

LYMPHATIC CONTRACTILITY

A POSSIBLE INTRINSIC MECHANISM OF LYMPHATIC VESSELS FOR THE TRANSPORT OF LYMPH*

By RALPH O. SMITH,† M.D.

(From the Department of Medicine and the Oscar Johnson Institute for Medical Research,
Washington University School of Medicine, St. Louis)

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Present knowledge concerning the transport of lymph has been gained primarily from study of the effect of extrinsic factors on lymph flow. The influence of muscular movement, respiration, pulse, vascular changes, massage, etc., has been extensively reviewed by Drinker and Yoffey (1). Study of the possible intrinsic mechanisms involved in the transport of lymph, on the other hand, has received but scant attention. During a recent investigation of acute popliteal lymphadenitis in rats (2), it was observed that peripheral afferent lymphatics leading to the popliteal lymph node contract rhythmically. Review of the scattered information relating to lymphatic physiology revealed that such rhythmic movement had not previously been recorded for the most peripheral lymphatics.

The Structure of Lymphatic Vessels.—The anatomy of the lymphatic system was first extensively reviewed by Poirier, Cunéo, and Delamare (3). The intima of lymphatic vessels is composed of a single layer of endothelial cells with many elastic tissue fibers in the adjacent subendothelial region. The media is formed of transverse and longitudinal muscle fibers and elastic tissue. The adventitia is usually the most prominent layer of the vessel and consists of interlacing collagenous tissue, muscle bundles, and elastic fibers. The largest lymphatic vessel, the thoracic duct, possesses the most extensive muscular development, but collecting vessels as small as 0.2 mm. in diameter are well supplied with muscle fibers (4).

The valves of lymphatics are usually bicuspid, lined with endothelium, and attached to the wall of the vessel by a connective tissue base (4, 5). Although filmy and fragile in appearance they are remarkably competent (6).

The blood supply of lymphatics has been thoroughly studied by Evans (7). A profuse arterial and venous circulation is found in lymphatics as small as 0.1 mm. in diameter, and in larger vessels several venules and arterioles anastomose freely throughout the adventitial tissue. Evans calls attention to the fact that the adventitial distribution of the vasa vasorum of lymphatics is identical with that found in arteries, but different from that of veins because in these latter vessels the vasa vasorum penetrate freely into the tunica media.

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Dogiel (8) investigated the nerve supply to lymphatics of the human prepuce and described in the tunica adventitia a dense plexus of nerves which impart frequent branches to muscle fibers. Concerning the origin of the nerve supply of lymphatic vessels he remarked, "It is noteworthy, that several nerves, which weave about the lymph vessel, branch off from trunks running about the length of the blood vessels." Kytmanoff (9) studied the nerve supply to lymphatic vessels of the spermatic cord of dogs and cats, and described superficial and deep adventitial plexuses with fibers extending into the subendothelial tissue. Many nerve branches appeared to end in muscle bundles while others terminated in twig-like, tufted, or varicose processes which he interpreted as sensory in nature. Large nerve trunks supplying adjacent blood vessels were also said by Kytmanoff to anastomose with branches of the lymphatic plexuses. Carleton and Florey (10) confirmed the presence of an extensive nerve supply to lymph vessels by histologic study of tissues stained supravivally with methylene blue, and noted, in addition, that lymphatics lacking muscle fibers were apparently devoid of nerves.

The foregoing anatomical description applied only to lymphatic vessels and not to lymphatic capillaries, for the latter are essentially only endothelial-lined tubes. Spontaneous movement has never been observed in lymphatic capillaries (11, 12).

Previous Observations of Spontaneous Contractility of Lymphatic Vessels.—Although lymphatics of the mesentery of dogs were first seen and described by Aselli in 1652 (13) it was not until 1774 that Hewson first reported briefly of having seen actively contracting lacteals in horses and dogs killed immediately after the ingestion of food (14). In 1784 Shelden described powerful contractions of the cervical lymphatics of dogs (15). Béclard (16) in an anatomical description of the lymphatic system stated that, "if the thoracic duct or any other vessel (lymphatic) be punctured after being tied, the liquid issues by jets, like the blood which comes from a vein (artery), while after death it only escapes in a sheet over the lips of the wound." Colin (17) noted movement of the lacteals of dogs after ligating the blood vessels to the mesentery. In 1869 Heller graphically described rhythmical contractions of lacteals of guinea pigs (18). He likened each segment between two valves to a lymph-heart as seen in the amphibia, and stated that their contraction produced a peristaltic-like wave of motion in the vessel. Some years later Lieben (19) confirmed the observations of Heller and described similar contractions of the lacteals of rats and mice.

