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Effects of Calcium Deficiency and Pyridoxin Deficiency on Thymic Atrophy (Accidental Involution).

Herbert C. Storek.

From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York City.

In a variety of experimental conditions atrophic thymus glands have been described by many observers. In many of the cases this atrophy has been attributed to the variable introduced by the experiment. The specificity of the observed effect, however, was not ascertained by sufficient controls.

In the following it has been attempted:

1. To establish the approximate norm for thymus size in albino rats raised under con-

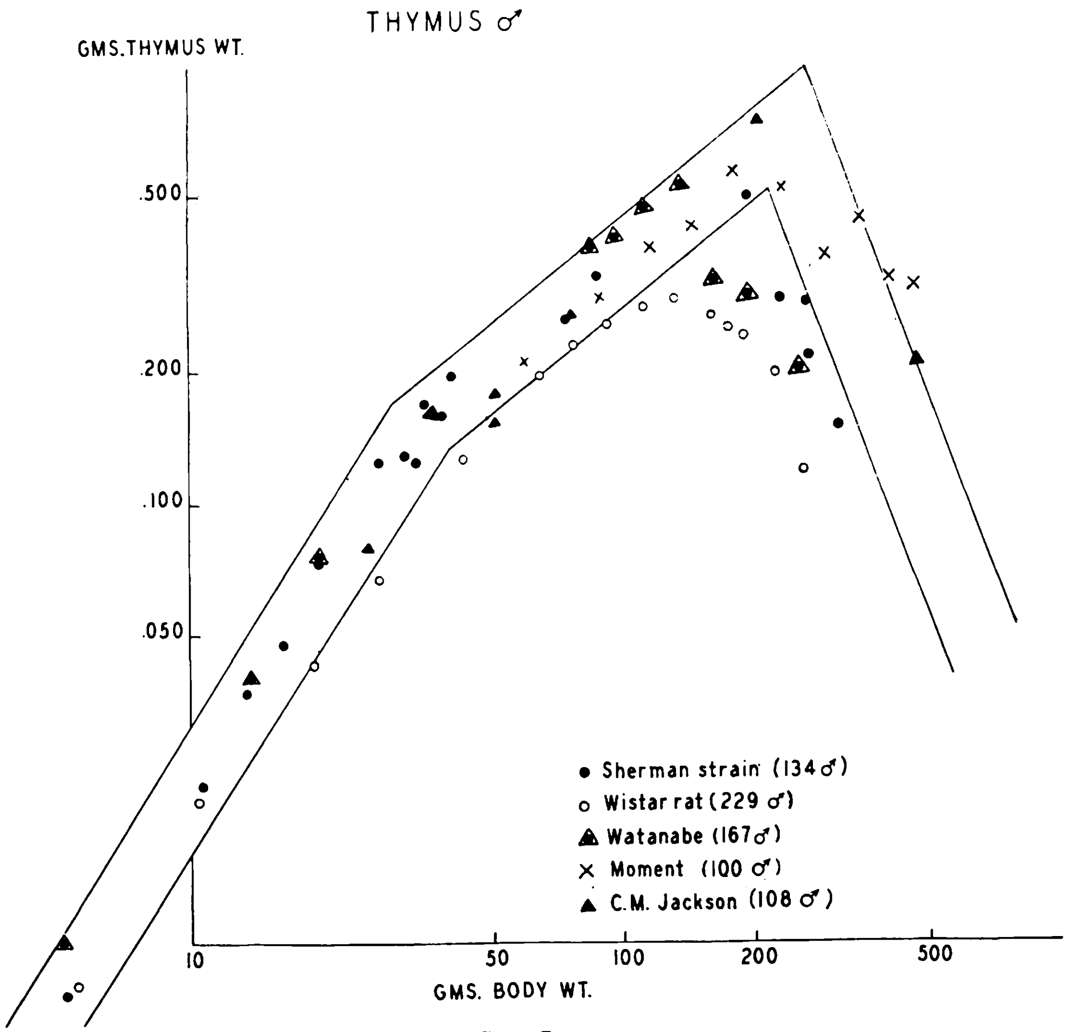

Chart I.
Log./Log. plot of thymus weight on body weight in male albino rats.

