Prolongation of Life in High-Leukemia AKR Mice by Cortisone.* (20094)

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This experiment is one of a series designed to further explore the mechanisms of action of hormones in cancer processes, especially in relation to cancer prevention and cancer control. The study here reported provides evidence that chronic cortisone administration prolongs the life of female mice of the high-leukemia strain AKR. The prolongation of life resulted from prevention of spontaneous lymphoid leukemia deaths at the early age typical of this strain.

Materials and methods. Female mice of the high-leukemia strain AKR were given prolonged treatment with cortisone acetate starting when the mice were 4 weeks of age. Thirty-seven mice, 20 treated and 17 control, were observed until their death from leukemia or other causes. The data are incomplete as 2 treated animals are still alive at 16 months. The calculations are based on a terminal date of 16.4 months. The data are still further modified by the deliberate sacrifice and autopsy of 6 treated mice at 14 months of age. All other mice were, insofar as possible, autopsied and gross and microscopic examination of leukemic and suspected leukemic lesions conducted at time of death. The *treated mice* were injected subcutaneously with 1 mg/day in 2 divided doses of an aqueous suspension of cortisone acetate (Merck). Injections were given for 3 consecutive days, at monthly intervals, earlier studies having indicated this to be the maximum dose tolerated well when given at monthly intervals. Diet consisted of Purina laboratory chow and water fed *ad libitum*. All mice were bred.

Results. The mean length of life of the control females was 9.3 months and of the treated mice 14.3. The mean difference of 151 days was significant with $P < .001$. Fig. 1 shows the per cent mortality at different ages. Seventy-six per cent of the control animals had evidence of acute leukemia at death. Animals not exhibiting leukemia were only those unaccountably lost from the group. In the treated group, the usual macroscopic evidence of leukemia was absent. Histological evidence of mild infiltrating leukemia was found in a few animals. Often death seemed to be due to multiple infections and conditions related to cortisone treatment. Many bizarre lymphocytes, monocytes, and polymorphonuclear cells were seen in the older treated animals.

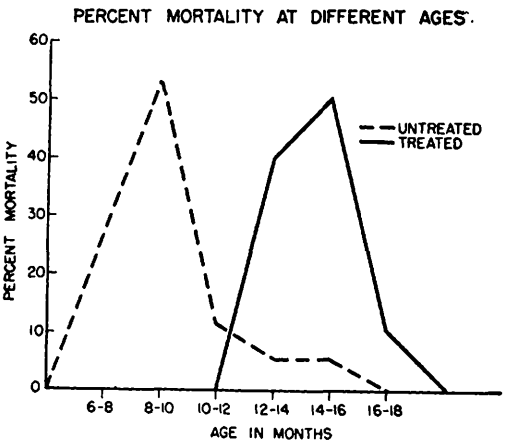

FIG. 1.

Discussion. The pronounced effects of pituitary adrenotropic hormone and adrenal cortical extracts on lymphoid tissues have long been known(1,2). A recent review of this subject is available(3). The effects of adrenal cortical and adrenotropic hormones on primary and transplanted lymphomas and leukemias indicate a possible relationship of the adrenals to the growth of these tumors(4-10). Recently, cortisone has been shown to inhibit significantly lymphoma development after x-radiation(11). Four cortical steroids were observed to be especially active in reducing the rate of transplanted lymphoid tumor growth in the mouse(12,13). In the present experiment cortisone was used because of its well-known ability to regress lymphoid tissues and,

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temporarily, lymphoid tumors. In selecting the high-leukemia AKR strain, consideration was given to the fact that in this case precancerous or early cancer changes would not have to be detected since leukemia at a relatively uniform age is an almost constant occurrence. The method of treating the animals periodically was chosen in an attempt to minimize the possible selection of cortisone resistant cell types as therapy proceeded. Preliminary tests indicated that 1 mg/day for 3 days was the maximum which could be used monthly with adequate survival. Prolongation of life with a decrease in the incidence of spontaneous leukemia has previously been reported as the result of (a) drastic caloric restriction in AK mice where the mean length of life was prolonged from 9.6 months to 14.0 months(14) and (b) total thymectomy at early ages in AK, RIL, and C58 strains where the mean length of life was prolonged from 7.6 to 12.7 months, 9.5 to 13.6, and 10.6 to 15.5 months respectively(15,16). The possible reasons for increase in longevity and reduction in occurrence of acute leukemia at early ages in the present study will be discussed in a later report.

Summary. Periodic administration of cortisone throughout life to high-leukemia AKR mice significantly prolonged their mean length of life from 9.3 months to 14.3 months. Prolongation of life resulted from prevention of spontaneous leukemia deaths at the early age expected in this strain.

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Life Span of the Red Blood Cell in the Hypophysectomized Rat.* (20095)

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The fundamental defect leading to any anemia must be either a decrease in rate of production of red cells or a decreased life span of red cells in the circulation or a combination of the two. Evidence in favor of each of these possibilities has been given to explain the anemia which characteristically follows hypophysectomy. Hypoplasia of the bone marrow(1) and a decrease in reticulocytes in the peripheral blood after hypophysectomy (2) are strong, but not conclusive, evidence that the post-hypophysectomy anemia results from a decreased activity of the bone marrow in producing erythrocytes. Hemosiderosis of the spleen of hypophysectomized rats(3) and a normal reticulocyte response after bleeding hypophysectomized rats(4) have been given as evidence that the pituitary is concerned with the control of blood destruction rather

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