MEGACARYOCYTES IN THE PERIPHERAL CIRCULATION.*

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PLATE 1.

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Immature forms of red cells and white cells which originate in the bone marrow are commonly observed in the peripheral blood in many pathological conditions. The presence of large numbers of such cells in the blood is a feature of myelogenous leucemia. It might be expected that similarly either true immature forms, or what correspond to immature forms, of the third formed element of the blood, which also originates from the bone marrow, namely the blood platelets, would be present under those conditions in which we find immature red and white cells.

The megacaryocyte (megalocaryocyte) of the bone marrow has been conclusively shown by Wright (1) to be a parent cell of the platelets. The appearance of megacaryocytes in the peripheral blood does not seem to have been noted in the English literature. Isolated observations that they do occur are reported in foreign literature by Oelhafen (2), Di Guglielmo (3), Cesaris-Demel (4), Kaznelson (5), and Nägeli (6). More recently an article has been published by Pianese (7) and another by Di Guglielmo (8) that also refer to the occurrence of megacaryocytes in the circulating blood. These authors found them in cases of myelogenous leucemia, polycythemia vera, and rarely with simple leucocytosis.

It is the object of this report to emphasize that megacaryocytes occur in the peripheral blood and that they occasionally appear in

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large numbers. I have frequently found these cells in the blood of myelogenous leukemia patients, and have observed them in two cases of polycythemia vera, one of lobar pneumonia, one of Hodgkin's disease, and one of sepsis.

Owing to the normally large size of the megacaryocytes, one can conceive that if they left the bone marrow they would be unable to pass through the finer capillaries of the lungs. There is ample proof, originally given by Aschoff (9) and since by Bunting (10), MacCallum (11), and Wright (1) among others, that megacaryocytes may become packed in the lung capillaries in various conditions calling forth abnormal or immature bone marrow elements.

The presence in the peripheral blood of immature megacaryocyte elements, namely undifferentiated bits of their cytoplasm, together with large numbers of platelets and the subsequent demonstration of megacaryocytes in the lung capillaries, has been noted in Hodgkin's disease by Bunting (10). Cytoplasmic bits of these bone marrow giant cells, which are misnamed giant platelets by Fonio (12) occasionally have been observed in the circulating blood in various other diseases. The presence of these cytoplasmic bits was associated with marked increase of the blood platelets. Variation in the histology of the platelets has received very little attention as compared with that given to the red cells and white cells. Rather marked pathological variation in the size, contour, and character of the granules of the platelets occurs, as shown in studying them in fresh vitally stained as well as fixed preparations. Some such changes in the platelets may be interpreted as indicating immaturity. I have observed frequently abnormal forms and found bits of megacaryocyte cytoplasm in the blood under a wide variety of conditions, including Hodgkin's disease, but notably in myelogenous leukemia. These abnormal derivatives of the megacaryocytes are seen particularly when there is a considerable increase of platelets. The more marked deviations from normal occur when there is other evidence of intense activity of a pathological marrow.

The character of the megacaryocytes seen in the peripheral blood is shown in the accompanying plate.¹ These giant cells have

¹ It is a pleasure to acknowledge that Dr. J. H. Wright has examined some of the preparations from which these cells were drawn and that he considers them to be identical with megacaryocytes seen in the marrow.

