Alterations of the Thymus and Other Lymphoid Tissue in Young Horses With Combined Immunodeficiency

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Combined immunodeficiency (CID) is a significant disease in terms of prevalence in Arabian foals and is a useful animal for study of a similar condition in children. Thymuses from all CID foals examined were extremely hypoplastic. Light and electron microscopic examination of thymuses from CID foals, as well as a thymus from an aborted CID fetus, demonstrate that the basic thymic structure is intact, despite a number of dissimilar morphologic appearances. From these data, we inferred that the thymic hypoplasia was caused by a failure of committed lymphocytes from the bone marrow to populate the organ. The lack of uniform organized lymphocytes in the spleen and lymph nodes provides considerable support for the absence of lymphoid precursors or their inability to respond to differentiating influences. (Am J Pathol 84:39–54, 1976)

THE MOST SERIOUS of the primary immunodeficiencies occurring in children are associated with the lack of development of both functional B and T lymphocytes. These have been variously designated as Swiss type agammaglobulinemia,[1] lymphopenic agammaglobulinemia,[2] and thymic alymphoplasia with lymphocytic hypoplasia.[3-5] These are now designated *severe combined immunodeficiency* (CID).[6,7] Affected children have decreased serum immunoglobulin concentrations and depressed cell-mediated immune responses, as well as having a paucity of lymphocytes in the lymph nodes, spleen, thymus, and blood.[1-7] Death ensues from a variety of infectious diseases.[1-4] The immunologic function of some affected children has been restored with bone marrow transplants[8,9] and with a fetal liver transplant.[10] Cell-mediated immunity, but not humoral immunity, has been reconstituted in CID children with fetal thymus transplants.[11,12] The decreased T and B lymphocyte responses in CID children and the ability of hemopoietic stem cells to correct both functional abnormalities has led to the concept of a stem cell defect (see Fudenberg *et al.*,[6] and Cooper *et al.*[7,10] for review). Whether the defect is

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a lack of lymphoid precursor cells or a failure of lymphoid precursor cells to respond to thymic influences and the influences of the inductive site for immunoglobulin-producing cells is not clear.

We have described an immunodeficiency syndrome in foals, which closely resembles CID in children.[13-15] Affected foals are born agammaglobulinemic, in contrast to normal foals that have detectable levels of serum IgM and sometimes IgG.[14] Nursing CID foals, like normal foals, usually absorb all immunoglobulin classes from ingested colostrum.[14] The maternal IgM and IgA are first to be cleared from CID foal sera and these immunoglobulins remain absent, demonstrating a failure of synthesis by CID foals. Of the other immunoglobulin classes, occasionally maternal IgG(T) is lost from CID foal serum, but none have lived long enough to clear all the maternal IgG.[14] Additional evidence of failure to make antibody by CID foals includes absence of a response to injections of sheep red blood cells (RBC) and an absence of "natural" serum antibody to rabbit RBC.[15] Lymphopenia (<1000/cu mm) occurs as well as a marked decrease in immunoglobulin-coated B lymphocytes.[15] Evidence for an absence of T-lymphocyte function includes the observation that lymphocytes from peripheral blood and lymph nodes of most CID foals fail to respond to phytolectins (phytohemaglutinin, concanavalin A, and pokeweed mitogen) when measured by *in vitro* lymphocyte transformation.[15] These foals fail to develop skin reactions to initial intradermal injections of phytohemagglutinin, to which normal foals do respond.[15] The affected foals we have studied died within 5 months after birth, and the causes of death included viral, bacterial, fungal, and protozoal infections.[13-15] Combined immunodeficiency in foals is transmitted as an autosomal recessive trait,[16] and all cases studied to date have been of the Arabian and part-Arabian breeds.[13-17]

Since CID in foals has considerable potential as an animal model of the human disease and is a significant disease of Arabian foals, the morphologic basis of the disorder needs careful delineation. During our studies with CID foals, we have noted considerable variation in the appearance of all the lymphoid organs, especially the thymus and lymph nodes. The purpose of this paper is to describe the alterations in lymphoid tissue which occur in this disease and to present evidence for a stem cell defect.

Materials and Methods

Foals With CID

The criteria for the diagnosis of combined immunodeficiency in the 34 foals in this study have been previously defined [13-15] and are as follows: a) lymphopenia (<1000/cu mm while the lower end of the normal range is generally greater than 2,000/cu mm), b)

absence of IgM by single radial diffusion (<2 mg/100 ml while the normal mean from birth to 4 months of age is >30 mg/100 ml), c) lymphocyte depletion in the lymphoid organs which is described in detail in this report, d) increased susceptibility to infections, and e) death or euthanasia in a moribund state before 5 months of age. The clinical documentation of a deficiency of cell-mediated immunity in foals meeting the criteria outlined has been reported.[15] One additional case was an aborted fetus which had an absence of IgM, which is synthesized by the normal equine fetus, as well as lymphoid depletion with thymic hypoplasia.

Sixteen CID foals were available for necropsy by the authors within 1 to 3 hours after death or euthanasia. Thymus tissue was found either macroscopically or microscopically in all these foals. These cases included an 8-month aborted fetus. (The gestation period of horses is 11 months.) Tissues from an additional 19 foals with CID were sent to us by veterinary practitioners from throughout the United States. In many instances, complete tissue samples from each of these foals were not saved. Of the later 19 cases, all had spleens saved, while lymph nodes were saved in 11 and thymuses in 9. The 35 total CID cases were of the Arabian or part-Arabian breeds. Tissues were formalin fixed, and histologic sections were stained with hematoxylin and eosin.

