The Incidence, Distribution and Significance of Megakaryocytes in Normal and Diseased Human Tissues

BY EDWARD B. SMITH, M.D. AND JAMES BUTCHER, M.D.

THE PURPOSE of this paper is to present certain statistical information regarding the sites and distribution of the megakaryocyte in normal persons and in patients with various types of disease.

There is a lack of basic information regarding the megakaryocyte even though it has been recognized as a distinct component of the bone marrow since the 1890's. Soon thereafter this giant cell was discovered in the capillaries of the lungs of man and in the circulating blood of animals and of man. There is now almost universal acceptance of the thrombocytogenic role of the megakaryocyte and its relationship to bleeding and to thrombosis. However, there is still need for information regarding the normal origin and residence of the cell, the mechanism of thrombocyte production, and the significance of circulating megakaryocytes. The need for basic information regarding the incidence of the megakaryocyte in human tissue provided impetus for the present study.

Numerous megakaryocytes may appear in the circulation in blood dyscrasias of various types. Certain observers have demonstrated the increase in megakaryocytes in sections of bone marrow of patients dying of infectious disease, especially pneumonia. In some of Gorony's cases megakaryocytes were demonstrated in various organs. In sections of bone marrow in idiopathic thrombocytopenic purpura Nickerson and Sunderland noted a preponderance of "functionally active" forms and a decrease of degenerating forms of megakaryocytes, the total numbers being widely variable. They regarded the presence of megakaryocytes in the sinuses of the spleen and in the vessels of other organs as a characteristic finding in idiopathic thrombocytopenic purpura. Hertzog also noted megakaryocytes in the spleen but did not consider this finding significant. Of more importance was the increase in megakaryocytes, especially the young forms, in the bone marrow in his study of 36 cases of essential thrombocytopenic purpura.
bocytopenic purpura. This is in agreement with the findings of most observers including Dameshek and Miller who noted an increase in megakaryocytes in aspirated marrow studied by various techniques.

It is probable that determination of the megakaryocyte content of the bone marrow can be done most accurately by means of histologic section of tissue sufficient to allow evaluation of 100 "high power fields." Examination of the bone marrow sections yields reliable results according to Krumbhaar and Custer. It is unfortunate that there is lack of correlation of results obtained by the several methods, i.e., examination of stained "smears," of sections of marrow, and of cell counts performed by using a hemocytometer.

In a recent study, Brill and Halpern demonstrated megakaryocytes in sections of the lungs in all of their 50 autopsied cases and in the spleen of about two-thirds of these cases. They noted that an increase in megakaryocytes in the lungs was roughly related to the simultaneous occurrence of these cells in the various organs. They stated that "under normal conditions megakaryocytes in small numbers circulate in the blood stream" although their series did not include normal individuals. Our material includes essentially normal human tissues from cases of traumatic and other types of "sudden death."

The present study was designed (1) to determine the incidence of megakaryocytes in "routine" histologic sections of normal human bone marrow and of normal human organs, (2) to determine the incidence of megakaryocytes in "routine" histologic sections of bone marrow and organs of ill persons dying of various types of disease and (3) to attempt to correlate any variations noted with the type of disease.

**Materials and Methods**

This study includes autopsied cases from the files of the Presbyterian Hospital in Philadelphia (PH), The Armed Forces Institute of Pathology (AFIP), Valley Forge General Hospital (VFGH), and the Department of Pathology of Washington University School of Medicine (WU).

The first group consists of "sudden" death cases which were selected to obtain representatives for all age groups when possible. These cases were nearly all from the AFIP, VFGH, and from the St. Louis County Hospital (in the files at Washington University School of Medicine). Various causes of the "sudden" deaths were: auto accidents, 33; gun shot wound, head, 12; gun shot wound, aorta, 12; hemorrhage into pons Varolii, 4; carbon monoxide poisoning, 3; stab wounds, heart, 2; slashed throat, 2; drowning, 2; barbitual, suicide, 2; old infarct of heart, 3; ruptured aortic aneurysm, 1; hanging, 1; electrocution, 1; run over by train, 1.

The second group of cases included hospitalized patients dying of natural causes in Presbyterian Hospital in Philadelphia or in the hospitals affiliated with the Washington University School of Medicine. These cases were largely unselected except for elimination

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*To calculate arbitrarily the number of megakaryocytes in a cubic millimeter of bone marrow (after Williams, 1942):

The volume of a cylinder equals \( \pi r^2 t \), \( r \) being the radius of the microscopic field, \( t \) being the thickness of the histologic section (approximately 5 microns). Using a Bausch and Lomb binocular microscope with 43X objective (N.A. 0.55) and 10X ocular, the volume of 100 such cylinders equals 3.1416 \( \times 0.172 \times 0.005 \times 100 \) equals 0.045.

