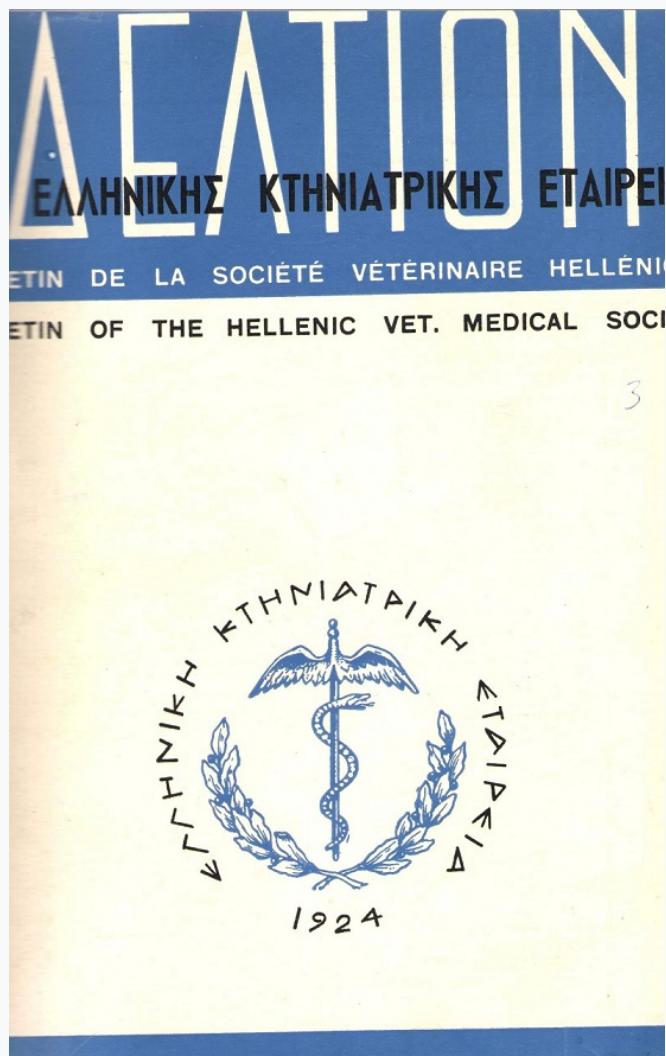


## Journal of the Hellenic Veterinary Medical Society

Vol 20, No 3 (1969)



### LYMPH NODE HYPERPLASIA IN A CONGENITALLY DEFORMED BULL INOCULATED AT BIRTH WITH BOVINE LYMPHOSARCOMA MATERIAL

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doi: [10.12681/jhvms.19988](https://doi.org/10.12681/jhvms.19988)

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#### To cite this article:

HATZIOLOS, B. C. (1969). LYMPH NODE HYPERPLASIA IN A CONGENITALLY DEFORMED BULL INOCULATED AT BIRTH WITH BOVINE LYMPHOSARCOMA MATERIAL. *Journal of the Hellenic Veterinary Medical Society*, 20(3), 125–135. <https://doi.org/10.12681/jhvms.19988>

<p><b>ΔΕΛΤΙΟΝ</b></p> <p><b>ΤΗΣ</b></p> <p><b>ΕΛΛΗΝΙΚΗΣ ΚΤΗΝΙΑΤΡΙΚΗΣ</b></p> <p><b>ΕΤΑΙΡΕΙΑΣ</b></p>	<p><b>BULLETIN</b></p> <p><b>OF THE</b></p> <p><b>HELLENIC VETERINARY MEDICAL</b></p> <p><b>SOCIETY</b></p>
<p><b>TOMOS 20</b></p> <p><b>ΤΕΥΧΟΣ 3</b></p> <p><b>ΙΟΥΛΙΟΣ - ΣΕΠΤΕΜΒΡΙΟΣ 1969</b></p>	<p><b>VOLUME 20</b></p> <p><b>No 3</b></p> <p><b>JULY - SEPTEMBER 1969</b></p>

