THE BONE MARROW ON STERNAL ASPIRATION IN MULTIPLE MYELOMA*

By Edwin D. Bayrd, M.D.

INTRODUCTION

THIS STUDY of the bone marrow on sternal aspiration in multiple myeloma is concerned primarily with three main points: (1) the type of cell or cells involved in the production of the disease; (2) the origin of this cell or these cells, and (3) cytologic criteria for the degree of malignancy.

As will be noted more fully later on, there seems to be no point of agreement on the first two aspects of this subject and almost no information whatsoever on the third.

An attempt will be made herein to elucidate all three of these issues insofar as a study of the available literature and material at hand permits.

All satisfactory sternal marrow smears available through February, 1947, were reviewed for cell type and indications of origin. These numbered seventy-one altogether. Fifty-one cases were studied completely with differential counts, as noted subsequently, and with attention to all morphologic detail. These observations were used in an attempt to correlate cytologic findings with clinical findings.

Forty-three cases had been seen long enough ago to be included in the follow-up study for indications of degree of malignancy. This last group includes all of those cases seen at the Mayo Clinic through December, 1945.

METHOD

The technics of sternal aspiration used have been various modifications of the Arinkin method1 (using a Klima and Rosegger needle2) and have been fully described previously.3–5 The present method employed is that used by Schleicher.3–6

One to 2 cc. of the marrow material was withdrawn with a dry sterile syringe from the gladiolus at the level of the second interspace after inserting the tip of guarded needle and stylet 1 to 2 mm. beneath the inner table of the cortex. In addition to the marrow blood withdrawn, small elements ("units") of bone marrow are apparently withdrawn intact. The whole is placed in a paraffin-lined heparinized glass tube. The use of these small "units" permits fixed tissue technics to be employed on the same bone marrow from which volumetric studies and smears are made.

Smears alone were available for review in the large majority of instances but in the few cases in which tissue was also available and of additional interest this fact is indicated. In addition to a general description of the sternal marrow smears that were made on each case after a period of study, differential counts of 200 marrow

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cells were made. Further "differential counts" were conducted on 100 "myeloma cells" in each case in an attempt to develop an objective method for determining the degree of anaplasia or immaturity.

A small, 200 cell differential count was considered to be adequate for this study, (1) because a larger 1,000 cell count run as a pilot showed less than a 3 per cent variation in the predominant cells present, (2) because the limits of normal are so wide that only gross changes are significant, and (3) because quantitative relationships in these marrows are of secondary importance. The number of nucleated erythrocytes per 100 myeloid cells was noted. The "myeloma" cells were classified as old if the nuclear chromatin was fairly compact and the nucleus small (usually eccentric), tending to resemble the ordinary plasma cells, whether or not a nucleolus was present. The intermediate stage cell, the type most often seen in multiple myeloma, usually had one or more large nucleoli and a vesicular, finer stranded nucleus with or without chromatin "dots" (small isolated, denser areas of chromatin). There was, in this group, less tendency toward eccentricity of the nucleus than in the old cells. The young or immature forms were those with a large nucleus, with a very fine chromatin skein, with or without nucleoli such as seen in the stem cell or the reticulo-endothelial cell. Here the nucleus showed the least tendency toward eccentricity. This division proved to be a workable, though, as might be anticipated, not an infallible one.

Historical Review

The significant clinical feature and gross morphologic aspects of the disease now widely known as "multiple myeloma" were developed largely during the latter half of the nineteenth century from the time of Macintyre, Watson, Bence Jones and Dalrymple in 1848 to 1850 to that of Wright in 1900. Macintyre described a case, appropriately enough of a man, 45 years old, who was seen in consultation with Dr. Watson, in whose urine Bence Jones noted some abnormal protein matter and on whom Dalrymple reported the microscopic findings in two affected ribs. Subsequently, Rustizky, Kahler and Bozzolo added coherence to the clinicopathologic picture of the disease and stimulated the reporting of more cases. Until 1900, when Wright published the studies he had made on a case of multiple myeloma that had come to his attention in February, 1898, no one had linked the offending marrow elements to the plasma cell. Shortly thereafter, however, Christian reported on 6 cases, all with this characteristic finding, although he later stated that he considered the myeloma cell to vary within the limits of plasma cell on one side and myelocyte on the other. Since that time, 75 to 80 per cent of reported cases have been of the plasmocytic type. It was during these formative years and the next two decades that most of our concepts of etiology, cell type and histogenesis were laid down. This was done in the main by pathologists utilizing fixed tissue sections. Subsequently, some of the other more bizarre manifestations of the disease were emphasized, such as hyperproteinemia, rouleaux formation, myeloma cells in the peripheral blood and associated amyloidosis. Two of the most complete reviews of the problem
to date include those of Geschickter and Copeland,36 and Atkinson.19 The relationship of the diffuse multiple myeloma to the solitary myeloma, intraosseous and extraosseous, and "plasma cell leukemia" has been discussed by many authors, a few of whom are noted.27, 29, 31, 37, 38 In 1929, Arinkin1 introduced his method for bone marrow aspiration and since then more attention27, 29, 34, 37, 39 has been directed toward this technic as a method of diagnosis and means of studying the histopathologic characteristics of this disease.

COMMENT ON THE LITERATURE

A. THE TYPE OF MYELOMA

It has been widely held since the concept of multiple myeloma was first formulated that several, if not all, types of marrow cells were involved in the production of the specific lesion. There were thus erythroblastic,44-46 lymphocytic,17, 49 megakaryoblastic,11, 49, 50 myeloblastic,46, 48, 51, 52 and myelocytic,39, 44, 46, 48, 52 as well as plasmacytic, "lipoblastic"43 and osteoblastic types.53 Of the current texts in pathology or clinical pathology this opinion finds support among Bell,55 Wood,56 Moore,57 MacCallum,58 Oertel,59 Gradwohl,60 and Kolmer and Boerner61 and further acceptance by other authors.16, 37, 62-77 Boyd78 seems to support those whose contention it is that all types are but a variation of one cell type when he remarks (having previously listed the usually accepted types) that "on the other hand it is equally possible, indeed probable, that the apparent variety is merely due to anaplastic changes in one fundamental cell type."

By the time Wright11 made his first observations incriminating the plasma cell in 1900, the following histopathologic diagnoses had been made on the lesions of cases accepted as multiple myeloma: lymphosarcoma, myelogenous pseudoleukemia, lymphadenoma, hyperplasia of marrow, vascular endothelioma, sarcoma, small round cells and lymphoid cells. In 1904, Weber17 reviewed the literature (38 acceptable cases) and reported one of his own. This case he classified as a "myelocytic" myeloma. He also recorded a second previously reported case, which he designated as "lymphocytic" although he mentioned the presence of more than the usual amount of cytoplasm and occasionally eccentrically placed nuclei.

