BIOLOGIC PROPERTIES OF ISCADOR: A VISCUM ALBUM PREPARATION

I. Hyperplasia of the Thymic Cortex and Accelerated Regeneration of Hematopoietic Cells following X-Irradiation

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We demonstrated that a preparation of *Viscum album* (Iscador) has unusual effects on the immune system. In CD-1 mice, the mean weight of the thymus increased from 45 to 85 mg. following six daily intraperitoneal injections of 2.5 mg. of Iscador. The thymic trophic influence was maintained over a long period of time. Sprague-Dawley rats treated with Iscador for 16 weeks showed an increase of 78 per cent in thymic weight over controls. The increased weight of the thymus was due to increased proliferation of cortical thymocytes. The number of blast cells in the outer cortex of the thymus increased within 2 days of the first injection and remained at high levels. Thymocytes of Iscador-treated animals were 29 times more responsive to Concanavalin A than those of untreated controls. Iscador increased the amount of antibody produced by animals injected with sheep red blood cells if it was injected after the antigen. Iscador also had effects on hematopoietic cells. It accelerated the recovery of hematopoietic tissue in bone marrow and spleens of irradiated animals. We believe that *V. album* preparations may be valuable reagents for perturbing thymus function.

Additional key words: Bone marrow, Thymus hypertrophy.

Viscum album, mistletoe, is a toxic plant which has been used in medicine for centuries. In 1926, during the first era of intense interest in tumor immunology, a product made from crude press juice of the plant called "Iscador" was introduced in Europe as an immunotherapeutic agent for cancer (5). This work was carried out under the direction of Rudolph Steiner, and Iscador was produced commercially in Arlesheim, Switzerland. Like Colley's bacterial toxins (20), which were introduced during the same era in this country, injections of Iscador reportedly produced regression or remission of some tumors, but few patients were cured, and the preparation soon fell from favour. However, the production and clinical evaluation fo Iscador has continued in Arlesheim. Two aspects of the published work on Iscador aroused our interest. First, repeated intraperitoneal injections of Iscador reportedly produced enlargement of the thymus (21); and second, similar injections suppressed the growth of certain experimental tumors (11).

The thymus has been considered to be a central lymphoid organ which produces T lymphocytes under the control of various hormonal and cellular stimuli, but independently of external antigenic stimulation (16). The evidence for autonomous function of the thymus is convincing. If thymus tissue is transplanted from one animal into another of different age or compatible strain, its rate of growth or involution follow the pattern characteristic of the donor, not the recipient in which the graft is placed (18, 19). In experiments involving transplantation of many thymuses into mice, Metcalf (15) demonstrated homeostatic controls governing the total tissue mass of the spleen but not of the thymus. Most of the lymphocytes produced by the transplanted thymuses remained in the thymus where they were destroyed. Additionally, most investigators have found that injection of antigens which cause marked proliferation of the lymphoid tissue in the spleen and lymph

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nodes have little or no demonstrable effect on the thymus (14, 17). However, recent evidence suggests that the thymus may play an active role in the generation of specific suppressor cells (10) and in contact sensitivity (4). There are scattered reports that cells in the thymus proliferate following some types of antigenic stimulation. Injections of Pertussis (6), dansyl chloride (8), organ grafts (27), phytohemagglutinin (1), sheep red blood cells (22), and an SV40-induced tumor (13) have all been reported to stimulate proliferation of lymphoid, reticular, and/or epithelial cells in the thymus. Stimulation of thymocyte proliferation by these agents was detected by histologic or autoradiographic techniques. It was seldom, if ever, clearly detected on gross examination. Nienhaus, Stoll, and Vester (21) reported that extracts of *V. album* have far greater effects on the thymus than any of these other materials. They found that injections of Iscador caused the thymus to double in size within a few days. We are unaware of reports of any other material with this activity. This paper reports our confirmation and extention of the work of Nienhaus. We found that Iscador stimulates a striking proliferation of cortical thymocytes, increases their reactivity to the mitogen and Concanavalin A, enhances antibody production to sheep red blood cells, and accelerates the recovery of bone marrow following sublethal x-irradiation.

Materials And Methods

Iscador is the trade name for *V. album* preparations intended for parenteral injection. We obtained Iscador Mali from Arlesheim, Switzerland. The extract were received in glass vials of 10 ml. containing a 10 per cent solution (100 mg. of fresh plant per ml.). They were stored at 4°C. throughout the experiments. The required dilutions were made daily, and the unused portions of the original vials were stored in sealed plastic containers.