Foals Without CID

Tissues from 25 foals (1 to 120 days of age) dying from a variety of causes were compared with tissues from the CID foals. Twenty-two of the non-CID foals were Arabian.

Electron Microscopy

Tissues from CID and non-CID foals were excised, fixed in 1.5% phosphate-buffered (0.1 M, pH 7.3) glutaraldehyde containing 1% dimethylsulfoxide and 1% sucrose, post-fixed in 1% phosphate-buffered (0.1 M, pH 7.3) osmium tetroxide, stained *en bloc* in a 1% solution of aqueous uranyl acetate, dehydrated in a graded series of ethanols and propylene oxide, and embedded in Epon-Adraldite.[16] Thick sections were prepared and stained with toluidine blue for examination by light microscopy. Ultrathin sections were cut with a diamond knife and stained with uranyl acetate and lead citrate. Micrographs were taken with a Philips EM-200 electron microscope.

Results

All of the CID foals in this study (with the exception of the aborted fetus—cause of death was unknown) died of infections. Pneumonia caused by adenovirus, *Pneumocystis carinii*, or various bacteria was the most prominent disease. Other foals succumbed to hepatitis, enteritis, and other infections. Consequently, it is important to consider two catagories of pathologic changes in CID foals: a) alterations of lymphoid tissues resulting from the genetic defect, and b) lesions caused by various infectious diseases as a result of the primary genetic defect. Since the secondary infections are numerous and control of such infections is important in maintaining foals for transplantation studies, they are the subject of another report.

Normal foals are born with well-developed lymphoid tissues that resemble lymphoid tissues of other young animals and humans. In fact, by 7 months into the 11-month gestation period, the equine fetal lymph nodes,

spleen, and thymus resemble those of a neonatal foal.[19] The lymph nodes from birth onward have defined follicles and germinal centers with a lymphocyte-filled paracortical area. The spleen of young foals has both follicles with adjacent arterioles and arterioles with lymphocytic sheaths. The thymus of newborn foals has a clearly delineated cortex and medulla. The cortex is packed with lymphocytes, and the medulla contains easily identifiable Hassall's corpuscles of varying size. Subsequent paragraphs describe how CID foal lymphoid tissues contrast with those from normal foals.

Thymus

The presence of a morphologically identifiable thymus (macroscopically or microscopically) in all of the 16 cases of CID we necropsied revealed that thymic hypoplasia rather than thymic aplasia occurs in CID foals. The thymus was sometimes difficult to identify at necropsy. When identifiable, it was located in the thoracic cavity just anterior to the heart and was best visualized by removing the left side of the rib cage. Thymuses from 6 CID foals weighed between 4 and 15 g, while those from 4 non-CID foals dying of bacterial infections weighed between 28 and 50 g (Table 1). Thymuses from non-CID foals without infections, one from a foal euthanized after leg trauma and one from a foal dying of toxic hepatic necrosis, weighed 185 and 100 g, respectively. The thymus from an aborted Shetland pony fetus (approximately 9 months' gestation) weighed 65 g (Table 1).

The 24 CID foal thymuses examined microscopically were extremely hypoplastic; however, even the most affected organs possessed an outer

Table 1—Thymus Weights From Foals

Foal No.	Breed	Age	Cause of death	Thumus weight (g)
1	Arabian	1 day	Hepatitis (viral)	50
2	Arabian	2 days	Nephritis (bacterial)	40
5	Tennessee walker	3 days	Nephritis (bacterial)	28
8	3/4 Arabian	7 days	Pneumonia (bacterial)	30
9	Arabian	2 months	Toxic hepatic necrosis	100
13	Arabian	3 months	Euthanasia (leg injury)	185
15	Shetland pony	9 months' gestation	Abortion (unknown cause)	65
32	Arabian	104 days	CID	4
36	Arabian	19 days	CID	6
40	Arabian	30 days	CID	10
49	Arabian	60 days	CID	15
53	Arabian	81 days	CID	8
54	Arabian	84 days	CID	13

capsule, and some were divided into lobules by interlobular fibrous septa. None of the thymuses from foals with CID examined displayed a distinct cortex or medulla, but all of them contained an epithelial component with Hassall's corpuscles. Adipose tissue surrounded the epithelial and lymphoid cell islands and branches extended to the outer capsule.

Two thymuses from CID foals were examined by electron microscopy. Lymphocytes were sparse, and those present were interspersed between epithelial cells and trabecular elements (Figures 1 and 2). Epithelial cells were identifiable by cytoplasmic tonofibrils and desmosomes and were present around blood vessels and trabecular elements (Figures 3 and 4). Basement membrane was evident and appeared to separate the few lymphocytes present from blood vessels and stroma. Macrophages were present and did not contain excessive amounts of phagocytized lymphocytes or cellular debris (Figure 4). Normal foal thymuses resembled those described in rats [20] and humans [21] and differed from those of CID foals in the number of thymocytes present in the cortex and medulla and in the absence of adipose tissue.

Besides the general observations, there were a variety of microscopic appearances which require more detailed descriptions. Two thymuses from CID foals had a marked cystic pattern, which will serve as the prototype description and variations will be mentioned. The basic structure of these thymuses was an arborization of connecting spaces lined by epithelial cells that were sometimes flattened and other times round (Figure 5). Inside the epithelial cell-lined spaces were pink-staining debris, vacuolated epithelial cells, and occasionally an amorphous mass of blue-staining material. Outside the epithelial cell-lined spaces, whose walls were usually several cells thick, were three different kinds of cells. Some were obviously epithelial cells and were often arranged in structures resembling Hassall's corpuscles in various stages of formation and degradation (Figure 6). Another cell type resembled lymphocytes, while the third type was fibroblastic in appearance. These cells were surrounded by mature fat cells which extended to the capsule.

