Congenital Hereditary Lymphoedema in the Dog*

Part II. Pathological Studies

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In Part I of this study, the clinical and lymphangiographic features of congenital hereditary lymphoedema were described, and it was shown to be inherited as an autosomal dominant trait with variable expressivity (Patterson, Medway, Luginbühl, and Chacko, 1967). It is the purpose of this paper to describe the pathological findings in the offspring produced in the test matings described in Part I, and to compare them with the known pathological features of congenital hereditary lymphoedema in man, cattle, and swine.

Materials and Methods

Of the 44 offspring born of test matings, 14 died, and 19 were sacrificed for study. Necropsy material was fresh or satisfactory for study in 30 of these dogs, 7 of which were clinically affected with lymphoedema.

Pups which died in the neonatal period (3 weeks of age or younger) were preserved *in toto* in buffered 10% formalin after opening the abdominal and thoracic cavities. In larger animals, sacrificed for study, the posterior aorta was cannulated, and the rear limbs were perfused with 10% buffered formalin after injection of 10% Evan's blue dye into the interdigital space. The lymphatic vessels and lymph nodes of the limbs were then dissected after fixation. All dogs were examined grossly. Blocks were taken from the skin and subcutis of the limbs and lateral trunk region, and all abdominal and thoracic organs. One rear leg and one front leg of each of the severely affected pups was cut transversely into 5 mm. thick segments from a level just proximal to the popliteal or axillary regions (Fig. 2). All segments (some after removal of the bone) were processed for microscopical examination. Blocks of skeletal muscle were obtained from the thigh, pectoral region, and either diaphragm or tongue. Muscle biopsies of the thigh and pectoral regions were performed in all living dogs included in the study. Sections were stained with haematoxylin and eosin, elastica van Gieson, and Movat's

pentachrome stain. In addition, to selected sections, the Feulgen, Von Kossa, and Oil red O techniques were applied.

Results

Lymphatic Changes

Macroscopical Changes. These were similar in all affected dogs, but most marked in pups with generalized subcutaneous oedema of the trunk, limbs, and tail (Fig. 1 A and B). Gross abnormalities were largely limited to the skin, especially the subcutis, to the more superficial areas of the intermuscular stroma, and to the peripheral lymph nodes. Affected parts were moderately to severely swollen, and pitted on pressure. Upon cutting through the skin, the subcutaneous tissue was two to eight times the normal thickness (Fig. 2 and 3). The cut surface of the subcutis bulged and had a greyish, glistening, and translucent appearance. Clear fluid oozed, or could be squeezed out. There were also disseminated, discrete, or ill-defined areas of slightly darker, gelatinous appearance. Coarse and delicate tissue strands (muscle bundles, fibrillar structures) were present in areas of severe oedematous thickening of the subcutis, and wide, fluid-filled vascular spaces were detected with the dissecting microscope.

The dorsal view of the entire body, cross-sections of a rear leg distal to the popliteal region, and a vertical section through the thoracic area of a 3-week-old pup (pedigree No. 10, P.M. 2433) are shown in Fig. 1, 2, and 3. In this and other severely affected pups which died or were killed *in extremis* during the neonatal period, the paws were extremely swollen and the footpads were usually cracked and ulcerated.

All the affected dogs which were brought to necropsy, including those which had transient oedema in the neonatal period, had abnormalities of the popliteal lymph nodes (Table I). These were absent bilaterally in all but one of the affected

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FIG. 1. (A) Dorsal view of 10-day-old female pup (No. 10, P.M. 2433) with generalized subcutaneous lymphoedema. (B) Oedematous right hind limb of the same pup.

FIG. 2. Cross-sections through a rear limb from the popliteal area to the toes with severe oedematous thickening of the subcutis (arrows). Same pup as in Fig. 1 (No. 10, P.M. 2433).

FIG. 3. Transverse section through the thoracic wall of same pup as previous figures (No. 10, P. M. 2433). There is severe oedematous thickening of the subcutis (1). 2 = vertebra; 3 = obliquely cut rib.

animals: this dog had transient oedema early in life, and at necropsy, a mass 1 mm. in diameter, with the histological characteristics of a lymph node, was found in the usual location of the left popliteal lymph node. The axillary lymph nodes could not be found on examination of their usual location in any of the dogs with oedema of the front legs, and they were absent in 4 out of the 7 dogs in which clinically detectable oedema was limited to the rear legs. Other regional lymph nodes were present and appeared grossly normal in all affected dogs.

