# VIRUS LEUKEMIA (RECTICULOSARCOMATOSIS) OF MICE INDUCED BY HUMAN LEUKEMIC MATERIAL

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A new strain of leukemia of CC57BR mice is described. It differs from other strains of virus leukemias mainly in the fact that initially this leukemia was induced in mice by material from the spleen and bone marrow of a person dying from acute hemocytoblastosis after passage through a surviving tissue culture. Morphologically the leukemia, transplantable into CC57BR and C57BL mice by means of cellular and cell-free material, is a reticulosarcomatosis with a typical macroscopic and microscopic picture.

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More than 15 strains of virus leukemias of mice are now known (Gross, Graffi, Friend, Mazurenko, Rauscher, etc.). In this paper we describe a vew strain of leukemia (recticulosarcomatosis) of CC57BR mice differing from other strains primarily in the fact that the leukemia was induced initially in mice by material from human leukemic tissue after passage through a surviving tissue culture [1].

## EXPERIMENTAL METHOD AND RESULTS

A suspension of the spleen and bone marrow of a person dying from acute hemocytoblastosis was introduced into a surviving tissue culture of normal human spleen. After incubation for 4 and 7 days at 37° the culture was injected into the spleen of 3-month old mice of line CC57BR, with a low incidence of spontaneous leukemia. Of the 24 mice surviving for 10 months from the beginning of the experiment, 9 developed leukemia. In some cases of leukemia it was impossible to preserve the cell transplants. Most leukemias belonged morphologically to the group of myeloses with typical macroscopic and microscopic pictures. A fresh surviving culture of normal spleen from a CC57BR mouse was infected with suspension of spleen from one mouse with induced leukemia (tumor-like form). After three passages (total duration of incubation at 37°, 1.5 months) the supernatant of the 8-day surviving culture was injected intraperitoneally into 20-day old CC57BR mice. After 22.5 months, two of the three surviving mice developed leukemias. Transplantation of cells from a mouse with induced reticulosarcomatosis was carried out into mice of the same line. Reticulosarcomas began to appear 4-5 months later. In most mice transplantation of cells from these tumors caused the development of reticulosarcomatosis with a latent period of less than 30 days (usually 3 weeks).

Reticulosarcomatosis of CC57BR mice was adapted by transplantation of cells (after a latent period of 5 months) into C57BL mice. A cell-free supernatant was prepared from the liver, spleen, and tumor tissue of 4th generation mice and, when injected into newborn CC57BR mice, caused them to develop typical reticulosarcomas (the first case of leukemia was observed one month after inoculation of the mice).

In some experiments leukemias (reticulosarcomas) appeared 3-4 weeks (or later) after injection of Seitz filtrates of leukemic tissues into newborn (1-3 days old) CC57BR mice.

Induction of leukemia was also possible by material taken from animals before they developed morphological signs of leukemia. Leukemic cells were transplated into CC57BR mice. Forty days later, before any signs of leukemia had appeared, a suspension of spleen, liver, and bone marrow cells was transplanted from one of these mice intraperitoneally into adult CC57BR mice. After 8 months the mice developed typical reticulosarcomatosis.

Consequently, leukemia could be induced by virus isolated from an infected animal before any signs of leukemia appeared.

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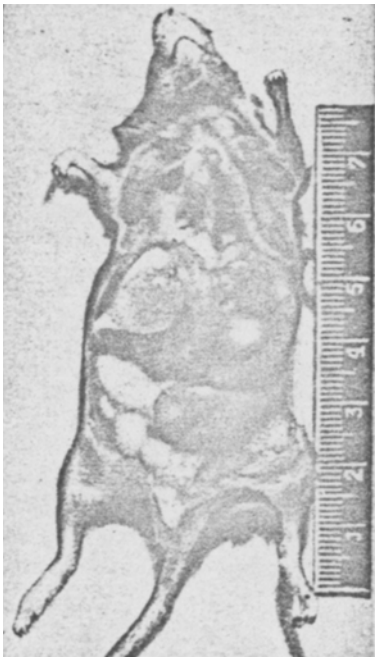

Fig. 1. Microscopic picture of reticulosarcomatosis of CC57BR mouse.