## **LYMPH NODE HYPERPLASIA IN A CONGENITALLY DEFORMED BULL INOCULATED AT BIRTH WITH BOVINE LYMPHOSARCOMA MATERIAL\***

**Basil C. Hatzios\*\***

During attempts to induce leukemia in cattle, a marked hyperplasia of the prescapular lymph nodes was found in a bull which had been inoculated at birth, in the thymus area, with a cell-suspension of bovine lymphosarcoma tissue. This animal, like the others used in these transmission attempts (10-13), had a known leukemia-free background. It was born, however, with minor skeletal and muscular anomalies. It is the purpose of this paper to report this unusual hyperplasia, which macroscopically resembled lymphosarcoma.

### **MATERIALS AND METHODS**

The tumorous mass used for the inoculum was obtained by biopsy from a 5 1/2 year old Holstein-Friesian cow severely affected with lymphosarcoma. Immediately after harvesting the material, an emulsion was prepared by

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Bull. Hel. Vet. Med. Soc., 1969, V. 20, No. 3.

Received for publication June 28, 1969.

\* Scientific Article No. A 1518. Contribution No. 4172 of the Maryland Experiment Station. Supported by research grant (D-65) of the State of Maryland.

The computer time for this project was made available through the facilities of the Computer Science Center of the University of Maryland.

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mincing and grinding in a sterilized mortar 10 Gm of the tumorous mass and suspending it in 50 ml of sterile saline. To this suspension of 20 per cent weight/volume, antibiotics were added to a concentration of 2,000 units of penicillin and 10 mg of dihydrostreptomycin per ml. The emulsion was then left in the refrigerator for 15 minutes to permit the coarse particles to settle. With the use of a 16-gauge needle, 10 ml of the supernatant suspension was inoculated immediately into the cervical thymus area of a 3-hour old male Holstein-Friesian calf. This calf had been born with a moderate atrophy of the pectoral muscles and with a heavy bone structure. A locomotor disturbance noted at birth was overcome within a week.

The animal was deprived of colostrum and was reared artificially. It was placed in a pasture where its skeletal condition appeared to improve, but at 1½ years it developed aggressive tendencies which necessitated confinement in the barn. There, malformations of the skeleton developed, such as thick and bulky epiphyses, moderate enlargement of the carpal joints, slight bending, and deformations of the metacarpuses. Much of the foreleg deformation was due to repeated knee injuries caused by the bull's restriction in a stanchion. The animal grew tall and thin. Its head became heavy with the cranial base reduced in length, and its facial tuberosities became prominent. No kyphosis was observed. At 2½ years, in spite of adequate food intake, the animal started losing weight. At 46 months, it suffered a fractured pelvis and was slaughtered four days later.

Body temperatures of the calf were taken twice daily during the first two months after inoculation. Blood samples were collected daily for the first week, weekly up to the first month, and monthly thereafter. Hematologic data were obtained by standard laboratory methods, as previously described (12,13). Bendixen's key (2) for bovine leukosis was used in evaluating the hematologic reaction. The cellular elements of the lymphoid series were expressed in circulating lymphoid cells (CLC) per cmm (13).

Necropsy was performed immediately after slaughter. Impression smears were made with material of carpal joints and stained according to the Macchiavello method for rickettsiae. Specimens of lymph nodes and organs were taken for bacteriological examination including mycoplasma. Homogenates from the prescapular lymph nodes were used for intraperitoneal inoculations in mice (3 passages) and intravenous in one calf. Specimens from all lymph nodes and organs were fixed in 10% formalin or Zenker's fixative, and processed for sectioning. Hematoxylin-Eosin, Giemsa, PAS, and Foot's modification of Bielschowsky's method for collagen and reticulum staining methods were used for differentiation and identification of cellular and stromatic elements.