In 1910, Williams and associates79-80 reported a case of plasmacytic myeloma and also reviewed the slides and tissue of a case reported by Moffatt84 in 1905 as lymphocytic. It was their expressed opinion that this, too, was plasmacytic. And even as early as that time they observed that "this suggests that further research will show that the differences in the type of cell are more apparent than real, and are the result of differences in fixation, staining and description, or perhaps in degree of anaplasia." Shennan,52 in 1913, also, in a good discussion of the early literature, reported 3 cases, the second of which he regarded as myelocytic, the other two probably being plasmacytic. At the same time he presented a classification which included "true myelocytes, premelocytes or myeloblasts, lymphocytes, plasma cells and megaloblasts (erythroblastoma)." However, it is interesting to see that though Shennan outlined a rather inclusive classification he did express some doubt that such a wide variety of types exists. "It is questionable
Bone marrow in multiple myeloma

whether all the different varieties of myeloma described in the literature of the subject can be clearly differentiated from each other. Possibly the apparent differences are due to the variability of one cell type.

In 1916, Vance reported a case which he placed somewhere between an erythroblastoma and a myelocytoma. He listed ten authors who had observed myeloblastomas, eight authors who had reported lymphocytomas, six who had noted myelocytomas, Ribbert's erythroblastoma, and several authors who had described plasmacytomas.

Wallgren, in 1920, in a widely quoted review of the problem, expressed the opinion that a lymphocytic type does not exist, that newer methods of staining have done away with it, and that all myelomas are made up of cells of the same fundamental type which may, however, show certain varying stages of development, differentiation or degeneration. In 1928, Geschickter and Copeland summarized the findings on 412 cases of proved multiple myeloma from the literature and reported on their findings in 13 of their own cases. They had this to say about myeloblastic and myelocytic types:

As for the so-called myeloblastic or myelocytic type of myeloma, we have repeatedly observed that concerning the same section two authorities will differ between these two terms. Ewing, in cases 8 and 11 in our series, used the term myelocytic or myeloblastic, while Bloodgood used the term plasma cell type. In running through a series of 22 proved cases in rapid succession, one finds that these 2 cases do not stand out especially as atypical and fit in well with the so-called plasma cell type, although superficially, the nuclei do not appear to be as typically spoke-like in arrangement. Many authors, in describing such cells in cases of multiple myeloma are uncertain whether to class these cells in the plasma or myelocytic series, and some of these authors have thought that the apparent difference was due to fixing or staining methods.

In some cases the differentiation was made on the basis of the oxidase reaction, and in other cases on the Unna-Pappenheim reaction for plasma cells. While the differentiation can thus be made in some cases, often it cannot be made either by oxidase reaction or by Unna-Pappenheim stain.

Wintrobe, while noting that the "literature refers to myelomas of various types: myeloblastic, lymphoblastic, lymphocytic, myelocytic, erythroblastic and even hemocytoblastic and megakaryoblastic," said, "Plasma cell myeloma is the most common designation. There is a good reason to doubt the identification of the cells in many of the reported cases. Even many of those who have referred to 'plasma cells' have admitted that those were atypical. Recent studies which have been aided greatly by the possibility of obtaining the tumor cells by sternal puncture, indicate that the myeloma cell is a peculiar form differing from any other cell type."

Cases reported in which tissue studies were responsible for diagnosis. Wood, Quinlan and Merrill reported a case of multiple myeloma in which the patient was a boy 19 years old. Tissue obtained for biopsy was submitted to four pathologists for their opinion because of the infrequency with which this disease occurs in the first two decades of life. Wood, Warren, and MacMahon expressed the opinion that this was a pleomorphic or atypical plasma cell myeloma, while Geschickter stated that it was of the "primitive myelocytic series." Donhauser and de Rouville in reporting four cases of multiple myeloma noted that two were of the
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plasma cell variety and that one was lymphocytic, while the other was myelo-
cytic. This last was felt by Parker to be Hodgkin's disease.

The foregoing 33 cases (table 1), reported since Wright made his observations
on the plasma cell character of this tumor, are cases in which the histopathologic
diagnosis is other than of the plasma cell type. It should be emphasized that in all
of these cases the diagnosis was based on the examination of tissue sections. It will
also have been noted that great difficulty frequently attends the classification of
these cells cytologically from tissue alone and that competent pathologists may
differ widely in their opinions of the same tissue. And this takes no cognizance
whatsoever of those cases in which a diagnosis of other than myeloma entirely
was made erroneously, as has undoubtedly occurred in some instances.

**Table 1.** Unselected Cases of Multiple Myeloma from the Literature which were Reported as of other than the Plasma Cell Type

<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>Cases</th>
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<tbody>
<tr>
<td>MacCallum</td>
<td>Myelocytic</td>
<td>1</td>
</tr>
<tr>
<td>Ribbert</td>
<td>Erythroblastic</td>
<td>1</td>
</tr>
<tr>
<td>Weber</td>
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<tr>
<td>Permin</td>
<td>Lymphocytic</td>
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</tr>
<tr>
<td>Moffatt</td>
<td>Lymphocytic</td>
<td>1</td>
</tr>
<tr>
<td>Shennan</td>
<td>Myelocytic</td>
<td>1</td>
</tr>
<tr>
<td>Vance</td>
<td>Myelocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Gunn and Mahle</td>
<td>Megakaryoblastic</td>
<td>1</td>
</tr>
<tr>
<td>Geschickter and Copeland</td>
<td>Myelocytic</td>
<td>2</td>
</tr>
<tr>
<td>Wood and associates</td>
<td>Myelocytic</td>
<td>1</td>
</tr>
<tr>
<td>Donhauser and de Rouville</td>
<td>Lymphocytic</td>
<td>1</td>
</tr>
<tr>
<td>Perillo</td>
<td>Lymphocytic</td>
<td>1</td>
</tr>
<tr>
<td>Batts</td>
<td>Myeloblastic</td>
<td>1</td>
</tr>
<tr>
<td>Symmers</td>
<td>Myeloblastic</td>
<td>1</td>
</tr>
<tr>
<td>Wilson</td>
<td>Lymphoid</td>
<td>1</td>
</tr>
<tr>
<td>Feller and Fowler</td>
<td>&quot;Elast cell&quot;</td>
<td>1</td>
</tr>
<tr>
<td>Rosenberg and Kirshbaum</td>
<td>Lymphocytic</td>
<td>1</td>
</tr>
<tr>
<td>Slavens</td>
<td>Myeloblastic</td>
<td>1</td>
</tr>
<tr>
<td>Rypins</td>
<td>Myeloblastic</td>
<td>1</td>
</tr>
<tr>
<td>Jacon and Kahn</td>
<td>Myeloblastic</td>
<td>1</td>
</tr>
<tr>
<td>Jenkinson and Foley</td>
<td>&quot;Without plasma cells&quot;</td>
<td>1</td>
</tr>
<tr>
<td>Cantarow</td>
<td>Granulocytic</td>
<td>1</td>
</tr>
<tr>
<td>Moore</td>
<td>Myeloid</td>
<td>1</td>
</tr>
<tr>
<td>Schwartz</td>
<td>&quot;Giant cell&quot; myeloma</td>
<td>1</td>
</tr>
<tr>
<td>Marchal and Mallet</td>
<td>Hemohistioblast</td>
<td>1</td>
</tr>
<tr>
<td>Stewart and Weber</td>
<td>Lymphocytoma</td>
<td>1</td>
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<tr>
<td>Smith and Silberberg</td>
<td>Hemocytoblastic</td>
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<tr>
<td>Mewburn and Vango</td>
<td>Lymphoid</td>
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*Cases reported in which diagnosis was based on sternal aspirations. The technic of
sternal aspiration is of relatively recent origin; yet, even so, enough cases of mul-