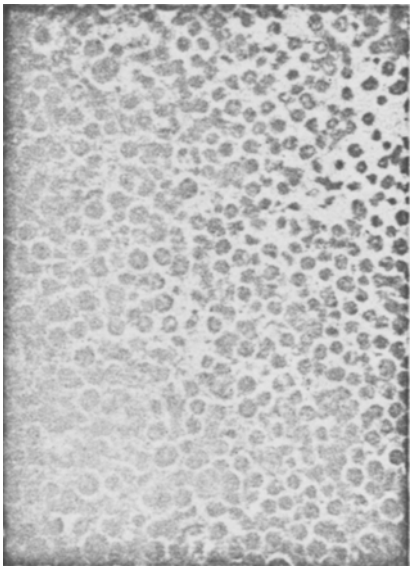

Fig. 2. Microscopic structure of tumor nodule from mouse with reticulosarcomatosis.

The typical macroscopic picture of this strain of leukemia is shown in Fig. 1. As a rule the liver of these animals was considerably enlarged, with numerous large white tumor nodules. Tumor nodules were also observed between loops of intestine. The spleen, kidneys, and thymus were sometimes enlarged, with white nodules. Often the spleen was small and macroscopically unchanged. The peripheral lymph glands were moderately enlarged.

Cytological investigation of the bone marrow, spleen, liver, kidney, thymus, and tumor nodules revealed a uniform picture of total metaplasia of the organs: young, large cells with an ill-defined border of cytoplasm, a round nucleus, in which numerous mitoses were present and could be seen. These young cells were identified as reticular cells of the hematopoietic system, but sometimes they resembled the germinoblasts described by Czech workers [2].

Histological investigation shows that the organs (liver, spleen, kidney, lungs, thymus) were intensively infiltrated or largely replaced by tumor of reticulosarcoma type (Fig. 2), with an extremely polymorphic cell composition, consisting of atypical polymorphic reticular cells with numerous mitoses, accompanied by malformed cells with giant hyperchromic nuclei.

A few days before death, the blood usually showed leukocytosis (up to several tens of thousands), with the appearance of immature cells. The antigenic spectrum of the strain of leukemia now being described, compared with other leukemic and normal tissues, is at present being studied in the gel-diffusion reaction.

Rabbit antisera against this strain of leukemia (reticulosarcomatosis) contained antibodies definitely reacting with antigens obtained from the spleen, liver, lungs, kidneys, and tumor nodules of animals with reticulosarcomatosis. As a rule this antigen was also detected in the spleen of normal mice of various lines. So far as other organs are concerned, only traces of this antigen could be detected in them. Traces of it were also found in certain organs of animals with transplanted and virus leukemias. In cases of Maloney, Mazurenko, Zil'ber-Postnikova, and Rausher virus leukemias, this antigen could not be found in the liver, kidneys, lungs, and tumor nodules, although it could be found in the spleen. It must be assumed that this antigen is not virus-induced, but is connected with the cell specificity of this strain of leukemia. Antisera against reticulosarcomatosis of CC57BR mice also reacted with antigens of normal and leukemic human tissues. However, antigens detected by our sera in human tissue differed from the antigens found in mouse tissues.

The following fact must be borne in mind when considering the mechanism of development of leukemia in the experiments described above. Leukemia unquestionably developed in the mice under the influence of virus, because the latent period of development of the disease produced by injection of leukemic material after three passages at 37° in the course of 1.5 months was 22 months, while after transplantation it was more than 4 months. In addition, reticulosarcomatosis can be produced by injection of cell-free centrifuged and filtered material into newborn CC57BR mice.

The experiments results show that leukemic human tissues contain an agent which is preserved in culture of surviving human spleen tissue and which induces leukemia in mice of line CC57BR with a low incidence of spontaneous leukemia. The fact that transplantation of cells of induced leukemias into other mice as a rule is unsuccessful may be indirect evidence that the tissues (antigens) of leukemias induced by tissues of mice of the same pure line are foreign in nature (this is confirmed to some extent by the gel-diffusion reaction).

The possible etiologic significance of the isolated leukemogenic agents for human leukemia remains unexplained, and no methods for solving this problem can yet be clearly visualized.

The similarity or difference between virus causing reticulosarcomatosis in CC57BR and C57BL mice and other leukemogenic viruses of mice has been studied only in the gel-diffusion reaction. A common antigen is present only in the spleen of mice with Moloney, Friend, and Mazurenko leukemia, but it is absent from other organs of mice with Rauscher, Moloney, Mazurenko, and Zil'ber–Postnikova virus leukemias.

## LITERATURE CITED

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