In all but one of the clinically normal pups, the popliteal, axillary, and other regional lymph nodes were present and of normal gross appearance. In one dog, both popliteal nodes were minute (about one-tenth the normal size), whereas all other lymph nodes were present and without gross lesions.

The thoracic ducts could be seen in all dogs sacrificed after 1 month of age, including dogs with lymphoedema. They were looked for in those that died or were sacrificed at an earlier age, but were not found, probably because of the small size of the animals. A few millilitres of clear fluid were present in the pleural and peritoneal cavities in three of the pups with generalized subcutaneous oedema. Other gross lesions, including focal ulcerative dermatitis, bronchopneumonia, pulmonary emphysema, focal ulcerative glossitis, subcapsular haemorrhage in the liver, and severe congenital hydrocephalus occurred inconsistently in both normal and oedematous dogs, particularly in those that died early in the neonatal period.

Microscopical Changes. They were similar in all affected animals, and in all affected organs of the same dog. They were mainly confined to the macroscopically oedematous areas, the lymphatic system, and in 9 of the 17 affected dogs, the skeletal and cardiac muscle (Tables I and II). In addition, in severely affected pups, varying degrees of oedema and lymph vascular changes were inconsistently

TABLE I
DISTRIBUTION OF OEDEMA, AND CHARACTERISTICS OF REGIONAL LYMPH NODES AND MUSCLE IN 30 NECROPSIED DOGS

Distribution of Oedema	Total	Absent Popliteal Lymph Node	Absent Popliteal and Axillary Lymph Nodes	Other Lymph Nodes Absent	Muscle Disease
Lymphoedema rear limbs only	7*	2†	4	0	1
Lymphoedema rear and forelimbs	1	0	1	0	1
Lymphoedema all limbs, trunk, and tail	9	0	9	0	7
No lymph-oedema	13	0‡	0	0	0
All dogs necropsied	30	2	14	0	9

* Four of these dogs had rear limb oedema in the neonatal period, but not at necropsy at 3 months of age.

† One dog which had transient rear limb oedema in the neonatal period had a minute popliteal lymph node; other lymph nodes were grossly normal.

‡ One dog, which was not clinically affected, had minute popliteal lymph nodes. Other lymph nodes were grossly normal.

TABLE II

DISTRIBUTION OF MUSCLE DISEASE AMONG DOGS DYING IN THE NEONATAL PERIOD AND THOSE KILLED FOR STUDY

		Muscle Disease	No Muscle Disease	Total
Neonatal death (1-21 days)	Lymphoedema	9	3	12
	No lymphoedema	0	1	1
Killed for study	Lymphoedema	0	5	5
	No lymphoedema	0	12	12
All dogs necropsied		9	21	30

present in the epicardium, the perivascular tissue of the aorta, large arteries, and the caval veins, the peri-oesophageal and peritracheal tissue, the tongue, intermuscular stroma, the hepatic triangles, the renal pelvis, and the renal subcapsular stroma.

In histological sections, the oedematous areas consisted mainly of a loose meshwork of connective tissue fibres with moderately to severely distended empty tissue spaces (Fig. 4, 5, 6, and 7). The oedema fluid apparently was of a low protein content in most areas, and was therefore absent in paraffin sections. In all affected dogs there were also small discrete, and larger ill-defined areas of eosinophilic, protein-rich oedema. This was disseminated without a specific pattern in the thickened subcutis of all parts of the body (Fig. 6A). The proteinaceous fluid filled distended tissue spaces or was confined to anomalous, dilated lymph vessels (Fig. 6B).

Areas of inflammatory reaction, consisting of protein rich oedema, fibrinous deposits, polymorphonuclear and mononuclear cells were seen in the skin as well as in the periosteum, perichondrium, synovial membranes, peritendino-vaginal and pericapsular tissues of the joints. A small number of inflammatory cells was scattered throughout the oedematous tissue but there was no appreciable fibrosis associated with the oedema (Fig. 4).

