) states regarding the etiology of multiple myeloma that it is unknown, but that the clinical picture often suggests infection as a factor in origin. He also states that the disease at times resembles a nutritional disorder, to be grouped with osteomalacia, rickets and so forth. As to a possible infectious origin in the case of multiple myeloma, Geschickter and Copeland conclude, "In patients with myeloma, the combined incidence of influenza,

malaria, and typhoid is approximately that of trauma. When one considers the frequency of these infections among all classes of patients, their special significance for this disease is doubtful. Tuberculosis, syphilis, osteomyelitis and infectious arthritis are found associated with myeloma and sometimes coexistent with it. These diseases have no demonstrable connection with the etiology of multiple myeloma and their association with it is coincidental. From time to time theories regarding the infectious nature of myeloma have been proposed and the occasional febrile course of the disease stressed. More plausibly, the elevations in temperature can be ascribed to intercurrent infections. All in all, the etiologic obscurity that is attached to malignancy in general seems to extend in no less degree to multiple myeloma."

Wallgren(1921), who is quoted by many writers throughout the literature, cleverly scans over the etiology of the disease in his article by saying that the etiology is a systematic metastasis of a condition which manifests itself as a tumor, and closely resembles sarcoma.

HISTOGENESIS AND MICROSCOPIC FEATURES OF MULTIPLE MYELOMA

In the year 1920 an excellent article appeared in the literature written by Morse on the nosology and histogenesis of multiple myeloma, and it is from that article that the following is quoted.

"The exact characteristics which allow a tumor to be admitted to the myeloma group have never been uniformly agreed upon in pathologic literature. The presenting symptom which brings the patient to the clinic is usually pain of a constant, distressing, and deep-seated character, associated with marked weakness and cachexia, and occasionally with complaints leading the physician to a consideration of organic disease of the cord.

Physical examination shows the emaciation, loss of weight and an anemia, usually of a severe grade. Careful and detailed inspection of the osseous system reveals the bone tumors usually most evident in the ribs, but often found in the other long bones by presence of pain or spontaneous fracture. The x-ray leaves no doubt of the condition, since the finding of circumscribed or diffuse bony tumors in practically all parts of the body makes the diagnosis. The Bence-Jones albumose may or may not be found in the urine. The relatively rare occurrence of the disease along with its present hopeless outlook has caused interest

to be centered chiefly in the histological pathology of the tumors and the discussion of their nosological relationships.

The name multiple myeloma was first applied by v.Rustizky who regarded the condition as rather a hyperplasia than a neoplasm and who believed that the characteristic cell was a marrow cell. This stand was taken because of the general resemblance both grossly and microscopically which the tumor bore to marrow tissue, rather than as a result of detailed microscopic study of the cellular elements involved. Indeed, at this time, the detailed histology of the marrow had not developed to a degree to make this sort of study possible.

Cases of myeloma had been described previous to v.Rustizky's account under various names, but taking the literature as a whole both preceding and following 1873, it becomes immediately apparent that if many cases are to be admitted into the myeloma group we must either interpret the term liberally to mean multiple tumors in general associated with marrow, or assume the differences of description and interpretation to result from the undeveloped state of histology at that time. Similar or related clinical conditions and pathologic findings are described under many names.

Several important considerations relating to classifi-

cation constantly arise throughout the series. One of the earliest of these was whether the disease should be considered as a neoplasm or as an inflammatory or hyperplastic reaction of normal marrow elements. v.Rustizky in his original description speaks of the condition as a hyperplasia rather than a heteroplasia, and separates the condition from the myelogenous sarcomata of Virchow on this point. Grawitz reports 3 cases which were probably not myelomata, under the name osteomyelitis maligna -- these were most probably aleucemic or chloromatous in nature. Abrikossoff believes the cells to be of a myelocyte type and discusses the position of myelomata relative to hyperplasia and neoplasia. Wieland reserves the term myeloma for those growths which are myelomatous in the anatomical sense, that is whose structure does not depart from the mother tissue.

It is of interest that, as time has gone on, the conception of neoplasia has become more fully developed and myelomata are admitted into the neoplasm family with the same watchful waiting regarding their ultimate disposal as in the case of the leucemias.

The main subject for settlement, however, has been the relation of these tumors to the myelocyte series of marrow cells. The possibilities presented are obvious. These tumors might have their origin:

1. From misplaced tissue not normally related to any marrow tissue.
2. From ordinary connective tissue elements.
3. From blood vessels especially.
4. From fat tissue.
5. From lymphocytes.
6. From cells normally present and characteristic of marrow, but not part of the myelocyte series.

There is nothing in the life history or histology of multiple myeloma to suggest any such degree of heterotopia as the first condition requires, and the possibility has never been discussed in the literature.

Before considering the remaining possibilities, the difficulty arises as to what we mean by the term myeloma and how great a diversity of structure and power of metastasis we are going to allow to a tumor and still call it a myeloma. The disagreements between pathologists regarding the position in nosology of this tumor are always going to reduce themselves to this matter of difinition until the matter of histogenesis is settled. For the present the condition should be defined liberally as a multiple primary neoplasia arising in the bone marrow, showing marked ability to erode and destroy bone with little or no tendency to reparative process or callus formation and with very limited powers of

metastasis.

The second possibility -- namely that we are dealing with tumors of ordinary connective tissue origin, can be discarded on the ground that in the first place the cellular content of myelomata is distinctive and not that of undifferentiated connective tissue. For sarcomata of a like degree of histoid structure they are far too benign and metastasize much too sparsely. Several characteristics set myeloma apart from ordinary sarcomata; their multiple primary occurrence; their distinctive and uniform cell type with a lesser degree of heteroplasia; their specific and marked ability to erode bone by lacunar absorption without producing a reparative action onthe part of the bone, associated with a very low degree of ability to metastasize in spite of their local destructive character.

The same considerations, together with the fact that hemangenic endotheliomata are recognized to occur in marrow as a distinct condition in no way resembling multiple myelomatosis pathologically, disposes of the third possibility.

In order to consider the fourth division, we must assume that fat is a distinct tissue of separate ancestry from connective tissue. Beside the fact that this idea is not generally accepted, we have the limitation of myelomata to

bones rather than a relation to fat tissue in general, and the fact that while there might be a fancied resemblance between the embryonic fat cell and the myeloma cell, the latter are more basophilic and do not differentiate like fat cells. In this connection it is of interest that Rustizky found cells in the tumors of his case that he interpreted as changed fat cells.

As to arguments against a lymphocytic origin we are in the same position as we are with regard to fat. The myeloma tumors are always primary in bone, never in lymph nodes. They do not show even a predilection to metastasize to lymph nodes. Moreover, multiple myeloma is not associated with lymphatic tissue abnormality, and the tumor cells do not differentiate like lymphocytes.

There remain, however, two additional possibilities which are most important.

1. Do multiple myelomata constitute a group by themselves, having origin from a distinct if unknown series of bone marrow cells, or --
2. Do they belong to the myelocyte series of tumors?

These two points of view are represented by Wright on the one hand, who described them as arising from bone marrow plasma cells, and by MacCallum on the other hand, who was satisfied as to the myeloblastic origin of his case even before the oxidase reaction came into use.

The question whether or not Wright and MacCallum were discussing different sorts of tumors is settled by Christian, who studies a series including the above two and concluded they were of the same type. Indeed from a perusal of the typical cases reported in the literature, such as those of Wright, MacCallum, Christian, Vance and Symmers, there can be little doubt that the multiple myelomata represent a distinct tumor type possessing distinctive histological features and differing from sarcomata in general, and from the leucemic types. There are no greater differences in members of individual cases, than between any other well-defined tumor group. Christian leans toward the view that they resemble plasma cells more than myelocytes. The oxidase reaction has added to our methods of investigation, but it must be kept in mind that a negative reaction does not prove that the tumor is not of myeloblastic origin.

