MONOCYTIC LEUKEMIA

A Case Report Illustrating Variations in the Clinical Picture

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The subject of monocytic leukemia is beclouded with controversy and unsolved biological, cytological, and clinical problems. The full understanding and solution of these questions can be furthered by the recognition of the variegated features of this disease. Conversely, failure to appreciate this aspect leads to erroneous conclusions and apparently irreconcilable divergence of opinion. Thus, a survey of the literature uncovers a variety of interpretations that are frequently diametrically opposed. We believe that this paradox is, in part, due to failure to appreciate fully the natural history of monocytic leukemia.

Although most authors agree that monocytic leukemia is a distinct entity, this has not been universally accepted. Myelocytes and immature forms resembling myeloblasts may be found in monocytic leukemia and, conversely, the transient or persistent appearance of monocytes in myelogenous leukemia has been reported frequently. Naegeli, Rosenthal, and others deny the existence of monocytic leukemia per se and admit only a monocytic phase of myelogenous leukemia. Naegeli believed the monocytosis in myelogenous leukemia is a "reactive monocytosis," while Hittmair suggests that it is a "mesenchymal reaction." Campbell, Henderson, and Croom, on the other hand, explain the myelocytic reaction during monocytic leukemia as an "irritative phenomenon (myeloid phase)" secondary to monocytic infiltration of the bone marrow. This antithetical argument, in which both sides utilize the same line of reasoning to support their views, stems primarily from the obscure origin of the monocyte and the lack of knowledge concerning its immature precursors (Jaffe). Thus, in 1934, only 21 years after the initial report of monocytic leukemia by Reschad and Schilling-Torgau, Forkner could enumerate 19 views as to the probable source of the monocyte.

The theories concerning this cell's origin fall into three main groups. Naegeli supports his concept that monocytic leukemia is a form of myelogenous leukemia by denying the existence of the monoblast and by declaring that the cell in question is a variant of the myeloblast. This cell he terms a para-myeloblast, a view which has secured considerable support. On the other hand, many authors believe that the monocyte can be traced back to one or more components of the reticulo-endothelial system (RES). Thus, either the reticulum cells or the endothelial cells individually have been incriminated by some writers, while others have felt that all parts of the RES can contribute to monocytopoiesis. The opinion is expressed frequently that the RES produces an immature cell, the hemohistioblast (which is identical with the monoblast), and that this cell subsequently...
develops into a monocyte. This immature cell is not identical with and does not resemble the other direct derivative of the RES, the histiocyte (macrophage).\textsuperscript{10,11,27} Other writers prefer to consider a stem cell as precursor.\textsuperscript{6,27,41} In a later publication, Doan and Wiseman\textsuperscript{14} state that the general, loose, reticular mesenchymal connective tissue is the site from which the monocytes develop. To a certain extent this opinion is shared by Bock and Wiede\textsuperscript{4} and Jaffe,\textsuperscript{24} who believe that fibrocytes may develop into monocytes. Jaffé\textsuperscript{24} considered this tissue to be an undifferentiated, blood-forming, germinal system which is not identical with the RES but which represents mesenchyma, a concept which concurs with the theory of Doan and Wiseman.\textsuperscript{14} Campbell, Henderson, and Croom\textsuperscript{4} also invoke the stimulation of a stem cell which differentiates either into monocytic or myelocytic cells.

An additional difficulty in securing a precise definition of monocytic leukemia is found in the indefinite descriptions of the histologic changes in this disease. Full use of supravital and differential staining technics has not been the rule. Jaffé\textsuperscript{24} states that many authors do not differentiate between stem cells and monocytopoietic cells nor do they draw a distinct line between myeloid hyperplasia and metaplasia. He and others, for instance, have observed erythrophagocytosis in the peripheral blood in the monocytic phase of myelogenous leukemia, while DiGuglielmo\textsuperscript{12} emphasizes that the cells of monocytic leukemia never contain red cells, cellular debris, or iron pigment; this is a typical lack of agreement which is reproduced so frequently in the literature.

While many authors state that monocytes and promonocytes are oxidase positive, there is no unanimity of agreement concerning this reaction. Foord, Parsons, and Butt\textsuperscript{17} failed to observe a positive oxidase in 3 cases. Campbell, Henderson, and Croom\textsuperscript{4} found the peroxidase reaction to be positive in only a minority of the cells; it was very fine and not the coarse, gross reaction seen in myelocytes. They thought that these cells resembled the blood histiocytes of Dameshek rather than true monocytes. Osgood\textsuperscript{14} did not believe that the peroxidase is of any value in differentiating monoblasts from myeloblasts or lymphoblasts and felt that the oxidase-positive granules found in monocytes are, in reality, engulfed inclusions of degenerating granulocytic cells. Doan and Wiseman\textsuperscript{14} considered the oxidase-positive granules in monocytes to be different in location and degree from those seen in the granulocytic cells.

It should be pointed out also that various authors admit the considerable difficulty encountered in distinguishing and identifying the various cells under discussion. Merklen and Wolf\textsuperscript{29} state that the only certain way they could identify the monoblast was by the presence of large numbers of monocytes. Isaacs\textsuperscript{23} thought that finding all gradations between monoblasts and monocytes was helpful in identifying the various cells. The fact that monocytic leukemia is a relative newcomer to the leukemias also indicates the difficulty in cytologic differentiation.

To establish some degree of order in this otherwise chaotic and contradictory mass of information, Gittens and Hawksley\textsuperscript{19} presented a classification of leukemic monocytosis based on the segregation into one group of those cases showing specific involvement of the RES or cases showing a generalized monocytic infiltration; the cases of monocytosis with the histological features of myelosis were placed in
another group. Using as their criteria the characteristic alterations of the reticulum in relation to the predominating blood cell, Campbell, Henderson, and Croom classified reported cases into those showing (a) hyperplastic reticulum without blood monocytes; (b) hyperplastic reticulum with increase in blood monocytes; and (c) no particular tissue or reticulum formation but demonstrating purely blood cell differentiation into monocytes and granulocytes.

