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Thymic Lymphoma and Myeloid Leukemia in the Rat Induced with Ethylnitrosourea

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Summary. A high incidence of thymic lymphoma and leukemias was observed in adult Wistar rats after i.p. injection of ethylnitrosourea. Among 10 rats given 30 mg ENU, thymic lymphomas developed in three rats and hyperplastic thymic lesions in other three animals. Among 20 rats receiving 50 mg ENU, thymic lymphomas developed in nine, myeloid leukemia in five and other malignant tumors in three animals. It is still unknown why in some cases the myeloid tissue appears more susceptible to the carcinogenic action of ENU than the lymphoid tissue.

A moderate yield of experimental leukemias in the rat following treatment with p-nitroso(methyl)aminoazobenzene, methylnitrosourea and ethylnitrosourea was reported (Ivancovic, 1964; Druckrey *et al.*, 1967). After oral administration of N-nitrosobutylurea (Odashima, 1970) or 4–7 injections of pulse doses of DMBA an incidence of 100 per cent leukemia in the same strain of animals was recorded (Huggins and Sugiyama, 1966). Using relatively small doses of ethylnitrosourea we have observed a high incidence of thymic lymphomas and myeloid leukemia in adult Wistar rats. The present communication reports some of the initial results of this study.

Male random-bred Wistar rats were only used. Experimental animals were injected i. p. with 10 mg ethylnitrosourea (ENU) in alcohol-saline 1:4 at monthly intervals. Group 1:Ten rats received 3 × 10 mg ENU. Group 2:Twenty rats received 5 × 10 mg ENU. Group 3:Ten animals were injected with alcohol saline only. Eight months later all animals with manifested splenomegaly and orbital

Table 1.

Histological findings	Group 1 30 mg ENU	Group 2 50 mg ENU	Group 3 control
		N° of rats	
	10	20	10
Hyperplastic thymic lesions	3	—	—
Thymic lymphoma	—	3	—
Thymic lymphoma with lymphoblastic leukemia	3	6	—
Myeloid leukemia	—	5	—
Other neoplasms	—	3	—

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hemorrhages were sacrificed. The experiment terminated at the tenth month following treatment. Histological studies were made of the thymus, lymph nodes, spleen, liver, kidney and tumor tissues. White blood cell counts and smears of the bone marrow, spleen, lymph nodes as well as of peripheral blood were prepared and stained by May-Grünwald-Giemsa and peroxidase methods.

The localization and histological type of the lesions are summarized in the table. In Group 1 (30 mg ENU) three rats developed large thymic lymphomas with lymphoblastic leukemia and three animals had hyperplastic thymic lesions. Nine rats in Group 2 (50 mg ENU) developed thymic lymphoma, five myeloid leukemia, three – other neoplasms. Among nine rats with thymic lymphoma three were with aleukemic leukemia and the remaining – with lymphoblastic leukemia. The histologic appearance of the thymic lymphoma is shown in Fig. 1. The thymic neoplasms were lymphoblastic sarcomas often displaying a "starry sky" pattern. Lymph nodes were considerably enlarged. The predominant cell type in the lymph nodes resembled the neoplastic lymphoblasts in the thymus.

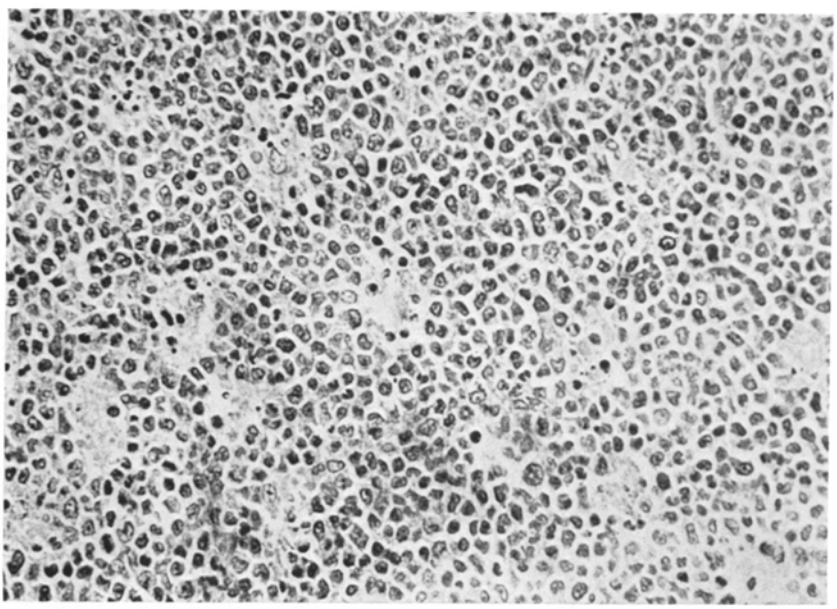

Fig. 1. Thymic lymphoma (lymphoblastic lymphosarcoma) displaying a "starry sky" pattern (50 mg ENU). H. & E. 200 ×

A moderate hepatosplenomegaly was also observed in these cases but splenic enlargement was not caused by a proliferation of lymphoid elements only. The peripheral blood smears in nine out of 12 rats (Groups 1 and 2) showed round mononucleated cells with a narrow rim of blue cytoplasm around the nucleus. Invasion of leukemic cells was seen perilobulary in the liver as well in the spleen, lungs and kidney. Among twenty animals of Group 2 five had myeloid leukemia apparently of induced origin. In these cases a characteristic feature of the disease

was an extreme splenomegaly, combined with enlargement of the mesenteric lymph nodes and liver. Histologically the typical findings in the liver was a diffuse proliferation of premature myeloid elements in the hepatic sinusoids and centrolobular veins. In the spleen an extreme proliferation of primitive cells led to disappearance of the normal organ structure. In the evaluation of femoral bone marrow smears some difficulties were encountered in distinguishing tumor cells from the normal marrow population when the proliferation of prematured marrow cells was not diffuse and well pronounced.

The main interest of these observations in relation to the problems of pathogenesis of rat leukemia is the high incidence of different proliferative lesions of the lymphoid-myeloid complex of tissues after the administration of a much smaller dose of the carcinogen ethylnitrosourea than in other studies (Druckrey *et al.*, 1967). It is still unknown why in some cases the myeloid tissue appears more susceptible to the carcinogenic action whereas in other the thymic neoplasmas prevail.

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