The "Morular Cell" and the "Grape Cell" in Bone Marrow and Peripheral Blood

By AVINOAM ZLOTNICK

THE association of hyperglobulinemia with an increase in the number of bone marrow plasma cells is a well-known phenomenon. Bing & Plum[1] first drew attention to this and noted that "a comparison of the various affections in which hyperglobulinemia is found, shows as a common feature an augmentation of the plasma cells and other cells belonging to the reticulo-endothelial system." Since then, many observations have substantiated this statement and have suggested that the plasma cells may be concerned in the formation of immune globulins and antibodies,[2-4] or that plasmocytosis and hyperglobulinemia may be associated with a hypersensitivity reaction.[5]

While examining some bone marrow smears and buffy coats of patients with hyperglobulinemia of non-myelomatous origin, it was noticed that beside the increased number of plasma cells, there were some plasma cells and plasmacytoid reticulum cells the protoplasma of which was full of hyaline-blue spheroid or polyhedral bodies. Since these cells have been described in the bone marrow of multiple myeloma,[11] purpura hyperglobulinemica,[16] as well as in normal bone marrows,[17] the purpose of this study was to find out whether these cells are only associated with hyperglobulinemia or whether they may be found in its absence.

MATERIAL AND METHODS

The material for this investigation consisted of bone marrow aspirations from 39 patients and buffy coat smears of 7 patients who were hospitalised in our department. Eight of the bone marrow aspirations were from patients who showed hyperglobulinemia of non myelomatous origin. Of these, five had hepatic cirrhosis, proved either by post mortem examination or by liver biopsy; one had juvenile rheumatoid arthritis, one acné conglobata which has been under observation for the last ten years, and one patient suffered from carcinoma of the thyroid, with metastases in bones, lungs, kidneys, and heart. This last patient showed a leukemoid reaction with 165,000 leukocytes per cu.mm., mostly adult neutrophils.

The other 31 patients suffered from different kinds of anemias, leukemia, Gaucher's disease, Hodgkin's disease, idiopathic thrombocytopenic purpura, hepatosplenomegaly of unknown origin, carcinoma of the lung, kidneys, or stomach, rheumatoid arthritis, infectious hepatitis in its early stages, bronchial asthma, exudative pleuritis, and pyrexia of unknown origin. None of these patients had an increase in the globulin fraction above the normal.

All the bone marrow aspirations were taken from the sternum, smears were prepared, dried in the air and stained with May-Gruenwald-Giemsa. Some of the smears were stained by the Sudan black stain for fat and the periodic acid Schiff reagent (P.A.S.)[21, 22] for polysaccharides. The percentage of the plasma cells was obtained by counting a total of 500 cells in 5 different areas of the smear.

Buffy coats were prepared according to Marten & Blackburn's[9] technic from seven patients with suspected systemic lupus erythematosus. All showed hyperglobulinemia.

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Results

Three kinds of cells with intracytoplasmic configurations could be found in the bone marrow smears of patients with hyperglobulinemia.

(1) Plasmacytoid reticulum cells, the cytoplasm of which contained closely packed polyhedral hyaline bodies or columnar crystals which stained faintly blue. These cells had the typical eccentric nucleus, usually single, of a plasma cell, but cells with several nuclei were encountered (figs. 1–4).

(2) Plasmacytoid reticulum cells with a single eccentric nucleus, the cytoplasm of which contained many hyaline bluish, transparent vesicles of different sizes. They were sometimes so numerous that they completely obscured the cytoplasm and covered parts of the nucleus. The vesicles were arranged in several layers which could be distinguished by altering the fine adjustment of the microscope. They were either small, so that the bluish cytoplasm of the mother cell was seen between them, or they were large and pressed together (figs. 5–8). The mature cell looked like a berry (fig. 8) reminiscent of the "morular cell" of Mott.[6]