The most popular classification at the present time is that of Downey, who divides monocytic leukemia into two main groups. The differentiation is based on (a) the derivation of the predominant cell, (b) the distinguishing characteristics of this cell, and (c) the histopathologic changes which occur in the blood-forming organs. The first group he terms the Naegeli type, since it is considered a variant of myelogenous leukemia, a view first expressed by Naegeli, who favored a myeloblastic origin of the monocyte. In this form transitional stages between myeloblasts and monocytes may be observed in blood and bone marrow. Often this type terminates without significant alterations in the blood picture. At autopsy, infiltration of large mononuclear cells unassociated with hyperplasia of the reticulum can be found in the hematopoietic organs. A small percentage of cases terminate with the picture of myelogenous leukemia with characteristic changes in the blood-forming organs.

The second, or Schilling type, on the other hand, shows transitions between cells of the RES and monocytes. This is associated with systemic and excessive hyperplasia and proliferation of the reticular tissue in blood-forming organs, with differentiation into monoblasts and the appearance of reticulo-endothelial cells, monoblasts, and monocytes in the blood. Because of this relationship, the terms "reticuloendotheliosis," "reticulosis," and "leukemia reticuloendotheliosis" have been used synonymously with monocytic leukemia by some authors, while others distinguish "leukemic or aleukemic reticuloendotheliosis" from "nonleukemic reticuloendotheliosis." Downey, Osgood, and others believe that these terms should not be used to denote monocytic leukemia.

Baserga introduces a line of reasoning in this problem which perhaps may serve to breach the schism. He states that the appearance of an erythroblast in myelogenous leukemia does not make this an erythro-myelogenous leukemia; therefore, the presence of myelocytes in monocytic leukemia does not necessitate the diagnosis of monocytic-myelogenous leukemia. It is still monocytic leukemia.

The hematologic differentiation of the Schilling type may be quite difficult from those instances of symptomatic, transient monocytosis due to sepsis lenta, in which an increased number of monocytes and hyperplasia of the RES are found. In instances of reticuloendotheliosis due to intoxications and granulomatous reactions (syphilis, tuberculosis, Hodgkin's disease, and lupus erythematosus), a marked leukemoid monocytic reaction may be encountered. Doan and Wiseman have indicated a possible relation between the monocytosis in Hodgkin's disease and that of monocytic leukemia. Ewing states that many authors have associated monocytic leukemia with tuberculosis. Rosenthal and Abel have indicated an allied phenomenon—leukopenic infectious monocytosis sometimes seen in agranulocytosis.
The literature depicting the clinical features is likewise contradictory. Forkner, Dameshek, Mitchell, Osgood, Campbell, Henderson, and Croom, and others have stressed the striking frequency of tumefaction of the gums and the presence of ulcerative mouth lesions in monocytic leukemia. On the other hand, Watkins and Hall, Wintrobe, Jaffe, and others do not regard these gum changes as characteristic or exclusively representative of this disease. The data of Watkins and Hall may clarify this divergency, however, inasmuch as 3 out of 9 acute, and 2 out of 14 chronic Naegeli types showed gum involvement in contrast to the complete absence of this change in all of the 6 patients of Schilling type. Doan and Wiseman originally believed that there is no clinical syndrome which is pathognomonic of monocytic leukemia and which can differentiate it from other types; however, recently they have reversed their previous stand and feel that gum changes are typical of this disease. Watkins and Hall affirm that there is no essential clinical difference between this and other leukemias.

The course of the disease is usually acute. Jaffé states that "true chronic monocytic leukemia has not yet been described, and I think that when a case of monocytic leukemia lasts long enough, it sooner or later turns into a myelosis." Naegeli also believes that "it [monocytic leukemia] is a temporary variant of myelogenous leukemia, into which it passes unless death intervenes." In Osgood's series of 147 cases, 77 per cent (acute group) lived six months or less, 13 per cent existed from six months to one year (subacute group), and only 10 per cent (chronic) lived more than one year. In Watkins and Hall's series there were 23 of the Naegeli type, with duration from five weeks to six years, while the 6 Schilling types lived from seven weeks to twenty-seven months.

Sex predilection in this disease seems to be agreed upon. Osgood noted that over two thirds of his cases occurred in males, a relationship which has also been mentioned by others. There is some tendency to remission in acute monocytic leukemia, as Campbell, Henderson, and Croom have indicated. The incidence of this disease is calculated at 3 per cent to 9 per cent of all leukemias by Osgood, and Rosenthal and Harris suggest that this relative incidence is about that of the various types of cells in normal blood.