Therefore, the megakaryocytes per cubic millimeter of bone marrow equal:

\[
\text{No. of megakaryocytes in 100 high power fields} = \frac{0.045}{100}
\]
of blood dyscrasias and for the inclusion of a few cases in the third decade which were chosen to cover these age ranges. The causes of death among those of the hospital cases were divided into four groups: (1) Infections: peritonitis secondary to various lesions, 9; bronchopneumonia, 4; acute rheumatic fever, 3; pyogenic meningitis, 2; tuberculous meningitis, 2; acute pancreatitis, 2; miliary tuberculosis, 1; disseminated lupus erythematosus, 1; brain abscess, 1; abscess of back, 1; osteomyelitis of the mandible, 1; typhoid fever, 1; infectious hepatitis, 1; acute enteritis, 1. (2) Thrombosis cases: phlebothrombosis incident to heart disease, 9; postoperative pulmonary embolism, 5; carcinoma and phlebothrombosis, 3; erythema nodosa with phlebothromboses, 1; polycythemia vera with phlebothromboses, 1. (3) Cirrhosis: cirrhosis of the liver, 13. (4) Miscellaneous: Malignant tumor of an abdominal organ 11; intracranial hemorrhage, 9; recent infarct of myocardium, 7; hypertension with cardiae failure, 4; hypertension with uremia, 2; valvular disease of the heart, 3; congenital heart disease, 3; chronic glomerulonephritis, 3; Hodgkin's disease, 1; malignant melanoma, 1; neuroblastoma of adrenal, 1; microcephaly, 1; hemorrhage from peptic ulcer, 1; dissecting aneurysm of aorta, 1; neonatal adrenal hemorrhage, 1.

The routine histologic sections of heart, lung, liver, spleen and kidney were studied microscopically in every case. Sections of brain and other organs were studied in about half of the cases but in general yielded few positive results. A section of vertebral bone marrow was examined when available. The sections were 5 microns in thickness in all of the Presbyterian Hospital and Washington University material and varied between 5 and 6 microns in thickness in most of the other cases. This variation is possibly of significance only in the determination of the number of megakaryocytes in bone marrow. All sections were stained by the hematoxylineosin method and in addition some duplicate sections of the bone marrow were stained by the May-Grunwald-Giemsa technic. The latter did not make available any additional desired information. It is true that the azurophil granules of the megakaryocytes and the specific granules of leukocytes were made visible by the May-Grunwald-Giemsa stain but visualization of these granules was not absolutely necessary for reasonable accuracy in identification of the megakaryocytes. Indeed, equivocal cells of immature or degenerated varieties have relatively obscure and indefinite granules.

Measurements of the histologic sections of the organs revealed a surprising uniformity in size of the usual autopsy section (about one square centimeter). This average section has a volume of about 0.5 cu. mm. (0.05 mm. thick x 10 mm. wide x 10 mm. long equals 0.5 cu. mm.). The wide variations in density and vascularity among tissues was recognized but there was sufficient uniformity to permit comparison of the same type tissue from different cases. In the examination of the bone marrow one hundred "high power fields" were counted in areas free of bony spicules and large blood vessels. In some cases only 50 such areas were available so that a calculation of the result to comparable terms was necessary. Primitive megakaryocytes and equivocal promegakaryocytes were not included in the counts of organs or bone marrow. The classical megakaryocytes presented a deeply basophilic nucleus with heavy chromatin network and irregular parachromatin patches. The nuclei were polymorphic and enormous (except in the case of elongated "naked nuclei" found conforming to the shape of a capillary of an organ, fig. 1). Smaller cells of the promegakaryocyte stage displayed

Fig. 1A.—A well preserved megakaryocyte in a pulmonary capillary.
1B.—A megakaryocyte in a pulmonary capillary. Only a small amount of cytoplasm is visible around the large, lobulated nucleus.
1C.—A well formed megakaryocyte in the splenic pulp.
1D.—The large nucleus of a megakaryocyte conforming to the contour of the space it occupies in the splenic pulp. Only scant cytoplasm is demonstrable.
1E.—A tortuous "naked nucleus" conforming to the shape of the capillary loop of a glomerulus.
1F.—A glomerulus containing a "naked nucleus" of a megakaryocyte.
1G.—A large, rectangular megakaryocytic nucleus lying in a sinus of the liver.
1H.—The nuclear remnant of a megakaryocyte in the heart. Such a nucleus resembles the nuclei of myocardial fibers in some instances. However, in this picture note the faint outline of the capillary wall, and the lymphocyte and neutrophil also present in the capillary.
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comparable tinctorial properties in their nuclei but sometimes had lymphocytoid cytoplasm. The "naked nuclei" mentioned above were regarded as pyknotic, megakaryocyte nuclei which had lost their cytoplasm in the formation of platelets.

