THE PEROXIDASE REACTION IN THREE CASES
OF MULTIPLE MYELOMA OF THE BONES WITH
REMARKS CONCERNING THE NOSOLOGICAL POSI-
TION OF THESE TUMORS

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The exact characteristics which allow a tumor to be admitted
to the myeloma group have never been uniformly agreed upon
in pathological literature. From a clinical point of view the
cases are fairly well defined. 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 the consideration of organic disease of the spinal
cord. Physical examination shows the emaciation, loss of weight,
and an anemia usually of severe grade. Careful and detailed
inspection of the osseus system reveals the bone tumors usually
most evident in the ribs, but often found in the long bones by
the 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 this disease
along with the present hopeless prognostic 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
(1), 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 re-
semblance both gross and microscopical which the tumor bore to
marrow tissue, rather than as a result of detailed microscopical 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 evident 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 pathological findings are described under many names.¹

Several important considerations relating to classification 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. Rustizky (1) 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 (13) on this point. Grawitz (2) reports three cases under the name osteomyelitis maligna which were probably not myelomata but aleucemic or chloromatous in nature. Abrikossoff (14) believes the cells to be of myelocyte type and discusses the position of myelomata relative to hyperplasia and neoplasia. Wieland (3) reserves the term myeloma for those new growths that are myelomatous in the anatomical sense, that is, whose structure does not depart from the mother tissue. Abrikossoff is not able to agree with Kauffman (15) and Wieland that a separation into myeloma on the one hand

¹ Myeloma multiplex (Rustisky) (1), Osteomyelitis maligna (Grawitz) (2), Lymphosarcoma multiplex ossium (Wieland) (3), Sarcoma multiplex ossium (Buch) (4), Pseudoleucaemia myelogenes (Runeberg) (5), (Zahn) (32), Ostitis sarcomatosa (Hammer) (6), Lymphadenia ossium (Nothnagel) (7), Endothelioma intravasculare (Markwald) (8), Myelosarcoma (Schmaus) (9), Erythroblastoma (Ribbert) (10), Plasmoma malignum (Hoffmann) (11), Myeloblastoma (Symmers) (12).
and multiple lymphosarcoma on the other is possible. He
thinks the essential point is the inability of the myelomata to
metastasize and compares them to lymphosarcomata of lymph-
nodes (aleuemic leucemia?) in this respect, but separates them
sharply from ordinary bone sarcomata. Since there are several
undoubted myelomata now in the literature which have shown
a certain degree of metastasis, Abrikossoff's basis for his con-
clusion is done away with. Relating to this question, it is of
interest that, as time has gone on and the conception of neoplasia
has become more fully developed, this matter has settled itself,
and myelomata are admitted into the neoplasm family with the
same doubts and reservations and the same watchful waiting
regarding their ultimate disposal as is the case with the leucemias.

The main subject for settlement, however, has been the rela-
tion 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 tissue of
the marrow.
2. From the ordinary connective tissue elements.
3. From the 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.
7. From the myelocyte series.

There is nothing in the life history or histology of multiple
myelomata to suggest any such degree of heterotopia as the first
consideration requires, and the possibility has never been dis-
cussed in the literature.

Before considering the remaining possibilities, the difficulty
immediately arises as to what we mean by the term myeloma
and how great a latitude regarding 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 definition until the
matter of histogenesis is settled. For the present, the author believes that a liberal conception is the best one in that the definition should contain no dogmatic statements regarding the histogenesis, and that the condition of "multiple myeloma of the bones" should be defined 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 histology of the tumors is characteristic and quite definite and uniform in different cases as regards the picture presented under the microscope, in spite of the uncertainty and disagreement regarding the origin of the cellular elements. On this basis we can discuss the remaining questions.

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 histioid structure they are far too benign and metastasize much too sparsely. Several characters set the 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 reaction on the 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 (Markwald (8), Berger (16), Thevenot (17), Symmers and Vance (18)) 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, as Mallory has suggested. 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 myeloma cells 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 the 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 myelomatosis is not associated with abnormalities of the lymphatic tissue, and the tumor cells do not differentiate like lymphocytes.

On account of the fact that some cases reported as examples of myelomata have apparently been of the lymphocyte type, such as that of Herrick and Hektoen (19), there has been a tendency in the later literature to restrict the conception of myeloma definitely to those tumors having a characteristic histology. Thus Symmers objects to the cases of Herrick and Hektoen, Weber, Scheele and Herxheimer, and Kahler being included as myelomata. Symmers believes that apparent secondaries found outside the marrow usually arise by stimulation of latent centers in extramedullary hemopoietic viscera, but that true transplantation metastases do occasionally arise.