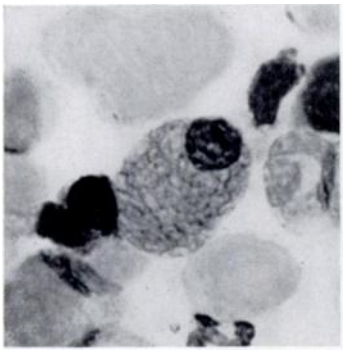


Fig. 1

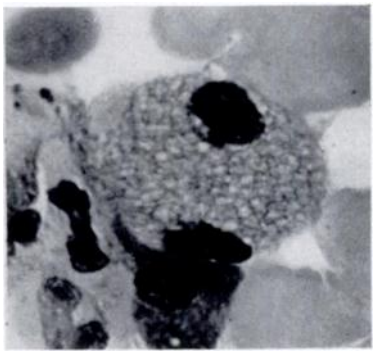


Fig. 2

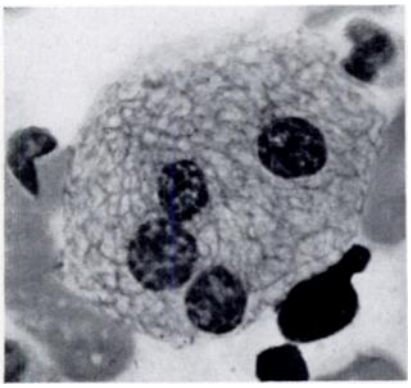


Fig. 3

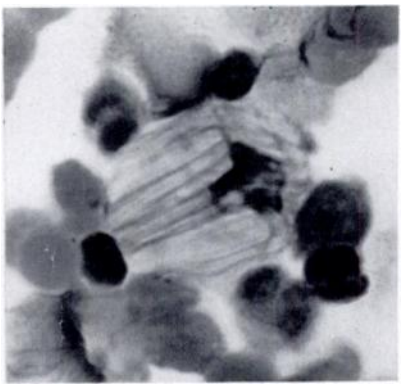


Fig. 4

Figs. 1–3.—Plasmacytoid reticulum cells containing crystal-like inclusions, from the bone marrow of a patient (No. 6) with acné conglobata. ×1000.

Fig. 4.—Plasmacytoid reticulum cell with columnar crystals, from the bone marrow of a patient (No. 4) with hepatic cirrhosis. ×1000.

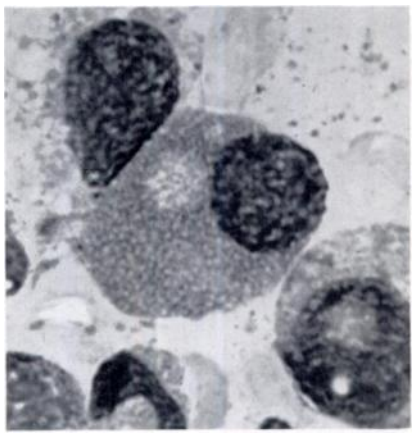


FIG. 5

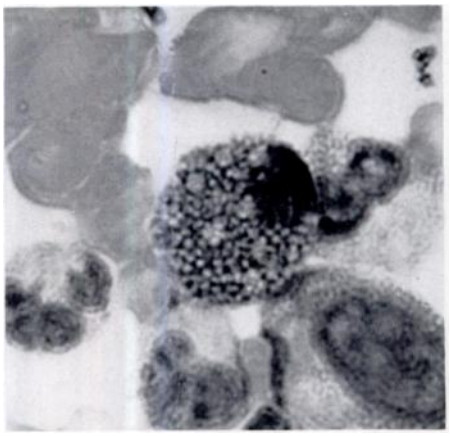


FIG. 6

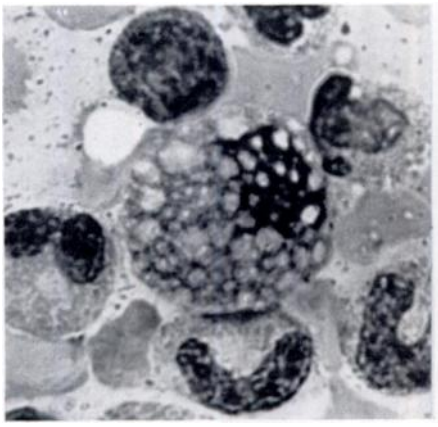


FIG. 7

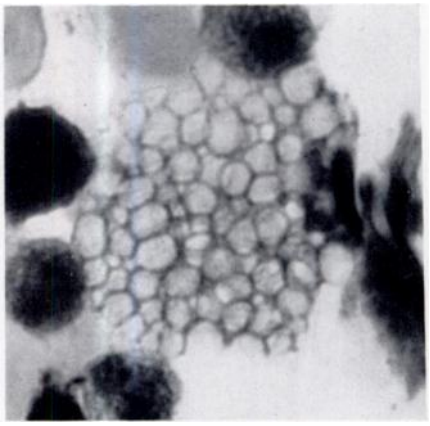


FIG. 8

FIGS. 5–8.—Stages in the development of a "morular cell" in the bone marrow of a patient (No. 5) with carcinoma of the thyroid accompanied by a leukemoid reaction. Note that as the vesicles increase in size, they partly cover the nucleus. ×1600 approx.