Thymuses from 7 foals with CID were similar to the preceeding 2 foals, except that the central spaces were less defined because they lacked an epithelial lining. The epithelial cells present were scattered in clumps and individually in the areas of lymphoid cells adjacent to the aborizing spaces. The thymuses in this group contained epithelial cell clumps resembling Hassall's corpuscles. Hassall's corpuscles, though present, were difficult to find in two of the thymuses. The thymus from the aborted fetus was very hypoplastic and the morphologic appearance resembled thymuses described in this group.

Another group of 11 CID thymuses displayed a branched pattern of lymphoid-appearing cells, epithelial cells and fibroblasts embedded in adipose tissue, surrounded by a capsule. They lacked, however, any type of space in the branches. All of these contained epithelial structures resembling Hassall's corpuscles. Two of the 11 thymuses contained large Hassall's corpuscles, the centers of which were filled with necrotic debris.

Two thymuses were so distinctly different that they were difficult to identify as thymus (Figure 7). They had only small amounts of identifiable epithelial and lymphoid components. Focal hemorrhage was noted and, microscopically, these foci resembled granulomas with epithelial giant cells, individual epithelial cells, and lymphocytes. Some of the lymphocytes were clumped, adding further to their bizarre appearance.

Two additional thymuses appeared embryonic in that most of the connective tissue was composed of spindle-shaped cells (Figure 8). Branches and islands of densely arranged spindle-shaped cells were present, and structures which resembled Hassall's corpuscles were included in these areas. Some cells resembling lymphocytes bordered the fibrous branches and islands.

Thymuses from non-CID foals with bacterial infections were smaller than those from normal foals (Table 1). Microscopically, the medullary areas were similar in appearance to normal foals with identifiable Hassall's corpuscles. The cortex, however, was depleted of lymphocytes. Macrophages with evidence of phagocytized lymphocytes were present in the depleted cortex. Even though the cortical depletion was severe, at no time did any of these thymuses resemble those from CID foals.

Lymph Node

A variety of different morphologic appearances were noted in lymph nodes from 26 CID foals and 1 CID fetus. In general, the morphologic changes were attributable to four basic alterations. a) The outer lymph node cortex was devoid of any type of B lymphocyte–dependent areas, including lymphoid follicles and germinal centers. b) The paracortical thymus-dependent areas of the nodes contained only a sparse population of lymphocytes, similar to that noted in the outer cortex. c) Variable accumulations of macrophages were present in the medullary sinuses. d) Plasma cells were absent from the lymph nodes. The composition of the cells in the affected lymph nodes were usually readily identifiable as macrophages, lymphocytes, and stroma. However, in some lymph nodes, the predominent nonstromal cells were spindle shaped and difficult to identify.

Many of the lymph nodes draining areas of inflammation contained

medullary sinuses distended with neutrophils and macrophages. In the more extreme cases, large numbers of macrophages were present in the cortex, especially in perivascular locations. In those lymph nodes associated with organs lacking inflammatory changes—such as the splenic lymph node and, in a few cases, the hepatic lymph node—the macrophage numbers were fewer. The medullary sinuses of the later lymph nodes were hypocellular, dilated, and empty, giving a cystic appearance (Figure 9).

Most lymph nodes from normal foals and from non-CID foals dying of infections were readily distinguished from lymph nodes of foals with CID by the presence of follicles and germinal centers, abundance of lymphocytes, and presence of plasma cells. The exception was lymph nodes from a few non-CID foals with severe generalized bacterial infections. These lacked well-defined follicles and germinal centers, making it difficult to differentiate them from lymph nodes from CID animals.

Spleen

The changes in the spleens from 34 CID foals and 1 CID fetus were easily identified on the basis of three morphologic features: a) absence of germinal centers and primary follicles, b) absence of periarteriolar lymphocytic sheaths (PALS), and c) lack of plasma cells. The B lymphocyte–dependent germinal centers were always absent, as was the scaffold where germinal centers were usually present. This observation was useful in distinguishing CID from other disorders with lymphocyte depression. In non-CID cases, there was always a remnant of stromal architecture of the germinal centers, even though lymphocytes were scarce. The PALS were invariably absent. In one case, however, some lymphocytes were found in association with splenic arteries. The splenic trabeculae in CID foals always appeared closer together than normal, and there was also a lack of lymphocytes in the red pulp. Only one of all the CID spleens examined had plasma cells and in this case they were very few in number.

Peyer's Patches

Intestinal sections containing Peyer's patches were available in 12 cases. These structures resembled the lymph nodes in that no primary follicles or germinal centers were present. There was an absence of plasma cells. Lymphocytes were sparse even in cases with enteritis.

Discussion

Similar to children with CID,[3-5,22,23] foals with CID have a detectable, though hypoplastic, thymus. The thymuses from foals with CID possessed

a capsule, an epithelial component with Hassall's corpuscles, and a paucity of lymphocytes. The epithelial cell–lined arborized spaces in two thymuses from foals with CID may have represented persistent central thymic canals. Thymuses with spaces lacking an epithelial lining could represent a more mature stage of development, where the epithelial cells have lost their orientation to the central canal and have become more disperse. Thymuses having branching without spaces would be a further step toward maturity, with complete obliteration of the canal. The embryonal appearing thymuses and the ones resembling granulomas represent distinct morphologic, though unexplainable, variations.