The differences in opinion as to which cases should be included as myelomata are well shown by the differences in the accepted lists of Symmers and of Pepper and Pearce (20).

The difficulty of sharply defining the limits of the myelomata has led many writers to make several groups. Thus Vance (21) distinguishes myeloblastoma, erythroblastoma, lymphocytoma, and plasmocytoma types. Christian (22), as heretofore mentioned, argues for the unity of the myeloma.

Pappenheim (23) considered them to be merely a special localization of processes belonging to the lymphosarcoma or pseudoleucemia group (Lymphosarcomatosis pseudoleucemica) and not a distinct entity in themselves.

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* Dr. Ewing in a personal communication states that there are a few cases of (myelomata?) arising in lymph-nodes.
Sternberg (24) admits four possible groups. His first and third groups are probably identical and would now be considered as myelomata.

Some growths have been diffuse in the bone marrow rather than represented by discrete nodules. Such cases are reported by Abrikossoff (14), Weber (25), Winkler (26), Kalischer (27), and Zochmann and Schumm (28).

Paltauf (29), Sternberg, and Kaufmann differentiate the primary multiple myelogenous sarcomata and lymphosarcoma from the group of true myelomata.

These were the easily settled questions which the literature has taken care of quite adequately and which have settled themselves as the cases have been reported.

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 (30) on the one hand, who described them as arising from "bone marrow plasma cells," and by MacCallum (31) on the other, 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 studied a series including both Wright's and MacCallum's cases and concluded that they were of the same type. Indeed from a perusal of the typical cases reported in the literature, such as those of MacCallum, Christian, Wright, Vance, and Symmers, and even the older cases of Rustizky, Zahn (32), and Wieland, 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 leuemic group. There are no greater differences in cell type in members of individual cases than between any other well defined tumor group. This idea has been especially developed by Christian,
who showed that there were not sufficient differences between Wright's and MacCallum's cases to warrant placing them in separate groups, in spite of the fact that the opinion of these two workers differed as to the resemblance of the cells to plasma cells on the one hand and myeloblasts on the other. Christian leaned toward the view that they resemble plasma cells more than myelocytes.

The oxidase reaction has added to our methods for the investigation of these tumors in that it may be applied now to each new case encountered. It must be clearly kept in mind, as Symmers pointed out, that a negative reaction does not prove that the tumor is not of myeloblastic origin. More than this, the author does not find proof in the literature that other cells of the marrow than the myelocyte series may not act positively to the oxidase reaction. It must be remembered that the lymphocyte series have been found to react negatively and the more differentiated members of the myelocyte series to act positively under normal conditions; and that while it is logical on these grounds to resort to this technique for deciding the origin of a circulating blood cell, it is quite another and unjustified leap of logic to assume that in the bone-marrow no cells but the myelocyte series give the peroxidase reaction even under pathological conditions. The point is that while the latter assumption may be true the question has not been studied.

In other words the peroxidase reaction applied to myelomata is productive of interesting information, but until we have more definite knowledge of bone-marrow histology nothing is actually settled by applying this reaction to a particular case. Furthermore there are other important general considerations which point toward a solution without the help of the oxidase reaction. To the writer's mind a very important point of view is that of Mallory (33), that these tumors do not consist of cells of the myelocyte series because they do not differentiate like them.

Since Wright claimed a "bone-marrow plasma cell" origin for myelomata there have been many reports either endeavoring to prove or taking it for granted that the tumor arises from the myeloblast series. The objection that has been raised to Wright's
view has been that the bone-marrow plasma cell is not a clearly defined entity. As Ewing (34) says, the histological structure of some of the cases so closely resembles plasma cells as to suggest that those who deny their existence have not encountered these cases. The oxidase reaction has revealed a few cases which have reacted positively and which, if we accept this reaction as positive proof of a myeloblastic origin, might be interpreted as myeloblastomata. Forman and Warren (35) report such a case and also Beck and McCleary (36). Both of Symmers' cases were negative as were also those of Pepper and Pearce, Bombard (37), and Vance along with three included in this report.

Aside from the occasional positive peroxidase reaction, the dictum that myeloma multiplex arises from the myeloblast series rests entirely upon an effort to show that the tumor cells resemble myeloblasts morphologically.