It is not always possible to identify large cells or large nuclear fragments. However, the identification of altered megakaryocytes is based principally on the nuclear features including the large size, the lobulation present in many instances, the characteristic dark purple (not blue) chromatin, and the general similarity to the nuclei of the megakaryocytes in the sections of bone marrow. Even the pyknotic nucleus of a megakaryocyte retains tinctorial qualities of purple to distinguish it from other cells in the sections. The greatest difficulty lies in distinguishing the nuclei of degenerating megakaryocytes from the nuclei of anoxic, degenerating myocardial cells. The intracapillary location of such nuclei is therefore an important point in their identification, especially in the heart and also in all other organs except spleen and bone marrow. In the hemopoietic tissues a greater number and percentage of megakaryocytes included intact cytoplasm to aid further in their identification.

**Table 1.**—Incidence of Megakaryocytes in the Tissues of Cases of "Sudden Death" as Compared with Cases of "Hospital Death"

<table>
<thead>
<tr>
<th></th>
<th>&quot;Sudden Death&quot; (79 Cases)</th>
<th>&quot;Hospital Death&quot; (111 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% incidence</td>
<td>Average number per case*</td>
</tr>
<tr>
<td>Lung</td>
<td>88</td>
<td>5.1</td>
</tr>
<tr>
<td>Spleen</td>
<td>90</td>
<td>3.5</td>
</tr>
<tr>
<td>Kidney</td>
<td>35</td>
<td>2.2</td>
</tr>
<tr>
<td>Liver</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>Heart</td>
<td>16</td>
<td>1.0</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>100%</td>
<td>2,970 per cu. mm. (i.e., about 134 per 100 &quot;high power fields&quot;)</td>
</tr>
<tr>
<td></td>
<td>(36 cases)</td>
<td></td>
</tr>
</tbody>
</table>

* One section of each organ was examined. Only those sections showing megakaryocytes were included in calculating the average number per case.

**Results**

One megakaryocyte or more was demonstrated in at least one case in the following tissues: bone marrow, spleen, lung, liver, kidney, heart, adrenal gland, pituitary gland, cerebrum, cerebellum, lymph node, pancreas, striated muscle, adventitial capillary of the aorta, mural thrombus in the heart, and thrombotic pulmonary embolus. The cells were located both intra- and extravascularly in bone marrow, spleen and lymph node. In the remainder of the tissues the megakaryocytes were intravascular only.

Confirming the work of previous observers it was found that the megakaryocytes in the bone marrow were virtually all large, adult cells whereas in the spleen and lungs about half and three-fourths of the megakaryocytes, respectively, were "naked nuclei" or apparently without cytoplasm. It was unusual to find an adult megakaryocyte in kidney, liver, or heart although "naked nuclei" were not uncommon.

**Control Series:** Table 1 shows the incidence of megakaryocytes in the major viscera and bone marrow in persons who were presumably well immediately
prior to death. It is interesting to note that in 90 per cent of the 79 cases the spleen showed megakaryocytes, averaging 3.5 such cells per case. Megakaryocytes were present in a section of lung in 88 per cent of cases, averaging 5.1 cells per case. Kidney, liver and heart followed with 35 per cent, 24 per cent and 16 per cent respectively. The “average normal” bone marrow of 36 cases presented 2,970 megakaryocytes per cu. mm. (varying from 1,422 to 4,800 per cu. mm. with only 3 cases being above 4,000).

Hospital Death Series: The incidence of megakaryocytes in the organs of 111 patients who died “slowly” of various diseases is summarized in table 1. The incidence and number of these cells in the capillaries of the lungs were greatly increased over the normal. One hundred per cent of sections of lung showed megakaryocytes, averaging more than 14 such cells per case.