Animals

CD-1 outbred, 18- to 20-g. female, albino mice were obtained from Charles River Breeding Laboratories, Wilmington, Massachusetts. Female C57BL/6 mice weighing 20 to 25 gm. were obtained from The Jackson Laboratory, Bar Harbor, Maine. Female Sprague-Dawley rats weighing 70 gm. were obtained from Sprague-Dawley Farms, Maidson, Wisconsin.

Toxicity Studies

The "therapeutic dose range" of Iscador is reported to be 5 to 15 per cent of the LD_{50} (29). To determine the LD_{50} for the particular batches of Iscador used, groups of 16 C57BL/6 mice, CD-1 mice, and Sprague-Dawley rats were injected intraperitoneally with doses of Iscador Mali ranging from 10 to 10,000 mg. per kg. The LD_{50} was found to be 700 mg. per kg. for CD-1 mice, 348 mg. per kg. for C57BL/6 mice, and 378 mg. per kg. for Sprague-Dawley rats. Animals injected with lethal doses of Iscador developed hemorrhagic peritonitis and died with tonic and clonic seizures. In most experiments, lower doses produced a transitory leukocytosis, but no peritonitis or seizures. White blood counts rose to around 50,000 cells per cubic mm 3 hours and returned to normal by 6 hours after injection. The dose of Iscador given to each group was a percentage of the LD_{50}, such that all animals were given Iscador in the therapeutic range but at different ends of the spectrum.

Radiation Experiments

C-57BL/6, CD-1 mice, and Sprague-Dawley rats were irradiated with a Maxitron 250, General Electric x-ray machine which produced 250 kilovolts potential, with a filter of 0.25 mm. of copper and 1 mm. of aluminum. The animals were placed in lusteroid centrifuge tubes that rotated on a Lucite platform.

Blast Transformation Assay

Rat thymuses were removed and placed in a sterile Petri dish containing Hanks balanced salt solution and teased apart. This suspension of thymocytes was washed twice and adjusted to a final concentration of 2×10^7 cells per ml. in serum-free medium (RPMI 1640, ISI, Carey, Ill.). Suspension (50 μl.) was placed into each well of a 96-well flat-bottomed microtiter plate (Linbro Chemical Company, New Haven, Connecticut) containing 100 μl. of serum-free medium and 50 μl. of a concentration of Concanavalin-A (Sigma Chemical Company, St. Louis, Missouri). Then, another 50 μl. of medium containing 80 per cent fetal bovine serum were added. After 47 hours incubation at 37°C., 25 μl. of tritiated thymidine (40 μCi. per ml.) were added. Twenty-four hours later, the plates were harvested on an Otto Hiller harvester, and the incorporated label was counted using a Searle scintillation counter.

Morphometric Analysis of Splenic and Thymic Tissues

The spleen or thymus was fixed in a 10 per cent neutral buffered formalin solution. Histologic slides were then prepared and stained with hematoxylin and eosin or methyl green pyronin. The slides were then examined with a microscope equipped with a grid that was divided into 36 equal squares. The relationship between the various components of the thymus (medulla, cortex, etc.) or spleen (hematopoietic tissue, lymphopoietic tissues, etc.) was expressed as the ratio between the numbers of squares occupied by the corresponding tissues. At least 10 representative microscope fields were assessed for each section.

Results

CD-1 mice were injected intraperitoneally daily with 72 mg. per kg. of Iscador Mali. Within 3 days, the gross weight of their thymuses began to increase. As seen in Figure 1, the thymus weight approximately doubled by day 9. In other experiments, mice were