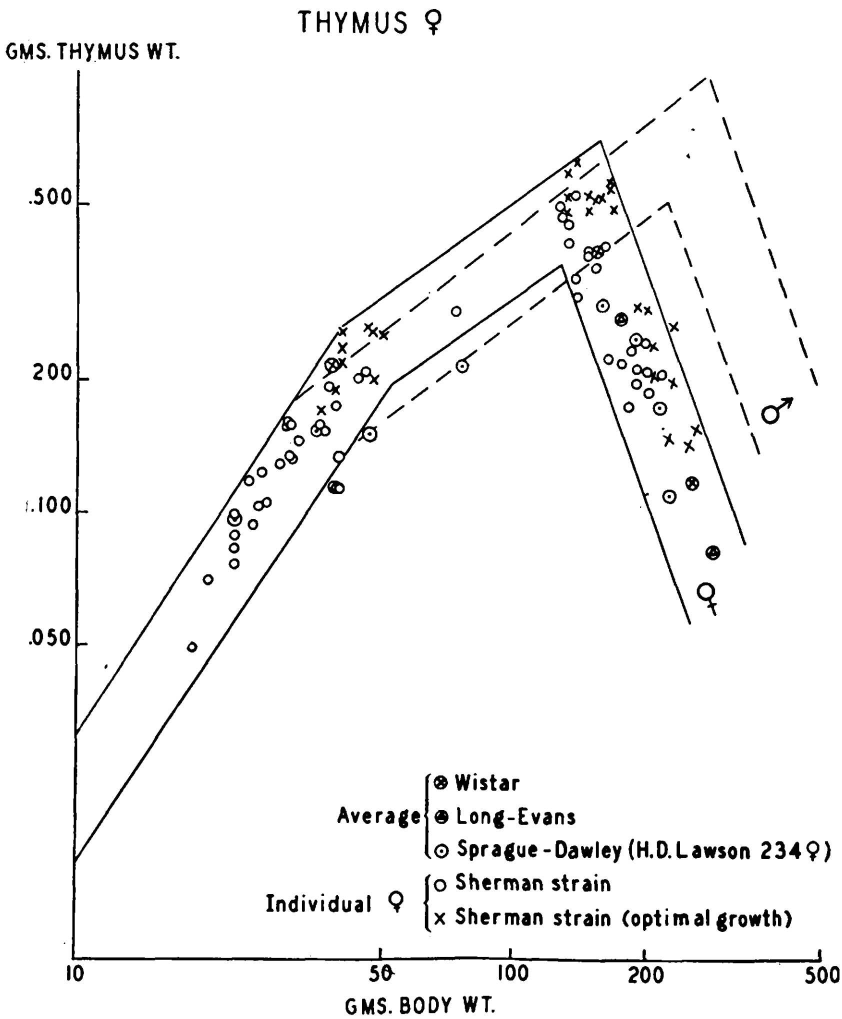

Chart II.
Log./Log. plot of thymus weight on body weight in female albino rats.

ditions probably close to optimal.

2. To study the extent of thymic atrophy (accidental involution) produced by closely controlled experimental conditions.

All of the experimental conditions induced, represented adverse bodily conditions and were associated with growth, retardation or body weight loss. The extent of the harmful stimulus was judged by its effect on body weight.

In all conditions where effects on thymic tissue were observed the lymphoid tissue appeared similarly affected. This was observed from the histology of lymph nodes and spleen.

Several attempts have been made in the past to determine the norm for thymus size in the rat over a range of age or body weight.[1-6] Only part of the data, however, were collected recently enough to take into account the newer knowledge of the dietary requirements in this species.