Abnormalities of the lymph vessels were consistently found in oedematous tissues. Confirming the lymphangiographic findings, the lymph vessels generally appeared to be increased in number and most of them were severely dilated and irregular in shape (Fig. 4, 5, 6B, and 7). The number, size, and shape of lymph vessels varied considerably at different levels of the same leg or trunk. Abnormal lymph vessels were found singly and in groups (Fig. 4 and 5). Groups of dilated lymph vessels were especially prominent in sections from the

normal location of the popliteal lymph node, and in the subcutis of the thoracic wall in those pups with generalized subcutaneous oedema. Sinusoid outpocketings of lymph vessels communicated with severely distended tissue spaces. Many dilated lymph vessels appeared ruptured but could be distinguished from tissue spaces by their structure (Fig. 4B and 6A). Valves or valve-like tissue strands and bridges, covered with endothelium, were frequently seen (Fig. 4B, 5, and 7). In some instances the valvular structures were covered with an increased number of enlarged endothelial cells; the underlying stroma, however, was normal or only slightly thickened (Fig. 7). Endothelial hyperplasia and hypertrophy in lymph vessels was occasionally observed in a segmental pattern, but rarely and only locally caused appreciable thickening of the vessel wall.

Many of the arteries and veins of the affected limbs and trunk were segmentally surrounded or ensheathed by anomalous, dilated lymph vessels (Fig. 4 and 5). Frequently an artery and its accompanying vein projected into a large space covered by endothelial lining, being connected to the surrounding tissue by a narrow isthmus of delicate collagen fibres (Fig. 4B). The larger and smaller arteries and arterioles were structurally normal, but the larger and smaller veins were often thick-walled in relation to their diameter, and to the accompanying arteries (Fig. 5A). Frequently the thickness of the wall of a vein exceeded by far the thickness of the wall of the corresponding artery, having two to three times as many layers of smooth muscle cells. This was true both for the veins of the extremities and of the trunk. Except for their unusual wall thickness, the veins appeared morphologically normal. This feature is still under investigation and comparisons are being made with the corresponding veins of unrelated pups of the same age.

In pups in which the popliteal and axillary lymph nodes were considered absent, based on lymphangiographic or gross pathological studies, the region of the usual location of these lymph nodes was examined histologically, but no lymphatic tissue was detected. The internal and external iliac and prescapular lymph nodes of affected dogs were frequently surrounded by dilated afferent and efferent lymph vessels, and intranodal sinusoids appeared distended. These lymph nodes were hypocellular but otherwise had a normal architecture. Similar changes were seen in the centrally located lymph nodes and in the thymus.

Striated muscle from the thigh, the pectoral region, the diaphragm or the tongue, and from the

FIG. 4. (A) Cross-section through proximal end of the tibia and fibula of the same pup as previous figures (No. 10, P.M. 2433), with the widened subcutis (1), consisting of a loose connective tissue meshwork containing thick-walled veins (2), and dilated lymph vessels (3), accompanying veins and arteries. (Low power, elastica van Gieson.) (B) Section through an area of the thoracic wall of a 1-day-old male pup (No. 33, P.M. 2644) with generalized lymphoedema. The subcutis (1) is thickened and contains oedema of a low protein content. There are many severely and irregularly dilated lymph vessels (2), some of which have valves (3), appear ruptured (4), or ensheath thick-walled veins and arteries (5, 6). The cross-cut bundles of the cutaneous muscles are separated by a widened oedematous stroma (7) and by dilated lymph vessels (8). (Low power, elastica van Gieson.)

heart was examined microscopically in all 30 dogs that came to necropsy. In 9 of the 16 dogs affected with lymphoedema there were muscular lesions in at least one of the sites sampled (Table II, Fig. 8, 9, and 10). All of these 9 animals were weak and died between the ages of 1 and 21 days.

Multiple sites of skeletal and cardiac muscle were examined from 3 of the 9 pups in which a myopathy had been observed. A wide spectrum of muscular changes was found in various body sites, including the legs, trunk, head, and tail, in the tongue, larynx, diaphragm, and all parts of the myocardium.

FIG. 5. (A) Irregularly dilated lymph vessels (1) with valvular structures, accompanying thick-walled vein of normal architecture (2) and structurally normal artery (3), surrounded by oedematous subcutaneous tissue (4). (B) Extensively dilated, anomalous lymph vessel with sinusoid outpocketing (1) and valvular structures (2). Thoracic wall of pup No. 10, P.M. 2433. (Medium power, elastica van Gieson.)