The differential diagnosis of monocytic leukemia, especially in the subacute stage, where atypical cases are more likely to be found, poses many difficulties. The group of cases displaying a normal or leukopenic white count and showing atypical, immature forms of monocytes, nucleated erythrocytes, and myelocytes requires intensive study and prolonged observation for eventual clarification. The degree of anemia has been noted frequently to be more severe and hemorrhagic phenomena are more likely to occur in such cases than in typical instances of chronic or subacute leukemia of other types. The differential diagnosis between monocytic leukemia and agranulocytosis, purpura, aplastic anemia, splenic neutropenia, splenic panhematopenia, and other leukemias often will depend solely upon the results of bone marrow examinations. The presence of "reactive" or "irritative" phenomena, as mentioned above in connection with "mixed" types, or the leukemoid reaction in those nonleukemic states of inflammation or intoxications, must be considered and evaluated in the differential diagnosis.
MONOCYTIC LEUKEMIA

In the last analysis, the diagnosis must be established by the morphological characteristics of the predominating cell as revealed by the fullest utilization of all applicable laboratory technics. These should include daily, complete blood counts, examinations of fixed and supravital smears of the peripheral blood, and frequent bone marrow aspirations. Biopsy of lymph node and skin nodules frequently offers valuable information, especially when Giemsa, azure-eosin, and reticulum stains are used. The oxidase test should be employed in fresh smears and frozen fixed tissues. Darkfield observation often clarifies the position, degree, and type of cytoplasmic granules within the monocytoid cell. We do not agree with Hall or Bloom as to the unreliability of the supravital technic in identifying these cells, although we agree that one should not attempt to establish the diagnosis by this single technic alone.

The purpose of the foregoing discussion has been to indicate the difficulty in delineating the clinical syndrome and the cytologic characteristics of monocytic leukemia. Aside from conflicting theoretical concepts, some of the confusion is due to incomplete reports in which necropsy descriptions are lacking or are sketchy, and the histologic analysis has failed to utilize the differential staining technics described above. In addition, continuity of observation of this disease, from onset of symptoms to eventual death, has often been lacking and, furthermore, the impression is gained that some observations are not as devoid of preconceived convictions as is desirable. We believe, as we shall illustrate by the case to be presented, that prolonged, intensive, clinical and laboratory observation will lead to an appreciation of the vagaries of this disease. Such observations have led us to the belief that some of the discrepancies in the literature can be synthesized into an organically unified and acceptable concept.

CASE REPORT

This 2.8 year old white male had been under intermittent observation for over nine months (because of headaches resulting from repeated head injuries) before the initial manifestations of his eventually fatal illness became apparent. Figures 1-3 and Table 1 chronologically present the voluminous clinical and laboratory data in graphic form.

In November 1943 the blood count was normal. At that time the headaches were found to be due to traumatic encephalopathy. Four weeks later the patient contracted an apparently simple upper respiratory infection. Within 24 hours he was acutely ill and febrile and he developed cervical adenopathy and a palpable spleen. A blood count revealed a relative leukopenia and severe granulocytopenia. No etiologic factor could be ascertained as responsible for this granulopenic state. Penicillin was administered for seven days in adequate dosage but the illness progressed alarmingly with increasing toxicity, fever, tachycardia, pharyngitis, tonsillar ulceration, hyperplastic gingivitis, regional adenopathy, and splenomegaly. On the fourth day of illness, penicillin therapy was instituted, the patient receiving 2,500 units intramuscularly every three hours. Clinical improvement was evident in the next 24 hours, although he developed an additional tonsillar ulcer and a harassing cough. In 48 hours the patient was no longer critically ill; the ulcerations began to heal and the fever diminished. Penicillin was administered for a total of ten days and was finally discontinued when all signs and symptoms disappeared.

During this remission the patient was asymptomatic, afebrile, and revealed no abnormalities on physical examination. Blood counts, however, disclosed slowly progressive anemia and leukopenia. Thus, the second attack of agranulocytosis, of 18 days' duration, was established by laboratory studies 9 days prior to the onset of signs and symptoms. On the 37th day of illness (January 23, 1944) sepsis was
evident. There were fever, early gingivitis, mild pain in the neck and jaw, and rectal discomfort from perianal inflammation. Increasing pharyngitis, cervical adenopathy, and trismus soon became evident. Intramuscular penicillin therapy was resumed on the 39th day and the patient received a total of 160,000 units daily. At this time the gingivae were inflamed and hyperplastic so that the teeth were partially buried, an erosion appeared at the angle of the mouth, there was a necrotic ulceration behind a left lower molar tooth, and the perianal inflammation had spread extensively. After 48 hours of penicillin therapy, in the presence of a maximum white blood count of 1,800 with 4 per cent granulocytes, there was striking clinical improvement; the temperature did not rise above 100.6 degrees F., and there was notable recession of the mouth lesions and the perianal inflammation. Despite the fact that the white blood count did not rise above 2,000 cm. with 12 per cent granulocytes, the mouth and anal lesions healed promptly although the lip erosion required another week for epithelization.

The first sternal marrow aspiration was performed after this second agranulocytic episode on Febru-
MONOCYTIC LEUKEMIA

ary 7, 1944, the 54th day of illness (table 1). The peripheral blood and sternal marrow smears were submitted to several consulting hematologists. All opinions were conflicting and differed in the classification and interpretation of the cells of the mononuclear group. The majority opinion was that the findings were suggestive of, but not conclusive for, leukemia.

The peripheral blood and sternal marrow smears were submitted to several consulting hematologists. All opinions were conflicting and differed in the classification and interpretation of the cells of the mononuclear group. The majority opinion was that the findings were suggestive of, but not conclusive for, leukemia.

The third and longest period of granulocytopenia began on the 58th day of illness (February 7). Similarly, it was detected initially by the serial blood counts. For 30 days the total circulating granulocytes were never greater than 155 per cm., and they usually ranged around 75 per cm. For five days no granulocytic cells could be found in the peripheral blood. Because of the hematologic warning of impending sepsis, penicillin therapy was instituted prior to the development of signs and symptoms, the patient receiving a total of 3,820,000 units in a period of 11 days. No other medication was employed, and for 10 days the only abnormalities detected were a single temperature reading of 100.0 degrees F., a thermal reaction due to a transfusion, a mild hyperplastic gingivitis, a soft apical systolic murmur, and the development of a palpable liver and spleen two finger-breadths below the costal margins.