## RESULTS

**Body temperature :** For 12 days following inoculation, the temperature varied between 38.4° C and 38.9° C. It rose to 39.2° C at the end of the 2nd week, and to 39.8° C during the 3rd week, at which time the animal developed a slight diarrhea. On the sixth week, the animal experienced a mild upper respiratory infection. It had a temperature of 40.0° C, a light mucopurulent nasal discharge, and a moderate cough. The animal responded promptly to antibiotic therapy\*. No other acute febrile incidence was noted thereafter; nor was there a reaction at the site of the inoculation. A moderate enlargement of the prescapular lymph nodes occurred approximately 10 days after inoculation.

**Hematologic changes :** The erythrocyte count varied little and remained within normal range during the period of observation. Packed-cell volume and hemoglobin value, however, were lower than normal (Table 1).

The leukocyte count varied considerably. It reached its peak during the 6th month with a high percentage of granulocytes, indicating stress or mild infection. As the animal advanced in age, the leukocyte count gradually decreased. There were,

TABLE 1. DATA CONCERNING VARIOUS BLOOD VALUES DURING THE 46 MONTHS OF OBSERVATION

Hematologic Tests	1st Year		2nd Year		3rd Year		4th Year	
	Range	M±m	Range	M±m	Range	M±m	Range	M±m
1. Erythrocyte count X 10 <sup>6</sup> cmm	6,100— 9,560	8,333±215	6,730— 8,650	8,083±754	6,680— 10,530	8,583±319	6,630— 10,910	8,583±384
2. Packed cell volume (in %)	26.0—33.5	29.116±0.682	29.3—37.5	33.575±0.648	32.4—41.9	37.500±0.333	28.1—38.2	33.332±0.912
3. Hemoglobin value Gm/100 ml	8.5—12.0	10.417±0.319	10.5 12.0	11.500±0.204	11.5—14.0	12.917±0.249	10.5—12.0	11.417±0.302
4. Leukocyte count (per cmm)	11,500— 18,550	14,267±550	10,000— 13,050	11,583±248	9,167— 11,850	9,167±287	8,200— 14,400	11,500±315
5. Circulating lymphoid cells (per cmm)	8,960— 12,064	9,920±335	6,900— 10,338	8,113±301	4,510— 6,927	5,815±219	4,176— 6,735	5,100±212
6. Average % of circu- lating lymphoid cells	46.2—80.6	69.52	62.2—83.8	70.05	50.4—72.6	63.43	29.0—67.0	48.57

\* Achromycin, Lederle Laboratory Division, Amer. Cyanamid Co., Pearl River, N. J.



however, 2 instances of leukocytic elevations, one in the 2nd month and the other, shortly after the pelvic fracture (Figure 1). The eosinophil count reached 12.6% during the 15th month and 13.0% during the 36th month.

The number of CLC also varied considerably paralleling, with some exceptions, the course of the leukocyte counts, at least during the first year. During this period, the number of CLC reached a positive level only once (4th month) and a suspicious level 6 times. In time, the CLC decreased disproportionately with the decrease of the leukocytes (Figure 1).