(3) Typical plasma cells with a characteristic eccentric nucleus and a deep blue cytoplasm, which contained globular bodies of different sizes. These bodies took an opaque blue stain. Their number varied from several globules in a cell to many, forming the "grape cell" of Stich et al.[7] Figures 9–12 clearly show the typical cytoplasm of the plasma cell between the globules, but in figure 13 only the globules can be seen, the cytoplasm between them having disappeared. Here the globules adhere loosely to one another and the cell may disrupt, isolated globules being visible in parts of the bone marrow smears. Figure 14 shows a cell which has apparently undergone disruption. The globules of these cells are negative with Sudan black and P.A.S. (fig. 15).

The cells described were found only in patients with hyperglobulinemia. Table 1 shows the occurrence of these cells in the marrows of the different patients. "Grape cells" were found in 5 cases, who besides the hyperglobulinemia had a

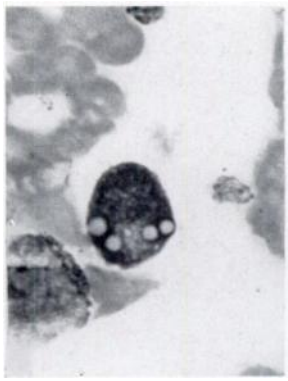


FIG. 9

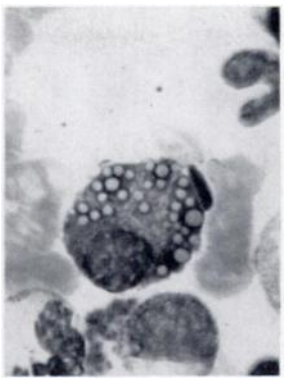


FIG. 10

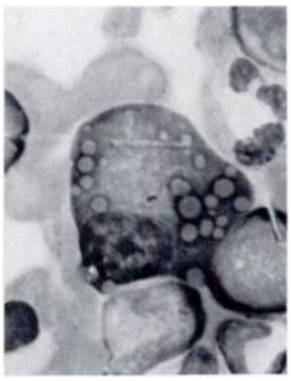
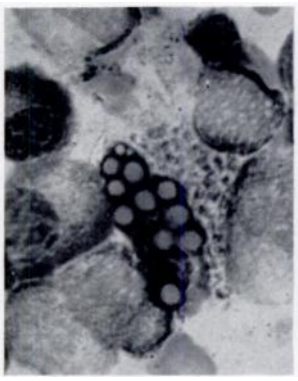


FIG. 11



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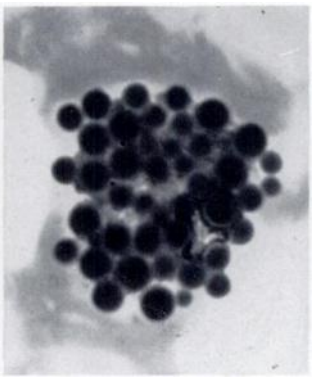


FIG. 13

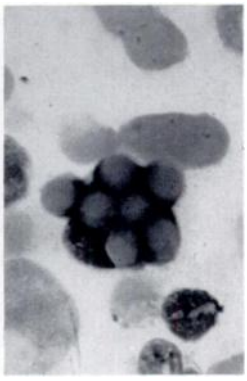


FIG. 14

FIGS. 9-14.—Stages in the development of the "grape cell," from the bone marrow of a patient (No. 6) with acné conglobata. The dark globules of the grape cell in figure 13 are due to overstaining. ×1000.