Examination of CID foal thymuses by electron microscopy indicated that the basic structure, including separation of residual lymphocytes from other structures by a basement membrane, was intact. Macrophages in CID foal thymuses did not have the excessive amount of phagocytized cells noted in atrophied or involuted thymuses from non-CID foals dying of infections. These data, taken together, suggest the hypoplasia was caused by an absence or inability of committed lymphocytes from the bone marrow to populate the organ. The thymic hypoplasia noted in a CID fetus aborted 3 months before term provides strong evidence for a failure of lymphoid cells to populate the thymus in CID foals. It also provides evidence against the thymic hypoplasia being caused by involution of a normally developed thymus as has been suggested in some CID children.[21]

Certain children with CID have an adenosine deaminase (ADA) deficiency, and a cause and effect relationship between absence of ADA and CID has been proposed.[24,25] Thymuses from CID children with normal ADA levels have been described as embryonal and lacking Hassall's corpuscles.[23] In contrast, thymuses from CID children with an absence of ADA were described as appearing extremely involuted and containing Hassall's corpuscles.[23] Foals with CID have normal levels of ADA,[26] and their thymuses have Hassall's corpuscles. These closely resemble the thymuses from ADA-negative CID children. However, the wide variation in morphology of the 25 CID foal thymuses makes this type of comparison difficult to evaluate. The description of a possible intrathymic defect associated with some CID children suggests that the thymus may be defective,[27,28] in contrast to those CID cases that apparently have normal thymic function as indicated by the ability of bone marrow cells to reconstitute T lymphocyte function.[29] It would be quite interesting to measure the functional capacity of the epithelial component in CID foal thymuses to produce substances such as thymosin. The functional ability

of CID foal thymic epithelium is extremely important when considerations for immunotherapy are made.

The absence of B lymphocyte areas of the lymph nodes and spleen was consistent throughout all the cases of CID examined. No evidence of primary follicle or germinal center formation was obtained in either organ, with the possible exception of one spleen which contained small clumps of lymphocytes and cells resembling plasma cells. This is compatible with failure to form specific antibody following antigen injection, absence of IgM and, sometimes, IgA and IgG(T).[14] It seems likely that if CID foals survived longer, all maternal immunoglobulins would be eliminated. The lymph node changes in CID foals are severe, but the lymphoid depletion accompanying severe bacterial infections can resemble those seen in lymph nodes of animals with CID. The alterations of spleen morphology in CID foals were not observed in non-CID foals. Spleens from non-CID foals with infections always possessed an identifiable area representing germinal centers, even though most of the lymphocytes were depleted. It appeared from preliminary observations that the absence of germinal centers, PALS, and plasma cells with a paucity of lymphocytes in the spleen were unique to CID foals. However, a recent case of agammaglobulinemia in a horse, with an absence of B lymphocytes and apparently normal T lymphocyte function,[30,31] displayed alterations in spleen morphology similar to those occurring in CID. Thus, based on the present information, spleens of foals with CID can be distinguished morphologically from spleens from non-CID foals with infections and lymphoid depression, but not from certain other immunodeficiency disorders of horses.

It should be emphasized that the changes described in lymph nodes and spleen from CID foals are very similar to those noted in children with severe CID.[3-5,22] The only observed distinction is that the variation of lymphocyte numbers in lymph nodes and spleens from children with CID appear to exceed those that have been observed in foals. Two explanations may account for this difference: a) Both sex-linked and autosomal forms of CID occur in children with similar functional abnormalities,[6,7] and there is an associated difference in the number of lymphocytes found in each. b) Additional variations of CID may occur in foals, and we have not, as yet, encountered the full spectrum of variations in lymphocyte numbers characteristic of this disease.

The data obtained thus far indicate that CID foals afford an exceptional opportunity to analyze the mechanisms causing a failure in the production of committed T and B lymphocytes. In addition, since this is the only

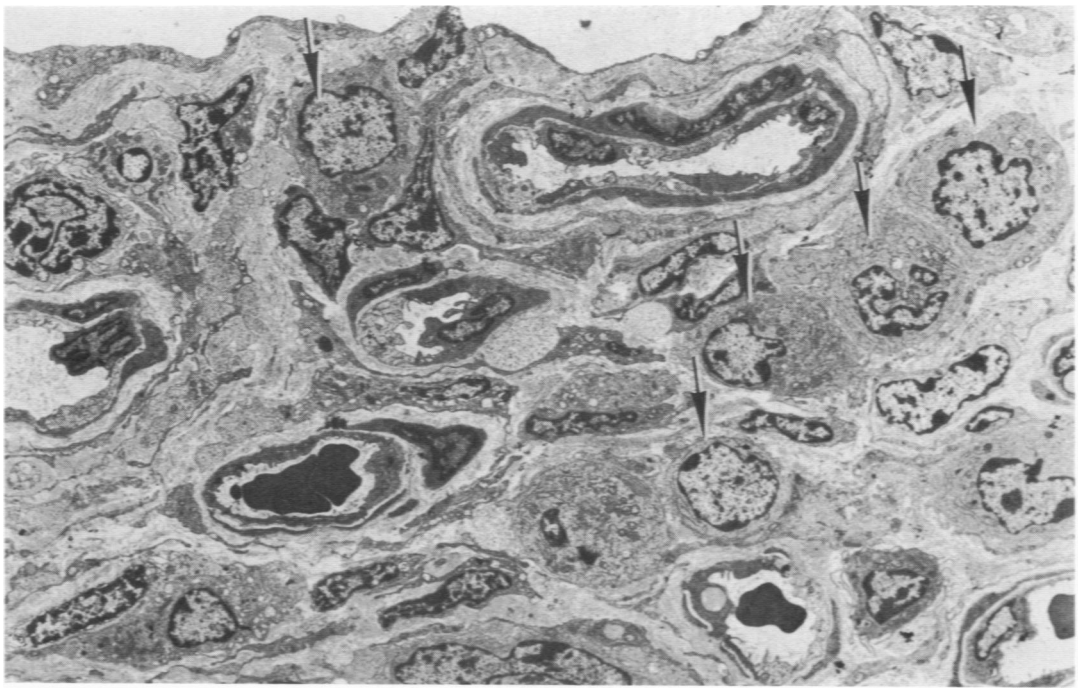
well-characterized immunologic defect in animals that resembles CID of children, new knowledge gained from immunotherapy studies in foals should be useful.