The prognosis was deemed poor at this time (February 12, 1944) in view of the weakness, marked
weight loss, and the progressive development of an aplastic anemia syndrome. From the 80th to the 119th day of illness, however, there was a spectacular improvement in the hematologic status. Blood smears showed a classical "leukemoid" reaction and all blood elements returned to normal limits rapidly associated with recovery of weight, strength, and sense of well-being. A sternal marrow aspiration was performed and it was reported that the previous provisional diagnosis of leukemia could not be substantiated.

There followed a clinical and hematologic remission of approximately three months' duration, during which time the patient was transferred to a hospital near his home where he was again under the observation of the same medical officer (VHK). The previous suspicion of leukemia could not be established by the admission studies.

A fourth episode of granulocytopenia began on June 26 and was treated promptly and exclusively with penicillin. Mild fever was the only clinical indication of possible infection. In view of a nondiagnostic sternal aspiration, a nondiagnostic thrombocyte count, the presence of phagocytosis of red blood cells and possibly of white blood cells, and the general nonconformance to a leukemic picture, consideration of splenic neutropenia (Doan and Wiseman15) was entertained. An exploratory laparotomy was performed for the purpose of securing diagnostic material. No abdominal adenopathy was observed; the liver was
**MONOCYTIC LEUKEMIA**

### Table 1.—Summary of Bone Marrow Studies

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<td>B)</td>
<td>0.5 - 3.0</td>
<td>4.2</td>
<td>3.6</td>
<td>3.5</td>
<td>4.5</td>
<td>9.0</td>
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<td>C)</td>
<td>5.0 - 19.0</td>
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<td>4.5</td>
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<td>Neutrophilic</td>
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<td>Metamyelocytes (juvenile forms)</td>
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<td>18.2</td>
<td>2.5</td>
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<td>3.5</td>
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<td>Polymorphonuclear leukocytes</td>
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<td>Monocytes: Typical</td>
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<td>Pronormoblasts (macroblasts)</td>
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<td>2.0</td>
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<td>Normoblasts</td>
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<td>Megaloblasts</td>
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<tr>
<td>Erythroblasts</td>
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<td>1.3</td>
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**FIG. 4. SMEARS OF THE PERIPHERAL BLOOD IN THE TERMINAL STAGE, SHOWING THE VARIATION IN APPEARANCE OF THE MONOCYTIC CELLS**

The lobulation and grooving of the nuclei, and the granulation of the cytoplasm are clearly demonstrated, while the irregular size and shape of the cells is evident. (X 1535.)
not unusual, but because of its increased size the spleen was removed. The results of the histologic examination of this organ are included in the autopsy report.

There was clinical and hematologic improvement for a short period after splenectomy. The white cell count rose to normal limits but significant numbers of immature monocytes appeared. After eight days, however, granulocytopenia recurred and penicillin was again administered. Although no overt signs of sepsis appeared, the course was now febrile and remained irregularly so until death.

In addition to loss of weight and strength, there were complaints of bone pain, mainly in the sternum and ribs, and left flank pain. Neither x-rays of the bones nor a complete genito-urinary survey yielded positive findings.

A fifth episode of granulocytopenia, without mucocutaneous lesions, occurred in the latter part of August 1944 and was again treated with penicillin, but with no effect on the elevated temperature. A progressive leukocytosis appeared, which eventually reached 180,000 cm., composed mainly of atypical monocytes and monoblasts. During this terminal phase there were severe vomiting, complete anorexia, constant pain in the ribs and sternum, abdominal pain, fever, tachycardia, and psychosis. An electrocardiogram obtained 10 minutes prior to death on September 22, however, revealed only tachycardia and very low voltage of all waves. Death occurred from acute circulatory failure nine and one-half months after the onset of the illness.

HEMATOLOGIC FEATURES

Analysis of the hematologic data requires precise cytologic descriptions for an exact definition of the monocytoid cells concerned in this disease. The following characteristics are based on daily examinations of fixed and supravitally stained smears of peripheral blood and of periodic bone marrow aspirations over a period of nine and one-half months (fig. 4).

The monocyte is usually larger than the granulocyte; its cytoplasm is opaque, mottled, gray-blue, and contains azurophilic granules. The cell margins are serrated and irregular. The nucleus is reniform or horseshoe-shaped and possesses a lacy, skein-like, coarse chromatin weave. "Grooving," "crumpled appearance," "lobulation," "indentation," and "folding upon itself" are characteristic terms used in denoting this peculiar configuration. With supravital stain, numerous neutral red or salmon-pink colored bodies, vacuoles, are symmetrically arranged around a centrosphere located in the bay (Hof) of the nucleus. This structure is the rosette which is considered so typical of the mature monocyte. Green-tinged mitochondria are small, fine, and few, and are located peripherally to the rosette and nucleus. The cell’s motility is very typical and specific and is best described as a "sliding" or "gliding" motion, the cytoplasm flowing extremely sluggishly and the contour of the cell being wavy or undulating.

The monoblast measures from 15 to 20 μ in diameter. In fixed, stained smears it possesses a basophilic cytoplasm containing no granules and, distinctively, no Auer bodies. The nucleus is round, large, and centrally situated; its chromatin is fine, stippled, and sieve-like, and usually possesses two nucleoli. In supravitally stained preparations, motility, neutral red bodies, rosettes, and vacuoles are absent.