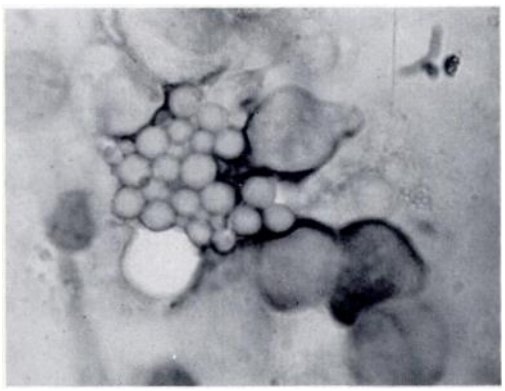


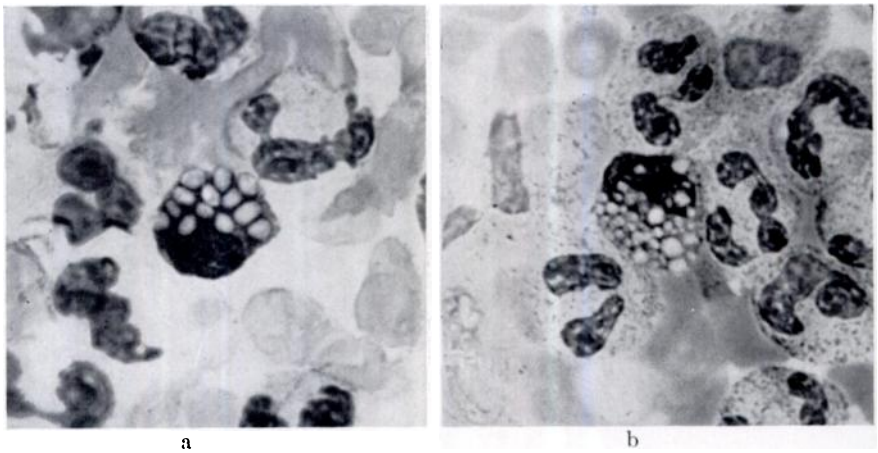
FIG. 15.—Negative stain with P.A.S. of a "grape cell" from the bone marrow of patient No. 6.

NOTE: With the exception of figure 15 all other figures represent cells stained with the May-Gruenwald-Giemsa combination.

TABLE 1.– *Hyperglobulinemia, Plasmocytosis and the Presence of Intracytoplasmic Inclusions in 8 Patients*

Case No.	Sex	Diagnosis	Serum Albumin Gm. %	Serum Globulin Gm. %	% B.M. Plasma cells	Morular cells	Grape cells	Crystals
1	M	Hepatic cirrh.	2.5	3.8	2.2	+	+	–
2	F	Hepatic cirrh.	1.8	4.6	0.8	+	–	–
3	M	Hepatic cirrh.	2.1	4.1	0.2	–	–	–
4	M	Hepatic cirrh.	3.5	3.7	1.2	–	–	+
5	F	Ca of thyroid	2.8	2.8	2.2	+	+	+
6	M	Acne conglobata	2.3	7.0	8.4	+	+	+
7	M	Biliary cirrh.	2.3	5.0	2.0	–	+	+
8	F	Juvenile rheumatoid arthr.	3.3	3.7	2.0	–	+	–

+, cells present; –, cells not present.



a b

FIG. 16.— "Grape cells" in buffy coats: (a) patient with suspected systemic lupus erythematosus, (b) patient with rheumatoid arthritis, ×1000.

plasmacytosis of 2 per cent or more. "Morular cells" were found in 4 patients, and plasmacytoid reticulum cells with cytoplasmic inclusions were also found in 4 patients. Only in one patient were none of these cells found. The number of "grape cells" was very small, and frequently one or two cells only could be found in a smear. Case No. 6, however, with a hyperglobulinemia of 7 Gm. per cent and a plasmacytosis of 8.4 per cent, showed numerous "grape cells" in different stages of development. In case No. 5, "grape cells" were found in the absence of hyperglobulinemia, but the albumin globulin ratio was 1:1. Here again there was an increased plasmacytosis.

"Grape cells" were further found in two buffy coats: one from a patient with juvenile rheumatoid arthritis, and the other from a suspected case of systemic lupus erythematosus (fig. 16 a–b). In the patient with rheumatoid arthritis (case No. 8, table 1) grape cells were also found in the bone marrow. This was the only case in which both examinations were made simultaneously. In a third patient, suffering from an unusual parasitic disease,[8] a typical morular cell was found in the buffy coat smear, which was erroneously described previously as a lipophage.

These cells could not be found in any of the 31 patients without hyperglobulinemia.

Discussion

The presence of hyaline vesicles in the protoplasm of plasma cells was first described in 1904 by Christy[10] in the cerebrospinal fluid of patients suffering from trypanosomiasis. A year later, Mott[6] described this cell in detail in perivascular infiltrations of the meninges and brain substance of patients dying of this disease. He called it the "morular cell," and it has since then been frequently referred to as Mott's cell. Intracytoplasmic vacuoles in bone marrow plasma cells were first described by Leitner[11] in a case of multiple myeloma. He considered the vacuoles to be protein bodies because of the negative results of staining with iodine (for carbohydrates) and Sudan black (for fats). Rohr[12] considers these cells to be lipophages, as does Möschlin,[13] who found them in smears of splenic punctures. Neither of these authors tried special stains to prove the nature of the substance in the vacuoles. Azerad et al.[14] and Gelin et al.[15] each described one case of multiple myeloma in which the bone marrows contained 73 per cent and 70 per cent of Mott cells, respectively. Horster[16] noted in the bone marrow of a case of purpura hyperglobulinemica an increase in plasma cells, some of which contained spherical or cuboidal crystalline bodies. Kabelitz[17] described similar cells in normal bone marrows, but did not record whether his patients had hyperglobulinemia or not. In his paper, the bone marrow was either normal or showed multiple myeloma. Snapper[18] in his monograph on multiple myeloma gives some excellent color plates of this cell and stresses the common mistake of identifying the spherical inclusions in the plasma cell with Russel bodies; with the Romanovsky stain, the Russel body being fuchsinophilic while these bodies stain grayblue. Stich et al.[7] described the "grape cell" which they found in the bone marrow of patients with multiple myeloma. They differentiated it from the Mott cell, contrary to Bessis,[19] and Snapper,[18] who regard the two as identical. Van Oye et al.[20] studying the "morular cell" of Mott in the cerebrospinal fluid of patients in the terminal stage of the sleeping sickness, found that the vesicles of this cell consist of a glyco-phospholipid. They doubt whether the "Mott cell" described by Bessis and by Azerad et al. in the bone marrow of multiple myeloma is identical with the "morular cell" of Mott.

