Effect of Thymectomy on the Golden Hamster (Mesocricetus Auratus). I. Wasting Disease

By Joseph D. Sherman, Marvin M. Adner and William Dameshek

A FATAL WASTING DISEASE in the hamster following thymectomy in the perinatal period was described in a preliminary report. When the thymus was removed either shortly after birth or within a period of 4 weeks, there followed within 7–14 days a severe, progressive disease characterized by weight loss, lethargy, dorsal kyphosis, periorbital edema, ruffled fur, alopecia, ataxia, diarrhea, pancytopenia and absolute lymphocytopenia. The unique features of this wasting disease in the hamster as distinct from other animals, such as the mouse, were its development in the relatively mature thymectomized animal, i.e., up to at least 4 weeks of age, and its occurrence in males, but not in females. This report extends our observations on the wasting disorder of thymectomized hamsters and indicates its close analogies to certain pathologic conditions found in man.

The important role of the thymus gland in the development of immune processes was shown originally by Archer and Pierce of Good’s Laboratory and by Miller. In a subsequent paper we will show that the thymectomized, non-wasted hamster has an impaired ability to make humoral antibodies as well as an impaired delayed hypersensitivity mechanism.

MATERIALS AND METHODS

Golden hamsters (Mesocricetus auratus) ranging from the newborn to animals 12 weeks of age were used. They were quartered in an air conditioned animal room and fed Purina Laboratory Chow and water ad lib. They were weighed at weekly intervals and weaned at 5–6 weeks.

The technic of thymectomy varied with the age of the hamster. Animals up to 48 hours old were placed in plastic ice cube containers, as ordinarily used in domestic refrigerators. These were then placed in the freezing compartment of the refrigerator for 9 to 11 minutes at which time the animals stopped breathing and became slightly pale. They were then secured to a board and the surgical field visualized with a binocular, stereoscopic microscope. The skin and underlying sternum were split down to the second or third rib, and the incision was then widened with an iris forceps. The bulbed thymus was easily visualized and removed by mechanical suction. The sternum was closed with a single suture and the skin closed with a plastic adhesive dressing (Aeroplast, Aeroplast Corp., Dayton, Ohio). The animals were then warmed intermittently under an electric lamp (100 watt bulb), and when fully active were returned to their mother. To avoid cannibalization when the thymectomized hamsters were returned to their cage, it was necessary to distract the mother with such articles of food as ground meat, lettuce, potato, etc.

Hamsters older than 48 hours required intraperitoneal Nembutal (pentobarbital sodium, Abbott, 0.75 gr. per ml.), 0.1 cc./100 Gm. body weight for anesthesia. Animals with fur
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were shaved with an electric razor, and the sternum and cervical area prepared with tincture of iodine. With the animal’s head facing the operator, a skin incision was made from the midcervical area to the fourth rib. The trachea was exposed down to the sternal notch by gentle dissection of the overlying strap muscles. The sternum was then split in the mid-line from the sternal notch to the third rib, thus exposing the thymus. The gland was freed by blunt dissection from its fascial attachments in the anterior mediastinum. Removal of the gland was accomplished with the aid of a forceps and cotton applicator stick, although in some cases removal of the gland was facilitated by the use of mechanical suction. Minimal bleeding was readily controlled with the cotton applicator stick. The sternum was closed with two or three interrupted sutures, and the skin approximated with continuous sutures. Sham-thymectomy was performed as above, but the gland, once exposed, was left intact.

Thymectomy and sham-thymectomy were performed on animals of both sexes at the following ages: < 24 hours, 24 – 48 hours, 1, 2, 3, 4, 8 and 12 weeks. Experimental groups consisted of litters comprising totally thymectomized, sham-thymectomized and unoperated controls.

When it was noted that female hamsters did not develop the wasting disorder, a series of experiments were carried out to evaluate the role of oophorectomy and the administration of sex hormones on thymectomized and non-thymectomized hamsters. In these studies, animals of both sexes, 2 and 8 weeks of age, were used. The table below indicates the various experimental groups established for each sex. The technic of bilateral oophorectomy was essentially the same as that described for the mature rat4 except that only the ovary and its surrounding fat were excised, while the remainder of the genital tract was left intact. Oophorectomy or sham-oophorectomy was performed on the same day as thymectomy.

