

EFFECT OF CHRONIC HYPERIMMUNIZATION WITH
DTP VACCINE ON DEVELOPMENT OF LEUKEMIA
IN PURE-LINE AKR AND CC57BR MICE

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After chronic hyperimmunization of AKR and CC57BR mice there was an increase in the incidence of leukemia compared with the control. Vaccinated mice developed neoplasms which differed qualitatively from the spontaneous leukemias found in mice of these lines (reticulososes, lymphoreticulososes, carcinoma of the liver in AKR mice) or appeared only after induction by carcinogens (reticulosarcomas, myeloid leukemia in mice of line CC57BR with a low incidence of spontaneous leukemia). In AKR mice there was some increase in the mean latent period of development of the leukemias.

Many modern methods of prevention and treatment of diseases (vaccination of the population, serum and antibiotic therapy, etc.) considerably modify the course of typical pathophysiological processes in the body and also the typical course of recovery and increase the incidence of abortive and subclinical forms of diseases. Recent times have also brought an increase in the number of harmful environmental factors, which are phylogenetically new and to which man is unaccustomed, and which are therefore frequently highly pathogenic (for example, ionizing radiation, magnetic and electric fields, active chemical carcinogens, and so on).

As a result of exposure to factors of this type the reactivity of the organism to external specific and nonspecific stimuli is frequently modified. Usually this state does not disturb vital activity to any marked degree, but under certain conditions or during exposure to additional factors it may lead to the development of a disease. This state of the body has been called premorbidity [5].

The comprehensive study of the consequences of sensitization, the pathogenetic role of which in the etiology of many diseases (including malignant tumors and leukemias) has been insufficiently investigated, is of the greater importance to medical practice. The importance of this problem is emphasized by the considerable growth in allergization of the population, one reason for which is the prevention of infectious diseases by means of vaccination.

Allergization can play an important role in the etiology of leukemia in man as clinical and experimental observations have shown. In particular, collagenoses, reactive reticulososes, and anaplastic states developing against the background of allergic changes not infrequently are combined with or precede leukemias [1, 2, 6, 8, 10].

A leukemogenic or leukemia-stimulating effect has been obtained by administration of various antigens to animals, and has also been observed in animals with experimental models of autoimmune processes [9, 11-14].

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TABLE 1. Neoplasms in AKR and CC57BR Mice during Hyper-immunization Experiment

Index	Animals observed for 12 months				Animals sacrificed at 7 months				Total	
	AKR		CC57BR		AKR		CC57BR		AKR CC57BR	
	con- trol	expt.	con- trol	expt.	con- trol	expt.	con- trol	expt.	con- trol	expt.
Total number of mice	18	23	25	25	15	16	14	16	72	80
Number of mice with neoplasms:										
leukemia	11	15	—	—	—	1	—	—	11	16
with lymphoreticuloses	—	2	—	—	—	—	—	—	—	2
with reticuloses	—	1	—	1	—	—	—	—	—	2
with myeloid leukemia	—	—	—	1	—	—	—	—	—	1
with carcinoma of the liver	—	—	—	—	—	1	—	—	—	1
Number of mice dying:										
from malignant tumors	11	18	—	2	—	2	—	—	11	22
from other diseases	2	2	—	—	—	—	—	—	2	2
Percentage of neoplasms*	69	85,5	—	8	—	12,5	—	—	14	27,5

$P < 0,05$

*Mice dying from other diseases were not included when the percentage of leukemias was calculated.

In the investigation described below the role of sensitization in the development of leukemias was studied. Combined diphtheria, pertussis, and tetanus (DTP) vaccine, widely used for the prevention of children's infectious diseases, was used as the antigen. According to data in the literature this vaccine induces a powerful allergizing effect [3, 7] and sharply reduces the lysozyme and complement levels of the phagocytic activity of the leukocytes.

EXPERIMENTAL METHOD

Altogether 152 female AKR and CC57BR mice were used in the experiments. A high incidence of spontaneous lymphatic leukemias and vertical transmission of leukemogenic virus to the progeny is observed with mice of line AKR. The incidence of spontaneous leukemia in line CC57BR mice is low, not more than 1% [4].

The animals were immunized with DTP vaccine at the age of 1.5 months in a dose of 0.2 ml intramuscularly. The first three injections were given at intervals of 2 weeks, and the subsequent revaccinations at intervals of one month throughout the period of observation. Control animals were not vaccinated.

Some of the animals were examined for the presence of leukemias in the course of the disease among the mice, which remained under observation for 12 months. In the remaining animals, which were sacrificed at the age of 7 months before any outward manifestations of the disease were present, leukemias were found at autopsy (cytological and histological material was subsequently investigated).

The diagnosis was made by a combination of methods: autopsy, inoculation, cytological and histological examination.

The χ^2 method was used for statistical analysis.

EXPERIMENTAL RESULTS

The results are given in Table 1.

In vaccinated AKR and CC57BR mice under observation for 12 months the incidence of leukemia was higher than in the control animals.

The vaccinated mice developed neoplasms which differed qualitatively from spontaneous leukemias in the mice of these lines (reticulosos, lymphoreticulosos, carcinoma of the liver in AKR mice) or which appeared only after induction with carcinogens (reticulosarcoma, myeloid leukemia in CC57BR mice with a low incidence of spontaneous leukemia).

The distribution of the leukemias in time in control and vaccinated AKR mice under observation for 12 months is interesting. The vaccinated AKR mice showed an increase in the mean latent period of the leukemias by 1 month: in the control animals the latent period was 7 months, while in the experimental animals it was increased to 8 months.

Different interpretations are possible to the increased frequency of leukemia following immunization. In particular, some authorities regard hypoplasia of the lymphoid and reticular tissues as a precancerous state [12, 14].

Other investigators consider that this hyperplasia is a manifestation of a "potentiation effect" based on stimulation of the formation by antigens of "blocking" antibodies, which weaken the lethal action of cytotoxic antibodies or lymphocytes on malignant cells [9].

The results of the investigations described above provide evidence of the complex changes taking place in the state of the protective mechanism in vaccinated animals.

Evidence of activation of the protective mechanisms in the initial stage of the process is shown by the increased latent period of the leukemias in the immunized animals. Cytological investigations of the hematopoietic organs showed that initially (until the age of 5 months) stimulation of the hematopoietic and immunogenic functions was observed in the vaccinated animals.

In the period of development of leukemia (7-12 months of life), however, gross destructive and proliferative changes were observed: systemic reactive reticulosos, disturbances of the tissue proteins, hypoplasia of the bone marrow, atrophy of the lymphoid follicles of the spleen, and suppression of the plasma-cell response in the lymph glands.

These changes, indicating a sharp decrease in the protective power of the body, evidently contributed to the increase in incidence of leukemia and to the development of neoplasms which do not normally arise spontaneously in the mice of these lines.

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