injected at least four times a week with the same dose of Iscador for periods up to 16 weeks. Their thymus weight stabilized at a level about 50 per cent above that of controls. Histologic analysis of the thymus confirmed the gross observations. The weight increase was due to hyperplasia of the cortex and could not be attributed to attached lymph nodes or other tissues. The earliest changes were seen at 1 day after the first injection, many of the thymocyte nuclei showed densely clumped and segregated chromatin which resembled mitotic figures. Some may have been mitotic figures, but most were probably lymphoid cells undergoing degeneration (Fig. 2). The reticulum cells in the cortex became much more prominent. They developed bulky cytoplasm with a foamy appearance, stained positively with periodic acid-Schiff and contained many pyknotic nuclei. By day 3, the number of large lymphoblasts in the cortex had increased dramatically. These cells stained strongly with methyl green pyronin. Peak cortical activity occurred between days 9 and 13 when most of the cells in the thymic cortex were immature pyroninophilic lymphocytes (Fig. 3). Mitoses and large lymphoid cells occurred throughout the cortex but were most prominent near the capsule. The ratio of cortex to medulla changed from about 3:1 in control animals to 7:1 in Iscador-treated animals at the peak response. We detected little change in the medullary portion of the thymus. With continued injections, the proliferative activity and pyronophylic cells of the thymus decreased but remained above that of controls.

Similar increases in thymic weight were observed in C57BL/6 mice and Sprague-Dawley rats. The weight of the C57BL/6 thymuses increased from 45 ± 6 to 80 ± 12 mg. following six daily injections of 75 mg. per kg. of Iscador Mali. The thymuses of Sprague-Dawley rats increased from 306 ± 10 to 546 ± 42 mg. following 16 daily injections of 19 mg. per kg.

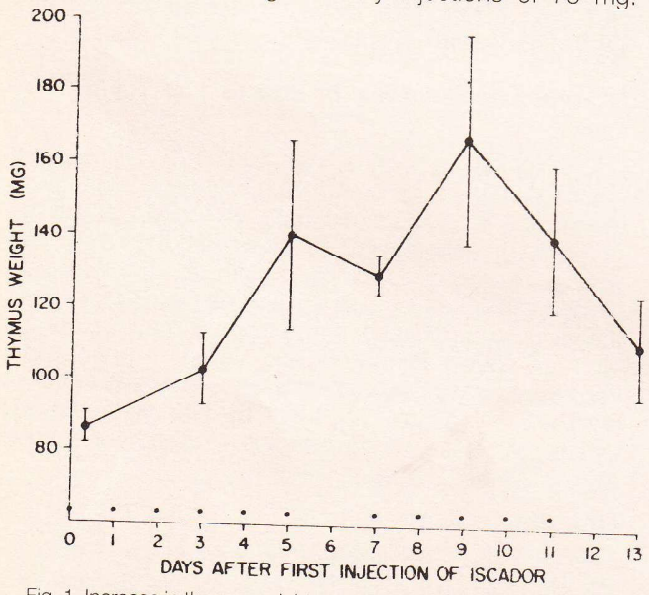

Fig. 1. Increase in thymus weight associated with daily intraperitoneal injections of 72 mg. per kg. Iscador Mali into CD-1 mice. The dots along with the base line show the days when injections were given. The means ± standard deviation for groups of three mice are shown.

Effects on Spleen and Lymph Nodes

Injections of Iscador Mali stimulated proliferation of lymphoid cells in the spleen and thoracic lymph nodes which drain the peritoneal cavity. The most pronounced proliferative activity was in the thymic dependent areas, the periarterial lymphoid sheath of the spleen, and the paracortex of the lymph nodes. There was also increased proliferation of germinal centers, the red pulp of the spleen, and medulla of the lymph nodes.

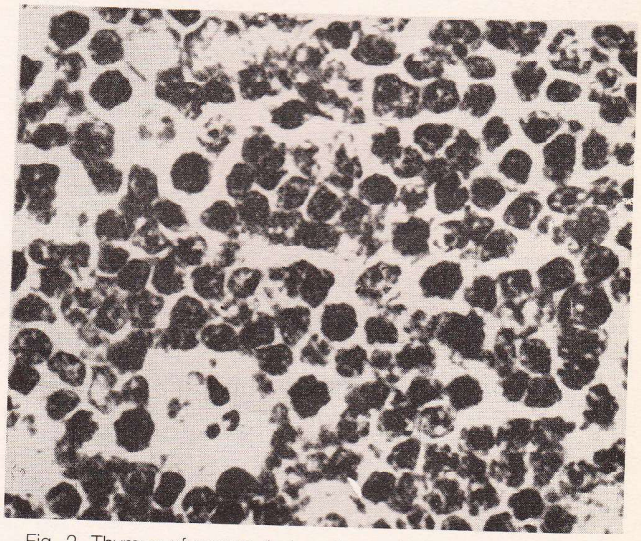

Fig. 2. Thymus of mouse 1 day after a single injection of Iscador. Note the increased number of mitoses and degenerating cells. Most lymphocytes are still small. Hematoxylin and eosin; x500.