Groups in Endocrine Experiments

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Normal)</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Thymectomy Oophorectomy</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Thymectomy Sham-oophorectomy</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Thymectomy Testosterone</td>
<td>×</td>
<td>×</td>
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<tr>
<td>Testosterone</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Estrogen</td>
<td>–</td>
<td>×</td>
</tr>
</tbody>
</table>

The estrogen used was conjugated estrogens (Premarin, Ayerst Laboratories, 1 cc. = 4 mg.) and 0.04–0.05 cc. (0.16–0.20 mg. intraperitoneally weekly) were injected for the entire experimental period. Testosterone propionate (Neo-Hombreol, Organon, 1 cc. = 50 mg.) was used and 0.01–0.02 cc. (0.5–1.0 mg. subcutaneously weekly) were injected for the duration of the experiment. The hormone injections were begun on the day of thymectomy.

Hematologic studies were performed on blood obtained both by direct cardiac puncture and decapitation. The following blood tests were done by previously described technics:8 hemoglobin, hematocrit, total red and white blood cell, reticulocyte, platelet and dif-
Table 1.—The Relationship of Post-thymectomy Wasting in the Hamster to Age and Sex

<table>
<thead>
<tr>
<th>AGE AT THYMECTOMY</th>
<th>THE NUMBER OF ANIMALS</th>
<th>FEMALE</th>
<th>MALE</th>
<th>% WASTED VARIOUS AGES</th>
<th>TOTAL GROUP % WASTED</th>
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</thead>
<tbody>
<tr>
<td>&lt;24 Hours</td>
<td>18</td>
<td>8</td>
<td>0</td>
<td>6 4</td>
<td>40</td>
</tr>
<tr>
<td>&gt;24 Hours to 48 Hours</td>
<td>16</td>
<td>8</td>
<td>0</td>
<td>2 6</td>
<td>75</td>
</tr>
<tr>
<td>1 Week</td>
<td>28</td>
<td>15</td>
<td>0</td>
<td>9 4</td>
<td>44</td>
</tr>
<tr>
<td>2 Weeks</td>
<td>50</td>
<td>17</td>
<td>0</td>
<td>21 12</td>
<td>36</td>
</tr>
<tr>
<td>3 Weeks</td>
<td>56</td>
<td>25</td>
<td>0</td>
<td>13 18</td>
<td>56</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>83</td>
<td>40</td>
<td>0</td>
<td>17 26</td>
<td>60</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>18</td>
<td>9</td>
<td>0</td>
<td>9 0</td>
<td>0</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>21</td>
<td>10</td>
<td>0</td>
<td>11 0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>290</td>
<td>132</td>
<td>158</td>
<td>44 24</td>
<td></td>
</tr>
</tbody>
</table>

ferential white blood cell counts. Anti-hamster serum was prepared in rabbits and erythrocyte agglutination reactions (Coombs tests) were done by a modification of the technic described by Betts et al.6

Post-mortem examinations were performed on all hamsters, and included gross and microscopic study. All surgical areas were examined grossly for sepsis and selected operated sites were cultured. Bacterial cultures were routinely done on heart blood and occasionally on stools. Viral isolation studies are in progress. Any potential focus of residual thymic tissue was checked histologically. Selected organs were weighed and all of the specimens were fixed in 10 per cent formalin and stained with hematoxylin and eosin.

Immunoelectrophoretic studies were performed on the sera of some wasted and non-wasted hamsters of both sexes.* The technic of immunoelectrophoresis was a modification of the microtechnic introduced by Scheidegger.7

RESULTS

Of 290 thymectomies performed on hamsters of all ages and both sexes, 70 animals (24 per cent) developed wasting disease. Table 1 shows the number of animals thymectomized and the percentage of wasting in each age group. There was a significant number of animals that wasted at each age, except at 8 and 12 weeks where no wasting was observed.

The first sign of the wasting disease following thymectomy was a failure to gain weight (fig. 1). This was then followed, during a period of 1–5 days, by an acute illness consisting of progressive weight loss, 50–75 per cent less than normal control or sham-thymectomized litter mates, (fig. 2), ruffled, unkempt appearance, hunched posture, lethargy, alopecia (especially in the cervical area), peri orbital and facial edema, occasionally epistaxis, diarrhea, or rarely, constipation. The end stage of the disease was charac-

*Kindly performed by Dr. F. Bruce Lewis, Blood Research Laboratory, Pratt Clinic-New England Center Hospital, Boston, Mass.
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Fig. 1.—Representative changes in body weights of normal and wasting hamsters.

