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Abstract

1) The influence of thyroid secretion upon the induction of leukemia in DbA/2 male mice by methylcholanthrene was investigated. Radiothyroidectomy significantly reduced the incidence of leukemia in these mice. This reduction in incidence did not occur if radiothyroidectomy was performed after the administration of the carcinogen. 2) Data indicated that hypothyroidism following radiothyroidectomy interfered with the initiation rather than the promotion of methylcholanthrene-induced-leukemogenesis. 3) No correlation between incidence of leukemia and body weights in the mice was noted.

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**INFLUENCE OF THYROID SECRETION ON THE
INDUCTION OF LEUKEMIA IN DBA MICE BY
METHYLCHOLANTHRENE**

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There has long been speculation regarding a possible relationship between hematopoietic tissues and thyroid function. Lymphocytosis has often been noted in patients with hyperthyroidism. Growth of lymphatic tissues in thyroxine-treated animals has been demonstrated. Elevation of metabolic rates has been observed in patients with leukemia. Blood iodine can be markedly elevated in the lymphoid leukemia patient. Striking remission after thyroidectomy has been reported in a patient with chronic lymphocytic leukemia.

GRAD(1955)^{1,2} investigated the influence of hyper- and hypothyroidism upon the incidence of mouse leukemia. He found that thyroxine decreased and thiouracil increased the incidence of spontaneous leukemia in AKR mice.

In 1953, BIELSCHOWSKY³ reported his studies of tumor induction with 2-aminofluorene and its acetyl-derivatives in thyroidectomized rats. In his experiment, the incidence of liver tumors was suppressed by thyroidectomy performed prior to the administration of carcinogen. No suppressive effect was found when thyroidectomy was done after the administration of carcinogen.

WOLFSON (1956)⁴ demonstrated that thyroidectomy by radioactive iodine shortened the interval between the onset of sarcoma and the administration of methylcholanthrene to rats.

Since these results appeared to show some discrepancies, the present investigations were undertaken to evaluate the influence of hypothyroidism upon leukemogenesis in mice.

In our experiment, DBA/2 male mice were used as the experimental animal, methylcholanthrene as the carcinogen, and radioiodine as the procedure of thyroidectomy.

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MATERIAL AND METHODS

Dda/2 male mice were divided into the following six groups :

1. Methylcholanthrene only.
2. I^{131} + Methylcholanthrene.
3. I^{131} + Isograft of thyroid + Methylcholanthrene.
4. Methylcholanthrene + I^{131} .
5. Methylcholanthrene + I^{131} + Isograft of thyroid.
6. I^{131} only.

Beginning at the age 6—10 weeks, generally at 8 weeks, Dba/2 male mice were given eighteen skin paintings (three times weekly for 6 weeks) of 0.25 % solution of methylcholanthrene in benzene. A number 6 camel's hair brush was used to apply the carcinogen at a different site for each successive skin painting.

To determine more clearly whether hypothyroidism interferes with "initiation" of carcinogenesis by methylcholanthrene or with the "promotion" of methylcholanthrene-induced carcinogenesis, radioactive iodine was administered either before or after painting with methylcholanthrene.

Male mice of the same age and strain were given three hundred microcuries of radioactive iodine, intraperitoneally, and skin painted 2 weeks later with methylcholanthrene.

Thyroid replacement therapy consisted of the subcutaneous implantation, in the axillary region, of both lobes of the thyroid glands of young adult mice of the same strain.

Thyroid isograft was made 2 weeks after radioactive iodine administration ; this was followed in one week by methylcholanthrene painting.

RESULTS

As shown in Fig. 1, 34 mice out of 49 painted with methylcholanthrene developed leukemia. This represented an incidence of leukemia of 69 % at 400 days of age (Exp. 1).

Male mice given 300 μ c of radioactive iodine, intraperitoneally, and skin painted 2 weeks later with methylcholanthrene showed a reduction in the incidence of leukemia to 12%. Only 9 out of 74 mice developed leukemia by 400 days of age (Exp. 2).

In 52 control mice receiving radioactive iodine alone, no leukemia developed (Exp. 6). Of the mice, which received isografts of thyroid tissue after radiothyroidectomy, 16 out of 30 mice (53%) developed leukemia after methylcholanthrene painting (Exp. 3).