distinctive characters more readily observed than described. In the bone marrow the megacaryocyte often characteristically develops a large amount of cytoplasm with ameboid activity so that it projects pseudopods into the blood channels. The formation of platelets results from the segmentation of the pseudopods. Pseudopods not connected with a nucleus are seen not infrequently and, as indicated above, may enter the blood stream. The cytoplasm when stained with Wright's stain contains numerous characteristic red to purple granules, and its edges often appear to be hyaline. Vacuoles occur in the cytoplasm. In the marrow the amount of cytoplasm associated with the megacaryocyte nucleus varies in consequence of the formation of platelets, and nuclei showing the usual signs of degeneration with little or no cytoplasm are frequent. In the peripheral blood the nuclei appear usually to be stripped of their cytoplasm, but as shown in the plate some retain a small amount, which is in the process of differentiation into platelets. In some instances formed platelets may become adherent to the nuclei when the preparation is made. In the bone marrow the nucleus of these cells often appears as a complicated pleomorphic structure that typically is lobate and basket-shaped. Owing to its character the nucleus may appear multiple; if it is actually multiple, this indicates degeneration. The nucleus in the marrow is frequently more vesicular than when seen in the blood stream. However, these nuclei seen in the peripheral blood are entirely similar to many of those seen in the marrow. They are of varying shapes and sizes, stain deeply, and present the characteristic spotty internal structure shown in the drawings. At times only a fragment of a nucleus occurs. Many of the nuclei seen in the peripheral blood are smaller than the majority of those seen in the marrow. At autopsy of three cases of myelogenous leukemia there were demonstrated in the lungs many much larger megacaryocytes than were found in the peripheral blood during the last days of life. The lungs of these individuals presented a remarkable appearance. The alveolar walls were thickened and many of the capillaries were plugged with enormous numbers of megacaryocytes. It would seem as if this capillary embolism might have embarrassed the pulmonary circulation and contributed to the dyspnea that these patients had during the last few days of

their life. However, they all had extreme anemia, which could account for their dyspnea. With an increased formation of megacaryocytes diminutive and atypical forms of megacaryocytes are frequently seen in the marrow. Increased numbers and diminutive and atypical forms are characteristic of myelogenous leucemia. This is in harmony with the conception that cells of tumors and tumor-like processes deviate from type and show atypicality. Thus it is not surprising that small megacaryocytes that can pass through the lungs occur in the blood of these cases. Many of the megacaryocyte nuclei observed in the peripheral blood are small, due to fragmentation in consequence of degeneration.

It is not at all uncommon to find an occasional small megacaryocyte (less than 1 per cent of the white count) in the peripheral blood in chronic myelogenous leucemia. During the continued study of some forty-five cases of this disease I have observed at one time or another megacaryocytes in thirty-five cases. In some instances these cells were observed before any form of radiation was given the patient, in others after such therapy. Certain cases showed these cells more persistently than others. When an occasional megacaryocyte was observed the patient was not so well as when they were absent and the white count was usually over 50,000 per c. mm. Even so, many patients showing an occasional one of these giant cells were not particularly sick. In six cases the megacaryocytes occurred in relatively large numbers. Two individuals, one who had had the disease for 4 years and the other for 6 years, showed from 1 to 8 per cent of these cells in white counts of from 50,000 to 150,000 per c.mm. during their last 3 months of life. Three others showed 1 to 4 per cent of these cells in white counts of from 75,000 to 400,000 per c.mm. All five of these cases were sicker than many of those who had an occasional megacaryocyte in their blood. They showed other evidence of unusual activity of the disease at the time the megacaryocytes were present as demonstrated by the presence of fever, a basal metabolism in the vicinity of +60, and numerous myeloblasts and other immature bone marrow cells in the blood stream. The sixth case that showed many of these giant cells was a most unusual one. The patient, who did not appear particularly sick, was a woman of 45 years, with an enormous spleen

and the symptoms of leucemia; before radium treatment she showed a hemoglobin of 75 per cent and a white count of 40,000 per c.mm. Many of these elements in carefully made preparations were broken, indicating their immaturity, and they could not be identified. The striking feature of the differential count of the intact cells was that 18 per cent were megacaryocytes and but 16 per cent myelocytes of various types. Myeloblasts were rare. The remaining cells were largely polynuclear neutrophils. Nucleated red cells were observed occasionally. The platelets were greatly increased. The patient, though continuing to have a large spleen, has been symptomatically very definitely benefited in the past 2 years by radium therapy. During this time the blood has shown no higher white count than 40,000 per c.mm., and seldom more than an occasional megacaryocyte, usually none. The immature white cells have fluctuated considerably in number, as have the platelets.