There are several difficulties in the way of considering myelomata as myeloblastic tumors. In the first place, if the cells of myelomata are myeloblasts or premyeloblasts and belong to the myelocyte series, why are these tumors not chloromata, and why do we not find transition stages in structure between myelomata and chloromata? In short, chloromata belong to the myeloblast series, are rapidly fatal, and always are, or become associated with characteristic leucemias. Myelomata do not differentiate like myelo-

cytes and never become leucemic. Chloromata metastasize widely and are associated with characteristic leukemic marrow, with lymph node and splenic changes. Myelomata do none of these things. This failure to differentiate like myeloblasts, and the absence of relation with leucemia are obstacles to accepting multiple myelomata as myeloblastic tumors, no matter how strong morphological evidence based on cytological comparisons may appear to be.

One most distinctive characteristic possessed by the myeloma is its ability to erode and destroy bone without a reaction being set up. The bone absorption goes on steadily and extensively without attempt at repair, and is certainly a specific property of the tumor cell. Neither normal nor neoplastic cells of the myeloblastic series possess this property, and the chloromata, although more malignant, possess little bone destroying power, and ordinary leucemias scarcely any. The albumosuria is no doubt associated in some way with this bone destroying power since other destructive bone lesions such as metastatic carcinomatosis sometimes show it, and the chloromata and other forms of leucemia only rarely. A point of view not before discussed in literature is that perhaps myeloma belongs to that series of reticulum cells whose function it is to absorb bone and regulate bone formation. Two types of cells

have to do with this regulation, osteoblasts, and osteoclasts. The classical cell to which osteoclastic function has been ascribed is the multinucleate, giant cell of the foreign-body type. These cells are numerous in areas where large amounts of bone are to be removed such as in healing fractures, but it is remarkable how scarce they are in many forms of bone formation where a very evident bone resorption is going on in the lacunae, thus bone absorption must go on without the intervention of the osteoclast. This leaves us with the alternative that in studying the situation, the so-called osteoblast must in some way regulate both absorption and deposition."

In his study of smears from myelomata, Morse states that he was notably impressed by the resemblance of tumor cells to osteoblasts. He concludes that the plasma cell myeloma springs from cells whose specific function is bone absorption and these may be heteroplastic osteoblasts.

This article written at somewhat of a midway spot in the files of literature on the subject, tends to give the reader a more or less comprehensive mode of approach on any consideration of the histogenesis of the condition. The article likewise exemplifies the more or less radical conclusions drawn by some of the earlier observers with but a limited scope of material available for study. Morse

rather emphatically concluded that but one type of cell fave rise to the tumor formation in all cases of multiple myeloma, his conclusion being based on his careful study of the three cases which came under his observation. A more careful review of the literature will bring out the fact that several and distinct cell types have definitely been shown to exist in different tumors, all in cases of multiple myeloma. The same error in conclusion was made by many of the early writers.

Since articles first began to appear in the literature on the topic of multiple myeloma there have been differences of opinion regarding the true histological structure of the neoplasm with numerous theories on the histogenesis being forthcoming. One writer would report a typical case of the entity with typical symptoms, physical findings and laboratory results and go on to describe the composite cells forming the neoplasm. The next writer would report exactly the same clinical picture in his case, but would differ extremely in the microscopic description of the tumor cells. Vance in 1916 made one of the earliest attempts to clear up this variation of reports. He states that although a variety of types of cells have been distinguished, the entire group, regardless of diversity, are derived from the undifferentiated bone marrow

cell, or myeloblast, which cell is the ancestor of both leukocyte and erythrocyte.

The cells of multiple myeloma, according to Vance, always resemble certain elements of normal bone marrow. In general, the tumor cells are composed of large spherical or polyhedral cells which lie without definite arrangement in a fine connective tissue stroma, separated from each other by a formless ground substance. The stroma contains a varying amount of thin-walled blood vessels, many of which are composed of but a single layer of endothelial cells. Five types of multiple myeloma have been distinguished on the basis of morphology by Vance.

The first type is composed of cells resembling myeloblasts. These are large spherical cells about the size of a lymphocyte with abundant, non-granular, lightly basophilic cytoplasm, and a large vesicular nucleus. The nuclei are either centrally or eccentrically placed, stain weakly basophilic, and possess a fine filamentous chromatous network in which lies the acidophilic nucleolus. Because of the similarity to the myeloblast, this specific tumor has been designated as a myeloblastoma.

The second type described in the early literature is that composed of cells with size and appearance of small lymphocytes. This type was early designated as lymphosar-

coma, or pseudo-leukemia confined to bone, but has come to be known in Vance's classification as the lymphoblastoma.

The third type described by Vance is composed of cells in which the cytoplasm contains neutrophilic granules. These may be equally distributed or clumped together in large irregular pigment masses. The cells of this specific type are considered atypical derivatives of the neutrophilic myelocyte, and the tumor has come to be described as the myelocytoma.

Type four is composed of cells containing hemoglobin which more or less closely resemble erythrocytes. Vance in his review of the early literature located only one such case reported. He designated the title of erythroblastoma to this group.

The fifth and final type as listed by Vance is the plasmocytoma. This tumor is composed of cells which resemble plasma cells. They are irregularly oval and approach the size of the large lymphocyte. The cytoplasm stains deeply basophilic at the periphery, but shows a clear area around the eccentrically placed nucleus. The nucleus itself is vesicular, shows dark chromatin clumps peripherally, and stains intensely acidophilic. These cells were first described by Unna in 1891, and called by him "plasma" cells due to the resemblance to the plasma cells of Waldeyer

found in the testicle. Various theories in the histogenesis of multiple myeloma suggest that this type are inflammatory in nature and arise primarily from bone marrow lymphocytes.

Vance summarizes his article as follows: "Multiple myelomata belong to a group of tumors which are composed of cells derived from primary mesenchymal 'Wanderzellen' and are closely related to leukemias, chloromas and other diseases of the lymphatic hemopoietic apparatus."

Wood and Lucke in 1923 state that myeloma cells are generally thought to be derivatives of specific marrow elements. They state that the specific cell type of multiple myeloma has been variously regarded as being identical with or related to the plasma cell, the myeloblast, the myelocyte, the lymphocyte, the erythroblast and the osteoblast, and the corresponding tumors have been named, respectively, plasmocytoma, myeloblastoma, etc. Most types of myeloma were, however, regarded as belonging to these latter two varieties.

Forman and Warren in 1917 reported on the infallibility of the identification of myeloma cells by means of the indol-phenol blue synthesis. They give a lengthy description of the procedure and report findings on various cases. In their belief tumor cells must, in order to be placed in

the myeloma group, show a positive reaction to the test which has been termed the oxydase reaction. Morse in 1920 gave a detailed account of the knowledge of the entity up to that date and reported three typical cases of multiple myeloma in which the test described by Forman and Warren proved to be negative.

Harbitz, in his report of 1923, gives colored plates of findings in his three cases in which the cells resemble a type of myeloerythroblastosis.

Ewing, in his text-book discussion of the histology of multiple myeloma written in 1919, states that while in some cases the cells of myelomata exhibit features of plasma cells, large or small, with single or multiple muclei, yet in the entire scope of tumors in this class, the cells vary widely in size and character. In some cases the entire tumor is composed of loosely packed typical plasma cells, 8 to 12 microns in diameter, round, oval, or polygonal, and with opaque amphophile, non-granular cytoplasm. A second group of cases shows larger cells, typical giant-cells, with multilobed nuclei. Multiple and vesicular nuclei are more prominent in this specific group. The resemblance to plasma cells is <u>not</u> striking and the tumors are more malignant and show considerably greater metastatic tendencies. Ewing compares this type to a lymphosarcoma with large cells. He classifies the myelomata as follows:

1. Plasmocytoma
2. Erythroblastoma
3. Myelocytoma (adult and embryonal)
4. Lymphocytoma

Regarding this classification, Evans in his discussion also written in 1919 states, "It is this difference in the type of cell producing the growth which explains the variation in the description of the condition by the several authors. It would also serve to explain why it is held by some that metastases may occur in tissues of the body other than bones." He reports three cases of the plasma cell type which are accordingly limited to the osseous system.