Fig. 2.—Larger sham-thymectomized hamster (left) compared to smaller wasted thymectomized litter mate (right). The wasted animal shows the characteristic hunched posture, alopecia, weight loss, ruffled fur and periorbital edema.

terized by profound lethargy, the animal responding only to direct painful stimulation, and finally by labored respirations and death.

The development of the clinical signs of wasting disease generally followed the same pattern, regardless of the age at which thymectomy was performed. Figure 3 depicts the relationship of age at the time of thymectomy to the onset of acute clinical wasting disease. It was noted that animals
that were thymectomized within the 1st week tended to show the acute signs of wasting at an earlier age than those thymectomized after 1 week.

The hematologic data on the wasted and control (sham-thymectomized and non-operated) animals are summarized in table 2. In summary, the wasted hamsters showed decreased hemoglobin, hematocrit and red cell values; the red cells were generally normocytic and normochromic; slight aniso- and poikilocytosis as well as punctate basophilia was often found. The platelet counts were reduced. There was mild leukopenia associated with a reversal of the normal lymphocyte to polymorphonuclear leukocyte ratio (L:P), and an absolute reduction in circulating lymphocytes. Mast cells were occasionally noted in the peripheral blood of some wasted animals. Occasional wasted animals showed large (20–25 μ) immature cells with slightly irregular to rounded or elliptical outlines, large round nuclei, one or two nucleoli, and pale, homogenous basophilic cytoplasm containing dark blue (with Wright's stain) granules. These immature ("blast") cells probably belonged to the myelomonocytic series. The monocytes and eosinophils were present in their usual number and showed no abnormality. The Coombs tests were negative in both the control and wasted hamsters.

The cellularity of the bone marrow of the wasted hamster was either normal or somewhat reduced with normal maturation of myeloid, erythroid and megakaryocytic elements. The precursors of these elements were present in normal numbers.

Post-mortem examination of the wasted animals revealed depletion of body fat (including brown fat), soft bones and generalized atrophy of lymphoid tissues. The most striking feature was the small, pale spleen that
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Table 2.—Summary of the Hematologic Data on the Sham-thymectomized and Normal Control Hamsters Compared to Wasted Thymectomized Litter Mates

<table>
<thead>
<tr>
<th>BLOOD VALUE</th>
<th>AVERAGE NORMAL (7 Days to 8 Weeks)</th>
<th>AVERAGE WASTED* (7 Days to 8 Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (Gm/100 ml)</td>
<td>16.2 ± 1.3</td>
<td>10.7 ± 1.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>48 ± 3.0</td>
<td>31 ± 2.7</td>
</tr>
<tr>
<td>RBC (M)</td>
<td>6.96 ± 0.7</td>
<td>3.3 ± 0.84</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>1.3 ± 0.32</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>Platelet Count (in thous.)</td>
<td>6.83 ± 1.4</td>
<td>1.77 ± 0.9</td>
</tr>
<tr>
<td>WBC (in thous.)</td>
<td>5.78 ± 1.29</td>
<td>3.17 ± 1.1</td>
</tr>
<tr>
<td>Total P.M.N. (%)</td>
<td>29.9 ± 5.5 Absolute (1800)</td>
<td>75.1 ± 4.6 Absolute (2400)</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>66.4 ± 5.9 Absolute (3960)</td>
<td>17.5 ± 2.8 Absolute (576)</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>2.6 ± 0.8</td>
<td>5.9 ± 1.9</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>1.1 ± 0.02</td>
<td>1.0 ± 0.01</td>
</tr>
<tr>
<td>Coombs Test</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*Values obtained at the time of sacrifice.

generally weighed 20-50 per cent of the spleen of control litter mates (fig. 4). No lymph nodes or Peyer's patches were found. Gross and microscopic search for thymic tissue was consistently negative. The spleen of both the sham-thymectomized and normal (non-operated) hamsters contained Malpighian corpuscles composed of small and large lymphocytes (fig. 5); plasma cells and their precursors were noted in the pulp, particularly along the trabeculae. In the wasted hamsters, the spleen showed an almost complete absence of Malpighian corpuscles and plasma cells and a relative increase in reticulendothelial cells (fig. 6). The normal hamster ileum contained Peyer’s patches and the lamina propria of the ileum contained many lymphocytes, monocytes and plasma cells (fig. 7). In the wasted hamster, the intestinal tract showed no Peyer's patches and the normal mononuclear infiltrate of the lamina propria was almost completely lacking (fig. 8).