1 Donaldson, H. H., *The Rat*, 1924, Mem. Wistar Inst.

2 Jackson, C. M., *Anat. Rec.*, 1937, **68**, 371.

3 Watanabe, T., *Trans. Jap. Path. Soc.*, 1929, **17**, 332.

4 Moment, G. B., *J. Exp. Zool.*, 1933, **65**, 359.

5 Lavson, H. D., *et al.*, *Endocrinology*, 1942, **31**, 129.

6 Stoerk, H. C., *Endocrinology*, 1944, **34**, 329.

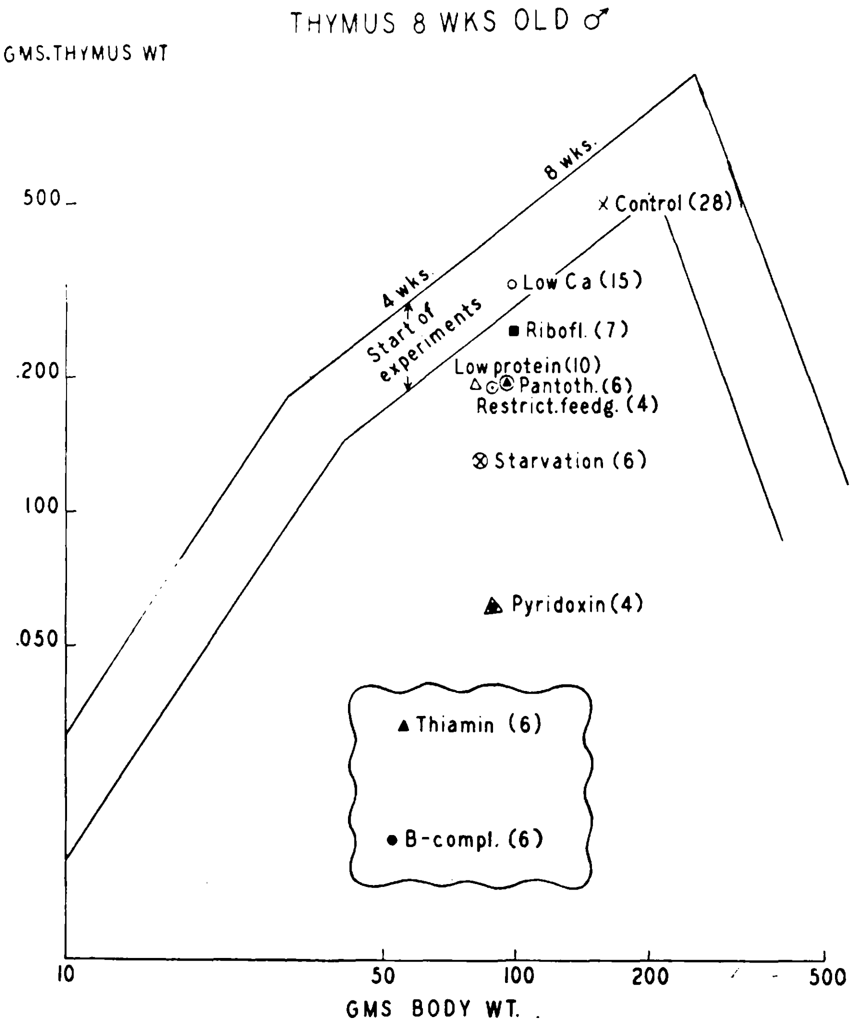

Chart III.
Range of thymus weights obtained from animals growing optimally (Chart I), compared with experimental data.

Recently Zucker and Zucker[7] have shown that in albino rats fed an adequate stock ration, there exists a simple body weight time relation. Their growth formula applied not only to large numbers of rats of their own colony but also to data of others who employed complete diets. This body weight time relationship, obviously cannot be obtained when factors other than dietary interfere with normal growth. Such a factor exists in most rat colonies in form of a large variety of known and unknown diseases.