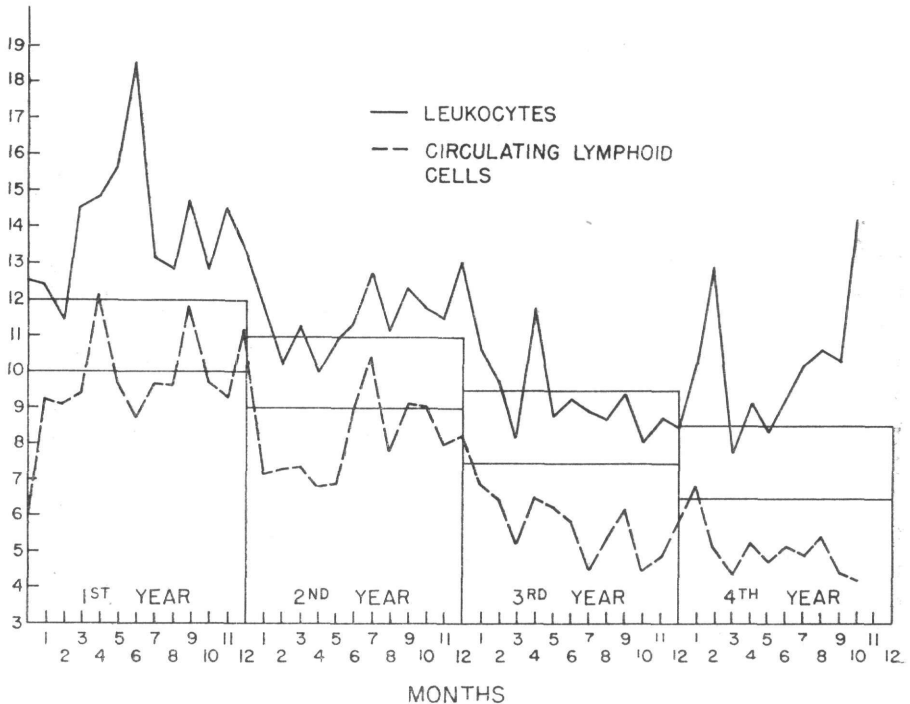


Figure 1. Variations of the leukocytes and circulating lymphoid cells (CLC) of bull #2 during the 46 months of observation.

Atypical lymphoid cells were present, but their number did not exceed 4 per cent. Morphologically, these cells were similar to those previously described (12).

**Necropsy findings :** The flesh condition was rather poor. Scattered bruises and areas of subcutaneous edema were noted in the thoracic and abdominal region and in the feet. The inner organs appeared to be normal. However, the lymph nodes, particularly the prescapular and sternal ones, were enlarged, but their surfaces were smooth.

Each of the prescapular nodes measured approximately  $13 \times 5 \times 4$  cm. The left one weighed 242 Gm., and the right one, 250 Gm. In cross section, the cortex was doubled and irregular, with tortuous greyish white bands extending to the medulla and a few scattered hemorrhagic areas (Figure 2).

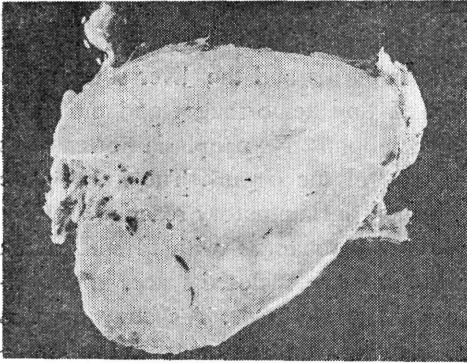


Figure 2. Cross section of one of the prescapular lymph nodes. The marked hyperplasia of the cortex gives the impression that it has doubled in width.

The sternal lymph nodes had attained the size of a walnut. There were also numerous hypertrophic or newly-formed lymph nodes, the size of a pea, along the alimentary tract and in the thymus area, where remnants of the involuted glands were present. However, no trace of the inoculated material was found.

The bones of the carpal joints were moderately enlarged. The skin over the area was scarred or bruised, the articular cartilage roughened, and the joint capsule thickened. However, there was little, if any, increase in joint fluid. In addition, enlargement of the costo-

chondral junctions of the ribs was observed, as well as hemorrhagic enteritis in a limited portion of the small intestine.

**Microscopic changes :** In the prescapular lymph nodes, the capsule was thick but smooth. Wide and tortuous cortical infoldings extending into the medullary zone rendered the demarcation line indistinguishable in many places (Figure 3). The cortical architecture in many places was overrun by, or thickly settled with, cells which appeared to be plasmocytes, although more hyperchromatic (Figure 4). In addition lymphocytes and some large lymphoid cells with bilobed and even trilobed nuclei were present. Mitotic figures were seen with varying frequency. Isolated macrophages with engulfed nuclear debris, such as normally encountered in the reaction centers, were scattered uniformly throughout the parenchyma. Only a few nodules with germinal centers persisted; they blended in smoothly with the surrounding cellular elements. The cords were prominent and hypertrophic (Figure 5). The outlines of the subcapsular and medullary sinuses were intact, although in many places they were noticeably compressed or dilated by plasmocytes which mingled with macrophages and, occasionally, eosinophils and neutrophils. The continuity of the parenchyma was interrupted by numerous trabeculae, some of which were thick and fibrotic. The reticular fibers were delicate, regular,