Geschickter and Copeland(1936) summarize the more modern views of the matter by saying that there are two distinct types of multiple myeloma, the plasma cell variety and another in which the cells resemble a normal lymphocyte. Between these two are all stages of gradual transition and gradation giving the impression that they are similar in derivation.

Burlend and Harries in 1923 describe a typical case of multiple myeloma in a child which showed numerous giant cells suggestive of osteoclasts. It is their opinion that these osteoclasts give rise to spindle cells and fibroblasts.

Geschickter and Copeland(1928) note further that a frequent observation in sections of the tumor studied is

the occurrence of apparent mitotic figures. The process is seen in many phases, and the frequency of its presence in the larger cells indicates that there is a relationship between this process and the multiple nuclei seen in the larger cells.

Myeloma tissue as a rule is rich in blood vessels. These are described by Geschickter and Copeland(1936) as being thin walled and lined with a single layer of endothelium. Around the blood vessels thin strands of fibrous tissue is often noted, and this fact is of interest because throughout the remainder of tumor tissue there is a noticeable lack of intracellular substance, with scattered fine fibrils being noted only here and there. Profuse hemorrhage into the substance of the tumor is a common finding due to erosion and rupture of the thin walled vessels described above. Erythrocytes thus are commonly found scattered rather profusely throughout. The presence of fat cells, giant cells, and eosinophiles has been rather consistently reported throughout the literature. These cell types are most commonly found at the periphery of the tumor and are thought to be the surviving cells of normal bone marrow.

The tumor nodule is but apparently circumscribed, and often in an examination of a section of tumor-invaded tissue it is difficult to determine just where normal tissue

ends and tumor tissue begins.

The tumor tissue according to Vance(1916) tends to entirely replace red bone marrow in the involved areas and likewise seems to have a corroding action on bone tissue proper.

Unlike the leucemias, in multiple myeloma only rarely do tumor cells enter into the circulating blood, as in the cases reported by Cabot, and by Beck and McCleary. From this fact Geschickter and Copeland conclude that the myeloma cell in itself is not of a circulatory variety, but is actually a peculiar marrow cell, restricted to some marrow function.

The blood picture associated with multiple myeloma is of a certainty far from typical, for cases have been reported in the literature in which almost any blood picture imaginable has been noted. Mills and Pritchard(1937) state that anemia is almost always present, and may be very severe. They state further that the anemia may be either of the hyperchromic or hypochromic varieties, and report 4 cases in which a moderate anemia was noted in all, and all were of the hyperchromic, macrocytic type. The differential counts in all 4 cases proved to be within normal limits, with low platelet counts in 2. Compiling all of the statistics available on the subject of white blood cell

counts, Geschickter and Copeland state that in 70 per cent the counts proved to be within normal limits. 23 per cent showed a leukocytosis, and the remaining 7 per cent showed a leukopenia. The subject of differential count on the other hand presents many and varied features according to these writers. In a series of 60 cases studied by them in which complete differential counts had been reported, myelocytes were found in 15, and they ranged in numbers from 1 to 10 per 100 cells. Eosinophiles varying from 3 to 5 per cent were noted in 5 of the 60 cases. Mononuclear cell increase commonly occurs and a relative lymphocytosis has not infrequently been reported.

Geschickter and Copeland likewise state that the finding of some degree of anemia is usual, but found that in 23 per cent of cases red cell counts proved to be over 4 million. In the majority of cases the red cell count proved to be between 2,000,000 and 3,000,000. These writers report finding cases in the literature in which the presence of normoblasts and megaloblasts have been noted. They further state that the usual anisocytisis and poikilocytosis of a marked anemia is also present.

The association of a hyperproteinemia with multiple myeloma offers the most recent of unusual findings which when sought in subsecuent cases have to be not at all un-

usual. Regarding this matter, Sweigert(1935) states: "Hyperproteinemia is decidedly uncommon. Its occurrence has been reported in several conditions other than multiple myeloma, for example, in large kidney tumors, and in certain of the infectious fevers, notably kala-azar. The most striking cases have, however, been found in association with multiple myeloma. The fact that this does occur has not long been known; the first case reported was in 1928, by Perlzweig, Delrue and Geschickter. Following this 15 have been reported in the literature of a total of 35 cases which have been adequately studied. The data on the subject is wholly inadequate for drawing any conclusions regarding the frequency of occurrence. Those cases thus far reported have been shown to be due either to hyper-- globulinemia or to actual Bence-Jones proteinemia. The presence of the latter was noted as early as 1917 by Jacobson, but he made no note of the excess above normal protein concentration."

Bannick and Greene(1929) found hyperproteinemia in 2 of the 13 cases which came under their observation, and of the 4 cases studied by Mills and Pritchard(1937), 2 presented the phenomenon, with the increase being due to an increase of globulin in both cases. Of interest is the fact that in both of these latter mentioned cases, serum

albumin content was reduced to approximately half the usual normal value. Little is known regarding the cause, frequency and type of the hyperproteinemia, as little study has been made on the subject, and that only in very recent years. Sweigert states in 1935 that as a result of the hyperproteinemia, unusual and variable clinical phenomena may be produced, notably; difficulty in counting red blood cells; autohemagglutination; accelerated sedimentation rate and abnormal blood coagulability.

CLINICAL PICTURE AND GROSS PATHOLOGY OF MULTIPLE MYELOMA

The patient suffering from multiple myeloma most frequently presents himself to the physician because of pain. This is not an infallible dictum, and the symptoms first noted in this disease may be extremely varied in any series of cases, but in general pain ranks first among the various characteristics noted by the patient. Of this pain Vance(1916) states that it is most frequently first noted on pressure to those bones most often involved, namely, the ribs, vertebrae, and the extremities. Vance describes the pain as of a deep-seated, persistent type, becoming more intense with motion, either active or passive. Referred neuralgic pain to the internal viscera is common and is explained by Vance as being due to pressure on the posterior nerve roots in the intervertebral foramina. According to Geschickter and Copeland(1936), the early characteristics of the pain associated with this entity are particularly vague and indefinite. These writers state that at the onset of the condition the pain is of a rheumatic type, wandering and intermittent, but usually confined to the back. In their review of the literature they found that in 70 per cent of the cases the

pain occurred in the lumbar or sacral regions, while in 20 per cent it first occurred in the chest, over the ribs or sternum. 5 per cent of their cases first noted pains in the legs, arms or shoulders, and the remaining 5 per cent were scattered throughout other regions of the body.

One of the very common characteristics of the pain associated with multiple myeloma is the aggravation produced by pressure or motion. The pains are often described as of a neuritic nature, with girdle sensations or radiations down the legs frequently taking place.

Discussing the subject, Symmers(1918) states that the patient often complains of a deep-seated, persistent pain with no apparent cause, which is often interpreted as rheumatic. He found that this most frequently made its appearance as a radiating pain down the legs, into the arms or around the trunk. Symmers brings outh further the resemblance of this early symptom to sciatica in many cases, and states that when this occurs, growths should be sought in the lumbar or sacral regions of the spine. The involvement of lower cervical or dorsal vertebrae is attended by pain corresponding to the distribution of superficial sensory nerves of the particular region, or even to visceral ramifications. Upper cervical involvement manifests itself by neuritic pains in one or both arms with occasional motor and trophic disturbances due to pressure of the

growth on the brachial plexus. A very excellent description of the various characteristics of the somewhat typical pain of multiple myeloma is that of Geschickter and Copeland(1936). They state,"Sharp accentuations of pain, brought on by sudden movement or muscular exertion, call the patient's attention to the severity of his illness. Most frequently such an unexpected climax of pain is brought about by the strain of lifting a heavy load or by some inexplicalbe fall. These attacks are exceedingly severe and the patient is usually in a state of prostration or collapse. In one case, the patient was chopping wood, when an effort precipitated pain which felled him to the ground, where he lay motionless for many minutes in a state of great pain and anxiety. In a case cited by Kahn in 1914, the sudden halting of a train in which the patient was seated was sufficient to bring on the attack. One of Wallgren's patients was seized by pain when going down some steps; he tumbled headlong down the remainder of the flight and sustained a fracture of the radius.