References

1. Hitzig WH: Swiss type of agammaglobulinemia. Immunologic Deficiency Diseases in Man. Edited by D Bergsma, RA Good. Birth Defects Original Article Series. New York, National Foundation Press, 1968, p 82–87
2. Lawton AR, Bockman DE, Cooper MD: Treatment of autosomal recessive lymphopenic agammaglobulinemia by transplantation of matched allogeneic bone marrow. Am J Med 54:98–110, 1973
3. Gitlin D, Craig JM: The thymus and other lymphoid tissues in congenital agammaglobulinemia. I. Thymic alymphoplasia in lymphocytic hypoplasia and their relation to infection. Pediatrics 32:517–530, 1963
4. Gitlin D, Vawter G, Craig JM: Thymic alymphoplasia and congenital aleukocytosis. Pediatrics 33:184–192, 1964
5. Blackburn WR, Gordon DS: The thymic remnant in thymic alymphoplasia. Arch Pathol 84:363–375, 1967
6. Fudenberg HH, Good RA, Goodman HC, Hitzig WH, Kunkel HG, Roitt IM, Rosen FS, Rowe DS, Seligmann M, Soothill JR: Primary immune deficiencies: Report of a WHO committee. Pediatrics 47:927–946, 1971
7. Cooper MD, Faulk WP, Fudenberg HH, Good RA, Hitzig W, Kunkel H, Rosen FS, Seligman M, Soothill J, Wedgwood RJ: Classification of primary immunodeficiencies. N Engl J Med 288:966–967, 1973
8. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA: Immunological reconstitution of sex-linked lymphogenic immunological deficiency. Lancet 2:1366–1369, 1968
9. Dooren LJ: Bone marrow transplantation in combined immunodeficiency disease. Boll Ist Sieroter Milan 53(Suppl 1):245–258, 1974
10. Cooper MD, Keightley RG, Wu L-Y, Lawton AR: Developmental defects of T and B cell lines in humans. Transplant Rev 16:51–84, 1973
11. Ammann AJ, Wara DW, Salmon S, Perkins H: Thymus transplantation: Permanent reconstitution of cellular immunity in a patient with sex-linked combined immunodeficiency. N Engl J Med 289:5–9, 1973
12. Rocherefsky GS, Stiehm ER, Ammann AJ, Cederbaum SD, Opelz G, Terasaki PI: T-cell reconstitution by thymus transplantation and transfer factor in severe combined immunodeficiency. Pediatrics 55:114, 1975
13. McGuire TC, Poppie MJ: Hypogammaglobulinemia and thymic hypoplasia in horses: A primary combined immunodeficiency disorder. Infect Immun 8:272–277, 1973
14. McGuire TC, Poppie MJ, Banks KL: Combined (B- and T-lymphocyte) immunodeficiency: A fatal genetic disease in Arabian foals. J Am Vet Med Assoc 164:70–76, 1974
15. McGuire TC, Banks KL, Poppie MJ: Combined immunodeficiency in horses: Characterization of the lymphocyte defect. Clin Immunol Immunopathol 3:555–566, 1975
16. Poppie MJ, McGuire TC: Documentation of autosomal recessive inheritance of combined immunodeficiency and estimation of the prevalence. Unpublished observations
17. Thompson DB, Studdert MJ, Beilharz RG, Littlejohns IR: Inheritance of a lethal immunodeficiency disease. Aust Vet J 51:109–113, 1975
18. Mollenhauer HH: Plastic embedding mixtures for use in electronmicroscopy. Stain Technol 39:111–114, 1964

19. Perryman LE, McGuire TC: Unpublished observations
20. Hwang WS, Ho TY, Luk SC, Simmon GT: Ultrastructure of the rat thymus: A transmission scanning electron microscope and morphometric study. Lab Invest 31:473–487, 1974
21. Bockman DE, Lawton AR, Cooper MD: Fine structure of thymus after bone marrow transplantation in an infant with severe combined immunodeficiency. Lab Invest 26:227–239, 1972
22. Berry CL: Histopathological findings in the combined immunity-deficiency syndrome. J Clin Pathol 23:193–202, 1970
23. Huber J, Kersey J: Pathologic features. Combined Immunodeficiency Disease and Adenosine Deaminase Deficiency. Edited by HJ Porter. New York, Academic Press, 1975 p 279–288
24. Giblett ER, Anderson JE, Cohen F, Pollara B, Meuwissen HJ: Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity. Lancet 2:1067–1069, 1972
25. Parkman R, Gelfand EW, Rosen FS, Sanderson A, Hirschhorn R: Severe combined immunodeficiency and adenosine deaminase deficiency. N Engl J Med 292:714–719, 1975
26. McGuire TC, Pollara B, Moore JJ, Poppie MJ: Evaluation of adenosine deaminase and other purine salvage enzymes in horses with combined immunodeficiency. Infect Immun 13:995–997, 1976
27. Pyke KW, Dosch H-M, Ipp MM, Gelfand EW: Demonstration of an intrathymic defect in a case of severe combined immunodeficiency disease. N Engl J Med 293:424–428, 1975
28. Touraine JL, Incefy GS, Touraine F, L'Esperance P, Siegal FP, Good RA: T-lymphocyte differentiation in vitro in primary immunodeficiency diseases. Clin Immunol Immunopathol 3:228–235, 1974
29. Incefy GS, Boumsell L, Touraine JL, L'Esperance P, Smithwick E, O'Reilly R, Good RA: Enhancement of T-lymphocyte differentiation *in vitro* by thymic extracts after bone marrow transplantation in severe combined immunodeficiencies. Clin Immunol Immunopathol 4:258–268, 1975
30. McGuire TC, Banks KL, Evans DR, Poppie MJ: Agammaglobulinemia in a horse with evidence of functional T lymphocytes. Am J Vet Res 37:41–46, 1976
31. Banks KL, McGuire TC, Jerrells AB: Absence of B lymphocytes in a horse with primary agammaglobulinemia. Clin Immunol Immunopathol 5:282–290, 1976