Other Tissues

Skeletal Muscle. A great variety of muscular changes was seen to involve single muscle fibres, groups of fibres, muscle bundles, and larger areas in an irregular ill-defined pattern. Degenerative changes included a hyaline, eosinophilic appearance with loss of striation in polarized light of single muscle fibres or segments thereof, granular and floccular appearance, vacuolation, fragmentation,

and myolysis (Fig. 8). Dystrophic calcification of necrotic muscle was repeatedly seen (Fig. 9A). Mononuclear cells and macrophages sometimes occurred between and adjacent to diseased muscle fibres (Fig. 9C), and proliferating mesenchymal cells were observed singly and in small groups. Exceptionally, multinucleated bizarre giant cells with little sarcoplasm, interpreted as attempts of regeneration, were seen in an area of muscle

FIG. 6. (A) Oedematous subcutis of rear limb with distended tissue spaces (1) that are not lined by endothelium. In between there are areas of oedema with a higher protein content (2). (B) Group of dilated lymph vessels containing a proteinaceous fluid in subcutis of thoracic wall. Pup No. 10, P.M. 2433. (Medium power, Movat pentachrome.)

degeneration and fibrous tissue proliferation (Fig. 9B). The nuclei of affected muscle fibres often were hyperchromatic, of an irregular shape, fragmented, and in some instances conglomerated to large, Feulgen-positive masses (Fig. 8B). From limited comparisons with normal unrelated pups of the same age the impression was gained that myogenesis of skeletal muscle was less advanced in the dogs with congenital lymphoedema. This

feature is still under investigation and no definitive results can be presented.

Cardiac Muscle. Disseminated focal degenerative changes confined to single and small groups of cardiac muscle fibres were found in all parts of the myocardium (Fig. 10). These cells were swollen, of an irregular shape, and had a hyaline, granular, or vacuolated cytoplasm. The nuclei

FIG. 7. Dilated, small lymph vessel with valve (1) in an area of oedematous intermuscular stroma of a thigh of pup No. 10, P.M. 2433. There is obvious endothelial hyperplasia and hypertrophy. 2 = small artery; 3 = fat cells. (Medium power, H. and E.)

had irregular outlines, were pyknotic, or fragmented (Fig. 10). Mononuclear and polymorphonuclear cells were sparsely scattered.

Other Microscopical Changes were inconsistently found and included focal ulcerative dermatitis, especially in the interdigital region; unusually large numbers of mast cells in the dermis; necrosis of subcutaneous and intermuscular fat; bronchiectasis, bronchiolactectasis, bronchopneumonia, and pulmonary emphysema; focal cerebral oedema; and focal inflammatory changes in many organs and tissues.

Discussion

The oedema in affected dogs was found mainly in the subcutis and intermuscular stroma of the hind limbs, or involved all four limbs. In 9 pups it also involved trunk, head, and tail; in these pups, other sites, including the epicardium, periadventitial tissue of large vessels, the tongue, and hepatic triangles, were also inconsistently affected. Oedema of this wide distribution has not been reported in Milroy's disease of man, where the oedema is

usually restricted to the lower limbs below the knee joints, sometimes involves the male genital organs, and rarely is found in the upper extremities (Esterly, 1965). A generalized congenital lymphatic oedema, involving the head, trunk, and limbs has been reported in Ayrshire calves in several countries (Donald, Deas, and Wilson, 1952; Morris, Blood, Sidman, Steel, and Whitem, 1954), and a chronic congenital oedema of the hind and forelimbs (Dickbeinigkeit) is known to occur in swine (Wiesner, 1960).

According to published reports, the knowledge of pathological changes in Milroy's disease of man is fragmentary, and the findings made from a small number of biopsy specimens have not been consistent. Schroeder and Helweg-Larsen (1950) found the oedema to be of a low protein content, not enclosed in endothelial-lined lumina, and failed to demonstrate the monstrous lymphangiectases present in isolated cases of simple congenital oedema. In their description there were increased numbers of thick-walled blood vessels of a uniform size, resembling arterioles. These were arranged in groups in the deeper zone of the fibrosed cutis.

FIG. 8. (A) Muscle from the thigh of a 10-day-old male pup (No. 11, P.M. 2456) with generalized lymphoedema. There is granular degeneration and vacuolation of swollen muscle fibres. A number of macrophages and undifferentiated mesenchymal cells are present (arrows). (Medium power, Movat pentachrome.) (B) Muscle from tongue of an approximately 10-day-old male pup (No. 43, P.M. 2687) with generalized lymphoedema. There are some pyknotic and disintegrating nuclei and several large irregular masses of Feulgen-positive nuclear material (1). Cytoplasmic changes include granular degeneration (2), ballooning, and myolysis (3). Furthermore, proliferating mesenchymal cells and scattered macrophages (4) are present. (Medium power, H. and E.) (C) Muscle from thigh of a 1-day-old male pup (No. 23, P.M. 2495) with lymphoedema of rear and front limbs. Segments of cytoplasm with a hyaline appearance (1), some pyknotic and karyorrhectic nuclei, and many macrophages (2) can be seen in this area of muscular disintegration. (Medium power, H. and E.)