Between these poles of maturity, one notes a group of cells demonstrating a variable degree of differentiation. The cytoplasm displays a lesser degree of basophilism than the monoblast and occasional azurophilic granules are present. The nucleus is coarser than that of the monoblast but, in contrast to the monocyte, discloses a finer and more lacy chromatin network. Occasionally nucleoli are observed. The nucleus shows early indentation of its rather sharply delineated membrane. With supravital stain, neutral red bodies are present, although they are much finer and
more uniform in size and shape; they are more diffusely arranged throughout the cell and do not form the typical rosette of the mature monocyte. Motility is present at times but it is less active and often is not present. Occasionally in both fixed and supravital stained preparations, erythrophagocytosis is detectable. This intermediate form, which can be termed the promonocyte or immature monocyte, shows no transitional developmental forms to cells of the myelocytic series, and its relationship to the monoblast and the monocyte can be readily demonstrated. The presence of this intermediate atypical group has been mentioned previously by Osgood and Downey. A noteworthy characteristic of the promonocytic cell observed in this case is its unusual shape, since it may be elongated, tailed, grotesquely lobulated, or forked.

The qualitative and quantitative relationships of the monocytoid cells to the other blood constituents may best be demonstrated by inspection of figs. 1–3. For the purpose of analysis of this data, we have arbitrarily divided the discussion into two phases; namely, the initial period from the onset of the disease (December 1943) to the first prolonged remission (April–June 1944), during which time the clinical and hematologic diagnosis remained in doubt; and the second period, following the remission, during which the frank picture of monocytic leukemia finally emerged.

During this first period, the red blood cells underwent a progressive reduction in numbers, falling to a low of 1,700,000 cm. in February 1944, which continued for approximately six weeks. Erythropoiesis was heralded by the appearance of large numbers of nucleated red blood cells in the peripheral blood and by polychromasia and macrocytosis.

The granulocytes during the initial period underwent three distinct episodes of granulocytopenia, accompanied by an absolute increase in monocytic cells. This monocytosis prevented the fall of the total white cell count to a degree commensurate with the granulocytopenia. Similar to the erythropoietic reaction mentioned above, the remissions of granulocytopenia were introduced by evidence of granulopoiesis. Particularly in the recovery phase of the third episode of neutropenia, a very pronounced myeloid reaction was observed which was characterized by the appearance in the peripheral circulation of large numbers of myelocytes and promyelocytes.

Simultaneously with the ebb and rise of granulocytic cells, increased numbers of mature and immature monocytes appeared in the peripheral blood; these, intermingled with the myeloid elements, created a bizarre and confusing picture. The separate identity of both myeloid and monocytic cell types could be determined in later examinations by means of supravital stained smears. There appeared to be no transition between the monocytic and granulocytic series. The supravital technic seemed particularly valuable in securing evidence to demonstrate the relationship between the monocyte and the “blast forms.” The latter were present in large numbers and their identification as to whether they were monoblasts or myeloblasts was difficult. During the recovery phase of the third episode of granulocytopenia there was a progressive reduction of all monocytic cells.

The thrombocyte count disclosed moderate transient reduction in numbers on
A. E. RAPPOPORT AND V. H. KUGEL

343

repeated examinations. While the tourniquet test was moderately positive, there was only slight tendency toward purpura.

Following the remission of about three months' duration, the hematologic equilibrium was once again disturbed by the development of profound anemia, leukopenia, granulocytopenia, and the appearance of an abnormal number of mature and immature monocytes. After splenectomy there was a transient rise of the white blood cells. Attention at this time became focused on the disquieting behavior of the monocytoid cell, which now began to increase in numbers and to reveal evidence of immaturity and atypism. The previous hesitancy and uncertainty over the clinical diagnosis and hematologic classification disappeared as the clear-cut pattern of monocytic leukemia emerged. The terminal phase of the second period provided a dramatic scene of tidal flooding of the peripheral circulation by monocytic cells, with the white cell count attaining a total of 280,000 cells per cm.

This frankly leukemic reaction was not associated with striking myelocytosis, the granulocytic cells being mature and well differentiated. The clear-cut relationship of monocyte to monoblast through an intermediate promonocytic stage assured the accuracy of the identification of the "blast" cell. This evidence supplied confirmation of the tentative designation of "monoblast" to these cells in the first phase of the disease.

Table 1 reveals the findings of repeated sternal marrow aspirations. The first aspiration was performed on February 7, 1944, after the patient had experienced two episodes of granulocytopenia. Owing to the marked increase of monocytes in the peripheral blood, there was considerable doubt as to the correctness of the diagnosis of agranulocytosis, although leukopenic infectious monocytosis (Rosenthal and Abel) was considered. The marrow aspiration disclosed almost 33 per cent mature and immature monocytes and an increased number of myeloid elements. These findings, in addition to the other hematologic data, seemed to support a diagnosis of monocytic leukemia (Naegeli type). The resident hematologist was convinced that the "blast" cells encountered in such large numbers were of the monoblastic variety rather than the myeloblastic. On consultation, two other hematologists confirmed the predominence of "blast" forms, but both preferred to label them myeloblasts. While one consultant seemed in favor of a diagnosis of myeloid leukemia, the other consultant thought that the entire picture might fit either a monocytic leukemia or a myeloblastic leukemia.

The difficulty in distinguishing myeloblasts from monoblasts has been pointed out. In this case, however, the high percentage of mature and immature monocytes in the bone marrow offers a definite clue in identifying the "blast" cells, inasmuch as derivation of the former from the latter must have occurred in order to explain the presence of monocytes in an organ where they are normally rarely found. Thus, the presence of a maturation gradient of monocytic elements from the earliest stage to adult forms should permit the identification of the "blast" cells as monoblasts. We feel that the consultants, when they arrived at a diagnosis of myeloblastosis, neglected to evaluate the presence of the mature monocytes.

The second aspiration was performed two and one-half months later, at the height of the hematologic remission. The values of the various cellular constituents
of the marrow now approximated the normal range and the "previous provisional diagnosis of leukemia could not be substantiated."