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<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
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<td>Scott</td>
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<td>Reich</td>
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</tr>
<tr>
<td>Pearson and associates</td>
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<td>1</td>
</tr>
<tr>
<td>Rubinstein</td>
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<td>Ferrata and Storti</td>
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</tr>
<tr>
<td>Vogel and associates</td>
<td>Plasma</td>
<td>4</td>
</tr>
<tr>
<td>Markoff</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Gordon and Schneider</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Hertzog and Schleicher</td>
<td>Plasma</td>
<td>3</td>
</tr>
<tr>
<td>Beizer and associates</td>
<td>Plasma</td>
<td>9</td>
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<td>Berger and Goodman</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Brugman and Reich</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Wells and Goldish</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Russell and Jacobson</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Thannhauser and Berenstien</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Foord</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Váradi</td>
<td>Plasma</td>
<td>5</td>
</tr>
<tr>
<td>Fleischhacker and Klima</td>
<td>Myeloblastic</td>
<td>2</td>
</tr>
<tr>
<td>Rosenthal and Vogel</td>
<td>Plasma</td>
<td>5</td>
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<tr>
<td>Weissenbach and Lièvre</td>
<td>Stem cell</td>
<td>1</td>
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<tr>
<td>Young and Osgood</td>
<td>Plasma</td>
<td>12</td>
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<tr>
<td>Diggs and Sirridge</td>
<td>Plasma</td>
<td>2</td>
</tr>
<tr>
<td>Magnabosco and Francescon</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Du Bois</td>
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<td>55</td>
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<td>Mondor and associates</td>
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<td>1</td>
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<tr>
<td>Dreyfuss</td>
<td>Plasma</td>
<td>1</td>
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<tr>
<td>Suarez</td>
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<tr>
<td>Curtze</td>
<td>Plasma</td>
<td>3</td>
</tr>
<tr>
<td>Blackman and associates</td>
<td>Plasma</td>
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<tr>
<td>Bauer</td>
<td>Plasma</td>
<td>1</td>
</tr>
<tr>
<td>Marchal and Mallet</td>
<td>Plasma</td>
<td>1</td>
</tr>
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<td>Schleicher and Fahr</td>
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<td>1</td>
</tr>
<tr>
<td>Brass</td>
<td>Plasma</td>
<td>2*</td>
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<td>Erf and Herbst</td>
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<tr>
<td>Churg and Gordon</td>
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<td>Schindler</td>
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<tr>
<td>Bøe</td>
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<td>5</td>
</tr>
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<td>Moss and Ackerman</td>
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</tr>
<tr>
<td>Meyer, Halpern and Ogden</td>
<td>Plasma</td>
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</table>

* (overlapping).
Multiple myeloma have been diagnosed by this method to make a brief survey of available reports of interest (table 2).

Vărădi\textsuperscript{43} reported on 7 cases, 5 of which were considered to be typical plasma cell forms, the other 2 being myeloblastic. The illustrations suggest that they might also be more anaplastic, younger varieties of the myeloma plasma cell.

Of the 6 cases in which Fleischhacker and Klima\textsuperscript{42} obtained sternal aspiration material, five were classified as plasma cell types and one as "Stammzellen myeloma?" The question mark is theirs.

Rosenthal and Vogel\textsuperscript{39} reported on 13 cases, of which all but one were of the "plasma-cell" type. The exception, case 13, was called myelocytic, although 3 per cent of plasma cells were present in the marrow on two sternal aspirations. Two plasma cells pictured had three nuclei apiece and were vacuolated. In this case, three questions may be raised: (1) was this really leukemia with moderately increased plasma cells or (2) was this really multiple myeloma with a severe leukemoid reaction and, if so, would still another sternal aspiration (two were done) have shown a different spread of cells with more "myeloma plasma cells," and (3) would a diagnosis of multiple myeloma be justified in the complete absence of the "myeloma plasma cells"? In the author's opinion the mere fact of a cell's preponderance does not establish a cell type.

Weissenbach and Lièvre,\textsuperscript{118} in the 5 cases which they described, found 3 to be "histiocytoid" in type, and 2 plasma cell-like; again their description of the "histiocytoid" cells, "with eccentric nuclei, nucleoli, basophilic cytoplasm and frequently vacuolated," prompts the speculation that these cells were merely the unrecognized, more anaplastic forms of the "plasma cell."

Erf and Herbut\textsuperscript{40}.\textsuperscript{41} reported 7 cases of multiple myeloma: 4 were of the plasma cell type, 1 was designated as lipoblastic, 1 megakaryocytoid and 1 myelocytic. The myelocytic patient had osteolytic bone lesions alone to suggest multiple myeloma, whereas her age, sex, hepatosplenomegaly, petechiae, marrow (10 per cent myeloblasts) and blood (6 to 15 per cent myelocytes) certainly point strongly to a diagnosis of leukemia. In this instance, then, a leukopenic leukemia is scarcely excluded. The sternal marrow in the case reported as megakaryocytoid "disclosed many typical single or double nucleated plasma cells." It was because of the "many transitions from these to giant cells with as many as 22 nuclei" that it was considered to be megakaryocytoid. The mere hypernucleation of the plasma cells here would seem dubious justification for such a conclusion and certainly the absence of the "many typical single or double nucleated plasma cells" would have made the diagnosis of multiple myeloma itself suspect. The third unusual case involved a man forty-one years old who had bone tumors and anemia and died after a brief illness. No Bence Jones proteinuria was noted and his serum proteins were low. The sternal aspiration examination suggested to the authors a likeness to marrow fat cells though reference was made twice to "many cells that closely resemble plasma cells." It is not clear on just what ground—the presence of bone tumors, "lipoblasts" in the marrow, the resemblance of marrow cells to plasma cells or a combination of these—the diagnosis of multiple myeloma was made in this case.
If on the first two grounds alone, the evidence would seem rather tenuous; if on the third, then the myeloma could scarcely be other than a plasma cell type.