The result of such an attack leaves the patient for the next few hours or days with severe pains in the lumbar and sacral regions, or over the lower ribs. From this stage of relatively intense pain the affliction passes over into a period of intermittency, an asymptomatic period

which may last as long as several months or even a year. This period in which the malady is apparently arrested is fairly characteristic of multiple myeloma, and it is during this interval that many of the patients have been discharged from the clinics, to fall into the hands of charlatans when the later stages of the disease become manifest.

During the final stages of the disease the pain reaches a climax in which it is at a maximum. It is here that portrayals of suffering of the most agonizing sort are to be found in the literature, and it is in this state that the complicating root pains, paresthesia and neuralgia appear."

These two writers go on to summarize the characteristic course of the pains as follows:

Stage 1. Intermittent, insidious wandering pains, rheumatic or neuralgic, radiating or girdle in character, worse on motion or pressure.

Stage 2. A dramatic incident of aggravation; with increase of intensity, marked by collapse, prostration and bone-breaking pains.

Stage 3. Subsiding, intermittent pains.

Stage 4. Relative freedom from pain with symptomatic relief.

Stage 5. Recurrent, progressively intense pain, proceeding to death -- complicated by neurologic manifestations.

In not a small number of the cases reported in the literature, the discovery of the actual tumor growth proved to be the initial symptom. The locale of these as has been previously stated, is most frequently in ribs, sternum, spine, clavicles and long bones of the extremities, and the skull. Geschickter and Copeland state that in their series multiple involvement of the ribs, sternum or clavicles, and spine occurred in 90 per cent of the cases, while 40 per cent of these patients had in addition, either involvement of the skull or the extremities about the shoulder or pelvic girdle, besides involvement of the trunk. They found but one case in which the extremities alone were affected by the tumor, and rare cases in which the tumor involved only the spine or only the ribs. They state, "Exceptions are so rare that the statement that myeloma is always multiple and always involves the trunk is practically vindicated. It is confined for the most part to the red marrow."

Regarding the size of the tumors, Ewing(1919) states that they form small modules, multiple and bean sized, or bulky growths as large as an orange associated with smaller tumors. Great variety in size has been noted by the

various observers, but in general it may be stated that the majority of the growths range from pea to hazelnut size. In his description of the tumor, Ewing states that it may be soft or firm, translucent or opaque, and whitish, gray, or deep red, depending upon the degree of vascularity. Grossly, hemorrhage, infarction, necrosis and blood cysts may be noted. Geschickter and Copeland(1936) point out that in the examination of a tumor growth in a given case of myeloma, one may find it to be elastic, yielding, pliable or malleable. They further note that in many cases a parchment-like crepitation may be elicited over the thin bony shell of the tumor, and where a mass is not made out, the bones give the sensation of yielding and fragility. Regarding the question of pulsation of the tumors, these writers note that this characteristic occurs but rarely, and cite the classical case of Rustizky and the case recorded by Bruce in which semifluctuation was noted.

Thomas in 1901 noted a rather peculiar characteristic of the tumors in their tendency to decrease rather spontaneously, with complete disappearance and reappearance in some cases. This factor is theoretically explained by Geschickter and Copeland as being associated with hemorrhage and its absorption.

The question of deformity produced by multiple myeloma

was encountered only in the review of Geschickter and Copeland. Scattered reports of the occurrence of deformity were noted, but in no other discussion was any attempt made to emphasize the frequency with which this factor occurs. The above mentioned review points out that in all cases of myeloma, 60 per cent show thoracic deformity, and when this deformity extends to the extremities, it is confined to the regions of the shoulder or pelvic girdle. The deformities produced by this disease are for the most part thoracic, and are most frequently located about the sternum and spine. Geschickter and Copeland describe the more typical deformity as follows:

"At the sternum, in addition to tumor, there is often a sinking in at the angle of Ludwig, or more rarely, a 'wavy' deformity of the gladiolus. Parasternally, along the ribs and at the clavicles, multiple small tumor nodules may be palpated, and this multiple involvement is so frequent (approximately 50 per cent) that we have termed it the parasternal rosary, to call attention to its diagnostic importance.

In the spine, flattening of the lumbar curve, dorsal kyphosis, and actual telescoping of the spinal column due to infarction and collapse of the vertebral bodies occur. In Marckwald's case there was a maximum of shortening which

amounted to 20 centimeters, while in a case cited by Kahler and in one of our own there was nearly an equal amount. Scoliosis is not a rare observation.

These deformities of the trunk lead to a characteristic habitus or stance. The patient stands with protruding abdomen, his bulging lower ribs resting on the pelvic brim; his shoulders braced back and his feet set at a wide base to aid in maintaining his equlibrium. Fatigue and pain come on rapidly with standing. The patient walks with the utmost deliberation and caution, if his affliction does not confine him to bed. In some cases the chin rests continuously on the chest, giving rise to decubitus ulcers."

Regarding the question of deformity accompanying multiple myeloma, Vance(1916) states that the skeletal involvement tends to render the bones fragile with the result that more or less characteristic deformities tend to develop. Lesions in the dorsal and lumbar vertebrae according to this writer give rise to an angular vertebral kyphosis. Sternal lesions give rise to deformity varying in degree from a simple bowing to an extreme S-shaped curve. Soft tumor masses may project either anteriorly or posteriorly from the body of the sternum, and the ribs often show fusiform swelling near the costochondral and costovertebral junctions. Vance also states that tumor masses in other bones show no characteristic deformities.

In reviewing the three cases reported by Anders and Boston(1903) it was noted that in one case the patient's teeth fell out. Geschickter and Copeland(1936) cite the case of Schmorl, in which the skull is reported to have increased 3 centimeters in size during the course of the illness. This, they state, is a very rare occurrence in cases of myeloma, and is far more typical of Paget's disease.

The occurrence of pathologic fracture of bone in multiple myeloma is an extremely common though frequently unrecognized occurrence. This process occurs in a greater percentage in this particular disease than in any other tumor of bone. Geschickter and Copeland remark that in their study of the malignant tumors of bone they 33 per cent of pathologic fracture in metastatic carcinoma, 62 per cent in multiple myeloma, and but 8 per cent in osteogenic sarcoma. The occurrence of this process is readily explained when one considers the activity carried on by the neoplasm. Osgood(1923) describes this very adequately when he points out that gross specimens show a much thinned cortex, and the dark red, soft tissue of the tumor mass, somewhat vascular and containing trabeculae, remains. The trabeculae undergo simple absorption, and the tumor never produces bone; areas of necrosis occur, and an extensive fibrosis seems to be the natural termination of the process.

It can thus be readily visualized that when the above described process proceeds to a certain point, pathologic fracture might readily occur.

Compilation of statistics on the subject by Geschickter and Copeland(1928) show that in over 50 per cent of the cases in which pathologic fracture occurs in association with multiple myeloma, it is the ribs which are involved. The clavicles and sternum are less frequently involved. They report that in two of the thirteen cases under their observation clavicular fracture did occur. Meyerding, Symmers, and Bruce, Lund and Whitcombe also report cases in which this occurred. Evans, Beck and McCleary, report cases in which pathologic fracture of the sternum took place. Howard and Crile report a rather rare finding in their case in which they observed spontaneous dislocation of the sterno-clavicular joint.

Multiple fractures are rather frequent in occurrence in multiple myeloma. This most commonly occurs in several ribs, although rather frequent reports were noted in which multiple fractures were observed in the clavicles and sternum.