This is altogether insufficient evidence considering the fact that its champions object to assigning the tumors a plasma cell origin, although admitting a similar resemblance morphologically. If a resemblance to plasma cells is not a sufficient proof of plasma cell relationships, then a myeloblastic resemblance does not prove myeloblast relationships. Taking the literature as a whole we find both ideas with ample supporters. Thus Von Verebely (38), Thomas (39), Vance, Wright, Christian, Hoffmann (40), Aschoff (41), Pepper and Pearce, and Ewing recognize plasma cell types, while MacLeod (42) and Zininger (43) note a resemblance to plasma cells. Menne (44), MacCallum, Abrikossoff, Weber (45) (Muir), Ribbert (46), Scheele and Herxheimer (47), Sternberg, Jores (48), Symmers, Forman and Warren, Beck and McCleary, believe in the myeloblastic origin.

The question cannot be settled on morphological grounds because of the limitations of the method.

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? The fact is
that myeloma cases never become chloromatous and never become associated with true leucemias, as do all chloromas sooner or later. Furthermore, myeloma cases do not exhibit the changes in the spleen and lymph-nodes that chloroma cases do. It might be argued that the myeloma cell is a less differentiated member of the hemopoietic group and therefore does not possess the highly differential morphological characters of the chloroma cell. Against this is the fact that the chloroma is more malignant than the myeloma, both as regards rapidity of growth, metastasis, and a rapidly fatal issue; which does not argue well for the chloroma possessing a more highly differentiated cell.

In short, chloromata belong to the myeloblast series, are rapidly fatal, and always are, or become, associated with leucemias; myelomata do not differentiate like myelocytes and never become leucemic. Chloromata metastasize widely and are associated with characteristic leucemic marrow and with lymph-node and splenic changes; myelomata do none of these things.

If it were not for the definitely myelocytic or lymphocytic character of chloromata and the definite leucemic nature of these tumors, the possession of a green color alone would not be sufficient to separate them from the myelomata. To the writer's mind, this failure of myelomata to differentiate like myeloblasts, and the absence of a relation between myelomata and leucemic states are obstacles to accepting myelomata as myeloblastic tumors, no matter how strong morphological evidence based on cytological comparisons may appear to be.

One most distinctive character possessed by the myeloma is its ability to erode and destroy bone without a reaction being set up. This is striking throughout the literature if we disregard a few isolated cases like the atypical one of Hammers (49), which was probably not a myeloma. 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 have this property and the chloromata, although much more malignant than the myelomata, possess very little bone destroying power and the ordinary leucemias scarcely any. The albumosuria is probably
associated in some way with the bone destroying power since other destructive bone lesions such as metastatic carcinomatosis sometimes show it and the chloromata and other forms of leukemia only rarely. So far this is in support of the general view Ewing expresses regarding the different identity of typical myelomata and tumors of the leucemic (myeloblastic) group.

A point of view hitherto undiscussed in the literature is that perhaps myelomata belong to that series of reticulum cells whose function it is to absorb bone and regulate bone formation. The statements in the literature regarding bone absorption are unsatisfactory. Two sorts of cells having to do with bone formation have been described, osteoblasts and osteoclasts. By some these have been considered as the same and by others as representing distinct types. The classical cell to which osteoclastic function has been ascribed is a 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 sorts of bone formation where a very evident bone resorption is going on in the lacunae.

There has never been sufficient proof that the multinucleated giant cell, which since the work of Kölliker has been assumed to be the active agent in bone absorption, has in fact this function. A very casual survey of sections of actively growing bone, showing evident resorption around the marrow spaces, makes it evident that much bone absorption must go on without the intervention of the classical osteoclast.

This has been recognized by many authors. Arey (50) in a recent important article gives the literature and shows definitely that many workers have been of the opinion that classical osteoclasts are not important in ordinary bone resorption. He concludes that "Only indirect and insufficient evidence points to the osteoclasts as the active specific agents of bone resorption. That they are merely degenerating, fused osteoblasts accords better with known facts." This leaves us with the alternative that the so-called osteoblast must in some way regulate bone absorption as well as bone deposition. This view is favored by
Arey, who believes that bone absorption is brought about as Wells thought by \( \text{CO}_2 \), although he recognizes that it is "difficult to imagine the mechanism of the localization of carbon dioxide (or the stronger lactic acid) in sufficient concentrations to effect the selective erosion of small areas or to account for the frequent directional polarization of the resorptive wave."