Reviewing carefully, then, the 10 cases noted in which other than a plasma cell type was reported, in the light of the present study as will be subsequently noted, it is seen that one is probably a case of leukemia (Erf and Herbut’s case 5), one is doubtfully multiple myeloma (Herbut’s and Erf’s case 6), one (Rosenthal and Vogel’s case 13) plasma cell myeloma with a leukemoid reaction versus myelogenous leukemia or ‘‘myelocytoma,’’ and a fourth (Herbut and Erf’s case 7) probably a plasma cell type, though not so reported. The other 6 are all reported as immature types, 1 with excess plasma cells, 3 with a description that fits well the more anaplastic plasma cell and another with illustrations which, if accurate, depict ‘‘plasmablasts’’ as frequently seen in this series of sternal marrow examinations.

Haden and Rumsey, in 1940, reported on 16 cases in which sternal aspirations had been done. Individual cases were not reported as such, and hence will not be considered further here.

The difficulties inherent in the establishment of a cytologic diagnosis from tissue sections are evident and are emphasized by the experience of Geschickter and Copeland, Wood, Quinlan and Merrill, and Ulrich. This point gains added weight by the observation of Erf and Herbut’s case 4 which was designated as myelocytic from sections, although the sternal marrow clearly demonstrated that these were plasma cells. Scott and associates noted that ‘‘plasmablasts’’ are not easily distinguished by routine staining methods from any early form of the myeloid or erythrocytic series and that this is probably the cause of many of the errors made by the early workers in interpreting them as myeloblasts and erythroblasts. They also pointed out the unreliability of ‘‘specific’’ plasma cell stains and the oxidase reaction in determining cell type in this disease (as have numerous authors) because of the variableness of the cell to any of these tests.

Churg and Gordon in the same vein stated that ‘‘many cases [of multiple myeloma] have been reported in which the predominant cell was thought to resemble not the plasma cell but the myeloblast. This was true of many elements in our own material. If these cells had predominated, the case might have been called by some an instance of myeloblastic myeloma. However, all transitional forms between these and other cells resembling plasma cells were present. This statement is true in other reported instances. Apparently, many of the so-called myeloblastic cells are variants, perhaps younger forms of the typical cell of multiple myeloma. . . . It seems logical, therefore, to group all the cells under one term, ‘‘myeloma cell.’’’

Doan said: ‘‘A diffuse hyperplasia of cells more or less characteristic of the so-called plasma type make up the new growth . . . the cells may show differing degrees of maturity . . . the plasmablast may be sharply differentiated from the myeloblast, lymphoblast and monoblast by the characteristic filamentous mitochondria (Doan and Lewenstein, 1936, unpublished data).’’ And Jones noted that ‘‘others have reported myelomas composed of myeloblasts, lymphoblasts, lymphocytes and erythroblasts. Apparently this discrepancy is due to the un-
certain identification of these cells in section material. Fleischhacker and Klima point out that since the advocacy of sternal puncture the cells encountered in myelomas have been predominantly of the plasma cell type. Since these multiple myeloma cells may be immature they may present a picture similar to myeloblasts."

B. HISTOGENESIS

Many of the early conceptions of the immediate precursor of the myeloma cell depended on the accepted concept of multiple cell types and many authors have stated that a myeloma cell might arise from a lymphocyte,\textsuperscript{29, 48, 62, 69, 86, 92} lymphoblast,\textsuperscript{45, 46, 51, 52, 63, 66, 69} myeloblast\textsuperscript{45, 48, 51, 52, 63, 66, 69} or erythroblast.\textsuperscript{38, 44, 45, 46, 62, 66, 69} In addition, it has been conceived that the osteoblast\textsuperscript{54} or osteoclast\textsuperscript{53} might be the progenitor of the myeloma cell. This hypothesis has no adherents today and fails entirely to consider extraosseous plasma cell lesions which may clearly precede multiple osseous spread.

The conception of the relationship of myeloma to the erythroblast has developed on very frail evidence, has failed of corroboration with sternal marrow aspiration, and may be dismissed also without further discussion (even though Meyer and associates\textsuperscript{39} noted a confusing similarity between plasma cells and nucleated erythrocytes in their reported case of "plasma cell leukemia"). Since the origin of the plasma cell from the lymphocyte has long been authoritatively advocated, it is not necessary to believe that lymphocytic multiple myeloma exists in order to postulate a lymphocytic derivation for it. This has its adherents.\textsuperscript{29, 138}

Michels,\textsuperscript{139} in a detailed review of the morphogenesis, function and development of the plasma cell in 1931, discussed the early formulation of morphologic concepts, pointed out that amitosis leading to the formation of multinucleated cells is a "frequent phenomenon" and enunciated four main hypotheses of plasma cell origin (listing their proponents). These include: (1) "a histogenous origin from connective tissue cells, including tissue lymphocytes, fibroblasts, clasmotocytes, resting wandering cells, adventitial cells, hemohistioblasts etc." (Piney, Downey, Naegeli, Maximow and others); (2) a hematogenic origin from emigrated lymphocytes; (3) "mixed origin from emigrated lymphocytes (monocytes) or pre-existent tissue lymphocytes," and (4) an origin from immature blood cells (myeloblasts, hemoblasts—erythroblasts, granuloblasts) through aberration or abortion.\textsuperscript{29, 139} Michels also mentioned Maximow's tissue culture work (1922-1923) which "showed that in explants of lymphoid tissue plasma cells develop from local lymphocytes in the course of two days." Jackson, Parker and Eethea\textsuperscript{29} noted the similarity of multiple myeloma to lymphomas and said: "The type cell (plasma) belongs beyond question to the lymphoid series, and the clinical picture finds analogies throughout its course in the pathologic and symptomatic picture of the lymphomata."

In the recent literature, increasingly greater mention is made of the origin of these cells ("myeloma" or "plasma") from the reticulum, to the point now where the hypothesis has gained such widespread acceptance as the statement, "since the disease originates in the reticulum cell\textsuperscript{\textcopyright} Osgood\textsuperscript{110} stated that "it is commonly thought that plasmocytes develop from lymphocytes, but I have never
found any evidence of this from my studies of multiple myeloma, plasmocytic leukemia or marrow or blood cultures. It seems certain that they are a distinct and separate line of cells. Both Scott and associates, and Kracke and Garver, who shared this conviction, cited Doan as holding the belief that the myeloma-plasma cell arises from the reticular cells of the bone marrow and general connective tissue, Churg and Gordon stress the probable origin of the myeloma cells from the reticulum of the bone marrow and cited Klemperer and Rohr (as did Jones) as pointing out that the "plasma cell" of the myeloma is an abnormal hematic cell, the origin of which may be traced to the primitive reticulum cell of the bone marrow. Cappell said, in reporting 2 cases of multiple myeloma: "It might be considered that the abnormal myeloma cells are derived originally from the primitive reticulum cells. Some have differentiated through a myeloma cell of the common type or have even been further transformed into the plasma cell type."

