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Thymic Atrophy and Lymphoid Hyperplasia in Mice Bearing Sarcoma 180.

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The changes in the size or weight of the thymus induced by various endocrine factors have been assumed to parallel those occurring in lymph nodes.[1-4] This is instanced by the concurrent hypertrophy of these tissues following adrenalectomy[5,6] and the concurrent atrophy after thyroidectomy,[7,8] gonadectomy,[7,9] the administration of cortical hormones[10-12] and pituitary adrenocorticotrophin.[13-15] While this evidence strongly supports the contention that the thymus acts as part of the lymphoid tissue, opinions to the contrary are widely held[16-18] and have recently been reviewed.[19]

One of us recently described[20] the *pronounced hyperplasia* of, and the increased nitrogen deposition in lymphoid tissue (as represented by the combined thymus and lymph node weight and nitrogen content) of male mice of the CFW strain bearing implants of Sarcoma 180. Independently, the other of us observed that Sarcoma 180 in female mice of the same strain evoked a *significant atrophy* of the thymus.[21] It thus appeared that under the conditions of these experiments identical factors could produce a *simultaneous thymic atrophy and lymphatic hyperplasia.* The present study demonstrates this fact.

Experimental. Sarcoma 180 was implanted subcutaneously near the axilla[22] as previously described[20,21] into 12 male and 12 female CFW mice (Carworth Farm) of approximately 18-20 g body weight; an equal number of untreated mice of both sexes served as controls. The latter group (6 animals per cage) received an amount of Purina Fox Chow equivalent to that consumed by the corresponding tumor bearing group and all animals were given tap water *ad libitum;* this control of food intake was later found to have no apparent effect on the tissue changes observed.

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1 Dougherty, T. F., and White, A., *J. Lab. Clin. Med.*, 1947, **32**, 584.

2 Houssay, B. A., quoted *J.A.M.A.*, 1942, **118**, 833.

3 Li, C. H., and Evans, H. M., *Vitamins and Hormones, Advances in Research and Applications*, 1947, **5**, 197, Academic Press, Inc., New York.

4 Selye, H., *J. Clin. Endocrinology*, 1946, **6**, 117.

5 Reinhardt, W. O., and Holmes, R. O., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 267.

6 Houssay, B. A., *Rev. Soc. Argentina Biol.*, 1941, **17**, 26.

7 Chiodi, H., *Endocrinology*, 1940, **26**, 107.

8 Reinhardt, W. O., and Wainman, P., PROC. SOC. EXP. BIOL. AND MED., 1942, **49**, 257.

9 Chiodi, H., *Rev. Soc. Argent. de Biol.*, 1938, **14**, 74.

10 Ingle, D. J., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 443.

11 Ingle, D. J., PROC. SOC. EXP. BIOL. AND MED., 1940, **44**, 174.

12 Dougherty, T. F., and White, A., *Am. J. Anatomy*, 1945, **77**, 81.

13 Moon, H. D., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 42.

14 Dougherty, T. F., and White, A., PROC. SOC. EXP. BIOL. AND MED., 1943, **53**, 132.

15 Simpson, M. E., Li, C. H., Reinhardt, W. O., and Evans, H. M., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 135.

16 Best, C. H., and Taylor, N. B., Physiological Basis of Medical Practice, Williams and Wilkins Co., Baltimore, 1943.

17 Caffey, J., The Nelson Loose-Leaf Medicine, Thomas Nelson and Sons, New York, 1946.

18 Margolis, H. M., *Archiv. Path.*, 1930, **9**, 1015.

19 Andreasen, E., *Acta Pathol. et Microbiol. Scandinavia*, Suppl. XLIX, Dissertation 1943.

20 Homburger, F., *Science*, 1948, **107**, 648.

21 Savard, K., *Science*, 1948, **107**, 381.

22 Sugiura, K., *Radiology*, 1937, **28**, 162.

TABLE I. Weight Changes of Thymus and Lymph Nodes in Intact Mice Bearing Sarcoma 180.

Sex	Group	No. animals	Final body wt, g	Thymus wt		Lymph nodes wt	
				mg	mg/100 g B.W.	mg	mg/100 g B.W.
Male	Tumor bearing	10	16.1 ± 0.5*	9.8 ± 1.9	61 ± 10.5	54.4 ± 5.4	338 ± 28.9
	Controls	12	18.1 ± 0.5	27.0 ± 2.7	149 ± 12.5	30.5 ± 2.7	169 ± 13.3
Female	Tumor bearing	10	16.0 ± 0.5	16.4 ± 2.5	102 ± 14.0	63.6 ± 0.4	398 ± 19.4
	Controls	12	17.6 ± 0.5	30.9 ± 2.4	176 ± 12.9	34.8 ± 0.4	198 ± 20.3

* Mean ± standard error.

TABLE II. Weight Changes of Thymus and Lymph Nodes in Hypophysectomized Mice Bearing Sarcoma 180.