We agree with Stich et al. that the Mott cell with its clear, hyaline vesicles which hardly stain with M.G.G. has to be differentiated from the "grape cell" with its opaque, bluish globules. Whether the "morular cell" of Mott in the cerebrospinal fluid of patients with sleeping sickness is identical with the Mott cell found in the bone marrow of patients with hyperglobulinemia, has still to be proved. On morphologic grounds there seems to be no difference. In the present material "grape cells" were found in 5 cases of hyperglobulinemia of nonmyelomatous origin, contrary to Stich et al. who found them in multiple myeloma only. Thus this cell can not be diagnostic of multiple myeloma. Kabelitz[17] stresses that the plasma cells with crystal inclusions in their cytoplasm were not of myelomatous origin, but he does not state whether there was associated hyperglobulinemia. In our series these cells could only be found when hyperglobuline-

mia was present. The crystalline nature of the inclusions was clear in one case only.

Preliminary studies indicate that the inclusions contain neither fat nor polysaccharides. Their affinity for blue stain with M.G.G. may point to their protein nature, but further work is necessary to decide this. Kabelitz discusses whether these globules are products of absorption or excretion of a paraprotein. Since the plasma cell is considered to be responsible for the formation of globulins,[2-4] it could be reasoned that these cytoplasmic inclusions are secretion products of the cells, but this remains to be proved, as does the opposite view, that they represent products of absorption of the abnormal globulin.

The "grape cell" occurred twice and the "morular cell" once in buffy coats of peripheral blood, from 7 cases of hyperglobulinemia. The significance of this finding is not yet clear, and no comparative observation could be found in the literature.

Summary

Bone marrow aspirates of 39 patients with different diseases were examined. In 8 of these patients, who showed hyperglobulinemia of nonmyelomatous origin, three kinds of cells were found:

1) Plasmocytoid reticulum cells whose cytoplasm was filled with crystal-like configurations.

2) Plasmocytoid reticulum cells with hyaline transparent vesicles of different sizes in the cytoplasm. These cells resembled the "morular cell" of Mott.

3) Plasma cells the cytoplasm of which contained opaque bluish staining globular bodies varying in number and size. These cells were identical with the "grape cell."

The "grape cell" was also found in the buffy coat of the blood from 2 patients with hyperglobulinemia, and the "morular cell" in the buffy coat from a patient suffering from an unusual parasitic disease.

The protein nature of these inclusions is assumed, since they stained with the M.G.G. combination, but did not stain with Sudan black nor with P.A.S.

Summario in Interlingua

Esseva examinate aspiratos de medulla ossee ab 39 patientes con varie morbos. In octo de iste patientes, qui monstrava hyperglobulinemia de origine nonmyelomatose, tres typos de cellulas esseva notate:

1. Plasmocytoide cellulas de reticulo in que le cytoplasma esseva plenate de configurationes crystallin.

2. Plasmocytoide cellulas de reticulo con transparente vesiculas hyalin de varie dimensiones in le cytoplasma. Iste cellular resimilava le "cellula muriforme" de Mott.

3. Cellulas plasmatic in que le cytoplasma contineva opac corpores globular in varie quantitates e de varie dimensiones le quales acceptava un coloration blauastre. Iste cellulas esseva identic con le "cellula aciniforme."

Le "cellula aciniforme" esseva etiam trovate in le coagulo blanc de sanguine ab duo patientes con hyperglobulinemia, e le "cellula muriforme" esseva presente

in le coagulo blanc de sanguine ab un patiente qui suffreva de un inusual morbo parasitic.

Le natura proteinic de iste inclusiones esseva considerate como establite per le facto que illos esseva colorabile per le combination May-Grunwald-Giemsa sed non per nigro de Sudan o reagente acide periodic de Schiff.

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