[*Illustrations follow*]



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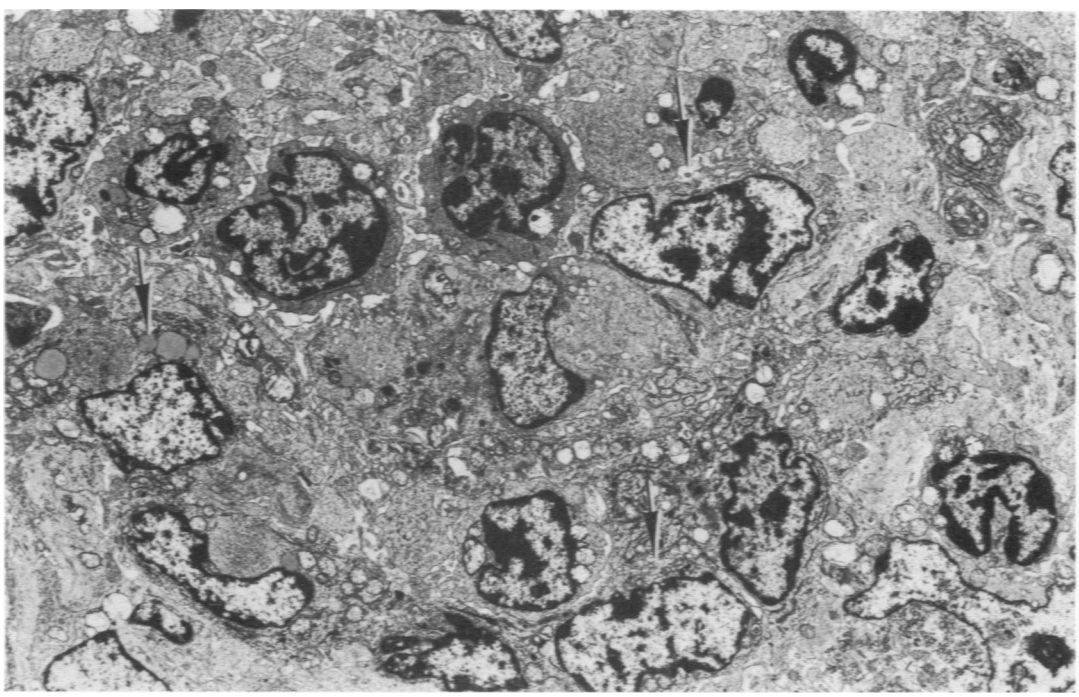

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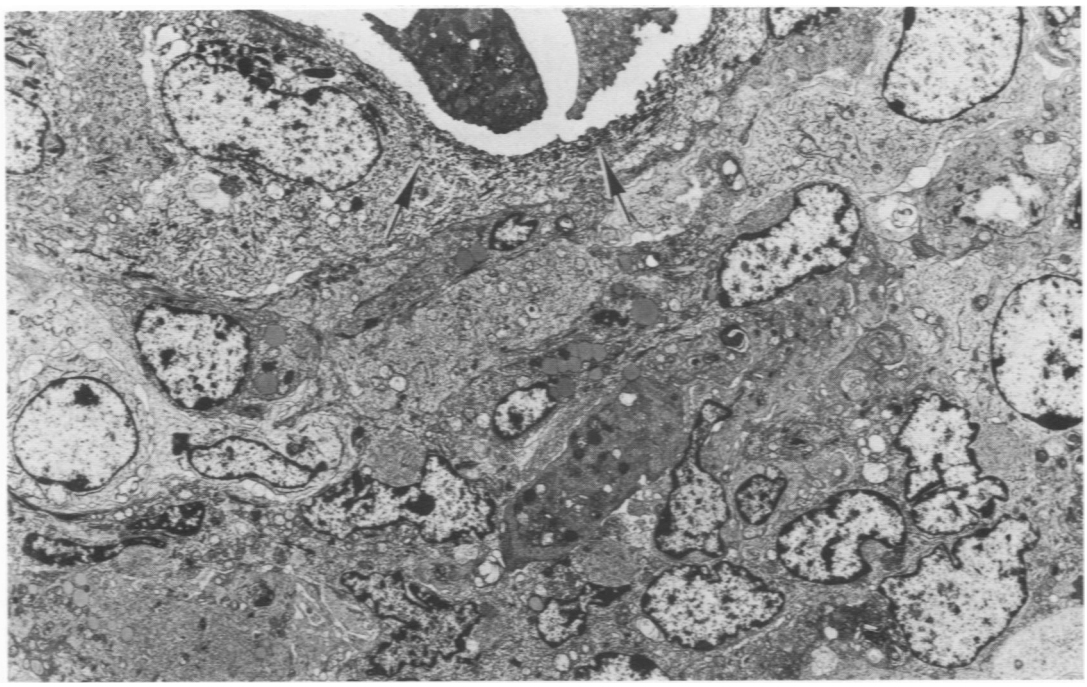
Figure 1—The outer region of the thymic tissue from a foal with CID contains a sparse popuiation of lymphoid cells (*arrows*) interspersed between epithelial cells and trabecular elements (Uranyl acetate and lead citrate, × 2900). **Figure 2**—Inner area of the CID thymus showing prominence of epithelial components (*arrows*) and absence of the large population of lymphocytes characteristically present in normal thymus (Uranyl acetate and lead citrate, × 3600).