Bacterial cultures of heart blood and surgical sites were uniformly negative. Stool cultures contained the same flora as the sham-thymectomized or non-operated animals.

Immunoelectrophoretic studies of the sera of wasted hamsters showed an abnormal pattern of the gamma-2-globulin line characterized by a change in shape and decreased length. These changes, indicating a deficiency of this protein, were not found in the non-wasted animals (fig. 9). Table 3
contains a summary of all the features of the wasting disease of the hamster.

Post-thymectomy wasting occurred only in male hamsters (table 1). Thus, of 158 thymectomized males, 70 (44 per cent) developed wasting; of 132 thymectomized females, none showed manifestations of wasting. Further studies to evaluate this striking sex difference are summarized in table 4. Thus, wasting was produced in 2 week old females treated with a combination of thymectomy and oophorectomy (3 of 15 hamsters or 20 per cent). In addi-
Fig. 6.—Histologic section of wasted hamster spleen (seen in fig. 4). There is an absence of Malpighian corpuscles and an almost complete absence of plasma cells. There is a relative increase in reticuloendothelial cells.

Fig. 7.—Histologic section of sham-thymectomized hamster ileum. Peyer's patches are present and lymphocytes, monocytes, and plasma cells are seen in the lamina propria.

tion, 8 of 24 (33 per cent) of the 2 week old females treated with thymectomy plus testosterone propionate developed wasting disease. It was not possible to induce wasting in females by sham-oophorectomy plus thymectomy or by testosterone alone. Wasting produced in the female was identical in all respects to that produced in the thymectomized males. In the male, thymectomy
Fig. 8.—Histologic section of wasted hamster ileum. No Peyer’s patches are seen. The lamina propria is almost completely free of mononuclear cell infiltrate.

Fig. 9.—Immunoelectrophoretic pattern of the normal (sham-thymectomized) hamster compared with the wasted hamster. The gamma-2-globulin (arrow) is shorter and has a different shape in the wasted animal.
Table 3.—Summary of the Clinical, Hematologic, Pathologic and Immunologic Features of Post-thymectomy Wasting Disease of the Hamster

<table>
<thead>
<tr>
<th>WEIGHT LOSS</th>
<th>LEUKOPENIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUNCHED POSTURE</td>
<td>LYMPHOPENIA</td>
</tr>
<tr>
<td>CERVICAL ALOPECIA</td>
<td>THROMBOCYTOPENIA</td>
</tr>
<tr>
<td>RUFFLED FUR</td>
<td>DIARRHEA</td>
</tr>
<tr>
<td>ATAXIA</td>
<td>CACHEXIA</td>
</tr>
<tr>
<td>LETHARGY</td>
<td>DEPLETION OF BODY FAT</td>
</tr>
<tr>
<td>EDEMA (EYES, FACE)</td>
<td>LYMPHOID TISSUE ATROPHY</td>
</tr>
<tr>
<td>ANEMIA</td>
<td>(Spleen, Nodes, Peyer's)</td>
</tr>
</tbody>
</table>

GAMMA GLOBULIN DEFICIENCY

alone induced wasting in 44 per cent of all animals studied. In the thymectomized males given estrogen or in males given testosterone or estrogen alone, wasting did not develop.

DISCUSSION

1. Post-thymectomy Wasting

In 1858, Friedleben removed the thymus gland of a young dog and 4 months later noted that the animal had become extremely emaciated, cachectic and had severe diarrhea. This may be the first report of post-thymectomy wasting disease or “thymic cachexia” as it was known for many years. Over the next 100 years several investigators noted a cachectic or wasting disorder following thymectomy in a variety of animal species including goats, dogs, rats, guinea pigs, mice, chickens and even frogs. The reports of these investigators indicate that the disorder was not systematically studied and, if reflected upon, was thought to be due to poor surgical skill, vague laboratory factors or ill defined “sepsis.” It was not until the work of Miller and Parrott and East with thymectomized mice that some features of the post-thymectomy wasting disease were evaluated and interpreted as a direct effect of thymectomy.