FIG. 9. (A) Muscle from foot of a 21-day-old pup (No. 9, P.M. 2364) with generalized lymphoedema. Dystrophic calcification of necrotic muscle with scattered macrophages (1) and degenerative changes in adjacent muscle fibres (2). (Medium power, H. and E.) (B) Pectoral muscle from a 10-day-old female pup (No. 12, P.M. 2457) with generalized lymphoedema. Large area of muscular degeneration with foci of dystrophic calcification (1), bizarre, multinucleated giant cells (2), indicating attempts of regeneration. (Medium power, H. and E.)

Heteroplastic smooth muscle cells were also seen in the subcutis and interpreted as indicating a disturbance of the development of mesodermal tissue in the subcutis of the lower extremity. It was thought that as a result of the apparent abnormality of arterioles, an abnormally high arterial pressure was transmitted to the capillaries, giving rise to filtration oedema. Thus, Schroeder and Helweg-Larsen suggested that the arteriolar abnormalities were the primary cause of hereditary lymphoedema in man, and that defective development of the lymphatics could hardly be considered as a patho-

genetic factor. Esterly (1965) found unusual vascular structures resembling those described by Schroeder and Helweg-Larsen in the proposita of the family he studied, but emphasized that the nature of these vascular changes was obscure and that the above hypothesis of pathogenesis remained unproven. In contrast, Kinmonth, Taylor, Tracy, and Marsh (1957), Wood and Esterly (1960), and Ersek, Danese, and Howard (1966) support the view that the lesion underlying Milroy's disease is hypoplasia or aplasia of peripheral lymphatic vessels. This view is based chiefly on failure to

FIG. 10. (A) Cardiac muscle, left ventricular wall, from a 10-day-old male pup (No. 11, P.M. 2456) with generalized lymphoedema. Disseminated single cardiac muscle cells or small groups thereof (arrows) undergo degenerative changes, including swelling, hyaline and granular change of cytoplasm, pyknosis, and karyorrhexis of nuclei. (Medium power, elastica van Gieson.) (B) Degenerating cardiac muscle cells in left ventricle of No. 10, P.M. 2433. Swollen cells with pyknosis, karyorrhexis (1) and hyaline (2) vacuolated cytoplasm. (High power, H. and E.)

demonstrate lymphatic vessels in the extremities by lymphangiography or intradermal injection of Evan's blue dye in the few cases that were studied by these methods.

Abnormalities were found in the peripheral lymphatic system in all of the 17 dogs with lymphoedema of the limbs, and only one of the clinically

normal dogs. One dog with no clinical signs of lymphoedema had hypoplastic popliteal lymph nodes, but otherwise was normal. In dogs with transient or persistent oedema of the hind limbs, the popliteal lymph nodes were absent (hypoplastic in one dog), while in dogs which also had forelimb oedema, the axillary lymph nodes were absent as

well. That the limb oedema did not result merely from the lack of regional lymph nodes, however, is evident from two observations. First, four dogs with rear limb oedema had no forelimb oedema, yet had absent axillary lymph nodes, and, secondly, four dogs had oedema of the rear limbs at birth which was no longer present at 3 months of age. Popliteal lymph nodes were absent in three of these animals and hypoplastic in one. This suggests that absence or hypoplasia of regional peripheral lymph nodes is one of the manifestations of a more generalized defect in the development of the peripheral lymphatic system. Absence of lymph nodes has not been reported in any other species affected with congenital lymphoedema, though pathological changes (diminished lymphopoietic activity, intra- and extra-nodal lymphangiectasis, oedema) were described in peripheral lymph nodes of two Ayrshire calves (Morris *et al.*, 1954).