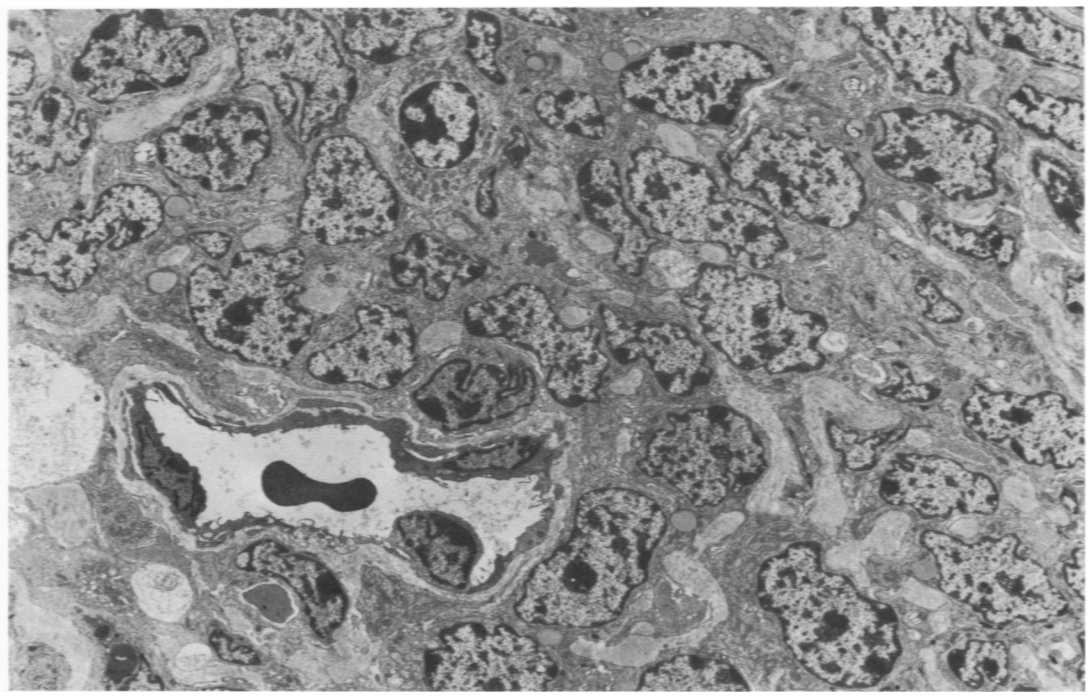
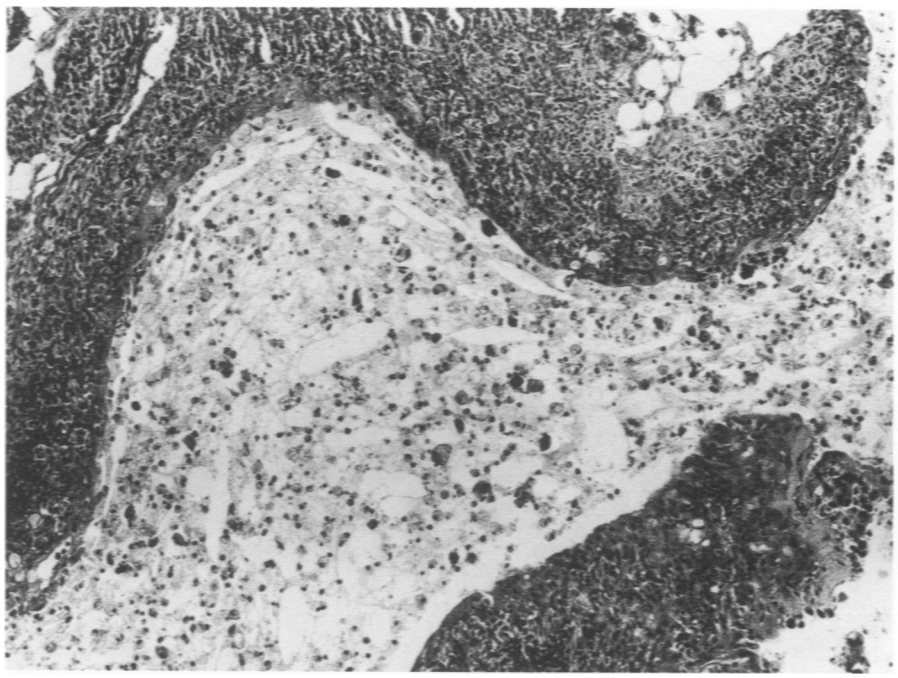


Figure 3—Central area of CID thymus adjacent to Hassall's corpuscle in an early stage of formation (*arrows*). The morphology of the epithelial cells and architecture of surrounding tissue is similar to that found in normal thymus tissue. (Uranyl acetate and lead citrate, × 2000) **Figure 4**—Central area of CID thymus showing abundance of epithelial cells and the presence of trabecular elements. No distinct zone delimits the medulla from the outer or inner cortex. (Uranyl acetate and lead citrate, × 2900)