Lymphocyte Stimulation Studies

Sprague-Dawley rats were injected with 38 mg. per kg. of Iscador 6 days per week for 8 weeks. At that time, the thymuses weighed 498 ± 59 mg. as compared to 327 ± 7.8 mg. for controls. As seen in Table 1, Iscador did not increase the spontaneous uptake of ^{3}H-thymidine by the thymus cells in culture. However, it did increase the amount of ^{3}H thymidine taken up in response to Concanavalin A by more than 15 times and the stimulation index by 29 times.

Effect on Antibody Response to Sheep Red Blood Cells

Injections of Iscador either enhanced or suppressed the production of antibody to sheep red blood cells depending upon the timing of injections. If animals were injected with a low dose of Iscador 3 days before injection of sheep red blood cells, antibody formation was suppressed on day 10. In contrast, if they were injected with the same dose on days 4 through 10 following sheep cell injecton, antibody titers were increased from 10 to 30, Table 2.

Effects on the Recovery of Irradiated Bone Marrow and Spleen

On several occasions, we separated plasma by centrifugation of blood in heparinized capillary tubes. We noted that the hematocrits of animals treated with Iscador for 2 or more weeks were higher by about 10 per cent than those of controls. Consequently, we performed experiments on the recovery of hematopoetic tissues following sublethal whole body irradiation to investigate this phenomenon. Animals were given whole body irradiation and then injected intraperitoneally with doses of Iscador as shown in Table 3. The femoral bone marrow and the spleen were studied at intervals by morphometric methods. As expected, the destruction of lymphoid and hematopoctic tissues occurred rapidly. Several days later, colonies of hematopoetic cells, especially etythropoetic cells, formed. The first colonies were observed under the splenic capsule and were only visible microscopically. In animals treated with Iscador, these colonies appeared in both the spleen and bone marrow and occupied a much larger area than those in controls. Six days after irradiaion, hematopoetic tissue occupied over 78 per cent of the spleen of animals treated with 37 mg. per kg. of Iscador as compared with only 6.6 per cent of the untreated controls (Fig. 4). In this same experiment, by 14 days postirradiation, the hematopoetic tissue in Iscador-treated animals occupied 13 per cent as compared with 43 per cent in untreated controls. We interpret this as a delayed recovery of untreated animals at a time when Iscador-treated animals had largely returned to normal. The recovery of lymphoid tissue as measured by the area of the white pulp of the spleen followed a slower course. Similar increases in the rate of recovery of hematopoietic and lymphoid cells were observed in CD-1 mice irradiated with 550 rads and Sprague-Dawley rats irradiated with 650 rads.

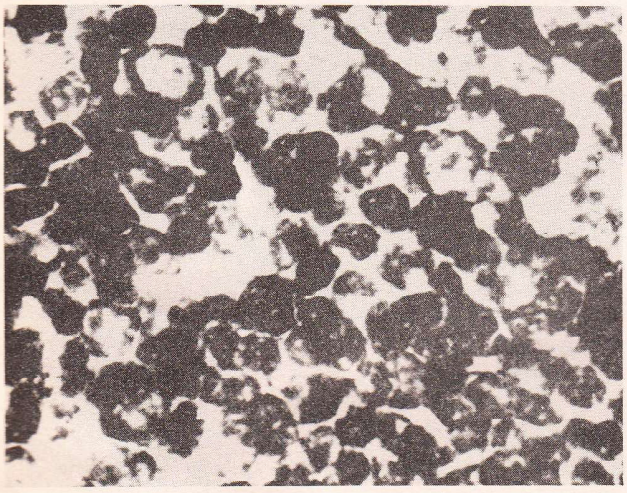

Fig. 3. Thymus of mouse after 9 days of Iscador treatments as shown in Figure 1. Most of the cells in the cortex are large lymphocytes. Hematoxylin and eosin, x500.

The changes in hematopoietic cells in the bone marrow of the various groups of animals were similar to those observed in their spleens.