Miller injected tuberculoprotein into the peritoneum of rabbits and observed that the precursor of the plasma cell was the reticular cell and its development could be traced through the blast stage to the typical mature Marschalko-type plasma cell, and finally into the degenerative phase with Russell-body formation. Lowenhaupt examined 12 cases at necropsy and found splenomegaly in all but one. The splenic follicles were separated by wide expanses of plasma cells. Because these germinal centers (and those in the lymph nodes) remained intact even when widely separated by plasma cells, she felt that a hypothesis of lymphoid origin was untenable. She felt that she could detect single plasma cells and clusters of plasma cells hanging from the "reticular framework" into the vascular stream and felt that a "histiocytic origin" was suggested.

Recently, too, Parsons, in a study of irradiated and tumor-bearing mice, arrived at much the same conclusion with regard to the plasma cells in these nodes. She observed that plasma cells develop locally in many inflammatory processes but that in these experimental mice it was systemic response, provoked by an agent acting on lymphoid tissue generally and primarily on the reticulum. Reticulosis was an early and constant feature and occurred coincidently with the disappearance of lymphocytes. She wrote:

Examination has given no evidence of the development of plasma cells from lymphocytes, which may indeed be entirely absent from the glands when plasma cells are abundant and active. Mitosis of lymphoid cells is rarely observed, even in the germinal centres where the reticulum cells appear to be in active proliferation and when karyokinesis of these and of plasma cells throughout the glands is marked. Proliferation of reticulum seems to start at the periphery and to spread inwards to the medulla, the existing plasma cells being in direct contact with these areas and having little relation to the diminishing lymphoid tissue.

In the early stages such glands show strands of branching cells forming a close network and staining more deeply with pyronin than normal reticulum. The nucleus is frequently eccentric. Later a perinuclear pallor develops in many cells, the nuclei of which are more darkly staining and have become more eccentric. . . . Around the hilum the intersinusoidal cords contain few coalescing reticulum cells but only free mature and immature plasma cells. Maximow and Bloom (1918) relate the plasma cell to the hemocytoblast, which they consider identical with the lymphoblast. No evidence has been found that this free mesenchymal cell is the direct
forerunner of the plasma cell, since the cells responsible for the plasmacytosis seen in the glands of the experimental mice appear to be the fixed reticulum cells of the stroma and identical with Maximow’s fixed undifferentiated mesenchymal cells.

Hertzog and Schleicher again stated "that the myeloma cells arise from the reticulum. This slide shows myeloma cells arising from vascular adventitial cells considered undifferentiated reticulum cells." Gordon and Schneider noted that Kracke and Garver, and Curtze had suggested that plasma cells originate from primitive reticulum cells. They then said: "The changes found in the hematopoietic organs in this case lend support to the view expressed by Kracke and Garver. At least strong presumptive evidence of this is supplied by the atypical reticulum cell hyperplasia found in the marrow, spleen and lymph nodes, and the transitional forms between reticulum cells and plasmablasts." Closely related to the concept of reticulum cell origin is that concept which holds that either the hemocyto- blast or the hemohistioblast is the parent cell.

C. DEGREE OF MALIGNANCY

In more than 230 references, only a handful of observers have commented on such aspects of the disease as they believed influenced the prognosis or mentioned factors which might be so implicated. In Morison’s fourth case, the disease was of brief duration and was "relatively anaplastic." Kolodny noted that "among plasmacytomata one encounters a small and large cell variety; the latter are said to be of more rapid growth and somewhat worse prognosis." Caylor and Nickel suggested that the "myelocytic" myeloma is more malignant than the plasma cell type. Gordon and Schneider’s case showed a very bizarre, anaplastic and pleomorphic marrow picture. The patient survived only about six weeks from the onset of symptoms. Mallory said: "I have never seen a bone marrow with so many immature plasma cell elements ... suggesting something very acute and very malignant." Moss and Ackerman remarked about the myelomas with large numbers of circulating myeloma cells: "Thus the readiness with which plasma cells tend to enter the blood stream should be a measure of malignancy. Such a statement seems logical, but it has not been proven." Hertzog and Schleicher in presenting 3 cases of plasma cell myeloma at a pathologic conference, stated that "the solitary types are of a high degree of malignancy," and "one can estimate to some extent the clinical degree of malignancy by the amount of secretory activity of these cells."

Nothing definite can be concluded from reviewing these brief remarks but the suggestion is present that pleomorphism, anaplasia and cytologic immaturity are associated with a shorter clinical course.

REVIEW OF CASES

In the normal bone marrow, plasma cells average approximately 1 per cent of the leukocytic series. In diseases other than multiple myeloma, such as chronic inflammations, granulomas, measles, roseola infantum, carcinoma, aplastic anemia, infectious mononucleosis, Boeck’s sarcoïd, cirrhosis, lymphogranuloma
BONE MARROW IN MULTIPLE MYELOMA

inguinale, monocytic leukemia, periarteritis nodosa and so forth, plasma cells may occur in excess numbers in the blood and bone marrow. Ordinarily this does not give rise to confusion with multiple myeloma, particularly if the diagnosis is clinically apparent. However, in an indeterminate situation, in which the bone marrow smear is expected to be of positive diagnostic value, some question may arise whether these excess and often abnormal plasma cells are not a part of a myelomatous process. This can not always be settled unequivocally on one examination, particularly negatively. However, in the great majority of cases little doubt remains.

The type of cell customarily found in smears of sternal marrow in multiple myeloma most resembles, of the normally occurring bone marrow elements, the plasma cell. The characteristics which distinguish the myeloma cell from the normal plasma cell have been described frequently in the past, and there is little that is new to be added to these descriptions. Nevertheless, setting down here again the observations made in these cases may prove useful in re-emphasizing the specificity of this picture as a pathologic, as well as a clinical, entity.

Sternal marrow aspirations in 51 cases were studied, 1 case twice with a three year interval, and 20 more subsequently reviewed after this study had been completed. These latter 20 cases will not be included except as has otherwise been noted.

The first sternal aspiration on a patient who had multiple myeloma was performed at the Mayo Clinic in 1939. In that year 2 cases were noted; in 1940, 5 cases were observed; in 1941, 3 cases; in 1942, 4 cases; in 1943, 6 cases; in 1944, 8 cases; in 1945, 15 cases; in 1946, 19 cases, and in 1947, at the time of this report, 9 cases. Follow-up reports were sought and obtained only on those patients studied who had been examined at the clinic prior to January 1, 1946.

GENERAL CONSIDERATIONS

The size of the cells found varied approximately from 12 to 60 microns, considering the longest diameter of the cell, multinucleated cells not included. This variation occurred within cases as well as between cases. In some instances a marked uniformity of size and shape was the rule (fig. 1), in some cases moderate variation occurred and in still others, very bizarre appearing cells (fig. 2) were observed, varying greatly in size and shape, with, however, almost indistinguishable gradations between stages.