Miller noted wasting disease following thymectomy in certain strains of mice. These animals developed lymphoid atrophy, lymphocytopenia, cachexia, emaciation, lethargy and death. The incidence of the disease decreased from 100 per cent if thymectomy was done at birth to nil if thymectomy was done after 7 days of age. Parrott and East confirmed Miller’s observations and further noted that wasting disease developed in an outbred strain of mice (TO) if the animals were thymectomized within the first 24 hours.
Table 4.—Relationship of Surgical and/or Hormonal Treatment to the Development of Wasting Disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2 WEEKS</th>
<th>8 WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEMALE</td>
<td>MALE</td>
</tr>
<tr>
<td>Control</td>
<td>A W A W</td>
<td>A W A W</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>17 0 21 12</td>
<td>9 0 9 0</td>
</tr>
<tr>
<td>Thymectomy and Oophorectomy</td>
<td>12 3 - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>10 0 - -</td>
<td>5 0 - -</td>
</tr>
<tr>
<td>Thymectomy and Sham. Ooph.</td>
<td>10 0 - -</td>
<td>4 0 - -</td>
</tr>
<tr>
<td>Thymectomy and Estrogen</td>
<td>- - 6 0</td>
<td>- - - -</td>
</tr>
<tr>
<td>Estrogen</td>
<td>- - 7 0</td>
<td>- - - -</td>
</tr>
<tr>
<td>Thymectomy and Testosterone</td>
<td>16 8 0 6</td>
<td>- - - -</td>
</tr>
<tr>
<td>Testosterone</td>
<td>10 0 5 0</td>
<td>- - - -</td>
</tr>
</tbody>
</table>

A = Alive  
W = Wasted

The features of post-thymectomy wasting of the hamster are similar in many respects to those described in the dog, rat, guinea pig, chicken and mouse. Thus weight loss, dorsal kyphosis, alopecia, unkempt fur, lethargy, lymphocytopenia, diarrhea, cachexia, atrophy of lymphoid tissue and soft bones have been noted in other animals. However, periorbital and facial edema, pancytopenia, epistaxis, ataxia, relative plasmocytopenia and gamma globulin deficiency have not been reported in other wasted, thymectomized animals. A unique feature of the wasting disease of the hamster was its development in a significant number of animals thymectomized even as late as 4 weeks of age. The high incidence of wasting at that age and the complete lack of wasting disease at 8 and 12 weeks of age suggested that post-thymectomy wasting disease would probably develop in some animals thymectomized at 5–7 weeks; studies are in progress to evaluate this possibility. Our data indicate that the interval between the time of thymectomy and onset of acute wasting disease was shorter when the animals were thymectomized during the 1st week of life, rather than at a later age (fig. 3), and a similar observation has been made in the mouse.3

Although it is apparent that removal of the thymus gland may produce a wasting disease characterized by the features summarized in table 3, some of these features are found in non-thymectomized animals suffering from a variety of conditions, viz., post-irradiation sickness,17 starvation,18 biotin deficiency,19 graft vs. host disease (runt disease),20 infection21 and malignancy,22 but all of these features occurring together have not been noted in any one of these diseases.

The similarity between some of the features of the graft vs. host disease (runt disease, homologous or secondary disease) and post-thymectomy wasting has been noted by us3 and by others.3,23,24 The two conditions may represent similar “end stages” produced by different mechanisms, or the fundamental mechanism may be the same.

The condition which has come to be known as runt disease (or running) is almost universally conceded to be a graft vs. host reaction produced by the administration of immunologically competent cells into an immunologically neutral recipient. The immunologic reactions of the genetically different grafted tissue acting against the recipient’s cells and tissues are thought to induce the experimental disorder. That a graft vs. host phenomenon plays a role in the pathogenesis of post-thymectomy wasting is hardly likely. Since both “runted” and “wasted” animals demonstrate a common abnormality, namely generalized lymphoid depletion, it is conceivable that this represents the common denominator of both the running and wasting disorders. In fact, they may represent the same disturbance with a certain number of differences due to immunologic abnormalities in the graft vs. host reaction, not present in the thymectomized animal.