Studying smears and teased preparations from myelomata, the author has been very much impressed by the resemblance which the cells from the tumors bore to the osteoblasts(?) which lie free in the connective tissue of the marrow and especially line the lacunae of rapidly growing bone. This is exemplified by figure 1, which is a photograph of a group of osteoblasts on the tip of a young bone trabecula in an area from the marrow of a rapidly growing ungual osteoma. The basophilic protoplasm, the eccentric nucleus of the vesicular type with peripherally arranged chromatin and central nucleolus are especially striking.
It is easy by measurements, staining reaction, and description of cytoplasmic and nuclear structure to show the similar appearance of the "osteoblast" and myeloma cell, but to use this method to establish the identity of the two cells is unjustifiable here as in the case of those who on similar grounds claim to show that myeloma cells are myeloblasts.

The important property of bone absorption which the myeloma cell so prominently possesses, accords well with an inferred relationship to cells of the osteoblastic series. On the grounds of the preservation of this function, we might infer a relative lack of anaplasia and consequent lack of malignancy which again accords with the facts. Only one difficulty arises. If these cells are osteoblastic in their relationships, why do we always find these tumors actively resorbing bone, but never building it?

Either of two assumptions might be favored. First that the cells of the myeloma differentiate in this special direction, and by this mode of differentiation bone absorption is made a hyperfunction just as the production of colloid material by some tumors arising from cells which normally produce it becomes an essential characteristic of their heteroplasia. This requires the conception of a constantly persistent "resorptive wave" to use the euphonic but somewhat vague term of Arey.

The second alternative we might use is to question the fundamental correctness of the idea that the so-called osteoblast is really a bone formative cell and suggest that it is always resorptive in function. This assumption is against the present conception of osteogenesis.

The clinical records of the three following cases have been left out for the reason that they contain no details bearing on the present study.

Case 1. Autopsy one hour after death.—The body is that of a very much emaciated man 37 years of age. A globular mass mentioned and described in the clinical history is found involving the left shoulder and clavicle. The seventh rib on the left is fractured in several places and is soft, easily broken, and paper-like throughout. Fractures can also be palpated in the fourth and fifth ribs on both sides.
On section the muscles are dark, dry, and small; the panniculus is absent. Superficial examination of the abdomen reveals the viscera in proper position and no fluid or exudate in the abdominal cavity. On removing the sternum we find it to be thicker than normal and soft and friable, so that large soft portions can be cut out with the knife. By making a mesial section and dividing the sternum in two portions the bone cortex is found to be a mere shell, largely decalcified, and the marrow to occupy almost the entire thickness of the sternum (about 4 cm.). The marrow is mottled pink in color and resembles the cut surface of a lymph-node. There are small hemorrhages and islands of bone fragments. Scarcey any areas of normal red marrow remain.

The ribs are thin-shelled, nearly decalcified, and there are nodules of tumor bulging and breaking through the bony cortex. Elsewhere the medulla of the ribs consists of dry, empty spaces. The right and left lungs are both adherent at the apex and present a low grade, nearly healed tuberculosis. There is anthracosis of the bronchial lymph-nodes.

The heart is of normal size. On section the muscle is deep brown. The aorta presents a moderate nodular sclerosis, evidenced by raised yellowish plaques. In the muscle of the ear of the right auricle, beneath the epicardium, is found a pinkish white plaque similar in appearance to the tumors found in the ribs and sternum. This plaque is about the size of a pea. The heart is otherwise normal.

There is no evidence of thymic remains and the thyroid is of the usual size and on section is found the usual colloid appearance without adenomata.

The gastro-intestinal tract including the liver and pancreas was examined in detail without any important finding. The liver is browner than normal, and appears slightly atrophic (brown atrophy).

The abdominal aorta is moderately sclerotic like the thoracic portion.

The spleen is of the usual size and consistency, and on section seems normal in consistency and appearance.
Both kidneys present numerous white nodules in the cortex. These vary in size from a pin-head to a hickory nut, and have a pinkish white color and lymphoid appearance. They are identical with the tumors found in the ribs and the sternum.

The prostate and bladder are found to be without unusual appearance.

The vertebrae can be freely incised with the autopsy knife. They have almost entirely lost their lime salts and are replaced by the lymphoid-like soft material heretofore described.

Microscopical findings.—The tumor nodules (fig. 2).

The sections of the tumor taken from all the different bones present the same picture. The structure is purely histioid consisting of a uniform mass of closely packed cells with a very delicate reticulum. The blood vessels are without walls, and are in the form of endothelium-lined spaces running through the tumor. All fields present the same picture. There are no areas of degeneration, necrosis, or fibrosis.