and unbroken (Figure 6). The vascularization was rich and the vessels were lined with increased, prominent, endothelial cells; many contained an unusually high number of leukocytes in their lumens. Tiny scattered hemorrhages were seen. Similar changes were also noted in the sternal lymph nodes.

The remaining lymph nodes had undergone mild changes of chronic inflammatory reaction. The spleen had prominent malpighian corpuscles and numerous germinal centers. The hematopoietic activity had been normal. The kidney had small foci of interstitial nephritis and the liver some areas of fatty phanerosis. The intestines showed tiny hemorrhages and moderate inflammatory reaction with presence of eosinophils. No neoplasia nor changes pertinent to leukemia was detected in any of the organs. The knees were the site of an extraarticular and non-purulent inflammatory reaction.

The long bones had undergone resorptive changes with rarefaction in certain areas of the original osseous structures. The enclosed spaces in the trabeculated bone showed highly vascularized fibrotic tissue. The bony margins were notched and irregular. Osteoclasts in interrupted rows marked the connections between the spicules and the fibrous tissue. In the compact zone, as well as in the bony spicules, there were cartilage cells in groups or in small island formations. The alignment of the epiphyseal cartilage cells was distorted and showed some discrete centers of irregular calcification. The bone marrow was normal.

Impression smears, lymph node cultures for bacteria and mycoplasma, as well as the homogenates inoculated in the mice and in the calf, were negative.

## DISCUSSION

The preservation of the normal architecture in many places of the enlarged preapular nodes, in association with the presence of inflammatory cellular elements, the persistence of phagocytosis, and the development of numerous fibrotic trabeculae indicate a hyperplastic process. Also, the normal size of the spleen with the presence of germinal centers and the lack of lymphoid cell aggregates in the organs exclude the presence even of a latent neoplastic condition of the lymphopoietic system. In addition, prominent among the cellular elements were the plasmocytes and, in some instances, other non-lymphoid cells. Generally, in inflammation of tissue, and particularly of the lymph nodes, the plasmocytes are prominent and sufficiently replace the lymphocytes in a large portion of the node (3). Plasmocytes, some of which are derived from free reticular cells (1), rather than lymphocytes, or macrophages, are the principal source of antibody formation (6, 7, 19, 23, 24, 30, 34). Plasmocytes elaborate gamma-globulin, either *per se* or in conjunction

with lymphocytes (4, 25, 26). This kind of globulin is to be found on the surface of plasmocytes and of cells forming the germinal centers of the lymphatic nodule (15, 21). Consequently the microscopic changes indicate a chronic immunological response. On the basis of these findings, the question arises as to the real cause of this immunological response.

It is doubtful that the inflammation which affected both knees was sufficiently intense to produce this lymph node reaction. It is true that in cases of transportation of bacteria or toxic substances through the lymphatic vessels, subsequent changes in the lymph nodes depend on the nature of the infecting organism, the animal's resistance, and other factors which affect the morphology of the cells produced by the inflammatory reaction. Therefore, the production of plasmocytes, which are said to have light phagocytic properties, was influenced in the present case by both the type of injurious agent and the part of the body involved. However, it is uncertain that these factors contributed to so great an extent in the development of the changes.

Infection of the carpal joints by psittacosis-like agents (14, 28, 32, 33), mycoplasma (17), or other organisms (31) is very improbable in view of the negative results of the cultures and the inoculations, and the absence of other signs usually accompanying these infections.