Many dilated, fluid-containing lymph vessels were found in the oedematous portions of the extremities of affected pups. Morris *et al.* (1954) observed in their extensive study of two Ayrshire calves that some lymph vessels were dilated and thin-walled, whereas in most of these there was extensive proliferation of the endothelium, leading to the formation of strands of tissue which in many cases divided the lumen. While they found these strands to have a relation to the valves normally present in lymph vessels, they considered their structure more complex than valves and presented the view that these tissue strands provided a considerable resistance to lymph flow. These abnormalities, and the presence of a tortuous thoracic duct in one calf, were thought to occur during the development of the lymphatic system, resulting in obstruction to lymph flow. Valvular structures were very frequently observed in the anomalous lymph vessels of the dogs which we studied, but areas of endothelial hypoplasia and hypertrophy sufficient to cause lymphatic obstruction were not seen. According to a brief description of hereditary lymphoedema (Dickbeinigkeit) of swine, thickening of the limbs is associated with an irregular, abnormal lymph vascular system, an accumulation of fluid in the connective tissue spaces, and a proliferation of fibrous tissue (Wiesner, 1960). The lymph nodes and other parts of the lymphatic system were not mentioned.

The significance of the unusually thick-walled, but otherwise structurally normal veins seen in affected dogs remains obscure. No evidence of arterial or arteriolar changes, as described by Schroeder and Helweg-Larsen in man, was found

in the dog, and heteroplastic smooth muscle cells were not present in the affected sites.

The lymphangiographic findings and the macroscopical and microscopical changes in the peripheral lymphatic system of the affected dogs provide an explanation for lymphoedema of the limbs. Major afferent lymph vessels draining the distal portion of the limb end blindly and there is absence or hypoplasia of the popliteal and axillary lymph nodes. Since central lymphatic vessels and nodes are present, and essentially normal, it appears that the peripheral and central lymphatic systems fail to make adequate connexions. As a result, there is obstruction to lymphatic drainage from the tissues of the limb. The basis for the oedema of the subcutis of the trunk and organs of the body cavities is less clear, since an assessment of lymphatic drainage by lymphangiography was not made in these areas. The affected tissues of the trunk and internal organs showed the same pattern of dilated, irregular lymphatic vessels seen in the legs, however, and thick-walled veins were also frequently observed in the subcutis of the trunk.

The significance of the myopathy observed in 9 pups which died during the neonatal period (1 to 21 days) is unknown (Table II). Muscle abnormalities were found only in dogs with lymphoedema, and only in those which died at an early age. Specimens from dogs sacrificed after the neonatal period, and muscle biopsies of living affected dogs were free of muscle changes. Both skeletal and cardiac muscle were affected, and a wide spectrum of acute degenerative cytoplasmic and nuclear changes occurred. Furthermore, some evidence was found that dogs with lymphoedema had a delay in the maturation of skeletal muscle.

The finding that muscle changes were present only in severely affected lymphoedema dogs which died during the neonatal period can be interpreted in two ways. (1) The muscle changes are not a primary feature of the disease, but are secondary to pathophysiological alterations in the dying pup affected with lymphoedema. (2) The presence of muscle disease, whether a primary feature of congenital lymphoedema or not, results in disability (making normal crawling and nursing difficult) which contributes to death. In the latter interpretation, muscle disease might be a separate entity which coincidentally is found with lymphoedema in our dogs, or it may be an inconsistent feature of the disease.

Summary

The gross pathological and microscopical changes found in 30 descendants of one dog affected with

congenital hereditary lymphoedema are described. Lymphoedema and lymph vascular changes were present in 17 pups. They were limited to the rear limbs in 7 animals, involved the rear and front limbs in one animal, and were generalized, affecting the limbs, trunk, and tail in 9 animals. In addition, lymphoedema and abnormalities of lymph vessels occurred inconsistently in organs and tissues of the body cavities. When persistent lymphoedema of a limb was present, there was absence of the regional lymph nodes (popliteal and axillary) and extensive dilatation of the lymphatic vessels of the distal portion of the limb. The popliteal lymph nodes were also absent or hypoplastic in dogs with transient lymphoedema in the neonatal period. Acute myopathy was observed in 9 pups which died with severe lymphoedema during the neonatal period, but was not found in surviving dogs with lymphoedema, or their normal litter-mates.

The pathological findings are compared with the known pathological features of congenital hereditary lymphoedema of man (Milroy's disease) and with congenital hereditary lymphoedema in cattle and swine.

It is concluded that in the dog, congenital hereditary lymphoedema results from abnormal development of the peripheral lymphatic system, including

certain regional lymph nodes. There is apparent failure of the central and peripheral lymphatic vessels to make adequate connexions, resulting in obstruction of lymphatic drainage.

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