At first glance the cell type seems remarkably uniform. The cells are irregularly oval and fairly uniform in size with most of the nuclei eccentrically placed. The protoplasm is slightly basophilic and stains like the protoplasm of plasma cells, and the margins of the cells when not pressed on all sides by other cells tend to be somewhat ragged. On closer analysis the individual cells are found to vary from one another to a considerable degree, but no more widely than those of any tumor which is rapidly growing. The cells vary from an oval shape like that of the plasma cell, to an irregularly round or polygonal outline in those areas where they are pressed upon by other cells. They vary in size from 5.8 to 8 microns in the short diameter, and from 7.7 to 13 microns in the long. The nuclei are more variable in size than the cells themselves. Some of them are small and pyknotic and take up only one end of the cell and others occupy nearly all the cell body. They vary in size from 5.8 x 9.1 microns to round pyknotic forms measuring 3.6 microns. In some of the cells the nuclei have divided without cell division following, so that cells resembling bone marrow megakaryocytes are produced.
Though they vary somewhat in size and shape, the great majority of the nuclei are vesicular in character with definite nuclear membranes which take the stain deeply. The chromatin is rather small in amount, giving the nucleus the appearance of a clear granular vesicle; it is for the most part murally arranged, clinging to the inner side of the nuclear membrane with delicate spiderweb lines running centrally to the nucleolus, which is usually prominent, and varies in size from a tiny chromatin point to a mass measuring about 1.8 microns in diameter. Occasionally there appear to be two nucleoli.

The sections of tumor taken from the body of the vertebrae show the contiguous muscle to be diffusely invaded. In places bony trabeculae are still present, but undergoing absorption. There are no osteoclasts, but the tumor cells are present in the lacunae and canaliculae and appear to be performing the osteo-
elastin function. There is no effort at bone formation in any of the sections.

The peroxidase reaction applied by both methods, to smears and frozen sections, was negative.

**Kidney.**—There is no diffuse infiltration of the kidney parenchyma with the tumor, but there are discrete nodules beneath the capsule about the size of a pea. These nodules have the same histological characters as the primary tumors. Remains of kidney tubules are scattered through it, and glomeruli with their tufts containing many fatty droplets. The uninvolved portion of the kidney shows many areas where the tubular epithelium is completely calcified but no other important changes. An occasional thrombosed glomerular tuft with the capsule filled with wandering cells and an occasional hyaline glomerulus appears, but there are no diffuse changes which could be interpreted as a definite nephropathic condition.

**Lung.**—There is an advanced emphysema, with the usual accompanying histological changes and a diffuse anthracosis. There are a few heart failure cells. Some of the branches of the pulmonary artery show quite marked proliferation of the intima. The lung tissue as a whole is much more fibrous than is usual in even the more advanced types of emphysema.

The liver presents no important changes. The cells around the central vein contain a great deal of light brown pigment and there is some pressure atrophy of the liver cords in this region with many fat droplets in the cells (early nutmeg liver).

Gastro-intestinal tract negative.

In the heart muscle there is no change except many fine fatty droplets in muscle cells, and increased brown pigment at the poles of the nuclei.

**Thyroid.**—Moderate enlargement of the follicles. Apparent colloid retention.

**Spleen.**—The pulp is especially prominent. The Malpighian bodies are few in number and atrophic. The pulp appears remarkably cellular and there are wide sinuses running through it. There is no increase of connective tissue in the spleen pulp.
Bone-marrow.—In areas not grossly involved by tumor growth the normal marrow elements are replaced in part by tumor cells, interspersed in large numbers.

Pathological Diagnosis.—Multiple myeloma of the bones, metastasis to the kidneys and muscle of right auricle. Metastatic calcification of the kidney tubules.

Case 2. Autopsy.—Body is that of a man 35 or 40 years of age. Well formed, distinctly emaciated. Faint icteric tint to the sclera. Moderate purplish hypostasis on the back.

Palpation of the bony cage of the thorax shows many softened crepitating areas on both sides. The left femur just above the knee is fractured when the body is moved from the stretcher to the morgue table. There are no other external abnormalities of importance.

On section the tissue is dry, the muscles dark red. No gas or fluid escapes from the abdominal cavity. Superficial inspection of the abdomen shows no gross abnormality. There is a moderate pseudo-melanosis of the intestines. The fifth rib is softened at the costo-cartilagenous junction, crepitates, and feels irregular on palpation.

Dissecting the tissue away from this region, we find an opalescent bluish mass the size of a hickory nut, and from here to the fourth rib at the costo-cartilagenous junction the tumor mass extends. The tumor tissue found on the fourth and fifth ribs replacing the bony cortex, resembles lymphoid tissue in general. On taking off the lateral wall of the chest with rib shears we find the ribs involved throughout their length by nodules of lymphoid-like tissue, which shine through the pleura presenting a linear nodular appearance along each rib. The ribs are extremely fragile, containing very little lime salts. The tumor mass, primary in the ribs, has completely replaced the rib marrow, everywhere, and in certain places has broken through the cortex and appears as an external nodule.