The spleen was a close second, being considerably increased over the normal. There were megakaryocytes in 97 per cent of cases with an average of more than seven per case. The kidney, liver and heart were also increased. The bone

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Number of cases</th>
<th>Lung</th>
<th>Spleen</th>
<th>Kidney</th>
<th>Liver</th>
<th>Heart</th>
<th>Bone Marrow (number per cu. mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>30</td>
<td>17.6</td>
<td>10.1</td>
<td>2.6</td>
<td>3.2</td>
<td>1.7</td>
<td>4493</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>19</td>
<td>13.3</td>
<td>8.4</td>
<td>2.4</td>
<td>1.5</td>
<td>1.2</td>
<td>3066</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>13</td>
<td>12.5</td>
<td>6.4</td>
<td>1.9</td>
<td>1.6</td>
<td>1.2</td>
<td>2639</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>49</td>
<td>12.9</td>
<td>5.2</td>
<td>2.2</td>
<td>2.9</td>
<td>2.9</td>
<td>3846</td>
</tr>
<tr>
<td>All “Hospital deaths”</td>
<td>111</td>
<td>14.2</td>
<td>7.4</td>
<td>2.6</td>
<td>2.5</td>
<td>1.9</td>
<td>3766</td>
</tr>
<tr>
<td>“Sudden death”</td>
<td>79</td>
<td>5.1</td>
<td>3.5</td>
<td>2.2</td>
<td>1.2</td>
<td>1.0</td>
<td>2970</td>
</tr>
</tbody>
</table>

marrow increase to 3,766 megakaryocytes per cu. mm. (average normal 2,970) was striking.

It should be noted in the analysis (table 2) of the main types of disease (infections, thrombi, cirrhosis and other diseases) among the “hospital” cases that the infectious cases averaged highest in the parenchymatous organs and in the bone marrow. The bone marrow in the infectious cases averaged 4,493 megakaryocytes per cu. mm., varying from 978 per cu. mm. in a diarrheal case (age 2 years) and 1,622 per cu. mm. in an infectious hepatitis case to a high of 10,355 per cu. mm. in a case of pneumococcal meningitis in a child. Seventeen of 30 cases (i.e., over half) presented counts above 4,000 megakaryocytes per cu. mm. of bone marrow but the variation in the counts among the types of infection was considerable.

The group of thrombosis cases is a somewhat heterogeneous one despite the common feature of a significant thrombus somewhere in the body. The average count of megakaryocytes per cubic millimeter of bone marrow was 3,066 (average of the “normal” series was 2,970). The results in this group ranged between 889 megakaryocytes per cu. mm. of bone marrow in an emaciated, 79 year old man...
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with carcinoma of the stomach and a phlebothrombosis to a high count of 5,333 megakaryocytes per cu. mm. of bone marrow in a 64 year old man with polycythemia and multiple thrombi. The latter case was the only blood dyscrasia included in the study.

An analysis of the occurrence of megakaryocytes in the various organs (see table 2) shows that the average number found in "ill persons" in general is less than the average number present in the patients with infection. Low counts were found in the cirrhosis group. The miscellaneous group was near the average for all ill persons.

The group of cirrhosis cases is interesting because of (1) the low average number of 2,630 megakaryocytes per cu. mm. of bone marrow, (2) the unusual pattern of distribution with striking absence of megakaryocytes from the liver. The spleen and lungs of all 13 cases showed megakaryocytes but the heart, liver and kidneys showed such cells in only 5, 5 and 7 cases respectively. That is, the frequency and distribution of megakaryocytes in cirrhosis cases approaches that of normal persons.

The comparison of the average normal with the average ill person in this study shows a striking difference in distribution of megakaryocytes in the organs. In figure 2 the most common sites of occurrence are indicated. In cases of "sudden death" megakaryocytes were observed in only the lungs and spleen in over 40 per cent of cases. Cases in which one additional organ showed a megakaryocyte constituted another 20 per cent of cases. Such cells were widely distributed in only a minority of the "normal" cases. On the other hand, more than half of the

![Bar chart showing the distribution of megakaryocytes in different organs.](image-url)
“ill” persons displayed wide distribution of megakaryocytes and they were confined to lung and spleen in less than 10 per cent of these diseased individuals.

Attempts to show difference in distribution and incidence of megakaryocytes in the different age groups were unfruitful except as regards the bone marrow. Figure 3 shows that in every decade the average “ill” person had more megakaryocytes than did the average “normal” person. These results obtain in spite of the inclusion of cases of cirrhosis and other types of liver damage in which the number of megakaryocytes in the marrow was decreased. Figure 3 also shows that with increasing age there is a downward trend in number of megakaryocytes per cubic millimeter of bone marrow. This conforms to the commonly recognized decrease in the amount of cellular bone marrow with age.