In the early stages of this investigation a relatively large number of thymus weights was recorded from animals of our stock colony (Sherman strain) kept on a complete ration (Rockland rat diet). Growth records as far as available showed optimal growth only in isolated cases. Later care was taken to improve the living conditions of the animals and to follow their growth regularly. It became evident then that animals showing optimal growth had larger thymus glands than undersized rats. The cause of the growth retardation in the undersized animals was not known but the failure to obtain optimal

[7] Zucker, L., and Zucker, T. F., *J. Gen. Physiol.*, 1942, **25**, 445.

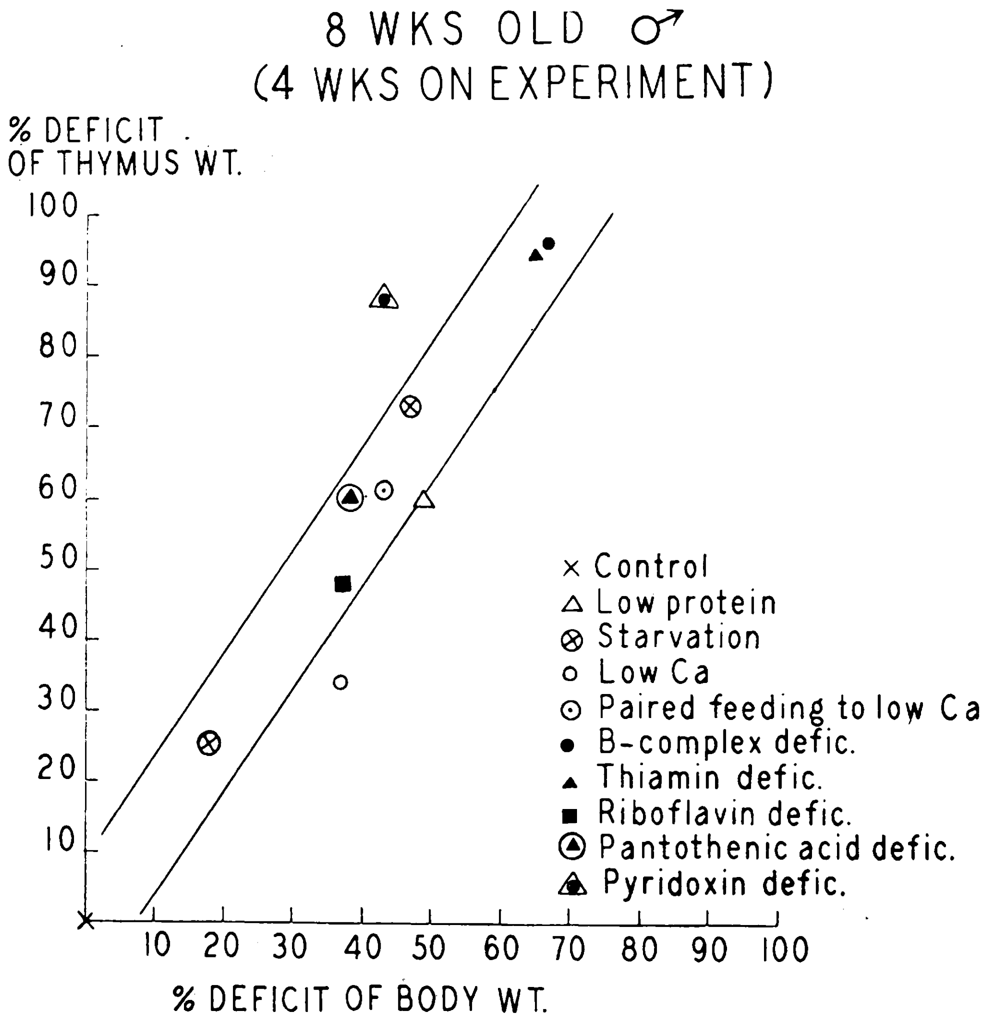

Chart IV.
Relationship between body weight deficit and thymus weight deficit.

growth on a complete ration was considered as an abnormality and thymus weights in such animals were excluded from the use as controls.