Removing the sternum with the attached costal cartilages, we find it very flexible, containing very little bone, and much thickened at the lower half. The sternum was split longitudinally with the autopsy knife. Scarcely any lime salts were present.
The marrow has been replaced by a lymphoid mass. The whole costal cage is replaced by lymphoid-like nodular tissue.

The apex of the heart is at the fourth interspace, apparently 1 cm. outside the nipple line. The right heart extends beyond the sternum. Both lungs are free and have collapsed about the hilus. The heart has a small soldier's spot on the right ventricle. The left ventricle is empty. The wall of the left ventricle is normal in thickness and color. The mitral valves admit two fingers. The flaps are normal. The right ventricle is empty. The tricuspid is relatively dilated. The right auricle contains a large post-mortem clot. The pulmonary artery presents no abnormality. The aorta shows a fine nodular type of sclerosis, not particularly advanced. The left coronary mouth is greatly dilated. There are patches of atheroma along the left coronary and also along branches of the right coronary. No gross evidence of syphilis is present in the heart. There is a patch of old adhesions on the posterior surface of the left lung near the vertebral. The adhesion seems continuous with the tumor in the rib. The tumor has slightly involved the pleura at this point. The lungs are small and dark in color, and on section fairly normal. Mediastinal lymph-nodes show no involvement. There is a purulent discharge from the bronchi. The right lung is small with a few subpleural nodules in the upper lobe. These nodules are calcified, the size of a pea, probably a healed tuberculosis. The right lung is otherwise negative.

The thoracic aorta is normal except for a slight nodular sclerosis.

The spleen is normal in size. There is considerable post-mortem autolysis and on section a distinct hyperplasia of the lymphoid tissue. The left suprarenal is normal in size, and on section shows no changes.

The left ureter is not dilated. The left kidney is small and has a scanty fatty capsule. On section the cortex is pale and swollen. Medullary rays are not well marked. The capsule strips easily.

The right adrenal is normal in size, and on section negative. The right kidney is about normal in size, and on section presents the same appearances as the left.
The mesenteric lymph-nodes are not enlarged. The intestines contain many fecal masses, but are otherwise negative.

Pancreas presents no abnormal gross changes.

There is a moderate purulent cystitis.

The prostate is normal in size.

The liver is of normal size and on section presents a slightly browner appearance than normal.

The gall bladder is distended, but contains no stones.

Pathological diagnosis.—Multiple myeloma of the bones, involving nearly all the bones of the body.

The x-ray report of a mass in the mediastinum was based upon an appearance due to the wide infiltration of the vertebrae in the thoracic region by the tumor. On either side of the vertebrae in the upper thorax the infiltration extends outward along the transverse processes and the proximal portion of the ribs in such a manner as to produce a large pyramidal-shaped x-ray shadow, which might very well be mistaken for a mediastinal growth.

The following is a summary of the histological changes.

The heart, lung, pancreas, bladder and adrenal present no changes of importance.

The spleen shows a distinct hypertrophy of the lymphoid follicles. There are no important changes in the pulp. No cells resembling tumor cells are found in the pulp. There are a few miliary tubercles in a moderate stage of fibrosis.

There is no increase in connective tissue in the kidney. Glomeruli appear normal. The cells of the tubules are granular from postmortem change. Throughout the cortex are many tubules which have been replaced by lime salts.

Pieces were taken from the tumor nodules of almost all the bones in the body, for microscopical examination.

The picture presented is uniform throughout (fig. 3). The tumor consists of a uniform histioid structure with a uniform type cell arranged on a delicate reticulum, with an intimate relation between the tumor cells and the blood-vessels. The blood-vessels have no proper wall, but pursue their course through the tumor lined by a simple layer of endothelial cells. The tumor
cells have the usual resemblance to plasma cells. They are of the same size and variation as in the previous case. In general they have eccentrically placed nuclei, basophilic protoplasm, with large vesicular nucleus showing the characteristic mural arrangement of chromatin with fine threads projecting inward toward the nucleolus. Although the ribs, vertebrae, sternum, long bones, and bones of the pelvis were involved in this case,

![Cells of Myeloma, Case II](image)

**Fig. 3. Cells of Myeloma, Case II**

there were no metastases to other organs as in the previous case. The metastatic calcification of the kidney was quite as striking as in case 1. There were no other pathological changes of importance found by microscopical examination of the sections.