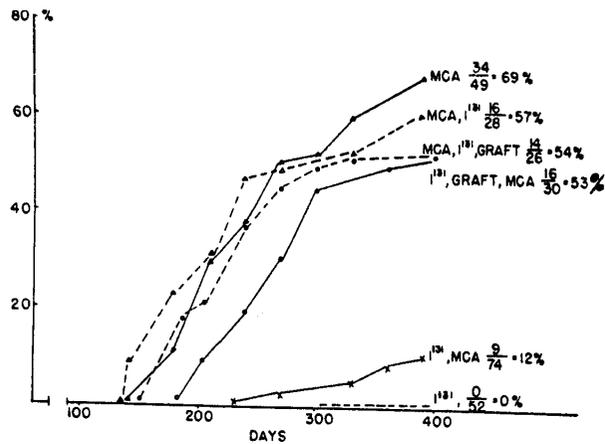


Fig. 1. Suppression of methylcholanthrene leukemogenesis in mice by radio-thyroidectomy

This suggests that the effect of radioactive iodine on methylcholanthrene leukemogenesis is related to its thyroidectomy effect, rather than to other pharmacological or radiological effects.

If radioactive iodine was not administered until 2 weeks after the last painting with methylcholanthrene, its suppressive effect on methylcholanthrene leukemogenesis was largely eliminated. Under these conditions, 16 out of 28 mice (57%) developed leukemia (Exp. 4).

In animals which were painted with methylcholanthrene first and subsequently underwent radiothyroidectomy and isograft, the incidence of leukemia was 54% out of 26 mice developing leukemia (Exp. 5).

BODY WEIGHTS

Body weights were routinely measured. No significant differences in body weights were found among the various experimental groups of animals until after 100 days of treatment. After this time the body weight data became distorted by the development of leukemia and the death of experimental animals (Fig. 2).

These data therefore appeared to indicate that in order to suppress methylcholanthrene leukemogenesis, the hypothyroid state must be present during the period of "initiation" of leukemogenesis; further, this effect is not dependent upon body weight changes.

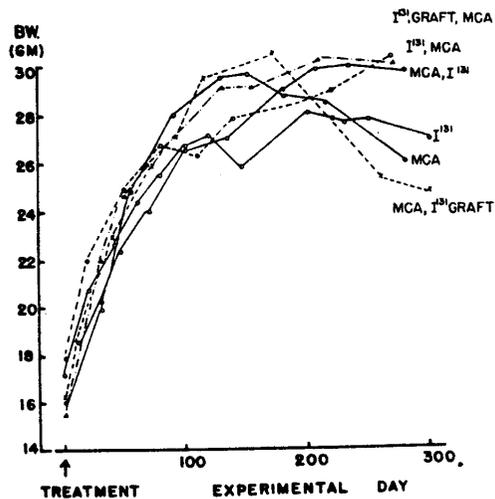


Fig. 2. Body weight of DbA/2 male treated with I¹³¹ and methylcholanthrene

DISCUSSION

According to our data, hypothyroidism showed a significant suppressive effect upon the induction of leukemia by methylcholanthrene.

As far back as 1909, STUART-LOW⁵ reported that cancer was rarely found among patients with myxedema. Surgical thyroidectomy was associated with regression in the size of tumors in his patients. According to HOHNENBURG, BULLOCK and JOHNSTON(1911)⁶, the removal of certain glands (i. e., thyroid, thymus and testes) appeared to decrease the susceptibility of rats to Flexner-Jobling sarcoma. MUROHARA (1930)⁷ demonstrated that thyroidectomy as well as the injection of large doses of thyroxine inhibited the growth rate of transplanted sarcoma in the rabbit. These data were confirmed by NISHIDA (1935)⁸, and KOSUGI (1937)⁹, LEVINE and KUGEL (1933)¹⁰, McJUNKIN, TEMPLETON and KRAVEC (1936)¹¹, and DARGENT, VIALIER and GUINET (1951)¹² also reported the suppressive effect of hypothyroidism upon implanted #180 mouse tumor, uterine spindle cell sarcoma in albino rats and inoculated tumor #8 of Guerin (uterine adenocarcinoma).

As cited earlier, BIELSCHOWSKY (1953)³ found that thyroidectomy resulted in the suppression of the induced liver tumor in rats by 2-amino-fluorene. In our experiment in which radiothyroidectomy significantly lowered the incidence of methylcholanthrene-induced leukemia in DbA/2 mice, the magnitude of the suppression was equivalent to that observed for

hepatic tumorigenesis in thyroidectomized rats fed acetylaminofluorene (KIRSCHBAUM, 1957)¹³.

