FOCAL LESION OF FRIEND’S DISEASE IN BONE MARROW*1

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Friend’s disease occurs in mice only a few days after the inoculation of Friend leukemia virus (FLV), and is characterized by the neoplastic proliferation of large polygonal cells in the red pulp of the spleen.

As to the origin of these cells, Friend,1) Metcalf, Furth, and Buffett,6) Kasuga and Oota,7) and Siegler and Rich8) have investigated it in detail, and concluded that it was a reticulum cell. Thus Friend’s disease has so far been considered to be a reticulum cell sarcoma. Recently, however, Friend et al.,2) noticed the erythrocytic maturation in the tissue culture lines of Friend solid tumors. According to the electron microscopic observation of the spleen foci of Friend’s disease, the authors concluded that Friend’s disease was an erythrogenic neoplasm.4) Furthermore, heme synthesis was proved by Takaku and the authors9) in the cells of the Friend ascites tumors, derived from the early splenic lesions in Friend’s disease,5) which supported the latter conclusion.

If Friend’s disease is an erythrogenic tumor as the authors have stated, the bone marrow must be involved. No detailed description, however, has been reported as to the changes of bone marrow in FLV-infected mice. Accordingly, the authors examined the sternal bone marrow of the mice which had been used for the spleen focus formation in the previous work.3,4)

MATERIALS AND METHODS

Animal DDD mice, male, 6-week-old, supplied by Institute for Infectious Diseases, University of Tokyo.

Preparation of Diluted Virus Solution
Ten-fold dilutions were made from the routine FLV inoculum.

Inoculation and Sacrifice Each 10-fold dilution of the original virus solution, 0.1 ml per mouse, was inoculated intraperitoneally or intravenously to each animal group consisting of 10 to 12 mice, splenectomized or non-splenectomized. The mice then were sacrificed serially.

Routine Methods for Histological Examination The viscera were routinely fixed in 10% formaldehyde solution and Orth’s solution for histological examination. For the examination of the bone marrow, the sternum, cut along the long axis, was used.

RESULTS

Spleen Focus Formation
Macroscopic spleen foci were well produced in the mice 9 days after the inoculation of 0.1 ml of \(10^{-3}\) to \(10^{-4}\) dilution of the routine FLV inoculum.3,4)

Focal Lesions in the Bone Marrow
In the sternal bone marrow of the mice with spleen foci, the focal accumulation of such large polygonal cells as seen in the spleen foci was frequently observed (Photos 1 and 2). The appearance of such focal lesions in the bone marrow was almost simultaneous with that of the spleen foci. The focal lesions in the

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bone marrow appeared in the pulp, not within sinusoids. They provided frequent mitotic figures (Photo 3). They were histologically identical to the focal lesions in the spleen (Photo 4).

In the splenectomized mice, the same focal lesions were observed in the sternal bone marrow. The frequency of the focal lesions in the latter groups was almost the same as that in the non-splenectomized groups. The focal lesions, consisting of large polygonal cells, appeared 7 to 9 days after the inoculation of 0.1 ml of $10^{-2}$ to $10^{-4}$ dilutions of the routine FLV inoculum.

**Changes in the Liver**

In the mice which had focal lesions of Friend's disease in the spleen and the bone marrow, the liver provided only slight infiltration of small erythroblasts in the sinusoids. In the animals inoculated with 0.1 ml of $10^{-4}$ dilution of the routine FLV inoculum, the focal lesions in the spleen and bone marrow appeared about 9 days after the inoculation, and the accumulation of Friend cells in the liver was noticed 14 to 17 days after the inoculation.

**DISCUSSION AND CONCLUSION**

Friend's disease has long been considered to be a murine viral reticulum cell sarcoma accompanied with prominent erythroblastosis. This consideration was chiefly based on the histological pattern of the FLV-infected spleen and the involvement of the spleen and the liver in Friend's disease.

In the present study, the focal accumulation of large polygonal cells was observed in the bone marrow of both splenectomized and non-splenectomized mice, inoculated with diluted FLV solution. In the non-splenectomized mice, the appearance of the bone marrow foci was simultaneous with that of the spleen foci. The cells in the bone marrow foci were histologically identical to those of the spleen foci. Judging from the electron microscopic observation of the spleen foci in Friend's disease, the cells in the foci in the bone marrow might resemble proerythroblasts or basophilic erythroblasts.

Thus, by applying the spleen focus method for the analysis of histogenesis of Friend's disease, the early sites of Friend's disease was proved to arise both in the spleen and in the bone marrow. This fact supports the conclusion that Friend's disease is a murine viral erythropoietic neoplasm.

Since the splenectomized mice with focal lesions of Friend's disease in the bone marrow provided the liver with only slight infiltration of the small erythroblasts in the sinusoids, followed by the true involvement of Friend's disease several days later, the hepatic lesions of Friend's disease in those mice are considered to be secondary to the bone marrow lesions.

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**REFERENCES**

9) Takaku, F., Ikawa, Y., Sugano, H., *This Journal*, to be published.

**EXPLANATION OF PLATE LII**


Photo 3. A high power view of Photo 2. Mitotic figures (M) observed. Formalin-fixed. Hematoxylin-Eosin stain. $\times 400$.

Photo 4. A focal lesion of Friend's disease in the spleen, shown for the comparison in the left upper portion. Formalin-fixed. Hematoxylin-Eosin stain. $\times 360$. 