The lymphoid depletion in the post-thymectomy state can be explained on the basis of current concepts of thymic function which indicate that the thymus gland is essential for the normal development of lymphoid tissue in the maturing animal. This could be exerted either through an endocrine action with one or more hormones regulating the development of lymphoid tissue, or by “seeding” of lymphoid tissue by thymic cells. One possible thymic hormone might be that of the “lymphocytosis stimulating factor” described by Metcalf.26 Other thymic hormones have been recently described by Szent-Györgyi.27 The apparent relationship of the thymus to the ovaries as indicated in our experiments might be indirect evidence for an endocrine function of the thymus. Actual migration of the thymic cells to the spleen and other lymphoid organs where the cells would then mature and be a potential source of immune cells has been suggested by several observers,28-30 even from the time of Hewson in 1777.31 Assuming either mechanism to be present, loss of the thymus gland at an early critical stage of development would, therefore, result in a lymphoid depleted organism. The reason for the lymphoid depletion in the graft vs. host reaction is not as apparent. It may be that there is a generalized destruction of lymphoid tissue of the host by the immunocompetent grafted cells. Another possibility could be that the grafted cells selectively
attack the thymic lymphocytes, producing, in a sense, functional thymectomy, and the organism develops the same abnormalities that result from surgical thymectomy. Thus, we have noted thymic atrophy in runted male F1 hybrid mice injected with parental strain spleen cells. Others have noted thymic atrophy in F1 hybrid rats. It may be that lymphoid depletion, regardless of its mechanism of production, is responsible for many common findings, and that the "wasted" and the "runted" states are at least physically identical.

The debilitated state which is characteristic of both the graft vs. host reaction and post-thymectomy wasting may be due to deficient protein synthesis because of atrophic lymphoid tissue. The thymus in particular is important for the synthesis and storage of deoxyribonucleic acid (DNA), and the gland plays a very significant part in nucleoprotein metabolism. As early as 1904, five times as much nucleic acid was reported in thymic tissue as in lymph nodes and this relationship has since been confirmed. Klose in 1910 expressed the opinion "that furnishing nucleic acid to the organism could be an important function of the thymus." Thus, the trophic (nutritive) function of the thymus may be important, particularly in growing animals, and wasting (or runting) may be a failure of the animal to produce lymphocytes and plasmocytes (which have been called trophocytes), and nucleoprotein in the absence of the thymus gland and lymphoid tissue.

The generalized atrophy of lymphoid tissue that follows thymectomy in the hamster, and particularly the absence of Peyer's patches and lymphocytes, plasma cells and monocytes in the lamina propria of the ileum are quite similar to the morphologic picture noted in the ileum of the germ-free guinea pig. The lack of lymphoid tissue may make the wasted hamster, like the germ-free animal, susceptible to its normal bacterial flora or their products. Death may therefore occur in the wasted thymectomized hamster as a result of infection by these supposed "non-pathogens." Our failure to culture "pathogenic" organisms from our wasted hamsters and the fact that bacterial and viral studies in the wasted mouse have also been unrewarding may be indirect evidence to support this proposition.

3. The Sex Difference in Post-thymectomy Wasting

One of the more unusual features of the post-thymectomy wasting disease in our hamster colony was its occurrence in males only. Normal male and female hamsters do not differ in body weight, hemograms, bone marrow, serum proteins, or spleen and thymus gland weights. Thus, the sex difference in the wasting disease following thymectomy cannot be ascribed to any of these factors. An increased susceptibility of the male to post-thymectomy wasting has not been noted by other investigators in other species. It was noted in studies of radiation-induced thymic atrophy in rats that there was a moderate retardation of body weight in males, but not in females or in controls; however, the other features of wasting disease, as recorded here, did not develop during an observation period of 70 days.