Sex	Group	No. animals	Final body wt, g	Thymus wt		Lymph nodes wt	
				mg	mg/100 g B.W.	mg	mg/100 g B.W.
Female	Tumor bearing	7	14.8 ± 1.2	26.1 ± 1.9	176 ± 12.5	65.9 ± 2.5	445 ± 17.1
	Controls	10	14.4 ± 0.3	36.4 ± 2.2	252 ± 14.3	45.0 ± 3.1	312 ± 22.8

Twelve days following tumor implantation, all animals were sacrificed by cervical fracture following a 16 hour fast, during which water remained available. The thymus and 3 lymph nodes (one axillary node from each side and one mesenteric node) were dissected from each animal and immediately weighed separately; other tissues were removed from these mice for additional studies which will be reported later. The weight of thymus and the combined weights of the three nodes, expressed in mg of fresh tissue and as mg per 100 g of final body weight are given in Table I.

In a second experiment, female mice of the same strain, weighing 12 to 14 g were hypophysectomized. Five days later Sarcoma 180 was implanted in the usual way in one half of the animals, the remainder serving as controls. From the time of pituitary removal the mice were maintained as described above except for the replacement of drinking water by physiological saline solution. The animals were allowed to survive for ten days following implantation and during this time one half of the tumor bearing group had died, while only 2 of the hypophysectomized control group were lost. Both groups were then sacrificed and the tissues dissected and weighed as described above. The completeness of pituitary removal, already indicated by the cessation of growth over the experimental period, was verified by histological examination of the base of the skull. Table II lists the weights of the thymus and the combined weights of the 3 lymph nodes of the hypophysectomized animals.

Discussion. The data shown in Table I and Fig. 1 demonstrate that mice of the CFW strain, bearing Sarcoma 180, exhibit atrophy of the thymus averaging 50% by weight, and an increase in lymph node weight of the order of 100%. No important sex difference was noted. Visual inspection indicated that the weight increase in the selected lymph nodes reflected a generalized change in the entire lymphatic system of the tumor bearing mice, a fact which has since been confirmed.[23] The

[23] Savard, K., and Tompkins, M., unpublished data.

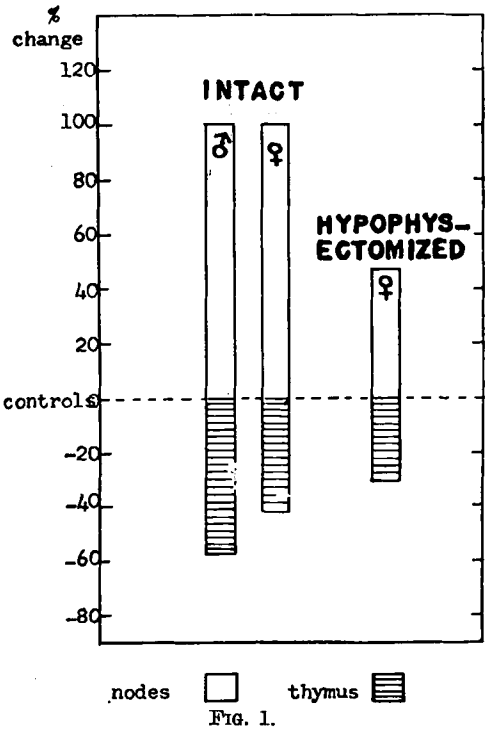

FIG. 1.

Per cent change over control values of thymus and lymph nodes weights expressed as mg per 100 g of body weight. The columns on the left refer to the intact animals; the one on the right refers to the hypophysectomized mice.

possibility of the hyperplasia being due to infection, regional lymphadenopathy or metastases of the tumor has been excluded in an earlier series by histological studies and a true lymphatic hyperplasia established by the clear cut increase in nitrogen content of these nodes.[20] There was thus, under the conditions of the experiment, a distinct dissociation of the response of the thymus and of the lymph nodes to the presence of growing Sarcoma 180.

In view of the fact that the growth of Sarcoma 180 in the CFW strain of mice is accompanied by adrenal changes indicative of an increased stimulation of the latter organ by the anterior pituitary[21] the possibility of a relationship between the endocrine system and the lymphatic and thymic changes was considered. The results of the second experiment shown in Table II indicate however that in the hypophysectomized animal, the growing tumor evoked a thymic atrophy and lymphatic hyperplasia, though to a lesser degree than in the intact animal; the adrenal hypertrophy and lowered ascorbic acid levels induced by the tumor in the intact animal[21] were, on the other hand, not observed in the hypophysectomized mice.[23] It is thus implied that the thymic and lymphatic changes are not mediated through the pituitary-adrenal system.

Summary. Transplanted Sarcoma 180 after 12 days of growth evokes thymic atrophy and lymphatic hyperplasia in mice of the CFW strain. These changes are not prevented by hypophysectomy, thereby excluding pituitary-adrenal mediation.

The authors wish to thank Dr. George Woolley and Miss Rosann Chute for the preparation of the hypophysectomized mice, and Miss Mary Tompkins and Miss Iris Forbes for their technical assistance.

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Response of Guinea Pigs to Diets Deficient in Choline.

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The hepatic choline concentration of the choline-deficient rat, when calculated on a fat-free basis, is not lower than that of normal rats.[1,2] This fact has been correlated with the observation that the choline oxidase activity of the fatty livers of choline deficient rats is markedly suppressed[3] and the suggestion advanced that it is the diminished choline

1 Jacobi, H. P., and Baumann, C. A., *J. Biol. Chem.*, 1942, **142**, 65.

2 Handler, P., and Dann, W. J., *J. Biol. Chem.*, 1942, **146**, 357.

3 Handler, P., and Bernheim, F., *J. Biol. Chem.*, 1942, **144**, 401.