The developmental disturbances and the structural changes of the bones are suggestive of a congenital disorder (12), somewhat reminiscent of chondro-osteodystrophy encountered in humans (18, 22). The condition of this bull, coupled with repeated light traumas of the knees, played a certain indirect role in the development of the lymph node changes, but certainly not enough to justify such scope.

A combination of the inoculation and the double carpalitis should not, in our opinion, be excluded as the cause of this unusual bilateral and symmetrical lymph node reaction. The hyperplasia of the sternal and other lymph nodes, which do not directly receive any lymphatic drainage of the forelimbs, might lend support to the idea that the injected material contained a lymphoproliferative agent. Conceivably, this hyperplasia could have evolved into true lymphocytic neoplasia, had the animal lived longer. On the other hand, there is no evidence suggesting that the inoculated material had a destructive effect on the thymus which could have resulted in alteration of the immunologic process. Nor is it possible that these changes might represent early manifestation of an immunopathic process or autoimmune response, as has been hypothesized with regard to the pathogenesis of leukemias (5, 8). It is also noteworthy that the lymph node hyperplasia was not reflected quantitatively in the blood tests; qualitatively, however, the atypical forms of lymphoid cells may be an indication, possibly not specific, of a disturbed lymphopoiesis.

Therefore, the lack of neoplastic changes and the negative blood reaction compel acceptance of the thesis that the existing nonspecific carpalitis was the origin of the lymph node hyperplasia. Moreover, the unsuccessful attempt at lymphosarcoma transmission by cell suspension injected in the thymus area immediately after the harvesting of the affected masses is in disagreement with positive results claimed by others (9, 16, 20, 27, 29).

The inflammatory nature of changes noted in the various organs was probably due to the animal's recumbency for a number of days before slaughter.

## S U M M A R Y

A Holstein-Friesian bull which was born with congenital, developmental, and locomotor disturbances, and which was inoculated 3 hours after birth with an emulsion of lymphosarcoma masses in the cervical portion of the thymus had, when slaughtered at 46 months, a marked hypertrophy and hyperplasia of the prescapular and sternal lymph nodes. Microscopically, the cortex and medulla were diffuse in many places, with loss of follicular pattern and replacement of the normal architecture by proliferation of plasmacyte-like elements. Lymphocytes were scattered about in small nodules. A limited number of histiocytes and granulocytes mingled in the medullary sinuses. The above reaction, indicating a strong immunological response, is attributable to foreleg injuries developed from the congenital skeletal abnormalities. However, in view of the intensity of the reaction, it is suspected that the injected lymphosarcoma material probably played a contributory role in the lymph node hyperplasia.

## Π Ε Ρ Ι Λ Η Ψ Ι Σ

**ΛΕΜΦΟΓΑΓΓΛΙΑΚΗ ΥΠΕΡΠΛΑΣΙΑ ΕΙΣ ΣΥΓΓΕΝΩΣ ΠΑΡΑΜΟΡΦΩΜΕΝΟΝ  
ΤΑΥΡΟΝ ΕΝΟΦΘΑΛΜΙΣΘΕΝΤΑ ΚΑΤΑ ΤΗΝ ΓΕΝΝΗΣΙΝ ΔΙ' ΥΛΙΚΟΥ  
ΛΕΜΦΟΣΑΡΚΩΜΑΤΟΣ**

Υπό Β. Κ. Χατζηόλου

Εἰς ταῦρος φυλῆς Holstein - Friesian, γεννηθεὶς μετὰ συγγενῶν διαταραχῶν εἰς τὴν ἀνάπτυξιν καὶ τὴν κίνησιν καὶ ὅστις ἐνωφθαλμίσθη 3 ὥρας μετὰ τὴν γέννησιν δι' ἐνὸς γαλακτώματος ἐκ μαζῶν λεμφοσαρκώματος εἰς τὴν αὐχενικὴν μοῖραν τοῦ θύμου ἀδέנוς, παρουσίαζεν ὅταν ἐσφάγη εἰς ἡλικίαν 46 μηνῶν, ἐκσεσημασμένην ὑπερτροφίαν καὶ ὑπερπλασίαν τῶν προωμοπλατιαίων καὶ στερνικῶν λεμφαδένων. Μικροσκοπικῶς



Figure 3. Same lymph node. Compact cellular elements and effaced demarcation line between cortex and medulla. Note partial obliteration of the normal architecture and diffuse hyperplasia of lymphoid cells. H & E X 100.