The third aspiration was carried out on June 21. The findings of this examination were interpreted as indicating a maturation arrest of the granulocytic cells inasmuch as there was an inordinate increase of promyelocytes. Four days later the fourth precipitous decline in total and granulocytic cells in the peripheral blood occurred. It is noteworthy that the bone marrow alterations preceded the changes in the peripheral circulation by an appreciable interval and heralded an impending leukopenia which was otherwise not apparent.

The fourth bone marrow examination, three weeks later, featured an even more marked reduction in the number of myelocytes and mature granulocytes. "Blast" cells were also increased and they were classified at this time as myeloblasts on the basis of their morphologic characteristics, since, unlike the initial sternal marrow examination, there was no accompanying monocytosis. Fig. 2, however, discloses the presence of large numbers of mature and immature monocytes in the peripheral blood, while analogous cells are conspicuously absent in the sternal marrow. Unless this absence were focal and not widespread throughout the bone marrow, it would appear that extramedullary monocytopenia was occurring in order to supply the peripheral blood with these elements. Similarly, myeloid metaplasia might be assumed to exist in foci other than the bone marrow.

The final bone marrow aspiration was performed about one month later, when the peripheral blood possessed its normal complement of white cells and granulocytes. In addition to this, the monocytes were markedly increased and comprised both mature and immature forms. The bone marrow picture at this time revealed an unequivocal monocytosis and granulocytopenia. These findings were considered diagnostic of monocytic leukemia, a conclusion subsequently confirmed.

ABSTRACT OF AUTOPSY PROTOCOL

**General.** The body was that of a 28 year old, somewhat emaciated, white male. Generalized lymphadenopathy was absent. The surface of the radix mesenterii was diffusely studded with small, dry, lusterless, firm, white-gray plaques possessing central, cherry-red areas. Many small, discrete lymph nodules could be felt in the intermesenteric folds.

**Lungs.** The lungs contained firm, circumscribed, moist nodules throughout.

**Thymus.** The thymus, markedly enlarged, weighed 65 grams. It was soft and contained many circumscribed firm nodules.

**Heart.** The pericardium and the myocardium were involved by diffusely scattered, irregularly sized, gray-pink plaques which extended into the subendocardial layer and the papillary muscles (fig. 5).

**Spleen.** Splenectomy was performed on July 7, 1944. Immediately after ligation and removal, the spleen weighed 468 grams. The organ was boggy, and its cut surface was moist, dark-red brown.

**Liver.** The liver weighed 2,400 grams and was enlarged. The surface was mottled by areas of yellow-gray which were distributed irregularly in a background of dark brown.
Gastrointestinal tract. The mucosa of the stomach contained discrete nodular masses. Several peripyloric lymph nodes of gray-white color were present. Peyer's plaques and solitary follicles were moderately enlarged.

Kidneys. The parenchyma was hazy and of light yellow hue. In the peripelvic fat of the left kidney there was a bean-sized, poorly demarcated mass of indurated tissue which possessed a gray-yellow, moist surface.

Pancreas. At the tail of the pancreas, in the region of the pedicle of the spleen, there was a poorly demarcated, plum-sized mass of red, moist tissue. At the site of ligation a mass of white, somewhat caseous necrotic tissue was present, in which suture material might still be recognized.

Bladder, testicles, prostate, brain, and adrenals revealed no gross abnormalities.

Bone marrow (sternum, vertebra, and tibia) was gray, red, and of mush consistency.

Microscopic Examination of Tissues. The common denominator of the changes in all organs was the presence of mononuclear cells. The organs were involved by these cells either by thrombosis of the blood vessels with resulting circulatory changes or by their infiltration in the interstitial tissues. The latter process led to architectural alterations which were either circumscribed or diffuse, causing compression atrophy, or necrosis of the native cellular components of the organ.

The prevailing cell was large and polyhedral (fig. 9). The cytoplasm was basophilic on polychrome stain and displayed a violaceous hue with eosin. Specific chromophilic granulation was usually absent, although occasionally faint red granules could be seen on Giemsa stain. The nucleus was eccentrically located, was of irregular size and shape, and might be round, oval, reniform, horseshoe-shaped,
lobulated, or folded upon itself. The chromatin was not densely packed and the nuclear membrane was sharply defined. At times multiple nucleoli were noted. The chromatin formed a lacy pattern composed of very fine intertwining strands with some thickening at the nodal points. Mitotic figures could be observed with moderate frequency. The size, shape, and appearance of the nucleus, and the tinctorial reaction of the cytoplasm, especially in Giemsa and oxydase stains, differentiated these cells from those of the granulocytic series.

Lungs. The lungs showed good aeration. Nodules composed largely of mononuclear cells were distributed throughout the parenchyma.

Heart. The heart exhibited considerable infiltration by large mononuclear cells which were diffusely distributed throughout the epicardial surfaces, fat, and myocardium (fig. 6).

Spleen. There was marked disturbance of the architecture. The malpighian bodies were small and sparsely distributed throughout the parenchyma. They were composed, in the main, of both lymphocytes and reticulum cells distributed irregularly throughout the nodule. In the center of the follicle there was a striking deposition of acidophilic, albuminous material which formed clumpy masses between the cells. With reticulum stain, there was no notable increase in the argyrophilic fibrils. The capillaries were dilated and engorged; the endothelial cells were swollen and were desquamating into the lumen of the sinusoids. There was striking proliferation of the entire reticulo-endothelial system; the cells were very pleomorphic,
many multinucleated giant cells were present, and phagocytosis of iron, as shown by the Prussian blue reaction, was prominent. There was mobilization of the fixed reticulum cell elements and transformation, into free monocytoid cells which were similar to the monocytes found in the peripheral blood. Mitotic figures were numerous. Fresh smears of the surface of splenic pulp demonstrated many large bizarre-shaped reticulo-endothelial cells in a state of hyperplasia and displaying erythrophagocytosis. These cells were closely related to the large peripheral blood monocytes.