With involvement of the extremities pathologic fractures are prone to occur. Union of fractures may occur, as is shown in the cases of Ellinger, Jellinek, Bruce, Scarlini, P. Weber, Ledingham, and Dialti, all cited by Geschickter and Copeland. Moore reports another case in which union

occurred in a clavicle which had undergone pathologic fracture, and in this case the union occurred rather rapidly. In one of the cases reported by Meyerding, both femora were fractured, the left proceeded to unite, the right failed to do so. Geschickter and Copeland report some success in aiding this union with deep x-ray therapy.

While dealing with the deformity and frequency of pathologic fracture associated with multiple myeloma, it may be well to consider any pulmonary changes which might go hand in hand with the disease. The frequency of pulmonary change has been considered by Geschickter and Copeland to appear in 55 per cent of cases. They found in their review that the prevailing pulmonary changes were a chronic bronchitis and emphysema, the former being the most common. This bronchial involvement is of a diffuse, persistent, mucopurulent variety which is characterized by a productive cough. It has been explained by these observers as the result of the debilitated and cachectic condition of these patients giving rise to hypostatic pulmonary changes dependent on the bed-ridden state of the individual. With the restricted alveolar ventilation brought about by painful respiration, the bronchial pathology develops.

Emphysema is next in frequency among the various pulmonary changes which have been observed. Dyspnea and

asthmatic attacks are often accompanying features. In these cases, the anginoid attacks of pain emphasized by such violent expiratory efforts as sneezing and coughing, cause the patient to breath shallowly with the chest held in an inspiratory state. The emphysema develops due to nutritive changes which give rise to weakening of the alveolar walls. Cases in which this condition was observed have been reported from the very beginning when MacIntyre noted the condition in his patient. Morse(1920) and Wallgren(1921) also report the condition in several of the patients under their observation.

Vance(1916), Wells(1921), Symmers(1918), Beck and McCleary(1925), and Wallgren(1921) all report finding various forms of pleurisy in their patients.

In all of the various conditions of pulmonary change, Geschickter and Copeland state that there is a fatal progression generally to a terminal pneumonia.

The appearance of vague neuralgic symptoms has already been discussed, but when one considers the frequency in which other neurologic symptoms occur in this disease, it seems obvious that in any comprehensive discussion of the entity some mention of these should be made. With the attack of the tumor on the sefense structures of the nervous system, the bony framework, it is readily conceivable that pressure on nerve cords will ensue. Geschickter and Copeland state

that neural disturbances are to be found in fully 40 per cent of the cases. Morse(1920) states that the presenting symptom which brings the patient to the physician is usually pain, as has been previously mentioned, but he continues in his article to state that occasionally the patient consults his physician because of complaints which lead the examiner to a consideration of organic disease of the spinal cord. Many and varied may be the neurologic symptoms which result from the erosion of the vertebral body, but most common of all is a paraplegia which develops due to compression of the spinal cord in the region of the lower dorsal or lumbar vertebrae, this being the most common site for tumor along the spine. Geschickter and Copeland state regarding this paraplegia that the onset is usually insidious, marked in the early stages by weakness of the legs with a tendency to stumbling. In the case reported by Bruce, Lund, and Whitcombe(1904), these observers especially noted the marked lassitude exhibited by the patient. In the early stages of the compression in the lower dorsal or lumbar regions, Geschickter and Copeland report also that there is a dwindling of sexual appetite, hesitancy in starting the flow of urine and diminished epicritic sensation over the lower extremities. Following this early stage the symptoms noted next are a generalized exaggeration reflexes, with a positive Babinski sign and ankle or patellar clonus. Finally

a flaccid paraplegia develops, incontinence is noted, and the patient is apt to develop decubitus ulcers. Meyerding (1924) reports a rather unusual case along this line in which the patient developed a unilateral involvement, and in still another case observed by that writer a paraplegia developed following a fall then gradually disappeared.

Other varied and more rare findings have been reported in the literature. Anders and Boston(1903) cite a case in which their patient developed a definite alteration of the voice which was attributed to a neurologic lesion. Meyerding reports still another case in which he noted anisocoria and failing vision. This occurred in a patient where a definite tumor of the skull had developed. Bloodgood(1906), and Anders and Boston report cases in which the patients developed diplopia.

Geschickter and Copeland(1936) state that although the mind remains clear in most instances, terminal confusion and coma are not rare.

In not a few of the cases reported in the literature has mention been made of a co-existing nephritis in patients suffering from multiple myeloma. One of the earliest of these is the case reported by Jacobson in 1917, in which he pointed out definite clinical evidence of a nephritis with which was associated retention of a large measurable amount

of Bence-Jones protein in the blood. Groat and Brewer(1915) had earlier reported a typical case with an associated nephritis, but made no mention of the possibility of some connection between the two conditions. Ewing in 1919 rather definitely linked the two conditions in his attempt to explain in some measure the peculiar Bence-Jones proteinuria. He stated that although neither exact nature, position or origin of the urinary protein are fully understood, it bears some relation to a severe but non-specific nephritis which commonly marks the disease, and other proteins may appear in the urine as a result. Wood and Lucke in 1923 also suggest the possibility that there may be some linkage between the two conditions which are so frequently co-existent. An estimate at the frequency with which this co-existence occurs has been set at 70 per cent of cases by Geschickter and Copeland. These authors state that clinically, the usual occurrence is a nephrosis with albuminuria and anemia, although in one of their own group of cases, the patient dated the onset of his symptoms to an attack of acute nephritis with chills and fever, anasarca, throbbing headache and hematuria. He was diagnosed on admission as having a nephritis of the chronic, hypertensive, non-protein nitrogen retention type. Hammond in 1924 rather definitely concluded that a chronic nephritis with non-protein nitrogen retention and an associated low blood pressure is typical of

multiple myeloma. The associated low blood pressure has not been conceded to be so constant a finding by Geschickter and Copeland who state that in general a low blood pressure is associated, but report two cases with systolic pressures of 165 and 158.

Describing the kidneys grossly in these cases, the above authors state that the organ is usually smooth and white, with almost invariably an associated decrease in size.

Bannick and Greene in 1929 made a rather comprehensive study of the association between the nephritis and the Bence-Jones proteinuria. Geschickter and Copeland compiled statistics from 150 cases studied and report that in 92 of these the above mentioned association was exhibited. This amounts to approximately 62 per cent of the cases, and whether this amount is sufficient to bear any special significance is a matter of question.

As to the origin of the nephritis, many theories have been propounded, no one of which seem to completely explain all of the cases reported. Geschickter and Copeland point out that because in over 60 per cent of the cases studied as mentioned above, there was an associated Bence-Jones proteinuria, there is a possibility that the constant foreign protein shock to the renal tissue may bring about repeated damage and ultimate dysfunction.

Symptoms arising in the gastro-intestinal tract of pa-

tients with multiple myeloma have been computed to occur in 20 per cent of cases.(Geschickter and Copeland,1928) These authors explain that in a disease running a fatal course, many terminal complications are to be expected, and certain of the gastro-intestinal symptoms exhibited in myeloma are to be considered as such. Chief among the gastro-intestinal symptoms are nausea, vomiting and colicky pains. The same authors, as well as Meyerding(1924) and Jacobson(1917), report cases in which vomiting occurred without any associated nausea. This they attributed to compression of the spinal cord, analagous to the gastric crises found in tabes dorsalis.

The question of whether multiple myeloma in itself ever gave rise to metastases was, in the earlier days, a matter of much debate. Writing in 1917, Pepper and Pearce stated as follows:

"The view that true myeloma does not form metastases has been emphasized ever since the first recognition of this condition, and doubt has frequently been cast upon the few cases of myeloma in which it was claimed that metastases were found. Myeloma with its characteristic diffuse or multiple primary involvements of bone marrow has by many authors been considered a disease limited to and involving only hemopoietic tissues."