The cytoplasm was abundant as a rule, even in the very immature cells, usually equaling the size of the nucleus and often exceeding it fourfold to fivefold. It stained deeply basophilic, when the usual Romanowsky stains were used, often staining more deeply at the periphery to form a sort of "rim" (fig. 3). In color it varied from a deep, slaty, cloudy blue to a rather bright and somewhat clearer blue. The cytoplasm was somewhat granular or pock-marked in appearance and not a clear homogeneous medium as is seen in the lymphocyte. Occasionally a perinuclear light, clear area or Hof was seen but this was inconstant. The character of the cytoplasm was one of the most persistently uniform and striking features of these
cells which held them together as a class, and impressed one with their similarity
to the normal plasma cell.

The nucleus was often eccentric and, in some cases, almost constantly so. Here
again the relationship to the plasma cell was emphasized. However, at this point,
nuclear similarity usually ceased. Most nuclei had a finer chromatin pattern than
the plasma cell, and this usually contrasted sharply with the parachromatin. A
few had well-differentiated nuclei with heavy chromatin blocking (fig. 1). Among
the rest were fine reticular patterns (fig. 4), diffuse stranded chromatin (fig. 3), or a
granular chromatin background surrounding islands of condensed chromatin
"dots" (fig. 5). As the cellular differentiation decreased, the tendency to eccen-
tricity seemed to be proportionately reduced, though this still did occur in obvi-
ously immature or poorly differentiated cells.

One, and occasionally more, large clear nucleoli were seen in the nuclei of most
myeloma-plasma cells. These usually stained a pale sky-blue, lighter than the rest
of the cell, although occasionally of a deeper blue. In all but two of the 51
cases studied there were more than 5 per cent of nucleolated myeloma-plasma (per
100 myeloma) cells. In six instances, nucleoli were noted in virtually all of the mye-
ломa-plasma cells, and in about 57 per cent (29 of 51) of cases there were nucleoli
in at least half of the myeloma cells present.

As might be expected, if amitosis were as common in myeloma-plasma cells as it
is in normal plasma cells,139 many multinucleated cells would be seen. This was so.
At least one multinucleated cell was noted in each case studied, and the frequency
rose to more than 5 per cent of all myeloma cells present. (The number of nuclei
per cell was noted to exceed twelve, although two to three were more usual.) This
tendency to "giant cell" formation has led to various diagnostic difficulties, as these hypernucleated cells may give rise to the belief that they are megakaryocytes, 

or (in tissue) tumor giant cells, or Sternberg-Reed cells. Mitoses were not common, but in those cases in which they were seen easily, the outlook was grave.

In all but 2 cases (rarely in 2 others) "cytoplasmic extrusions" were noted dis-

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Fig. 1a and b. These illustrations were both made from the same smear on the same patient and demonstrate vividly the degree of anaplasia and pleomorphism which may exist in the bone marrow in this disease (X 735).
seminated freely through the marrow field. These extrusion bodies were identical in all respects with the cytoplasms of the myeloma cells. They stained alike, had

![Image](image_url)

**Fig. 3.** Myeloma cells here constituted 2.5 per cent of leukocyte elements; lymphocytes 41 per cent. Note "rim" at periphery of myeloma cell (X 900).

the same internal "granularity," contained vacuoles when the myeloma cells did and even contained Russell bodies in one case in which they were numerous. In
several cases they seemed to arise from buds or pseudopodia extending from the myeloma cell. These same extrusions have been seen in the peripheral blood in such cases. That this has special diagnostic value, however, is doubtful as the same phenomenon may be seen in other conditions, particularly the lymphocytic and mono-
cytic leukemias. In this connection, it is of some interest to note that Sabin is quoted by Lowenhaupt as showing that release of globulin by clasmatocytes is associated with the shedding of cell cytoplasm into the blood stream. However, despite the attractive possibility that it might, no relationship could be noted between the rate of occurrence of these cytoplasmic bodies and the presence of Bence Jones proteins in the urine, or the degree of elevation of the serum proteins.

Among the common degenerative changes, so-called, that occur in plasma cells, vacuolization was noted often in the myeloma-plasma cells. In some instances, cells were literally riddled with vacuoles, and in at least two instances the nuclei were involved as well. An effort to stain such nuclear vacuoles with amyloid stains met with negative results in a recent case in which this was attempted. Appreciable vacuolization was noticed in more than half of the cases (29 of 51). Russell bodies (fig. 6) were not as numerous, however, even in those cases in which they were seen, although there were two instances in which this was not so. They were observed in 11 cases altogether, a trifle more than a fifth. It may be mentioned in passing that as recently as 1937, it was stated that Russell bodies had not been demonstrated in the myeloma cell.

As might be expected, rouleaux formation in the sternal marrow aspiration was noted with approximately the same frequency as it was in the peripheral blood, 78 per cent.

An attempt was made to correlate the cytologic findings with the presence of Bence Jones proteins in the urine, according to Hertzog and Schleicher's method, or any other that might suggest itself. No consistent cytologic property was noted, the occurrence of Russell bodies was without significance, as was the presence of vacuoles, or cytoplasmic extrusions. The state of cellular differentiation likewise was immaterial.

Schleicher suggested that during the “phase of growth” in which the cells are uniform in size and the cytoplasm stains deep blue no Bence Jones protein will appear in the urine. On this basis he correctly predicted that Bence Jones proteins would be absent from the urine in a case described. “When the cells secrete globulins they become larger and vary in size. The cytoplasm appears to be vacuolated and stains irregularly.” Disappointingly, in several of our most monotonously uniform cases Bence Jones proteinuria occurred as it did in the case with the clearest, bluest cytoplasm. Conversely in some of the cases with large, pleomorphic cells with deep, irregularly staining and vacuolated cytoplasm, Bence Jones proteinuria was not present. Hence it has been impossible at present to duplicate Hertzog and Schleicher’s results.

**CELL TYPE**

Myeloma-plasma cells were seen in every case, now totaling 71, without fail and consequently a diagnosis of plasma cell myeloma was made in each instance. There were no exceptions. However, it should be noted carefully that the myeloma-plasma cell was not the predominant marrow cell in every case. In fact, it was not the predominant cell in more than a quarter, or 13, of the cases. Lymphocytes were present in equal or greater numbers in 11 of these 13 cases. Figure 4 shows the char-
acteristic myeloma-plasma cell which was present in a smear in which 41.5 per cent of the cells were lymphocytes, while only 2.5 per cent were myeloma cells.

Fig. 7. Fixed Tissue Section from Bone Marrow. Same Case as Fig. 2

Fig. 8. Typical myeloma-plasma cells from a case interpreted as Hodgkin's disease on the basis of examination of fixed tissue (X 850).

Of these, 39 of the 100 myeloma cells enumerated had nucleoli. This patient was a man, aged 50, who had suffered from low back pain associated with progressive
weakness and paralysis of his legs for a year prior to his admission to the clinic. Osteolytic lesions were noted in the roentgenograms of his thorax, thoracic and lumbar segments of the spinal column, pelvis and femora with compression of the eleventh and twelfth thoracic vertebrae. No test of his urine for Bence Jones pro-

**Fig. 9. Binucleate "Myeloma" Cell in Sternal Marrow (X 1,000)**

**Fig. 10. Typical "myeloma" cell from marrow, same case as figures 9 and 11 through 16. Prominent, single nucleolus (X 1,100).**
BONE MARROW IN MULTIPLE MYELOMA

Fig. 11. More mature "myeloma" cell shows definite plasma cell characteristics now. Shrivelled nucleolus still can be made out at the 5 o'clock position (X 1,120).