The accepted norm of thymus weight was obtained with any of several complete diets, provided that growth was optimal. None of these diets had an apparent effect *per se* on thymus weight.

Chart I presents a log/log plot of thymus weight on body weight of male albinos of the Sherman strain from our stock colony as compared with other data from the literature. The band includes the range of our data obtained from 115 animals that grew either optimally or recovered from previous growth disturbance. As reported previously an identical range of thymus weights on body weight was obtained in 56 male rats, castrated or adrenalectomized 3-4 weeks before killing.[6] Jackson and Moment who employed animals growing close to optimally have obtained thymus weights as high as those found in our controls, or even somewhat higher. Fair agreement of all data is evident in the earlier part of the rat's life. The thymus weights from about 100 g of body weight on in Donaldson's (Wistar rat) and Watanabe's data and in our own earlier observations are sig-

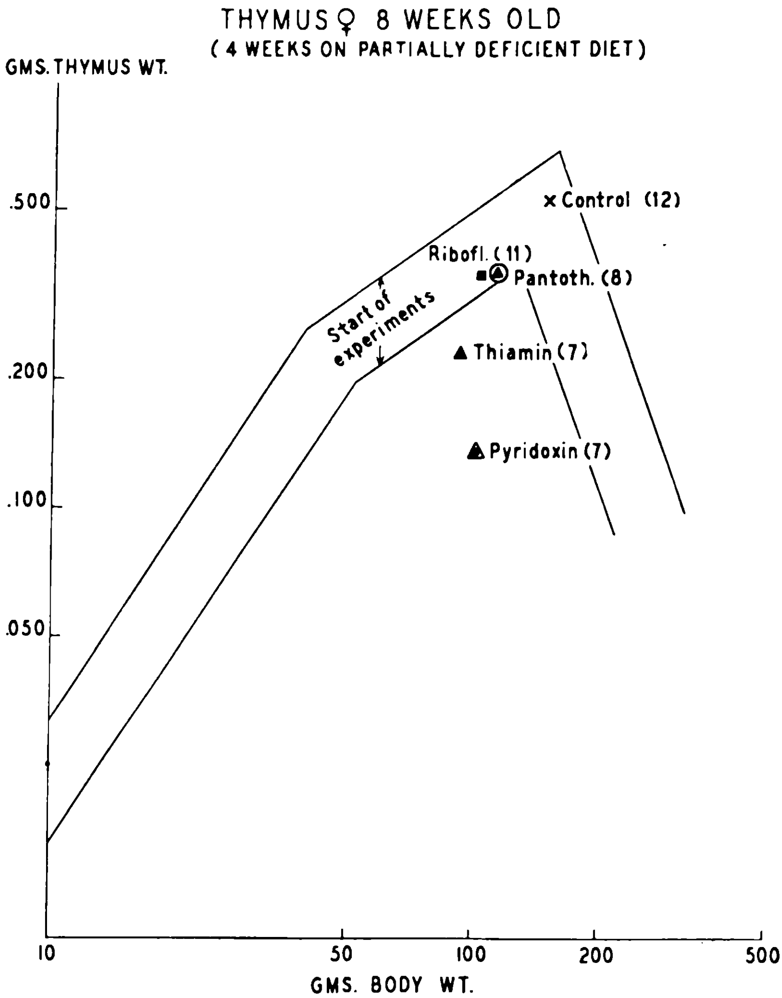

Chart V.
Range of data in Chart II compared with experimental data.[9]

nificantly lower than the accepted norm. In these 3 groups the growth of the animals was below optimal.

Chart II presents a similar plot illustrating thymus growth on body weight in the female albino.