These men state further that there is a small group

which belong to the myeloma class which do give rise to foci of identical tumor tissue at some distance from the site of bony involvement. They report a case in which they definitely showed it to belong to the plasma cell type of multiple myeloma, and in which at autopsy they found identical cells in the liver and spleen. Furthermore, these authors agree with the earlier reports in the literature in which foci of cells appeared in liver, spleen, ovary, tonsil and lymph glands of patients with authentic cases of multiple myeloma. All of these they opine are metastases rather than homologous new growths. Ewing in 1919 conclusively stated that although many of the cases terminate without metastases in the organs, distand secondary growths have been found in liver, spleen, kidney, lung and ovary. Symmers(1918) in one of the early articles on the subject states that multiple myeloblastomata are capable of originating growths in the extramedullary hemopoietic viscera by hyperplasia of pre-existing myeloblastic foce, and in certain other tissues by the process of metastasis by cell transplantation. In more recent studies on the subject it has been found that the occurrence of metastases to internal organs are not at all rare. No effort has been made up to the present time to compute the percentage of cases in which metastasis actually does occur, but many cases have

been reported throughout the literature citing the occurrence. Usually hemopoietic tissues are the favorite site for the spread of the tumor -- the spleen, liver and lymph glands predominate as metastatic sites. Geschickter and Copeland in their review found cases of metastasis to the spleen reported by Arnold, Aschoff, Verse, Askanazy and Reach. The cases they found in which the condition had developed within the substance of the liver were reported by Hoffmann, Mieremet, Scheele, Herzheimer, Shennan, Arnold and Kudrewetsky. The cases of Arnold, Christian, Lubarsch, Lunghetti, Charles and Sanguinetti, Harbitz, Devic and Beriel, Mieremet, Scheele, Herzheimer, Sternberg, P.Weber and Bechtold were observer by Geschickter and Copeland to exhibit evidence of metastasis to various lymph glands. Beck and McCleary(1925) report a case which they consider to be of special significance due to the fact that bone marrow plasma cells were found in the circulating blood. This has been cited by certain authors to explain the origin of the various metastases. Rarely do the metastatic growths provoke the initial manifestations of the disease according to Geschickter and Copeland, but in two of their particular series this actually was the situation. In one of these the first manifestation noted was the enlargement of cervical lymph glands, and in the other the discovery of a tumor of the testicle afforded the initial symptom of the disease process taking place.

BENCE-JONES PROTEINURIA

Mere mention of Bence-Jones proteinuria has come to be considered synonomous with multiple myeloma by many students. That this is definitely not the case has been conclusively proved by many authorities, and in the ensuing paragraphs the highlights of these proofs will in part be brought out. First, however, it might be of interest to consider the origin of this association of the substance with multiple myeloma. In an article published in 1847, a man by the name of Henry Bence Jones wrote as follows:

"On the first of November, 1845 I received from Dr. Watson the following note, with a test-tube containing a thick, yellow, semi-solid substance: 'The tube contains urine of a very high specific gravity; when boiled it becomes highly opaque; on the addition of nitric acid it effervesces, assuming a reddish hue, becomes quite clear, but, as it cools, assumes the consistence and appearance which you see: heat reliquifies it. What is it?' A few hours later a specimen of the same urine, passed by a grocer forty-seven years of age, who had been out of health for 13 months, was sent to me by Dr. MacIntyre. He being in attendance on the same case with Dr. Watson, had two days previously first observed the peculiar reactions of the urine.

The specimen of urine was slightly acid; specific gravity 1034.2; it contained a sediment consisting of crystalline phosphate of lime, oxalate of lime, and cylinders of fibrin. The urine became thick with heat from a deposit of phosphates, but cleared with a drop of acid. It gave no precipitate with an excess of nitric acid, unless left to stand, or unless heated and left to cool, when it became solid. This solid redissolved on heat, and again formed on cooling. Continued boiling with strong nitric acid evolved but little gas, and did not quickly hinder this reaction. Hydrochloric acid gave the same solid precipitate, which redissolved by heat. Caustic potash, and sulphate of copper gave a splendid bright blue, clear liquid, passing over, when heated, to claret colour."

The article continues with a discussion of the reactions of the various other specimens collected, and then:

"January 2 -- The patient died -- the following day I saw that the bony structure of the ribs was cut with the greatest of ease, and that the bodies of the vertebrae were capable of being sliced off with the knife."

Thus it was that the presence of the peculiar substance which has since become known as Bence-Jones protein became associated with the disease then known as "mollities and fragilitas ossium", which is now called multiple myeloma. The work done by Henry Bence Jones at this early date was

really remarkable, and the report published by him will be of express interest to anyone wondering just how some of the earlier scientists attacked new problems. The patience exhibited by this man, and the completeness of his experiments and reports is to be commended. He tested and retested the substance with many and varied chemicals under all conceivable conditions in his effort to solve the mystery of its composition and origin. In all available methods at his command at that early time, he chemically analyzed the substance and published the following conclusions:

"1. The substance is a protein containing 1.03 per cent sulphur and 0.19 per cent phosphorus. Hence it is an oxide of albumen, and from the ultimate analysis, it is the hydrated deutoxide of albumen.

2. In the above case of mollities ossium, 66.97 parts of the hydrated deutoxide of albumen were passing out of the body in every 1000 parts of urine. Hence, there was as much of this peculiar albuminous substance in the urine as there is ordinary albumen in the healthy blood. So far, then, as the albumen alone is concerned, each ounce of urine passed was equivalent to an ounce of blood lost.

3. The peculiar characteristic of this hydrated deutoxide of albumen was its solubility in boiling water, and the precipitate with nitric acid being dissolved by heat and

reformed by cold.

4. This substance must again be looked for in acute cases of mollities ossium. The reddening of the urine on addition of nitric acid might perhaps lead to the rediscovery of it; when found, the presence of chlorine in the urine, of which there was a suspicion in the above case, should be a special subject of investigation, as it may lead not only to the explanation of the formation of this substance, but to the comprehension of the nature of the disease which affects the bones."

Since the time of this original work, volumes have literally been written regarding the nature of this peculiar substance with little actual fact being forthcoming. Jacobson in his article published in 1917 summarized the theories of the origin of the substance which had been propounded prior to that time. He states, "Bence-Jones thought it to be an albumose. Magnus-Levy showed it to be a heteroalbumose. Kuhn and Chittenden believe that it is closely related to globulins. Simon thinks that it is probably derived from blood albumins through the action of enzymes from the abnormal plasma cells of the bone marrow. Austin states, 'The prolonged action of bacteria on fibrin and nucleins and possibly other proteins, produces protoalbumoses and heteroalbumoses.' DeCastello regarded the protein as a product of diseased renal epithelium, claiming it was

never described in urine when kidneys were normal. Abderholden holds that it is a foreign protein in tissues."

Regarding his own opinion on the subject, Jacobson states, "The fact that it yields albumose on digestion, and metaproteins on treatment with acids and alkalies, indicates that it is higher in the scale of protein decomposition products than the proteoses." He further states that the bulk of opinion at his time is that it is of endogenous origin, probably derived from blood proteins through the action of the abnormal cells of the bone tumor, and having properties which place it nearer albumin than proteose.

Cathart and Henderson in 1912 reported a record of very widespread experimentation with Bence-Jones protein in the urine. Aside from listing the results of numerous tests with various chemical substances, their article throws little light on the true nature or origin. Vance, who covered the subject of multiple myeloma rather completely in 1916 states that on the whole, researches on the composition of Bence-Jones protein have been quite unproductive, and all that can be definitely said is that it is probably an albumin manufactured in the body under pathological conditions, which is different in composition from any of the other body proteins. In his textbook published in 1919, Ewing says, "Neither exact nature, position or origin of

the urinary portein are fully understood. It bears some relation to a severe, but non-specific nephritis which commonly marks the disease, and other proteins may occur in the urine."