**FIG. 7. PHOTOMICROGRAPH SHOWING THE DIFFUSE ACCUMULATION OF MONOCYTIC CELLS IN THE SINUSOIDS OF THE LIVER ASSOCIATED WITH ATROPHY AND NECROSIS OF THE LIVER CORDS (X 200)**

**Liver** (fig. 7). There was marked necrosis of the liver cells. The cords were shrunken and compressed. The Kupffer cells were markedly swollen and were choked with pigment, usually hemosiderin. The sinusoids were packed with freely circulating mononuclear cells, but the portal triads possessed large accumulations of fixed elements. Cells of the myelopoietic series were entirely absent.

**Splenic Pedicle.** Sections through the localized tumor of the tail of the pancreas, in the region of the ligated pedicle of the spleen, demonstrated large areas of foreign body reaction to the suture material. This proliferating granulation tissue was characterized by the presence of many engorged capillaries, pigment-containing macrophages, and multinucleated foreign body giant cells. Very noteworthy, how-
FIG. 9. High power photomicrograph of tumor of postoperative splenic bed, showing the characteristic monocytic proliferation.

Note that the cells are not derived from peripheral blood by migration through the capillaries, but are products of the local connective tissue. (X500).
ever, is the fact that the predominating cell was the large monocyctic cell which has already been described in other organs (fig. 8), and many of which demonstrated active phagocytosis and a greater degree of pleomorphism than heretofore observed. It can be clearly demonstrated that the interstitial accumulation of these cells was not the result of migration of blood monocytes through the capillary walls but that it represented active adventitial proliferation (fig. 9). This admixture of monoblastic elements with other derivatives of mesenchyma represents clear-cut evidence of the ability of reticular connective tissue stem cells to differentiate into monocytes, thus supporting the previously expressed theory that

monocytes are derived from mesenchymal tissue. Granulocytes, eosinophiles, and lymphocytes were almost entirely absent.

The brain, adrenal, and pituitary glands were not abnormal.

*Lymph Nodes (Para-aortic and Mesenterial).* The lymph nodes disclosed almost complete obliteration of the follicular structure. The bulk of the parenchyma was replaced by large, loosely packed sheets of monocyctic cells which resemble those seen in the peripheral blood and other organs. The littoral and the reticulum cells showed marked numerical increase. The few vestiges of germinal centers were composed of swollen reticulum cells surrounded by deposits of fibrinous exudate. Phagocytosis of red cells, pigment, and nuclear remnants could be observed.

*Kidneys.* There was a diffuse and focal monocyctic infiltration in the interstitium
CELLS FILLING THE BONE MARROW SPACES

FIG. 11. PHOTOMICROGRAPH DEMONSTRATING THE BROAD SHEETS OF UNIFORM
CELLS FILLING THE BONE MARROW SPACES (X 75)

There is almost complete absence of myeloid and erythroid elements, while only occasional normoblasts are seen. (X 1515.)

FIG. 12. PHOTOMICROGRAPHS OF BONE MARROW, SHOWING THE UNIFORM
MONOCYTIC PROLIFERATION

of the adventitial tissues in the mid-portion of the organ. The subpelvic nodule and the large node in the renal pelvis were composed of monocytic cells similar to those already described (fig. 10).
Bone Marrow. Sections of medullary tissue of sternum, vertebra, and tibia displayed solid sheets of mononuclear cells which exhibited, in very typical manner, the morphologic characteristics concerned in this disease (figs. 11, 12). Cells undergoing mitosis could be found in abundance. Plasma cells and megakaryocytes were extremely rare. Except for an occasional eosinophilic myelocyte or granulocyte, there was almost complete absence of granulopoietic and erythrocytic precursors. A few monocytic cells possessed very faint, red granulations on Giemsa stain. This phenomenon may represent stem cell proliferation with slight differentiation toward the myeloid series. Oxidase stains of lymph node, liver, spleen, and bone marrow were completely negative.

Thymus. The normal architecture of the gland was altered by the presence of large sheets of pleomorphic monocytes which replaced the normally present thymocytes and medullary cells.

Pituitary. The pericapsular tissues and the anterior lobe were infiltrated by monocytic cells while none were seen in the posterior lobe.

DISCUSSION

The foregoing clinical and laboratory observations clearly indicate the erroneous conclusions which might have been drawn from single observations limited to a particular phase of this disease. Thus, at various times the features of agranulocytosis, aleukemic myeloid leukemia, aplastic anemia, leukemoid monocytosis, leukopenic infectious monocytosis, chronic splenic panhematopenia, and reticuloendotheliosis were depicted. Since monocytic leukemia can pursue such an erratic course, it is not surprising that attempts to confine this syndrome within rigid limits have been unsuccessful.

Certain clinical features merit comment. The frequency and significance of hyperplastic gingivitis in this disease have been the subject of debate. A well marked gingivitis was recurrently present in this case in the earlier phases of the disease. Why, however, did this feature disappear when the full-blown manifestations of monocytic leukemia became apparent? It is clear that the statistical presence or absence of this sign depends somewhat on the period of observation. The striking clinical and hematologic remission is also noteworthy.

Granulocytopenia as an expression of occult leukemia is well recognized. Nevertheless, the clinical picture here was initially that of "idiopathic" agranulocytosis. The abrupt febrile onset, the rapid appearance of necrotizing and ulcerative lesions, and the prompt response to penicillin therapy favored this impression.