The lymphocytolytic effect of adrenal corticosteroids has been well defined. It is not so well known that the sex hormones may also have a
lympholytic effect. Testosterone propionate and estrogenic hormones have been stated to produce thymic and lymph node atrophy in both sexes in rats, and in some cases greater atrophy in males than in females. Estrogens have been stated to increase the content of gamma globulin in the blood. It is possible that the lymphoid tissue of the female hamster is less reactive than the male to thymic ablation. However, the addition of a further lymphocytolytic agent such as testosterone propionate or adrenal cortical hormone might produce further lymphoid depletion, enough to produce wasting disease. Another interpretation would be that testosterone and oophorectomy “masculinize” the females, thus rendering their lymphoid tissues more susceptible to the effects of thymus gland extirpation. It is also conceivable that the female hamster has ectopic thymic tissue (like the bursa of Fabricius) which is not removed at the time of thymectomy and that this tissue prevents the development of wasting disease. Administration of testosterone propionate or exposure to the stress of surgery in the thymectomized female might produce further destruction of the thymic lymphocytes in these ectopic foci with the production of wasting disease. However, careful search for such ectopic thymic tissue at post-mortem examination has been unproductive. Thus, we are led to the conclusion that the presence of ovarian tissue and apparently of estrogen is, in some manner, protective to the lymphoid apparatus and thus, indirectly, to immunologic competence. Conversely, male sex hormone seems to have a lymphoinhibitory effect, thus resulting in a reduction of immunologic activity.

These experiments may have some bearing on the results of certain studies involving the bursa of Fabricius. The bursa, which is found only in Aves, is a pear-shaped sac at the dorsal aspect of the cloaca. Morphologically, it is identical with the chick thymus gland and the two organs appear to have a similar embryonic origin. Functionally, however, the bursa appears to be involved in the production of circulating antibody, while the thymus gland is concerned with delayed hypersensitivity reactions. The injection of testosterone propionate into the allantoic cavity of the 12 day old chick is followed by “bursectomy” of the animals at hatching and moderate to severe thymic atrophy occurs in some cases. The spleen and lymph nodes are decreased in weight with some of the birds showing the features of wasting disease. If the chick is injected with 19-nortestosterone at the 5th day of incubation, there is a lack of bursal development at birth and the animals develop a progressive wasting disease, one manifestation of which is chronic diarrhea. Furthermore, the simple dipping of fertile eggs for only 5 seconds in a testosterone propionate (methyl alcohol solution) has also produced marked bursal atrophy. Bursal atrophy can also be induced by ACTH, corticosteroid, exercise, restraint, starvation, estradiol and thiouracil. The results with estrogen have not been as carefully studied as with male sex hormones. Thus, no definite statement can be made at this time regarding the exact mechanism of medical “bursectomy” in the chick, although the weight of evidence is in favor of a masculinization effect resulting in atrophy of the bursa. The entire subject of the endocrinologic, particularly the sex
hormone, relationship to the thymus needs more intensive study. The work of Szent-Györgyi27 with two hormones derived from the calf thymus may be related to this problem.

4. Plasmocytopenia in Wasting Disease

Simultaneously with the striking generalized reduction in lymphoid tissue and in blood lymphocytosis following thymectomy in the hamster, an almost complete absence of plasmocytes was encountered. This is of interest and indicates strongly, as suggested by Michels,50 the close relationship between the lymphoid and plasmocytic systems. As a matter of fact, it seems likely that the plasmocytes are derived from lymphoid tissue, perhaps through the intermediary of large, primitive appearing cells called variously undifferentiated, basophilic reticular cells,60 hemocytoblasts,61 or immunoblasts,62 and that plasmocytes arise in response to certain antigenic stimuli. The relationship of plasmocytosis to the development of 7S gamma globulins (humoral antibodies) is well known, and their disappearance in the condition known as agammaglobulinemia has been thoroughly documented.63 From the academic standpoint it is of considerable interest that in the absence of the thymus with consequent lymphoid atrophy, there is a disappearance as well of plasmocytes. It is probable that this reduction of plasma cells in our wasted, thymectomized hamsters may be responsible for the observed reduction in gamma globulin.

5. Certain Clinical Correlations

We have previously noted81 that certain human diseases such as agammaglobulinemia61,65 and “lymphocytophthisis,”64 or “alymphocytosis”68 may be associated with a congenital atrophy or dysfunction of the thymus gland. In addition, another familial disease (ataxia telangiectasia or Louis-Bar disease66) has been associated with thymic atrophy. This disorder is characterized by ataxia, peculiar postural attitudes, facial wasting, oculocutaneous telangiectasia, frequent sinopulmonary infections, dermatitis, and retardation of growth; one autopsied case showed an absence of the thymus gland and ovaries.