Chart III gives a comparison of experimental data in the 8-week-old male. The band again represents the range of the accepted norm. A number of adverse dietary conditions, mostly produced by the omission of a single substance, from the diet, have been induced for a period of 4 weeks.* It is seen that in most of these conditions the thymus ceased to grow or was slightly atrophic when body growth was retarded. In deficiency of B-complex and in thiamin deficiency growth retardation was marked and was followed in the latter part of the experiment by body weight loss. In these 2 cases, thymic atrophy was extreme. Advanced thymic atrophy without marked effect on body weight was observed only in pyridoxin deficiency. Similar findings in the female rat have been reported previously.[8] No retarda-

* The basic diet was the same as used by Berg, B. N., and Zucker, T. F., Abstracts 107th A. C. S. Meeting, Cleveland, O., April, 1944. The thymi of the animals deficient in single B-factors were kindly given to us by the above authors.

8 Stoerk, H. C., and Zucker, T. F., PROC. SOC. EXP. BIOL. AND MED., 1944, **56**, 151.

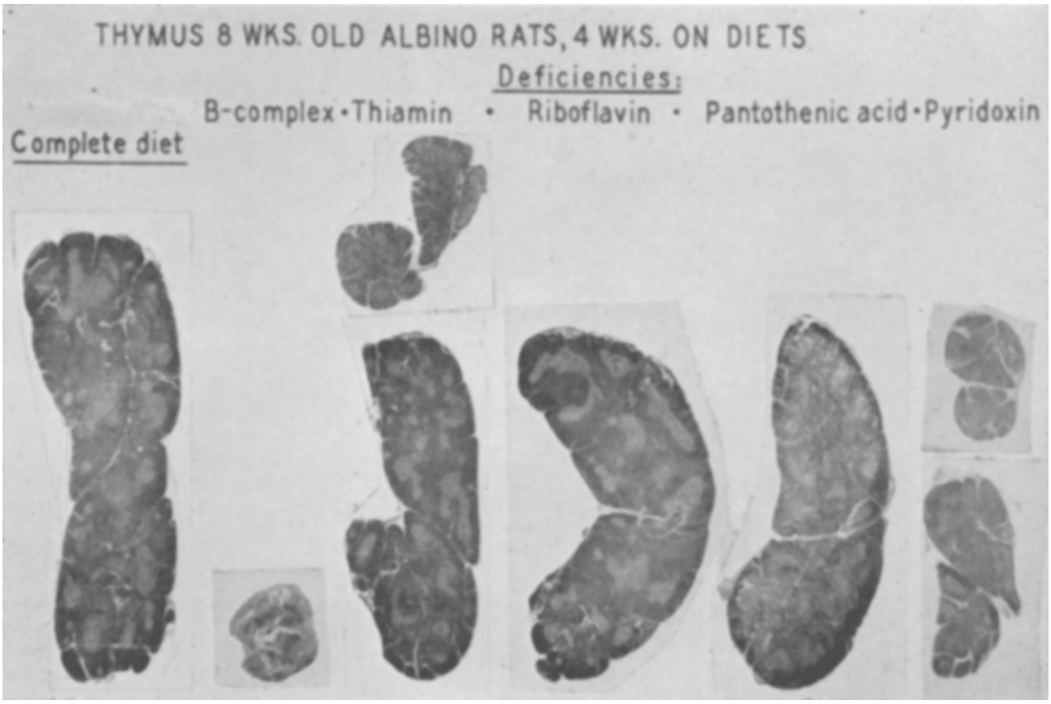

Fig. 1.

The sections of thymus are representative of the glands closest to the average weight in the respective group, except for those in thiamin and pyridoxin deficiency where the smallest and the largest gland in the group have been photographed. (Actual maximal diameter of control gland 10 mm).

tion of thymus growth was evident when body growth retardation and even weight loss was produced by calcium deficiency.