The frequency with which Bence-Jones proteinuria accompanies multiple myeloma was early claimed to be very high, and throughout the literature figures around 80 per cent have rather consistently appeared. In the complete study of Geschickter and Copeland they report but 65 per cent of the cases in which a definite association was shown. An early case of the presence of multiple myeloma with no associated Bence-Jones proteinuria was reported by Charles and Sanguinetti in 1907. Hansen(1922) reports seven cases which were under her direct observation in which cases the presence of the proteinuria was repeatedly sought. Of these, 4 male patients and 3 female patients, but one showed an associated Bence-Jones proteinuria, and that only after many tests were found to be negative. Walkey's case(1923) in a twelve year old boy showed no Bence-Jones bodies in the urine although repeated tests were performed. Berkheiser(1924) commented that absence of Bence-Jones protein does not eliminate myeloma, and the characteristic proteinuria is found with greater frequency in reports of patients of greater age. Boggs and Guthrie(1912) in contrast to the observers listed above found the proteinuria in all of

their cases.

Another point which should be brought out to show the reader that Bence-Jones proteinuria and multiple myeloma do not of necessity go hand in hand, is the fact that the proteinuria has in numerous cases been reported in conditions other than myeloma. As early as 1902 Simon reviewed the literature to find that 22 cases had been reported in which the presence of Bence-Jones bodies was detected in the urine, and of these in only 13 was the diagnosis of myeloma definitely established. He states that there is definite evidence pointing to the fact that the substance may occur in other diseases affecting the bone marrow. In 1903, Anders and Boston report that the finding may also be noted in the various cirrhoses of the liver, in acute yellow atrophy of the liver, in gastric carcinoma, in gangrene, in acute or chronic suppuration, in acute inflammations of the serous surfaces, in leukocythemia, in acute infectious fevers, after foetal death, and normally during involution of the uterus. Geschickter and Copeland report that in 107 cases of diseases other than multiple myeloma in which they found a record of determination, Bence-Jones bodies were found in 26 cases. The following table published by these observers points out the various conditions in which they found the substance.

BONE DISEASES

DISEASE	REFERENCE	CASES
Metastatic tumors of bone	Orrum, Bradshaw, Boston Boggs and Guthrie, and the authors	9
Multiple sarcoma of bone	Seegelken, Gilmore	2
Senile osteomalacia	Raske	1
Polyfibrocystic disease	Groves	1
Comminuted fracture	Campbell and Horsfall	1
Caries of the spine	Wallgren	1
Tumor of the jaw	Fitz	1
	TOTAL	16

BLOOD DISEASES

Lymphatic leukemia	Herz, Frohman, DeCastello, Askanazy	4
Myelogenous leukemia	Simon Moore, the authors	3
Chloroma	Weinberger	1
Polycythemia	Pribram	1
Experimental aplastic anemia in a dog	Zeulzer	1
	TOTAL	10
	TOTAL ALL CASES	26

Regarding this table Geschickter and Copeland go on to state that despite the fact that twelve different conditions are enumerated, the striking feature that all of these diseases involve either the bone or bone marrow is well emphasized.

Coriat in 1903 reported a finding of Bence-Jones bodies in a pleuritic effusion and only in that site. This case according to Geschickter and Copeland has been referred to by some as miliary tuberculosis, by others as multiple sarcomas. Coriat did not describe the symptoms of either, but wrote only on the rare and obscure nature of the patient's condition.

The above paragraphs make evident that fact that the presence of Bence-Jones bodies in the urine is of a certainty not specific for multiple myeloma.

Of the nature of the substance in question much has been written with little addition of fact to that laid down by Henry Bence Jones in his original article. Ewing states that the presence of the substance is shown by the fact that on heating, it precipitates slightly at 55 degrees Centigrade, becomes most abundant at 65 degrees and gradually dissolves at 85 degrees, reappearing on cooling. These figures do not apply in all cases, as considerable variation is shown by the substance in its physical properties. It may begin to precipitate as low as 43 degrees,

and may resist going back into solution until boiled. In some cases in which the precipitate does not clear on boiling, the addition of a few drops of 5% acetic acid will dissolve the turbidity. If serum albumin is present in the urine, a few drops of acetic acid should be added, the serum albumin coagulated and filtered off at boiling, and the foregoing procedure then carried out.

Geschickter and Copeland state that it should be borne in mind, in testing for these bodies in patients with myeloma, that they usually appear late in the course of the disease; at first they are present only intermittently, and generally are a constant occurrence only in the terminal stages.

ROENTGENOGRAPHIC PICTURE OF MULTIPLE MYELOMA

As early as 1906 the rather typical x-ray findings usually associated with multiple myeloma were described by Bloodgood. Since that time the findings have been confirmed in numerous of the cases reported. Regarding the relationship of x-ray to the condition, Meyerding(1924) wrote:

"To the Roentgenologist, multiple myeloma presents a most interesting problem. He must bear in mind this rather rare condition in his interpretation of apparent single tumors, injury and disease of the spine, suspected carcinoma, and those more vague complaints, such as backache, in which he is called upon in hope of clearing up the diagnosis. Not infrequently the roentgenogram gives the first information as to the true nature of the complaint, and no doubt it is largely responsible for the increased number of case reports found in the literature. Especially important is the ability of the Roentgenologist to determine the local or general character of the neoplasm. The finer determinations of differentiation from carcinoma, metastases, endothelioma, chloroma, etc. may baffle the most expert, and at times be impossible."

The changes which usually take place are characteris-

tically distributed in the trunk, in the sternum, in the skull, in the ribs and in the spine. The long bones of the extremities, the pelvis and shoulder girdle are less frequent, although far from rare, sites of change. The actual findings are described by Osgood(1923) as punched-out areas which are especially clear cut in the skull, and which have a well-defined margin. He further states that as the tumor proper is of an osteoclastic nature, little or no shadow is cast. The size of the typical punched-out areas vary from pea size to that of an orange.

By far the most comprehensive discussion of x-ray findings in the disease is that published by Geschickter and Copeland(1936), and it is from their work that the following is quoted.

"The ribs are most frequently diffusely mottled, but at the site of the ossified costochondral junctions, there is a tendency for the tumor nodules to stand out more distinctly as areas of bone absorption. Not infrequently, tumors about the size of an almond are to be seen lying on the ribs, rather than appearing centrally. At autopsy, these can be found projecting inwardly as subpleural nodules.

Pathologic fractures occur most frequently from the fifth down to the twelfth rib. The break is generally not

a clean one, but a default through a widened and rarefied area of rib, easily overlooked. In some cases, there are noticeable fracture deformities, but not the extreme bending seen in osteomalacia or the multiple globoid enlargements and distortions seen in von Recklinghausen's disease at the site of repeated fractures.

The clavicles may be expanded and rarefied at either the sternal or acromial ends. They are sometimes fractured or sublúxated at the sternoclavicular joint. In the sternum, unless lateral views are taken, involvement of this bone may be mistaken for mediastinal shadow when the tumor is sufficiently large.

Rarefaction and globular tumor formation are both to be found in the spine. In the rarefied vertebra, infraction and collapse lead to shortening, disappearance of the intervertebral disks and twisting of the spinal column with scoliosis. Involvement is most frequent in the lower dorsal and lumbar regions. There is a tendency for more than one vertebra to be involved.

When tumor formation is found in the skull, the roentgenogram is of great diagnostic value. Unlike the typical furry thickness of the skull in Paget's disease and sarcoma and sometimes in metastatic carcinoma from the prostate, there is no increase in the width of the tables.

Multiple punched-out areas are found confined mainly to the frontal and upper parietal regions, generally not as large as in cases of metastatic carcinoma or as mottled as in advanced cases of syphilis of the bone. Large frontal sinuses somewhat like those found in cases of acromegaly have been observed in three or four cases. This is in contrast to the condition found in Paget's disease and leontiasis ossea in which the size is decreased.

The pelvis is sometimes diffusely affected together with the rest of the skeleton, giving the impression that the bone is bloated or puffy, with an attenuated structure like edematous tissue.

When the long bones are affected, they show, in the early stages, either the multiple punched-out areas, or more rarely an expanded cystic change. Sooner or later, however, they assume an attenuated appearance, in which there are large areas of rarefaction, rather than expansion within a shell.