The peroxidase reaction applied to smears of the tumor as well as to frozen sections of tissue fixed in formalin were negative by both methods.
CASE 3. Autopsy findings.—The body is that of an adult male, about 40 years of age, 5 feet 11 inches tall. Greatly emaciated. The bony landmarks are normal throughout.

About 10 cm. to the right of the mid-sternal line on the third rib is a subcutaneous lump the size of a hen's egg and a smaller lump in the same region in the first rib under the clavicle. These lumps are connected with the rib and continuous with it.

There is some enlargement of the left testis, which is soft and elastic.

The abdomen is slightly distended. On section the panniculus is found practically absent. Tissues are moist and the muscles dark red. Superficial inspection of the abdomen shows a small amount of fluid in the abdominal cavity, but the gross relation of the organs is normal.

On stripping back the muscles from the thoracic cage we see the nodules above described developing from the ribs. The bony structure of the ribs is soft and friable. The mass is enlarged, has broken through the bony cortex of the ribs, and on section one obtains a thick semi-gelatinous substance, somewhat resembling pus.

The right lung is adherent in the upper portion and laterally by well organized fibrous tissue.

The left lung is free, but throughout there is considerable hypostatic congestion.

The right lung shows marked congestion, some edema. There are no solid areas of pneumonia and the bronchial lymph-nodes are not enlarged. There is considerable anthracosis. The left lung is less congested than the right. Both lungs crepitated throughout.

The heart lies free in the pericardial sac. There are no adhesions. There is a small amount of free fluid in the pericardial cavity. The mitral valves admit the tips of two fingers. There is marked sclerosis of the mitral cusps. The tricuspid valves are negative. The right orifice is empty, the left orifice admits two fingers, but there is no evidence of sclerosis. There is considerable edema of the walls of the coronary arteries. The aortic semilunars are slightly sclerotic. The first portion of the aorta
is somewhat dilated. The intima has a slight reddish discoloration, from a post-mortem imbibition of hemoglobin. There are no other changes of importance in the thorax.

In the abdomen there is about 200 to 500 cc. of clear fluid. The relation of the abdominal viscera is not disturbed. The liver is slightly enlarged, extending about two finger-breadths below the costal margin. It is smooth, the capsule somewhat thickened. On section the liver bleeds easily, and the centers of the lobules are dark red in color. The spleen is normal in size; the capsule somewhat thickened. On section there are no important gross changes. On removing the intestines we find the pyloric end of the stomach adherent by a mass of soft friable tissue. The mass involves the wall and the pyloric ring, and on section has the same general character as the mass found in the rib. This mass is continuous with the posterior wall of the abdominal cavity where it extends into the 8th and 9th dorsal vertebrae. These vertebrae are completely destroyed by the tumor, and the mass in the stomach and the abdomen is evidently a direct extension from this point.

Inspection of the vertebral bodies as a whole shows practically the whole spine involved in the process, with some areas of fairly normal vertebral tissue between the nodular masses of tumor substance.

The retroperitoneal lymph-nodes are somewhat enlarged.

The pancreas is soft, slightly displaced by the mass adherent to the pylorus.

The kidneys are somewhat congested, but show no other gross changes.

The prostate is slightly enlarged.

There is a large right-sided hydrocele of the testis, with some atrophy of the organ. The left testicle is slightly enlarged, but shows no gross changes.

*Pathological diagnosis.*—Multiple myeloma of the bones. Direct extension to the stomach. Hydrocele of the right testis.

*Microscopical findings.*—The lung shows a distinct emphysema with areas of atelectasis. There is fibrosis of the interalveolar septa, and many heart failure cells in the alveoli. The
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bronchi are filled with a thin mucous secretion. There is an advanced anthracosis. There is a considerable hyperplasia of both the spleen pulp and the Malpighian bodies. The spleen pulp shows an increase in its cellular content, and under high power many of these cells resemble those of the tumor. In the margins of the Malpighian bodies are also large numbers of large mononuclear cells, identical morphologically with those found in the tumor nodules. There is considerable increase of connective tissue in the pulp. The kidney presents an appearance of post-mortem disintegration of the protoplasm of the tubules. No changes are found which can be interpreted as nephropathic.

In sections of the prostate there are found no inflammatory areas or areas of glandular hyperplasia.

There are no changes of note in the heart muscle.