Fig. 12. Cell very suggestive of reticulo-endothelial cell. The nuclear pattern is fine and skeinlike; there is no blocking of chromatin nor any evident tendency to condensation. The cytoplasm is pale. The outline of a large nucleolus may be seen. This and the following four cells were noted in the peripheral blood of the patient whose sternal marrow was illustrated in the preceding three figures (X 1,000).

In 4 of the 11 cases mentioned, the lymphocytes exceeded the myeloma-plasma proteins was made. The concentration of protein was 10.2 Gm. per 100 cc. of serum and albumin-globulin ratio was 1:3.9. The patient died at home four months later.
cells by less than 5 per cent, which actually means that they occurred with approximately equal frequency in these cases. In the other 2 of the 13 cases, nucleated erythrocytes were present in numbers approximately three times as great as that of any other cell. In these 2 cases, characteristic myeloma-plasma cells were present to the extent of 16.5 per cent and 42.5 per cent of the leukocyte line.

The implications of this in the examination of fixed tissue should be apparent; namely, the possibility of designating the case as one of lymphocytic, erythroblastic, or myelocytic myeloma (here the oxidase reaction would be positive) on the basis of the predominant cell type.

Another of the hazards of tissue diagnosis is exemplified by the following case: A man sixty-five years old presented himself at the clinic with a three week history of back pain which he first noticed after climbing a fence. Rapid progression and deterioration ensued until the patient was disabled by his pain at the time of admission, just three weeks after its onset. He had been "completely well" prior to that time. An intensely tender tumor was noted medially in his right clavicle and roentgenographic examinations of his skull, thorax, and spinal column revealed multiple discrete osteolytic lesions. Bence Jones proteins were noted in his urine. His serum proteins were normal and the concentration of urea was 110 mg. per 100 cc. of blood. He died at home within the following week.

Examination of sternal marrow smears from this patient showed an extreme degree of pleomorphism (fig. 1). Eighty-five per cent of the myeloma cells present were immature or poorly differentiated and virtually all contained nucleoli. Although the more differentiated cells (15 per cent) in the smear (fig. 1.2) clearly established the identity of these cells, sections of tissue secured at the time of sternal aspiration would have been called "myeloblastic" (fig. 1), if, indeed, a diagnosis of multiple myeloma had been sustained at all.

More recently a 48 year old man appeared at the clinic with a four month history of thoracic and back pain, and severe anemia. His liver was enlarged and he had axillary adenopathy. On roentgenography his skull, ribs and spinal column were observed to be involved with multiple punched-out osteolytic lesions. The concentration of hemoglobin was 4.35 Gm. per 100 cc. of blood; erythrocytes numbered 1,390,000 and leukocytes 3,800 per cubic millimeter. Excessive rouleaux formation and promyelocytes were seen in smears of his peripheral blood.

Albuminuria was graded 2 to 3 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition), but the urine was negative for Bence Jones protein on two occasions. The erythrocyte sedimentation rate was 172 mm. in an hour (modified Westergren) and the total proteins were 9.2 Gm. per 100 cc. of serum. He had an albumin-globulin ratio of 1:1.51, and a concentration of urea of 81 mg. per 100 cc. of blood.

Sternal aspiration revealed a typical plasma cell myeloma of a poorly differentiated type with 30.5 per cent of myeloma-plasma cells with 2.5 per cent multinucleated (fig. 8). However, at necropsy, the examination of the fixed tissues presented a picture which was interpreted by the pathologist as being that of Hodgkin’s disease, including a heavy reticulum and “Dorothy Reed” or “Sternberg-Reed” cells (that is, multinucleated cells with two or three nuclei).
It may be seen, then, that though the degree of plasma-cellular differentiation may vary strikingly between cases and even within cases, a strong bond of cytologic similarity exists between all cases, and the transition from cell to cell can be observed to proceed through scarcely perceptible gradations. Three important pitfalls to proper diagnosis were recognized: (1) immaturity, (2) multinuclear plasmagiant cells, and (3) lack of preponderance of myeloma cells in some cases.

HISTOGENESIS

One looks to the more differentiated cells in a tumor to indicate its destination, and to the least differentiated cells to reveal its origin. In the immature myeloma cell, a granular, finely reticular (leptochromatic), skeinlike chromatin is frequently encountered. In certain cases (fig. 4), seen even in the late phases, it is strikingly apparent. This in itself would seem to be strong support for the hypothesis that the myeloma cell is derived from the reticulum, as has been so often stated by others and noted earlier in this paper.

Further strengthening this conclusion are the findings in the following case which I believe is, in many ways, unique. When first examined in the spring of 1940, the patient, a woman 60 years old, had moderate hepatosplenomegaly, osteolytic lesions in her skull and extremities (the only regions of which roentgenograms were taken), repeatedly positive reactions for Bence Jones proteinuria, albuminuria, grade 4, moderately severe anemia and the peripheral blood picture of...
leukemia. A sternal aspiration at that time showed 11.5 per cent of characteristic myeloma-plasma cells (figs. 9, 10 and 11), and a diagnosis of multiple myeloma was made. A review of the peripheral blood smear taken at that time shows characteristic myeloma cells present as well as myeloid immaturity (leukemoid reaction). Subsequently, however, the patient's liver was found to "fill her whole abdomen" and the peripheral blood contained many cells almost indistinguishable from (if, in fact, they were not) reticulo-endothelial cells. These final developments were so marked as to cause the clinician to change the final diagnosis to reticulo-endotheliosis.

Repeated careful reviews of all the slides made on this case from the marrow and peripheral blood emphasize that myeloma-plasma cells were present from the start to the finish and that an imperceptible transition existed between the most reticular cell, the completely characteristic myeloma cell (figs. 12 to 16) and the well-differentiated (though atypical) plasma cell. Clinically, this case fitted best a diagnosis of multiple myeloma in a "plasma cell leukemia" phase. Histologically, the suggestion was almost inescapable that this was a multiple myeloma; that multiple myeloma arose from the reticulo-endothelial cell and that here, in a profound instance of such a disturbance, in which the marrow elements were being liberated into the peripheral blood, the almost completely undifferentiated reticulo-endothelial cell itself was finding its way into the circulation along with its more differentiated counterpart, the myeloma-plasma cell. No other explanation so well satisfies the known facts about multiple myeloma, the experimental studies on the origin of the plasma cell and the very unusual findings in the case mentioned.