Some formation of bone occurs, as is proved by the healing of pathologic fractures and by microscopic examination, yet the roentgenogram rarely shows the formation of new bone in the reviewed cases. This absence of sclerosis about the areas of bone resorption is helpful in distinguishing this condition from metastatic carcinoma in the roentgenogram."

Little new regarding x-ray findings in multiple myeloma has come forward since the writing of the above article, and as recently as December of 1937, Mills and Pritchard reported the same findings as were listed above in the skull, pelvis and vertebra of their patient.

DIAGNOSIS

After having read the foregoing pages, the reader is well aware that the picture presented in myeloma is indeed a varied one, and the early symptoms may readily point to some condition far removed from this disease. In reviewing the literature one commonly encounters cases in which no accurate ante-mortem diagnosis was made, and only after post-mortem examination was the true entity brought out. The condition is commonly mistaken for Pott's disease, lumbago, nephritis, pleurisy, osteomalacia, osteitis fibrosa cystica, visceral c rcinoma with skeletal metastasis and tabes dorsalis. If the onset be characteristic with a symptom group which points specific lly to disease of bone, the diagnosis will more often be made with a minimum of difficulty. It is in those cases, rare to be sure, but present nevertheless, in which the initial symptoms are far removed from bony sites as have been described in the preceding pages in which diagnosis is often missed or not made until late in the course of the disease.

Of the rather detailed account of the various symptoms and signs of multiple myeloma already described, the following characteristics are listed by Geschickter and Copeland as being outstanding in giving the observer some presumptive evidence of the disease.

"1. Foremost in the series stands multiple involvement of the skeletal trunk in an adult. Spinal deformity should not be examined without including in that examination the ribs and sternum. If this had been done in nearly every case in the series studied in which a diagnosis of spondylitis deformans or Pott's disease wase made, the correct diagnosis of malignancy at least, would probably have been hit upon, and in all likelihood myeloma itself diagnosed. Deformity of the spine, the parasternal rosary of tumor nodules, bulging and deformity of the ribs these indicate multiple involvement of the trunk and are characteristic of the disease. Usually such multiple involvement is demonstrable in the x-ray films. An occasional case may run its entire clinical course with but a single focus in the bones, or the marrow involvement may be clearly demonstrated only at autopsy.

2. Occurring less frequently, but even more typically peculiar to this disease, is the pathologic fractures of a rib. Pathologic fracture of a rib in an adult is ample presumptive evidence for suspecting myeloma. In no other disease does it occur with a semblance of the frequency found in this condition.

3. The outstanding feature detracting from the diagnostic value of the Bence-Jones bodies in the disease is

the failure to carry out this test as a routine in bone diseases and tumors of bone. This test is so simple, implying watching for an early precipit te when the usual test for albumin is carried out by slow heating, that it should not be omitted as a routine in diseases of the skeleton. The albuminoid bodies are presumptive evidence of this disease. Their true diagnostic value, however, will not be known until this test is more often applied in skeletal disease.

4. Although backache and radiating rheumatic pains are commonly found in myeloma, backache is sufficiently widespread clinically almost completely to nullify the diagnostic importance of thi symptom. If in realization of the possibility of tuberculosis, metastatic carcinoma, sarcoma or myeloma of the spine, however, the clinician elicitis a history of early compression of the cord (such as beginning loss of sexual potentia, difficulty in starting urination, or loss of power in the legs), this type of backache, exacerbated by movement, with radiating pains and associated signs of early paraplegia should be suggestive of multiple myeloma.

5. In some cases, an otherwise inexplicable and increasing anemia of the primary type will lead to roentgen-ray study of the bones when the facilities are available.

Under these conditions, the possibility of multiple myeloma should be considered.

6. Finally, although adequate information is still lacking on this point, the presence of a chronic nephrosis with non-protein nitrogen retention and low blood pressure should arouse suspicion. In such cases the urine should be tested for Bence-Jones bodies. The plasma proteins may be markedly increased with inversion of the albumin-globulin ratio, and an analysis of the blood chemistry including such determinations should be made if possible."

It should be remembered that the most definite finding in the diagnosis of multiple myeloma lies in the x-ray which seems to be one of the most definite and characteristic of all the various symptoms and signs cited. In the article written by Morse in 1920 he makes the following rather radical statement which bears out this point:

"The x-ray leaves no doubt of the condition, since the finding of circumscribed or diffuse bony tumors in practically all parts of the body makes the diagnosis."

A more recent point of view on the subject of diagnosis is that brought out by Reich in 1936, who states that cases with typical x-ray findings in the bones and Bence-Jones proteinuria are in the minority and it is usually quite late rather than early in the course of the disease that the true picture is discovered. This author advocates the

use of sternal puncture as an early diagnostic procedure. He cites a case in which a biopsy of the lower portion of the sternum was done, microscopic examination of obtained material showed an enormous number of plasma cells, many of which were dividing and atypical. From his findings, Reich concluded that it is possible to make a diagnosis of multiple myeloma by a sternal puncture earlier than by other usual means. He states further that myeloma cells are commonly present in sternal marro early in the disease, and routine sternal puncture in obscure cases of this type will usually aid in the diagnosis. He cites no authority for this latter statement, and no other such statement was encountered in this review of the writings on the subject. If Reich's findings prove true in a majority of cases it will be a contribution of much import, for the procedure is a relatively simple one, can be performed on ambulatory and clinic patients as readily as can other routine blood tests.

PROGNOSIS AND TREATMENT

Little need be written regarding prognosis in multiple myeloma. It is generally conceded that the condition is always fatal and according to Geschickter and Copeland (1936) this fatal termination occurs on an average two years following the onset of the disease. Koch and Kuegle (1936) concluded that from the onset of symptoms death may occur at any time within a period of four years.

Regarding treatment Geschickter and Copeland offer the rather discouraging information that thus far no definite proof of a cured case could be found in the literature. Thus with little hope of giving the patient any permanent benefit from any type of therapy, the physician must turn to palliative symptomatic treatment. Bloodgood in 1905 stated in regard to treatment that the only type was excision of the tumor in the event that there happened to be but a single focus. Nothing further has been mentioned in the literature regarding this matter. Ehrlich in 1934 made the statement that x-ray treatment alleviates the clinical symptom of bone pain, when pre ent, and may temporarily retard the progressive bone destruction. Koch and Kuegle in 1936 state that although no treatment has ever arrested the progress of the disease permanently and the prognosis is hopeless, nevertheless, cobra venom given intravenously tends to relieve the pain. They further state that liver

therapy may be used to advantage to combat the anemia. Geschickter and Copeland add to the above, that in case of fracture fixation should be done, and a high calcium diet along with sufficient vitamin D should be administered. Morphine should be used to control pain when necessary, and inhalations may be given to benefit any complicating respiratory pathology.

The clinician is further instructed by Geschickter and Copeland to assume an attitude that is not too pessimistic, since much can be done to add to the comfort and cheerfulness of these patients.

SUMMARY

1. Multiple myeloma is a rare tumor causing death, developing in many foci, most commonly in the ribs, spine, pelvis, vertebrae, skull and upper portions of the femurs, affecting the red bone marrow primarily in these sites, and occurring most often in adults in the sixth decade.

2. Common clinical characteristics include; rheumatic pains, skeletal deformities, pulmonary changes with emphysema, and neurological manifestations such as radiculitis and paraplegia.

3. Associated findings often inclued; nephritis with non-protein nitrogen retention and low blood pressure plus Bence-Jones proteinuria, hyperproteinemia, pathologic fractures commonly in the ribs, typical punched-out areas of bone destruction shown roentgenographically, and anemia with unusual and varied cells appearing in the differential white cell count.

4. The disease is always fatal, terminating almost always within four years following the onset of symptoms.

5. Deep x-ray therapy is the most valuable form of treatment in bringing about temporary symptomatic improvement.

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