Infants with “alymphocytosis” are emaciated, develop numerous infections, show lymphocytopenia in the blood and marked atrophy of lymphoid tissue including the spleen. The Swiss authors, Barandun et al.67 and Hitzig and Willi68 have noted a complete absence of all immunoglobulins (gamma 2, beta 2A, beta 2M) in children with “alymphocytosis.” This condition appears to be far more severe than the “agammaglobulinemia” first described by Bruton69 and extensively studied by Good.68 The status of the thymus gland was first described as atrophic by Cottier63 and later confirmed.68 It is of interest that in four autopsied cases of agammaglobulinemia reported by Gitlin et al.,70 the thymus was atrophic in all four cases and markedly so in two. In a recent case of “alymphocytosis and agammaglobulinemia” described by Rosen et al.,65 the thymus “was a small remnant of tissue weighing less than 1 gram.” It contained no Hassall's corpuscles and no small thymocytes. The association of thymoma and hypogammaglobulinemia has been noted in several reported
cases. In these cases, the enlarged thymus gland is principally composed of reticulum cells (epithelial or spindle cells) and only a few lymphocytes (thymocytes). The gland is therefore depleted of lymphoid cells and, in line with current concepts of thymus physiology, is functionally atrophic. The condition known as "alymphocytosis" or "lymphocytophthisis" may be construed as a clinical analogue of "wasting disease" in the hamster and other animals and therefore of extreme severity leading to death early in infancy. Hematologically it is characterized by complete absence of lymphocytes and plasmocytes and of all immunoglobulins. In "agammaglobulinemia," which is compatible with a relatively lengthy life span, there is a complete or almost complete absence of plasmocytes, but a (relatively) normal quantity of lymphoid tissue and of lymphocytes. In this condition, although humoral antibodies are greatly reduced, the phenomenon of delayed hypersensitivity, including the tuberculin reaction and homograft rejection, are usually present. Thus, the physiologic reaction of the lymphocytes may be unimpaired although that of the plasmocytes (gamma globulin production) may be greatly reduced. Thus, it may be said that the post-thymectomy wasting disease of the hamster has many features of the human disease, which has been described chiefly by Swiss authors, and may prove to be an excellent experimental model for this disease.

Summary

A fatal progressive wasting disease was produced in male hamsters by thymectomy. The disease was characterized by generalized atrophy of lymphoid tissue, pancytopenia and decreased gamma globulins. Two unique features of this wasting disease were its occurrence in a significant number of animals thymectomized at 4 weeks of age and its development in males only. The thymectomized female hamster could be made to waste if treated with testosterone propionate or bilateral oophorectomy. The mechanisms involved in the post-thymectomy wasting disease are discussed, as well as the relationship of runt disease (graft vs. host disease) to thymic wasting. The relationship of the thymus to lymphoid tissue, immune globulins, and certain diseases in man are pointed out. The possibility that the wasted thymectomized hamster may be an experimental model for the human disease known as "alymphocytosis" or "lymphocytophthisis" is discussed.

Summario in Interlingua

Un progressive e mortal morbo consumptiva esseva producite in hamsteres mascule per thymectomia. Le morbo esseva characterisate per un atrophia generalisate del tissus lymphoide, per pancytopenia, e per declino in globulinas gamma. Duo unic caracteristicas de iste morbo consumptiva esseva su occurrentia in un numero significative de animales thymectomisate al etate de 4 septimanas e su disveloppamento exclusivemente in masculos. In hamsteres feminin que habeva essite subjicite a thymectomia le occurrentia del morbo poteva esser fortiate per tractamento con propionate de testosterona o per oophorectomia bilateral. Le mechanismos interesate in iste morbo consumptiva post thymectomia es discutite. Es signalate le relation del thymo con
tissu lymphoide, globulinas immunologic, e certe morbos in humanos. Es
discutite le possibilitate que le consumptive hamster thymectomisate
pote
servir como modello experimental pro le studio del morbo human cognoscite
come alymphocytosis o lymphocytophthisis.

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Effect of Thymectomy on the Golden Hamster (*Mesocricetus Auratus*). I. Wasting Disease

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