TABLE 1. STIMULATION OF THYMUS CELLS FROM ISCADOR-TREATED RATS BY CONCANAVALIN A[a]

Treatment	Stimulation	
	Concanavalin A	None
Iscador	152,000 ± 7,000	2,500 ± 1,100
None	10,000 ± 4,000	4,200 ± 900

[a] Sprague-Dawley rats were injected intraperitoneally with 38 mg. per kg. of Iscador Mali for 6 days per week for 8 weeks. Their thymus cells were then stimulated with Concanavalin A in culture. The mean ± standard deviation of the counts per minute of ^{3}H-thymidine replicates are shown.

TABLE 2. ANTIBODY TITERS TO SHEEP RED BLOOD CELLS IN C57BL/6 MICE TREATED WITH ISCADOR[a]

Days of Iscador treatment	Sheep red blood cell injection (day 0)	Antibody titer (day 10)
None	None	Less than 1
None	+	10 ± 1
−3	+	5 ± 1
4 through 10	+	30 ± 10

[a] Mice were injected intraperitoneally with 14 mg. per kg. either 3 days before or on days 4 through 10 after a single intraperitoneal injection of 0.5 ml. of a 10 per cent suspension of sheep red blood cells. Hemagglutinin antibody titers 10 days after injection of sheep red blood cells are shown as the mean ± standard deviation on groups of six mice.

TABLE 3. EFFECT OF ISCADOR ON THE REGENERATION OF THE SPLEEN OF C57BL/6 MICE FOLLOWING TOTAL BODY X-IRRADIATED WITH 400 RADS ON DAY 0[a]

Days after irradiation	Iscador treatment	Area occupied by hematopoietic cells	Area occupied by white pulp (lymphoid cells)
	mg/kg/day	%	%
Day 6	74	44.0 + 11.0	25.0 + 2.0
	37	78.5 + 3.0	10.5 + 0.7
	0	6.6 + 1.0	25.0 + 2.8
Day 14	74	29.0 + 5.0	27.2 + 2.0
	37	13.0 + 5.0	46.0 + 5.0
	0	43.0 + 3.0	18.0 + 3.0

[a] Daily intraperitoneal injections of Iscador Mali were begun on day 1. The percentage of the spleen occupied by hematopoietic cells in the red pulp and lymphoid cells in the white pulp were determined by morphometric methods. The results are shown as the mean per cent area ± standard deviation on groups of three animals.

Discussion

The principal finding of this paper was that repeated intraperitoneal injections of Iscador caused a proliferation of lymphoid and reticulum cells in the cortex of the thymus and a doubling of the weight of the gland in 9 days. Since changes in the survival and rate of emigration of cells from the thymus were not quantitated, the relative contribution of these factors to the hypertrophy of the thymuses in Iscador-treated animals is unknown. The pattern of proliferation of thymus cells