The above data are compared in Chart IV where the thymus weight deficit in percent below that of the controls is plotted against the body weight deficit calculated on the same basis. Roughly most values obtained fit a straight line, the slope of which is about 1.5. Marked deviations from this approximate straight line relationship are evident in 2 cases. In pyridoxin deficiency the thymus weight deficit in relation to body weight deficit was unduly high; in Ca deficiency this ratio was lower than expected. The latter finding is analogous to what is observed on proper comparison, in gonadal and adrenal insufficiency.[6] This occurrence in Ca deficiency is apparently not related to hypocalcemia since parathyroidectomized rats did not show a discrepancy between body weight and thymus weight deficit.[9]

The specific effect of pyridoxine deficiency in producing thymic atrophy is also brought out from the data plotted in Chart V. In this experiment partial deficiencies of single B-factors are compared in female rats. Body growth was almost identical in all groups except that the animals receiving low thiamin lost weight towards the end of the experiment. Actual thymic atrophy was found only in the animals partially deficient in pyridoxin.

In Fig. 1 the histology of glands, of female rats representative of their group, is compared in animals deficient in B-complex, and deficient in single B-factors. It is seen that the marked effect of pyridoxin deficiency on the thymus is also obvious from the morphology. Lymph nodes in these animals were likewise greatly depleted of lymphocytes.

Fig. 2 shows a microphotograph of an atrophic thymus gland representative of those of 10 mice fed a diet deficient in pyridoxin and injected with .2 mg Desoxypyridoxin (kindly supplied by Merck & Co.) 2 times

[9] Unpublished observations.

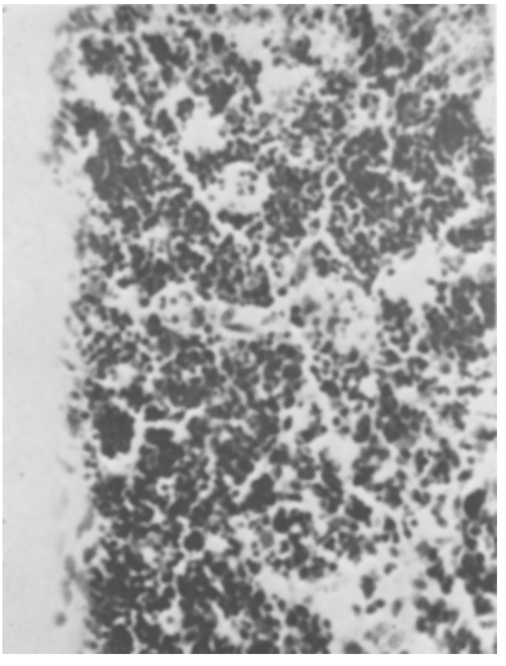

Fig. 2.
Thymus of mouse injected with desoxypyridoxin. Note pycnosis and fragmentation of lymphocytes. The cortical tissue was markedly reduced in amount.

daily over 3 days. The thymi of the injected animals weighed about 50% less than those of non-injected controls. Further studies are necessary to ascertain that no toxic effects are responsible for this change.

The apparently specific effect of even relatively mild pyridoxin deficiency in producing lymphoid atrophy suggests the possibility that pyridoxin may be essential for the maintenance of lymphocytes. This possibility has become of increased interest with the recent finding that a desoxypyridoxin is a powerful inhibitor of B-6.[10] This preparation may therefore perhaps be helpful in the treatment of tumors of the lymphoid tissue. The role recently attributed to lymphocytes in relation to antibodies, and the finding that pyridoxin deficiency suppresses circulating antibodies[11] suggests the possibility that desoxypyridoxin may be used in order to interfere with undesired antibody formation. Investigations in these directions are being carried out.

Summary. In male albino rats (8 weeks of age) exposed to a number of adverse dietary conditions, an approximately linear relationship was found between the amount of body weight deficit and the thymus weight deficit. There were 2 exceptions from this apparent rule: (1) in pyridoxin deficiency, the amount of thymus weight deficit was much greater than expected from the obtained body weight deficit; (2) in calcium deficiency an opposite effect was observed. Here the thymi of undersized animals were of the same weight as those of younger, normal animals of the same body weight.

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10 Ott, W. H., PROC. SOC. EXP. BIOL. AND MED., 1946, **61**, 125.

11 Stoerk, H. C., and Eisen, H. N., PROC. SOC. EXP. BIOL. AND MED., 1946, in press.