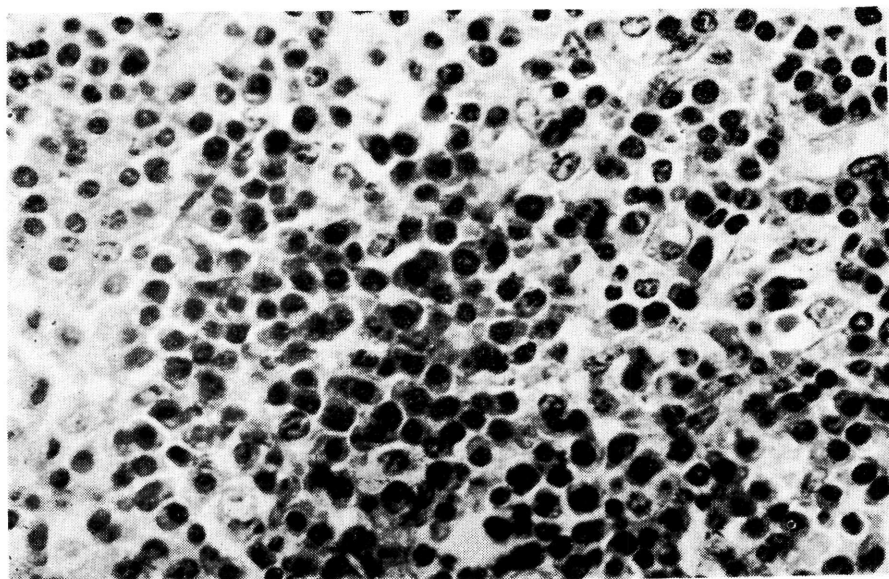


Figure 4 Proliferated and hypertrophic lymphoid cells having a dark and eccentrically located nucleus, a wheel-like arrangement of the chromatin, and a strong basophilic cytoplasm, characteristics of plasmocytes. PAS X 400.





Figure 5. Section of the same lymph node. Hypertrophic and compact cord surrounded by prominent trabeculae. Note compact lymphoid elements practically filling the medullary sinuses. H & E X 100.



Figure 6. Appearance of the stromal architecture normal. There is neither hyperplasia of reticular cells nor fragmentation of the reticular fibers. Foot's modif. Bielschowsky's method. X 100.



ή φλοιώδης και μυελώδης ουσία παρουσιάζοντο διάχυτοι εις πλείστα σημεία με άπώλειαν της προτύπου διατάξεως των λεμφοζιδίων και άποκατάστασιν της φυσιολογικής ύφης δια πολλαπλασιασμού στοιχείων προσομοιαζόντων προς τα πλασματοκύτταρα. Λεμφοκύτταρα άνευρίσκοντο διασκορπισμένα εις μικρά όξίδια. Περιωρισμένος αριθμός ιστιοκυττάρων και κοκκιοκυττάρων ήσαν άναμεμιγμένα εις τους κόλπους της μυελώδους ουσίας. Η άνωτέρω αντίδρασις, ύποδηλούσα ισχυράν άνοσοβιολογικήν αντίδρασιν άποδίδεται εις κακώσεις του προσθίου άκρου αί όποίαι έδημιουργήθησαν εκ των συγγενών σκελετικών άνωμαλιών. Έν τούτοις, λόγω της έντάσεως της αντιδράσεως, ύπάρχει ύπόνοια ότι το ένεθεν ύλικόν λεμφοσαρκώματος πιθανώς συνέβαλεν εις την δημιουργίαν της λεμφογαγγλιακής ύπερπλασίας.

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