Thymus and the Carcinogenic Induction of Mouse Leukemia*

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The thymus may under certain conditions determine susceptibility to the development of leukemia in mice. The incidence of spontaneous leukemia in Ak mice was remarkably reduced by thymectomy (2); extirpation of the thymus similarly reduced the susceptibility of C57BL mice to the induction of leukemia by x-rays (4) and of DBA/2 mice to the leukemogenic activity of methylcholanthrene (10). Although thymic involvement was observed infrequently in leukemia of C58 mice, thymectomy reduced the spontaneous incidence (9). For either the carcinogen-induced or spontaneous disease, susceptibility of thymectomized mice was restored by thymic grafting (9, 10).

The thymus was either exclusively or more extensively involved than other organs in leukemias induced by estrogenic hormone (3) or the combined action of estrogen and x-rays (7). When leukemia was induced in DBA/2 mice by feeding methylcholanthrene (1), the thymus was usually heavily infiltrated. The thymus proved to be more sensitive than other lymphoid tissues to the leukemogenic action of small doses of carcinogenic hydrocarbons which were injected directly into the tissue (11).

Apparently, the thymus provides a favorable environment in mice of certain genetic constitution for the transformation of normal to leukemic lymphocytes. When the thymus of a susceptible parent strain was grafted into thymectomized hybrids between this and a resistant-to-leukemia strain, the F₁ hybrid leukemias were transplantable only to the F₁ hybrids and not to the high leukemia strain which served as the donor for grafted thymus (8). This experiment indicates that the grafted thymus induced F₁ hybrid lymphocytes to become leukemic. Histologic studies suggested that the grafted thymus had invovled and become reconstituted by infiltration of F₁ hybrid lymphocytes.

Thymectomized C57BL mice were rendered susceptible to the leukemogenic action of whole-body x-radiation by grafts of nonirradiated C57BL thymus. The nonirradiated grafted thymus served as a focus for the neoplastic alteration of lymphocytes (5). Apparently thymic cells were "indirectly" induced by x-rays to become leukemic.

Since gonadectomized DBA/2 mice under specific conditions exhibited a greater susceptibility than intact animals to the carcinogenic induction of leukemia (11), gonadectomy-thymectomy experiments were planned. The objective was to determine whether the enhanced susceptibility of gonadectomized mice is mediated by the thymus.

MATERIALS AND METHODS

Methylcholanthrene-treated mice of the DBA/2 strain were either thymectomized, gonadectomized, or both operations were performed. Thy- mectomy was done between 35 and 50 days of age except in one group (Chart 3) thymectomized at 4 weeks of age.

Methylcholanthrene dissolved in thiophene-free benzene was painted on the skin with a #6 camel's hair brush, a different site on the mouse being used for each skin painting to avoid the induction of skin tumors.

Thymectomy was performed under urethane-anesthesia. The thymus was exposed by a mid-line, antero-posterior incision through the sternum from the manubrium half-way to the diaphragm. The left lobe was carefully brought to the exterior by gentle traction with forceps, and it was then usually possible to remove the right lobe together with the left. If the thymus was not identifiable in its entirety after extirpation, the operated mouse was discarded. Only the skin was sutured.

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Within a few days after operation (42–50 days of age) skin painting was begun.

**RESULTS**

Thymectomized DBA/2 mice receiving 36 skin paintings of a 0.25 per cent solution of methylcholanthrene in benzene were at least as susceptible as unoperated mice of this strain to the carcinogenic induction of leukemia (Chart 1). Initially, thymectomy had been done at 35–50 days of age, followed by skin painting at 42–50 days of age. Since Law (3, 4) had thymectomized at 4 weeks of age to demonstrate a thymic influence upon leukemogenesis, a group of mice was thymectomized at this age prior to the administration of 36 skin paintings. To parallel Law’s experiments further, a group of thymectomized animals was given eighteen instead of 36 skin paintings, since Law had used only twenty skin paintings of a 0.2 per cent solution of methylcholanthrene in benzene. That the thymus is frequently and primarily involved in our mice is suggested by the data from which Chart 2 was made.

Age at thymectomy did not alter the leukemogenic action of 36 skin paintings of a 0.25 per cent solution of methylcholanthrene in benzene administered to thymectomized mice. Of eleven males and eleven females thymectomized at 4 weeks of age, fifteen became leukemic when skin paintings were administered 3 times weekly for 12 weeks beginning at 42–48 days of age (Chart 3).

- **CHART 1.** —The incidence of leukemia in DB mice induced by 36 skin paintings of methylcholanthrene begun at 42–50 days of age was not reduced by thymectomy. Almost 100 per cent of gonadectomized-thymectomized mice developed leukemia. Thymectomy performed at 35–50 days of age.

- **CHART 2.** —Twenty-five per cent of DB male mice receiving eighteen skin paintings of methylcholanthrene had large thymomas suggesting that the thymus was the initial locus of neoplasia in methylcholanthrene-induced leukemia.

When thymectomized males were skin-painted eighteen rather than 36 times, however, the incidence of leukemia induced by methylcholanthrene was reduced (Chart 4), confirming the observations of Law. The incidence was higher and the age of onset earlier if the animals were gonadectomized as well as thymectomized (Charts 1 and 4). Leukemia
appeared in 45 of 46 thymectomized-castrated mice which received 36 skin paintings (Chart 1).

**DISCUSSION**

The thymus of DBA/2 mice was more susceptible than extra-thymic lymphoid tissue to the leukemogenic action of methylcholanthrene if the dose of the skin-painted carcinogen dissolved in benzene was relatively low (eighteen skin paintings). With a higher dose (36 skin paintings), no differential in susceptibility of thymus and extra-thymic lymphoid tissue was apparent. The action of methylcholanthrene was potentiated by gonadectomy in either thymectomized DBA/2 mice or animals of this strain with an intact thymus. Whatever influence the DBA/2 thymus exerts on leukemogenesis was exhibited by lymphoid tissue outside the thymus when 36 skin paintings were given. The disease occurring in thymectomized animals was in no way distinguishable from that induced in animals possessing a thymus.

The observations of Law on the leukemia-inciting action exerted by grafted thymus upon infiltrating host lymphocytes are fundamental. Since extra-thymic lymphoid tissue of thymectomized mice is independently susceptible to leukemogenic influences, it may be expected that this tissue should possess similar properties which have not as yet been demonstrated. Thymic and extra-

**SUMMARY**

The incidence of methylcholanthrene-induced lymphocytic leukemia was not reduced by thy-
mectomy when DBA/2 mice received 36 skin paintings of 0.25 per cent methylcholanthrene in benzene during 12 weeks, beginning at 42–50 days of age. When half this dose of carcinogen (eighteen skin paintings) was given, thymectomy reduced the incidence of induced leukemia, indicating a lower threshold of sensitivity of thymic lymphoid tissue to the leukemogenic action of methylcholanthrene. Gonadectomy enhanced susceptibility to the induction of leukemia whether or not mice possessed a thymus.

REFERENCES
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