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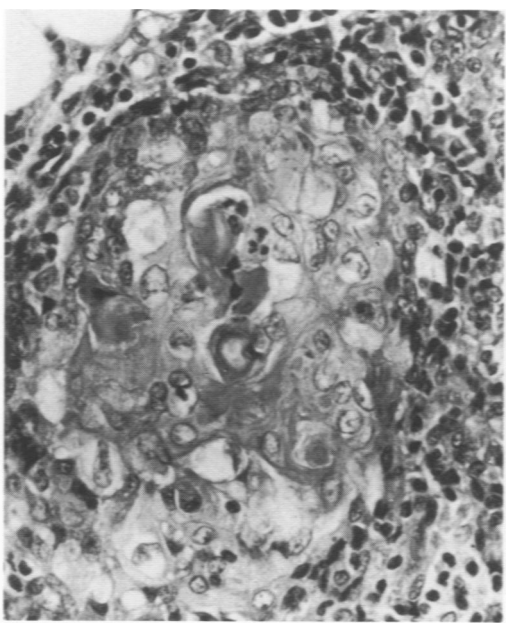

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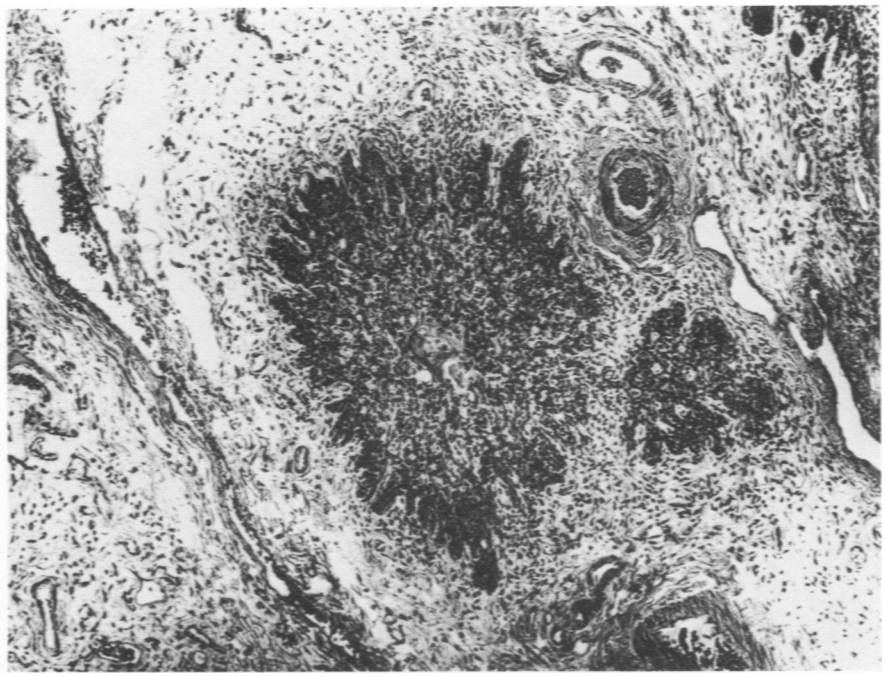
Figure 5—CID thymus with epithelial lined space surrounded by a few lymphocytes. The space contains vacuolated cells and debris. (H&E, × 100) **Figure 6**—Hassall's corpuscle in CID thymus (H&E, × 350). **Figure 7**—CID thymus containing very few lymphoid cells (H&E, × 350).



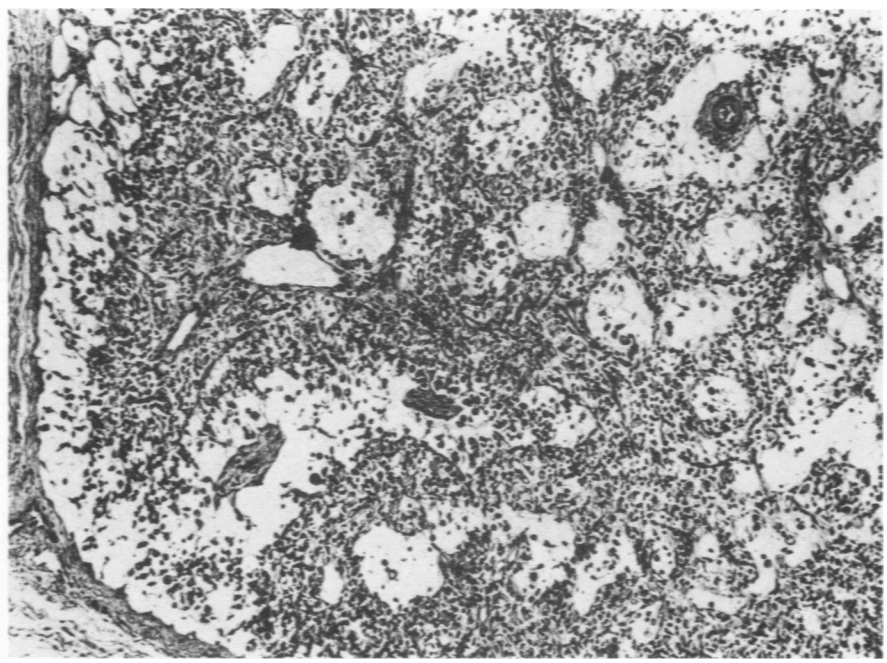


Figure 8—The connective tissue is this CID thymus appears embryonic. Note Hassall's corpuscle in center of tissue. (H&E, × 100) **Figure 9**—CID lymph node emphasizing lack of lymphocytes and large spaces (H&E, × 100)