Fig. 14. Here the trend becomes more pronounced. Three definite areas of condensation of chromatin are visible in the nucleus. Note also that the cytoplasm is darker and contains vacuoles (X 1,000).
ESTIMATION OF DEGREE OF MALIGNANCY

With the methods used, it was observed that those cases in which there was a marked degree of pleomorphism, often associated with frequent mitoses and notable immaturity, bore the poorest prognosis. Ten cases fell into this category. None of the patients in this group survived longer than twelve months after the onset of symptoms and the mean was 6.3 months. The patient who survived the longest in this group, twelve months, had the most uniform picture, despite the high percentage of myeloma cells present and the reticular, leptochromatic character of the nucleus (fig. 4) in almost all of the cells. The case of the 65 year old man previously described (fig. 2) most strikingly portrays this group. The total duration of this patient's disease from the onset of symptoms was one month and his marrow was most anaplastic and pleomorphic.

At the other end of the scale were the 7 cases in which uniform, mature-appearing plasma cells comprised almost the entire number of myeloma cells present, 96 per cent or more. Of the 7 patients, 3 died at the end of forty-two, sixty, and seventy-one months, respectively, and 4 were living when last heard from at the end of twenty-four, twenty-six, eighty-eight and sixty-seven months.

Typical, perhaps, of this group of patients is the case of a woman, 40 years of age, who was first seen in 1941, seven months after the onset of pain in the lower part of her back. She had a palpable liver. Roentgenograms revealed multiple punched-out osteolytic areas in her skull with osteoporosis involving her spinal column. Bence Jones proteinuria was present. Serum proteins were not determined. She was moderately anemic, the concentration of hemoglobin being 8.4 Gm. per 100
cc. of blood and erythrocytes numbering 3,410,000 per cubic millimeter of blood, and she had mild leukocytosis, the leukocytes numbering 11,303 per cubic millimeter of blood. There was albuminuria, grade 3 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition) and a concentration of urea of 38 mg. per 100 cc. of blood.

The patient’s only treatment consisted of orally and parenterally administered calcium salts prescribed by her veterinarian brother. Two years later she wrote that she felt better than she had in ten years and was mowing her own lawn. When heard from in 1945, fifty-eight months after the onset of her illness, she was hospitalized for a pathologic fracture of her left hip. She had had no treatment whatsoever in the preceding two years. She was last heard from in April, 1948.

Fig. 16. At this point a moderately well-differentiated myeloma-plasma cell emerges. It will be noted that there has been a gradual loss of cytoplasm, but in each instance the nucleus has tended to remain eccentric (X 1,000).

eighty-eight months after the onset of her illness, and was still feeling fairly well. Ninety-nine per cent of this patient’s myeloma-plasma cells were considered to be mature (fig. 1).

Of the remaining patients, 2 could not be traced and 2 were still living. The duration from the onset of symptoms regarded as referable to the disease varied from five to forty-four months. As was anticipated, the trend was toward a longer survival among those patients in whom the greater number of myeloma cells was mature. Of this intermediate group of patients, the following case history is probably most illustrative.

A man, 45 years old, was first seen at the clinic in February, 1945, with a history of anemia and weakness of one and a half years’ duration. For the preceding six months, he had manifested a marked tendency to bleed from his nose, gums, and
I012. BONE MARROW IN MULTIPLE MYELOMA

![Graph showing bone marrow findings in multiple myeloma]

Very immature cells present

Cells virtually all mature

Duration in years

Fig. 17. The column at the left represents a differential count of one hundred myeloma cells on each case followed for at least a year. The bars immediately to the right indicate the duration of the disease in the corresponding case from the onset of symptoms.

<table>
<thead>
<tr>
<th>Survival from onset, years</th>
<th>Grade 1*</th>
<th>Grade 2</th>
<th>Grade 3</th>
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<tr>
<td></td>
<td>Living</td>
<td>Dead</td>
<td>Living</td>
</tr>
<tr>
<td>0-1</td>
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<td>1</td>
<td>4</td>
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<tr>
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</tr>
<tr>
<td>5-6</td>
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<tr>
<td>Total</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* Graded 1 to 3 on the basis of 1 being the least malignant and 3 being the most malignant.
† Untraced.
lacerations of his skin. Osteolytic lesions were demonstrated in his roentgenograms. Bence Jones proteins were found in his urine and his total serum proteins were 11.8 Gm. per 100 cc. of serum with an albumin-globulin ratio of 1:2.19. The erythrocyte sedimentation rate (modified Westergren method) was 151 mm. at the end of an hour. Stem cells were occasionally seen in smears of the peripheral blood and there was excessive rouleaux formation.

The patient had no treatment other than local radium applications for severe epistaxis and died ten months later. Thirty-six per cent of the myeloma cells were of the moderately immature type, and the other 64 per cent were rather well differentiated.

All of the foregoing cases are summarized in table 3, and the duration of the disease in each case is graphically portrayed in figure 17.

It will be observed that several patients of the last-mentioned intermediate group lived only a very short time after the onset of symptoms. Since it is perfectly obvious that the onset of symptoms and the onset of the pathologic process in this disease do not correspond, it was not surprising to note some lack of correlation, and it was in this area that the value of the method used was most limited. It may also be mentioned, though this too, should be apparent, that the discrepancy between the onset of the disease and the onset of the initial symptom is not a constant. However, as will be noted from figure 17, the differential cytologic picture does bear a rather significant relationship to the expected duration of the disease in the group as a whole.

SUMMARY AND CONCLUSIONS

Generalizing, it can be said that the pathologic cells seen in smears of the bone marrow in multiple myeloma resemble the plasma cell and vary from the very anaplastic and immature cell to the well-differentiated and almost characteristic plasma cell.

The feature which the "myeloma" cell shares with the plasma cell is the abundant, granular, basophilic cytoplasm which tends to be fragile and undergo the same degenerative changes in each; namely, the formation of Russell bodies and vacuolization. Fairly frequently a perinuclear clear area or Hof is present and the nucleus tends to be eccentrically placed. Cytoplasmic extensions or pseudopodia may also be seen in either case, but they occur more often and more dramatically in instances of multiple myeloma. Multinucleated cells are commonly seen.

In addition, myeloma-plasma cells will often have a large clear nucleolus and a leptochromatic nucleus and will exhibit a tendency to the formation of isolated areas of condensed chromatin. Cytoplasmic extrusions, free cytoplasmic bodies, occasionally complete with Russell bodies and vacuoles are almost universally present.

All cases were of the plasma cell type; there was no exception. In these cases, the myeloma-plasma cell constituted from 2.5 to 96 per cent of the leukocytic elements present. The opinion was expressed that all so-called types of multiple myeloma are merely variations in differentiation of this same cell.

It was noted that anaplasia, hypernucleation and lack of plasma cell predomi-
nance in certain cases were diagnostic pitfalls. Additional evidence was adduced to confirm the reticulo-endothelial origin of the myeloma-plasma cell. It was further observed that certain prognostically valuable information could be gleaned from a careful review of the cytologic characteristics in these cases.

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