![Megakaryocytes per cu. mm.](image)

**Fig. 3.**—Average number of megakaryocytes in bone marrow of various age groups.

**DISCUSSION**

In our opinion the data of this study do not contain any significant evidence toward proving the site or the sites of origin of the megakaryocyte. However, it should be stated that not once did we observe a megakaryocyte attached to and apparently arising from the lining of a vascular channel.

The fairly old observation of circulating megakaryocytes has again been corroborated and some quantitative information is presented. Of significance is the repeated demonstration of megakaryocytes in the capillaries of the majority of cases of “sudden” death, whether of traumatic or natural cause. However, most of these circulating megakaryocytes were effete forms as represented by enormous nuclei with scant or no cytoplasm. Our observation of these cells in “normal” individuals confirms the conjectures of previous authors, notably Brill and Halpern, who believed that megakaryocytes circulate normally in the blood.
The increased number and wide distribution of megakaryocytes in the tissues of ill persons is probably due to abnormal liberation of bone marrow elements during periods of stress. The phenomenon is probably analogous to or part of a leukemoid reaction and may well be an expression of the agonal state. The spleen and lungs nearly always show megakaryocytes in both normal or diseased persons but this does not necessarily mean that either of these tissues generates these cells. The low blood pressure and wide vascular bed in the lungs is conducive to loitering of cells in the pulmonary circulation. The spleen is well known for its filtrative functions. However, well preserved, apparently normal megakaryocytes were found more frequently in spleen than in lung. Further, their not uncommon interstitial location in the spleen suggests origin there, as well as in the bone marrow.

The demonstration of megakaryocytes in other organs is more difficult and the mechanism for trapping the cells is less obvious except for the kidney. A megakaryocyte encountered in the kidney is almost invariably found in a glomerulus, suggesting that the cell was arrested during a phase of ischemia and rest for that particular glomerulus. In other organs of the body the demonstration of a megakaryocyte depends to a greater degree upon diligence and chance.

The bone marrow displays megakaryocytosis when stimulated by infection or by almost any disease in general. Pneumonia as a stimulus to proliferation of bone marrow elements including megakaryocytes has been noted particularly by Frey,21 by Williams22 and by Orbison and Laipply.23 Our studies confirm their findings as shown by our data in which infection caused an average increase of megakaryocytes in the marrow of almost 50 per cent (i.e., 2,970 increased to 4,470). Although diseased persons in general present high counts of these cells in the bone marrow, there is considerable individual variation among diseases and with aging of the patient.

Cases with cirrhosis tend to have a low content of megakaryocytes in the marrow, according to our results. This is in disagreement with Limarzi and co-authors29 and with Berman and his associates30 who found normal or increased megakaryocytogenesis in cases of cirrhosis. However, their determinations were made upon aspirated sternal marrow; therefore, one might question the adequacy of the method for precise quantitative study.

Age is well recognized as an important factor in the structure and function of the bone marrow (Custer, 1931–32).31 Study of the cases of “sudden death” makes it apparent that the megakaryocyte content of “normal” bone marrow decreases with increase in age (see fig. 3). This parallels the decrease in general cellularity of the marrow which has been recognized as a manifestation of aging. Our average normal of 2,970 megakaryocytes per cu. mm. of bone marrow among our 36 control cases is somewhat below that found by Williams22 who studied 16 “control” cases of traumatic death (ages 19 to 70 years). He established his upper limit of normal as 5,000 megakaryocytes per cu. mm. of marrow.

Determinations of the percentage increase in megakaryocytes in the bone marrow with illness shows no significant difference among the various age groups. A trend is indicated by the great difference between the normal and the ill of the earlier decade (fig. 3). However, statistical analysis (including data from
all individuals in both ill and well series) shows that this apparently exaggerated response is probably not significant.

**Conclusions**

1. Megakaryocytes are demonstrable in the tissues of essentially normal persons who have died suddenly.
2. Megakaryocytes are more abundant in the tissues of ill persons than in the tissues of normal persons. *
3. Megakaryocytes are more widely distributed in the tissues of ill persons than in the tissues of normal persons.
4. The average normal megakaryocyte content of the bone marrow decreases with advancing age. *
5. The bone marrow and other organs of diseased persons in general and of infected persons in particular show a numerical increase in megakaryocytes.
6. In cases of cirrhosis of the liver the megakaryocytic content of the bone marrow tends to be decreased.

**References**


* These data are statistically significant at the 1 per cent level.
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17 Wright, H. P.: Changes in the adhesiveness of blood platelets following parturition and surgical operations. J. Path. & Bact. 54: 461, 1942.
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