Kugel and Schnitker26 have reported the value of penicillin in agranulocytosis elsewhere. This case was unique in affording controlled studies of the therapeutic effectiveness of penicillin compared with the usual agents employed in this disease. Penicillin therapy, instituted after the development of severe oral and perianal inflammation, resulted in prompt and dramatic improvement despite continuing granulocytopenia. Subsequent episodes of agranulocytosis were treated by penicillin alone; neither mucosal ulceration nor sepsis was detected clinically or on postmortem examination. From these observations it was concluded that penicillin was effective in combating the bacterial invasion of mucous membranes which frequently occurs when there is marked diminution or absence of circulating granu-
locytes. A corollary observation is that the effectiveness of penicillin in vivo is independent of the granulocyte. Penicillin has no effect on leukemia per se, but the prolongation of life through control of sepsis permitted this case to pursue the full gamut of monocytic leukemia symptomatology.

Our case conforms with most of the previously reported instances of monocytic leukemia in that this was a relatively acute illness in a young male. A striking feature of this syndrome was the contrast between the paucity of clinical manifestations and the progressive severity of the disease. The extensive pancardiac involvement was not detected clinically although an electrocardiogram taken shortly before death revealed nodal tachycardia and low voltage of QRS and T waves. Changes frequently noted in leukemia were either absent or unimpressive. Lymphadenopathy, splenomegaly, and hepatomegaly were mild; purpura and leukemic infiltrations of the skin were absent. Sternal pain and bony tenderness were present terminally only, at which time the liver had enlarged to 2–3 finger-breathths.

Similarly to the granulocytopenia, the relationship of the anemia to the leukemic process was somewhat obscure. Whereas the anemia was most pronounced in the early stage of the disease, this degree of anemia was not approached in the terminal stage. Some factor other than mechanical displacement of erythroid tissue must be logically assumed to explain not only the early profound reversible anemia but also the striking erythropoiesis during the remission period. It was also observed that large numbers of nucleated red blood cells appeared in the peripheral circulation at a time when samples of the bone marrow showed almost complete effacement of erythropoiesis. Generally there were persistent attempts at regeneration of red blood cells as manifested by the presence of macrocytosis and polychromasia.

As previously noted, there are a number of conflicting interpretations of the myeloid component of monocytic leukemia. Support for several of these divergent opinions could have been obtained from our case depending on the moment of observation. Thus, examination of the peripheral blood at times suggested a Naegele type due to the increase of myelocytes compared to monocytes. Myelocytes were particularly numerous in the granulocytopenic episodes and even more numerous in the recovery episodes. It is significant that in the prolonged preremission period following the first 3 episodes of granulocytopenia, the peripheral blood assumed a strong leukemoid character that went hand in hand with the restoration of a normal hematologic status. On the other hand, in the later stages of the disease, as the frank monocytic leukemia progressed, this myeloid reaction diminished markedly. We believe that this myeloid reaction was, for the most part, an expression of the bone marrow reactivity to the agranulocytosis and was not an expression of the monocytic leukemia. In part, too, the appearance of myeloid elements in the blood may be an irritation phenomenon secondary to monocytic infiltration of the bone marrow as suggested by Campbell, Henderson, and Croom.

The contention of Baserga, previously quoted, is certainly pertinent here.

Supravital and Romanowsky stains proved adequate for the identification of the monocytic cells in the peripheral blood. In addition to the morphologic characteristics of these cells, the simultaneous appearance of monocytes, promonocytes, and monoblasts in the bone marrow further the identification of the "blast" cell,
one of the main stumbling blocks in the establishment of monocytic leukemia as an independent entity. This association of mature and immature forms in the bone marrow deserves emphasis. Because of the sporadic appearance in the blood of bizarre-shaped, forked and tailed mononuclear cells, one might have interpreted their presence as representing a benign reticulo-endotheliosis rather than monocytic leukemia. But, again, this impression would have been based on momentary observation and could not be borne out by prolonged study.

The gross findings at autopsy were generally unimpressive. As usual in monocytic leukemia, the involvement of the liver and lymph nodes was relatively mild and did not approach the degree usually found in either myeloid or lymphatic leukemia. Rather unusual, however, was the extensive leukemic infiltrations of the heart and thymus. The diffuse leukemic alterations in the omentum and the renal pelvic tissues are noteworthy, and the monocytic tumor formation at the site of ligature of the splenic pedicle is believed to be particularly significant. These monocytes are believed to have been derived from the local mesenchymal, adventitial, or reticular connective tissues. Their presence is therefore an indication of the retention of monocytopoietic potency by this tissue and may be looked upon as an expression of mesenchymal proliferation, a belief that has been advanced by Doan and Wiseman,11 Jaffé,24 Hadfield and Garrod,29 and others. The site of origin of the monocyte should not be limited specifically to the RES, as many writers have proposed, but should be included in the broader concept of mesenchymal proliferation and differentiation. This concept would aid in resolving many of the conflicting opinions concerning the origin of the monocyte.

From all of the foregoing observations, it appears that the distinction between the Schilling and Naegeli types of monocytic leukemia is more apparent than real and does not deserve the rigid segregation frequently employed. A similar contention has been advanced by Campbell, Henderson, and Croom5 and Custer.9

SUMMARY

Monocytic leukemia is an entity that has engendered a variety of divergent clinical and histologic opinions. A case is presented in which prolonged and intensive clinical and laboratory observations demonstrate the erratic course of this disease and illustrate the erroneous conclusions that may be derived from inconstant, momentary observations of this dynamic process. Study of the ‘natural history’ of monocytic leukemia yields observations which tend to reconcile many of the hitherto conflicting opinions regarding this disease.

The origin and characteristics of the monocytic cell are discussed, and its probable derivation from mesenchyma is emphasized.

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