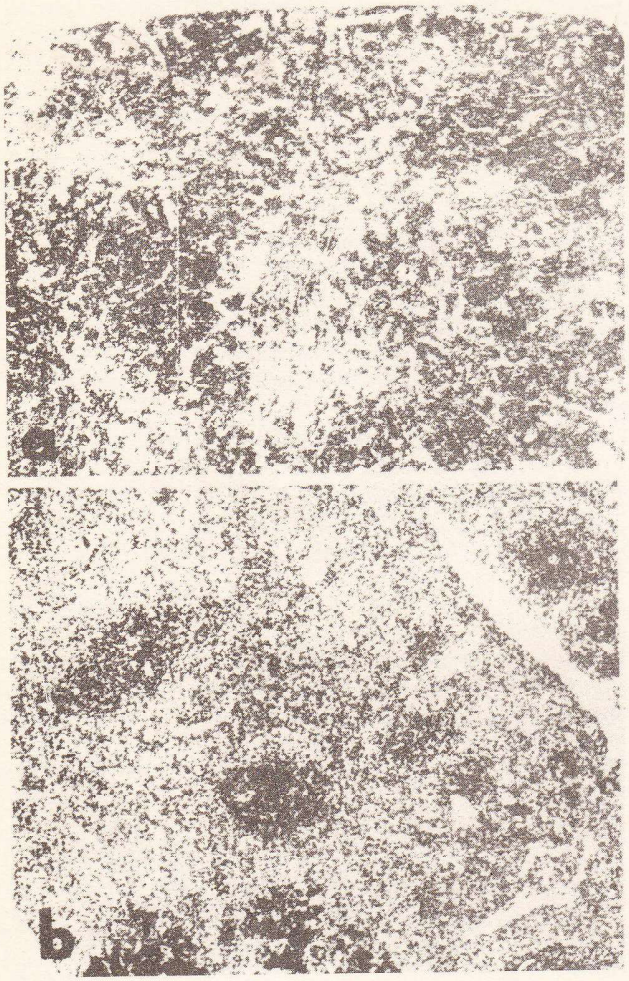

Fig. 4. Effects of Iscador Mali on the proliferation of erythropoietic cells in the spleen of x-irradiated animals. C57BL/6 mice were irradiated and injected with 37 mg. per kg. of Iscador as shown in Table 3. Spleens were removed 6 days after irradiation. *a*, Iscador-treated animal. The red pulp is nearly filled with erythropoietic cells. *b*, Irradiated animal not treated with Iscador as control. Hematoxylin and eosin; ×40.

induced by Iscador was an accentuation of that described during normal thymic activity (16). Mitotic figures and pyroninophylic cells developed vacuolated reticulum cells. They then spread throughout the cortex. As discussed in the introduction, increased proliferation of cortical lymphocytes and epithelial cells have been described following the injection of some antigens. The effect of Iscador appears similar to, although quantitively much greater, than that of these antigens. The type of proliferative activity in the thymus in autoimmune diseases and following direct antigen injection is different. Direct injection of antigen into the thymus causes the proliferation of lymphocytes, germinal centers, and plasma cells in the medulla (24). The thymic changes found in myasthenia gravis and other human autoimmune disorders and animal diseases such as the lupus-like syndrome in NZB mice also consist of germinal center and plasma cell hyperplasia, in addition to an infiltration by small and large lymphocytes (2, 3, 12).

If an animal is subjected to severe stress such as starvation or injection of corticosteroids, its thymic cortical lymphocytes are lysed and the gland shrinks to less then 25 per cent of its normal weight in a few days. On cessation of the stress, the cortical lymphocytes proliferate, and the gland rapidly recovers. The doubling time of the weight of the thymus of 2-month-old female C3H mice recovering from cortisone acetate is less than 2 days (16). It is evident that cortical thymocytes have a tremendous but tightly controlled capacity to proliferate.

Thymic lymphocytes became 29 times more responsive to Concanavalin A as a result of Iscador treatments. Since thymocytes normally develop increased responses to Concanavalin A as they mature, this suggests that Iscador stimulates maturation of thymocytes(7). Iscador caused a suppression of antibody production when injected before immunization with sheep red blood cells but caused an augmented response when injected after the sheep cells. These effects are typical of many adjuvants which may either enhance or suppress antibody responses depending on the timing of injections (9). They are not necessarily related to the effects on the thymus. Finally, Iscador caused an acceleration of regeneration of hematopoetic cells following sublethal x-irradiation. The relationship between the effects on bone marrow and the effects on the thymus is unknown. However, these experiments demonstrate that Iscador is able to stimulate a variety of cell types which are not stimulated by most antigens.

These experiments confirmed and extended the work of Neinhaus, Stoll, and Vester (21) which demonstrated that Iscador can cause thymic hyperplasia. Not all investigators have found these results. In particular, Stettler (26) performed similar experiments with Iscador Mali and found no significant increased weight or proliferative activity of the thymus. They did find a marked hyperplasia of the perithymic lymph nodes which they thought others might have misinterpreted as thymic lobules. They used doses of Iscador comparable to those use in the present experiments and two strains of mice. Although there may be strain differences in the response to Iscador, the fact that we have found similar changes in the thymus of two strains of mice and in Sprague-Dawley rats makes it unlikely that this is the entire explanation. It seems more likely that there were differences in the batches of Iscador used.

The nature of the active components of Iscador is uncertain. *V. album* has long been recognized as a toxic plant. It contains several protein toxins (23, 25). Vester (28) has reported that the tumor-inhibiting material in Iscador is a protein with a molecular weight of 60,000. In addition, it has been reported that Iscador contains a lectin which is specific for D-galactose (30).

There is no evidence that any of these materials are responsible for the effects of Iscador on the thymus. Nevertheless, the proliferation of cortical thymocytes produced by repeated injections of Iscador is far greater than that reported for any other known substance. Consequently, Iscador provides a new probe for perturbing thymic function in ways that are likely to have both theoretical and practical importance.

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"It is good to rub and polish your mind against the minds of others."

Michel de Montaigne