Sections were made from the tumor nodules of the rib of the involved vertebrae, and of the stomach region involved by continuity with the vertebral tumors. The tumor is of a pure histioid character, consisting of round cells arranged on a delicate connective tissue reticulum (fig. 4). There are some larger bands of hyaline connective tissue running through the tumor. The blood-vessels have delicate walls consisting of a few connective tissue strands and lined by a delicate endothelium. The cells in general closely resemble plasma cells. They are somewhat ovoid in shape with an eccentrically placed nucleus and a basophilic protoplasm; their margins tend to be somewhat ragged where the cell is not pressed upon from all sides. The nucleus is vesicular with murally arranged chromatin and fine bands of chromatin running toward the center to a rather large nucleolus. The structure is typical of a myeloma of the so-called plasma celled type.

In none of these three cases were abnormal cells observed in the peripheral blood. The many cases in the literature in which myelocytes in small numbers have appeared along with a terminal polymorphonuclear leucocytosis are explained on the ground that such terminal blood pictures are common with advanced tumors, especially when the bone-marrow is involved. Our cases show the terminal leucocytosis common to late malignancies, as pointed out by Vaughan (53).
The author does not find convincing statements in the literature that "plasma cells" or cells of distinctive type may be found during life in the circulating blood and used for diagnosis. The case of Beck and McCleary is certainly open to question regarding the interpretation of the origin of the cells found at autopsy in the blood-vessels. In the first place these cells had already been interpreted as ordinary blood cells during life, and not until after death was it decided that they represented distinct tumor cells. Further, although the patient is said to have died of acute lobar pneumonia, the white blood count is recorded as 8800. The tumor cells in their case gave the indophenol blue synthesis, but they do not record its result with blood smears.

The finding of abnormal cells in these cases must be interpreted as a result of combined reaction to late malignant disease in general and to non-specific bone marrow involvement in particular.
The peroxidase reaction, both on frozen section and on smears from the tumor surface, was negative by both methods tried. The methods in detail are given below.

THE PEROXIDASE REACTION

Two methods were used on both smears and frozen sections. The technique used by Forman and Warren was applied, which is similar to the one used by Evans (51) except that some steps are omitted.

The frozen sections from formalin-fixed tissue were placed in equal parts of 1 per cent alpha-naphthol in 1 per cent KOH and of 1 per cent dimethylparaphenylendiamin for two minutes. The section was then washed and examined in water on a slide with a coverglass. Smears were fixed in formol-alcohol for two minutes, washed, and the same technique applied.

The second method used was that of Goodpasture (52). The stain is prepared as follows:

- Alcohol 95 per cent ........................................ 100.0 cc.
- Sodium nitroprusside ...................................... 0.05 gm.
- Benzidine (C. P.) ........................................ 0.05 gm.
- Basic fuchsin .................................................. 0.05 gm.
- Hydrogen peroxide ........................................ 0.5 cc.

The sodium nitroprusside is dissolved in as little water as possible and then added to the alcohol; the other ingredients are then included. Goodpasture's solutions retained their activity for several weeks. I have not been able to get the reaction except with freshly prepared solutions.

Smears are allowed to dry and then covered with the reagent for one minute; an equal quantity of water is added and allowed to remain three minutes when the preparation is washed, blotted, dried, and mounted in balsam.

Frozen sections of formalin-fixed tissue are placed in equal parts of the reagent and water for five minutes, washed in water, dehydrated in acetone, cleared in xylol, and mounted in balsam.

The oxidase granules are blue, the nuclei red, and the protoplasm pink.
Blood smears and frozen sections from an inflamed Fallopian tube and appendix were used to control the stain.

In all three cases only a few scattered leucocytes showed the characteristic granules in either sections or smears. From this result we can only conclude that if the cells are of the myelocyte series they are too imperfectly differentiated to give the reaction.

**SUMMARY AND CONCLUSION**

1. Three cases of non-oxidase reacting myelomata are reported.
2. The histogenesis of these tumors is discussed, and data presented which is interpreted to support the theory that the so-called "plasma cell" type of myelomata is not of myeloblastic origin and has no relation to the leucemic group.
3. It is suggested that the "plasma cell" myelomata spring from a series of cells whose specific function is bone absorption, and that the myeloma cell may be a heteroplastic "osteoblast."
4. The finding of abnormal cell types in the peripheral blood of myeloma cases has not been demonstrated by the published examples to be specific and characteristic of this form of tumor. The myelocytes, "plasma cells," and other abnormal cell types, together with varying degrees of leucocytosis and disturbances of the percentage relationships of the various normal leucocytes, are adequately accounted for by the condition of malignancy accompanied by wide-spread bone-marrow involvement, and is found in non-myelomatous conditions.

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