WOLFSON (1956)⁴ noticed that sarcoma in rats was induced by 3-methylcholanthrene and that the onset of the disease was delayed when radioactive iodine was injected into the animals. According to MORRIS, WOLF and UPTON(1957)¹⁴, average survival time of rats and mice with transplanted lymphoma was prolonged if hypothyroidism was induced by either propylthiouracil or surgical thyroidectomy. These data cited above seemed to be quite similar to the results obtained in our experiment.

GRAD (1957)², however, reported that AKR mice rendered hypothyroid by thiouracil developed spontaneous leukemia at a significantly higher rate than AKR mice rendered hyperthyroid by the administration of thyroxine. KAPLAN (1954)¹⁵ has pointed out that although these contrasting data were significantly different from each other, neither result differed significantly from the incidence in untreated controls. GRAD² further concluded that the influence of hyper- or hypothyroidism on the incidence of spontaneous lymphatic leukemia of AKR mice depends on what effect these states had on the body weight of the animals.

In our experiment, no significant difference in body weight was noted between the radioiodine-treated mice and non-radioiodine-treated mice. Therefore, body weight may not be the important factor in the induction of leukemia in mice.

In 1942, SMITH, WELLS and D'AMOUR¹⁶ reported that thyroidectomy did not influence the induction of tumor by methylcholanthrene in rats. However, in their study, methylcholanthrene administration preceded thyroidectomy. BIELSCHOWSKY and HALL (1953)³ investigated tumor induction by 2-aminofluorene and its acetyl derivatives in thyroidectomized rats. In their experiment, thyroidectomy prior to the administration of the carcinogens prevented the development of neoplasms of the liver; thyroidectomy performed after the administration of the carcinogens did not modify carcinogenesis. These data, as well as ours, suggest that the time of thyroidectomy was the critical factor in the induction of neoplasms by carcinogens.

In our experiment, a dose of 300 μC of I^{131} was used to destroy thyroid function. GORBMAN (1947)¹⁷ has shown that 100 μC in normal adult mice produced almost complete and 200 μC complete thyroidal destruction. In addition, he (1949)¹⁸ reported that following doses of radioactive iodine sufficient to cause destruction of most or all of the thyroid, tumorous enlargements were found in the pituitary gland of mice. In our experiment, pituitary gland tumors were noticed in 6 out of 52 mice given radioiodine

only and in 4 out of 74 mice given radioiodine plus methylcholanthrene.

GOLDBERG and CHAIKOFF (1949)¹⁹ have shown that thyroidectomy without parathyroidectomy can be achieved with intraperitoneal radioactive iodine, when newborn rats are injected with I¹³¹, in a dose of 80 to 150 μ c, or adult rats in a dose ranging from 300 to 875 μ c (GOLDBERG and CHAIKOFF 1950)²⁰. In view of these data, it could be assumed that parathyroid function in our animals was not significantly influenced by the dose of 300 μ c.

No significant influence of hypothyroidism upon neoplasm was reported by MORIMOTO (1932)²¹ BISCHOFF and MAXWELL (1932)²² and VAZQUEZ-LOPEZ (1949)²³, using rabbits, rats and R III strain of mice respectively. Since the animal used in these experiments and the treatment which caused hypothyroidism were different from those in our experiment, different results might be expected.

SOLVITER (1951)²⁴ was among the first to study the effect of radiothyroidectomy on the survival of tumor bearing mice. No noticeable effect was found in his experiment. However, his experiment differed from ours in that he used implanted, rather than chemically induced tumors.

Recently, NAGAREDA and KAPLAN (1959)²⁵ studied the effect of radiothyroidectomy and thyroid grafts on the incidence of lymphomas in the thymic implants in thymectomized irradiated C57BL mice. Hypothyroidism significantly inhibited thymic implant tumor development in females; a similar reduction of lymphoma incidence in hypothyroid males was not statistically significant. In our experiment, only Dbal/2 male mice were used in order to avoid the complication of mammary cancer in evaluation of the incidence of leukemia.

SUMMARY

1) The influence of thyroid secretion upon the induction of leukemia in Dbal/2 male mice by methylcholanthrene was investigated. Radiothyroidectomy significantly reduced the incidence of leukemia in these mice. This reduction in incidence did not occur if radiothyroidectomy was performed after the administration of the carcinogen.

2) Data indicated that hypothyroidism following radiothyroidectomy interfered with the initiation rather than the promotion of methylcholanthrene-induced-leukemogenesis.

3) No correlation between incidence of leukemia and body weights in the mice was noted.

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