In two cases of typical polycythemia vera, one of Hodgkin's disease, one fatal case of lobar pneumonia, and one of sepsis, I have found an occasional, usually small, megacaryocyte. The blood in all of these cases showed increases of platelets with bits of megacaryocyte cytoplasm. The two cases of polycythemia were not particularly sick. Both showed various early forms of nucleated red cells and white counts of 25,000 to 40,000 cells per c.mm.; although no undoubted myeloblasts were present, 4 to 8 per cent of myelocytes occurred. The patients with pneumonia and sepsis both had a white count of about 90,000, consisting chiefly of polynuclears, but with a few myelocytes and normoblasts. The case of Hodgkin's disease, that died shortly after megacaryocytes were found in the blood, had a white count of 40,000. The polynuclears were 80 per cent, the large mononuclears 19 per cent, and the eosinophils 1 per cent, and a few normoblasts were seen.

Increase of platelets was the rule when megacaryocytes were found in the blood, but in some instances of myelogenous leucemia megacaryocytes were present when the platelets occurred in normal numbers and rarely when they were decreased. In all the instances in which more than an occasional megacaryocyte was found, there was a marked and usually an extreme increase of platelets, reaching to

over 3 millions in one case. In such cases bits of megacaryocyte cytoplasm were found frequently. When the giant cells were found there was usually other evidence of a serious alteration in the rate of emergence of the cells from the marrow as shown by the presence of many immature cells of both the white and red series, though the white count was not necessarily very high or the anemia marked. In myelogenous leucemia with the white count below 30,000, myelocytes less than 12 per cent, and no myeloblasts, the appearance of megacaryocytes and increases of platelets may be the first sign of increased activity of the disease, as shown in two cases. Usually myeloblasts and primordial nucleated red cells were found, in the cases of myelogenous leucemia when megacaryocytes were present. Of course, as is well known, myeloblasts and primordial nucleated red cells occur without megacaryocytes. None of these three elements normally occurs in the blood stream. Their presence in the blood stream is sufficient to indicate a serious alteration of the regulatory mechanism for the emergence of cells from the bone marrow into the circulating blood. The marrow in such instances is subject to great strain. The pathological process which underlies this altered regulatory mechanism is varied, since these immature cells occur in the blood not only when there are structural changes in the bone marrow, as in myelogenous leucemia, but also with other changes, probably largely functional, as in pneumonia and sepsis.

Apparently when megacaryocytes appear in considerable numbers in the circulating blood, the pathological process in the marrow particularly involves this element. In general the presence of these cells in the blood stream is not to be looked upon as indicative of a desirable type of marrow regeneration but more as indicative of a marrow disintegration, recovery from which may, however, occur.

CONCLUSIONS.

A megacaryocyte is seen commonly as an occasional cell in the peripheral blood of patients with myelogenous leucemia. Less commonly they appear in relatively large numbers.

These giant cells also may occur in the blood under other conditions.

Their presence is indicative of a bone marrow under intense strain.

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EXPLANATION OF PLATE 1.

This plate illustrates selected megacaryocytes found in ordinary cover-glass blood smear preparations of the peripheral blood from six different cases. The preparations were stained with Wright's modification of Romanowsky's stain. The drawings were made by the aid of a camera lucida. $\times 1,300$.

The seven megacaryocytes labelled 1 are from a case of myelogenous leucemia. Some are naked nuclei. The larger uppermost nucleus shows some adherent cytoplasm of a megacaryocyte.

The groups of cells labelled 2, 5, and 7 are also from cases of myelogenous leucemia.

In Group 2 megacaryocyte cytoplasm with its differentiation into platelets is distinct.

In Group 5 is shown a fragment of megacaryocyte nucleus with cytoplasm; differentiation into platelets is taking place.

In Group 7 two myeloblasts (the two central cells) are shown for contrast. On the left the large mass of platelets and megacaryocyte cytoplasm, associated with the somewhat degenerated megacaryocyte nuclei, may have come into approximation with the nuclei in the process of making the preparation.

The small megacaryocyte in Group 3 occurred in a case of lobar pneumonia, while that shown in Group 6 is from the blood of a case of polycythemia vera.

The red cells (Group 4) are inserted to illustrate the comparative size of the megacaryocytes.