An extensive investigation of the motion of lymphatics in various species of mammals was undertaken by Florey and coworkers (10, 11, 20-22). They noted that lacteals of guinea pigs, rats, and squirrels demonstrated active peristaltic-like motion, but stated that no similar activity was present in mice, cats, rabbits, dogs, or man (20, 21). The only available observation of contractility of lymphatics outside the abdominal cavity is that of Pullinger and Florey (11, 22) who described typical wave-like motion of thigh, spermatic cord, and diaphragmatic lymphatics in rats and guinea pigs. Pfuhl and Wiegand (23) published an excellent series of photographs of the lacteals of guinea pigs in various phases of contraction, and stated that muscle fibers were most numerous in the segments just proximal to the valves. Webb (24) used the technique of cinematography to study the movement of lymphatics in the mesentery of rats.

Physiologic Studies of Lymphatic Vessels.—Todd and Bowman in their textbook of physiology written in 1857 (25) describe slow contraction of the thoracic duct after

mechanical irritation and further stated that this "vital contractility" seemed to propel the contents of the vessel. Bert and Laffont (26) demonstrated that electric stimulation of the splanchnic nerve of dogs, horses, and asses caused contraction of the lacteals, whereas vagus stimulation produced fleeting dilatation and then contraction. Direct application of the electrode to the thoracic duct or lacteals produced a propagating contractile movement of the vessels. Stimulation of the trigeminal nerve of horses caused the lymphatic vessels of the upper lip to become engorged and varicose in appearance. Camus and Gley (27, 28) reported that electric stimulation of the splanchnic nerve of dogs resulted in dilatation of the cisterna chyli. Excitation of the cervical sympathetic nerve, superior to the first ganglion, usually produced dilatation of the thoracic duct, while stimulation of the vagus nerve constantly constricted the duct. In addition, Camus and Gley (29) demonstrated that asphyxia resulted in contraction of the thoracic duct and reported that the contraction could be abolished by sectioning the sympathetic trunk. Lieben (19) and Florey (21) found that topical application of dilute solutions of epinephrine, ergot, and pituitrin increased the rate of contraction of lacteals, whereas pilocarpine was without effect.

Materials and Methods

Subsequent descriptions apply mainly to observations of afferent lymphatic vessels to the popliteal lymph node of young rats, mice, guinea pigs, rabbits, and dogs, but were confirmed by similar studies of inguinal and cervical lymphatic vessels. All animals were anesthetized with either chloral hydrate, nembutal, or ether since none of these drugs appeared to modify lymphatic contractility.

Exposure of the popliteal space was accomplished by incising the skin over the medial aspect of the thigh just above the knee and by sectioning the lateral thigh muscles near their insertion. The popliteal lymph node was found to occupy a relatively constant position just above the belly of the gastrocnemius muscle and inferior to the popliteal artery.

After exposure of the node, all subsequent dissection was done with the aid of a binocular dissecting microscope at magnifications of 10 to 45 diameters. Under direct visualization the adipose tissue encasing the node was carefully teased away from the inferior aspect of the node exposing two large lymphatic vessels, which appeared as slightly opaque double-walled structures coursing through distinct layers of adipose tissue. For purposes of observation the vessels could be dissected distally for a distance of approximately 1 to 1.5 cm. from the node. Identification of vessels was facilitated by injection of minute amounts (0.01 to 0.05 ml.) of 0.1 per cent trypan blue in Locke's solution. The injection were made intradermally in the foot-pad through a No. 27 gauge needle.¹ During the periods of observation the area of dissection was kept at a temperature of 37.5°C. by irrigation with warm Locke's solution at pH 7.4. Although no direct method was available for measuring the contractions of the minute lymphatic vessels, contractile movements could be readily identified and recorded under the microscope. The ease with which results could be duplicated, from one experiment to another, attested to the accuracy of the method.

RESULTS

The spontaneous contractility of lymphatic vessels was first investigated in rats, mice, and guinea pigs, and the following complete descriptions apply to

¹ Immediately after intradermal injection the dye appeared in the lymphatic vessels and subcapsular sinus of the node, for intradermal injection likewise constitutes an intralymphatic injection (30).

experiments conducted with these animals. Attempts to extend the observations to rabbits and dogs, although attended by only partial success, provoked consideration of a possible intrinsic mechanism, less easily defined, which may play a rôle in the transport of lymph in higher mammals.

(a) *Characteristics of Spontaneous Lymphatic Contractility.*—The spontaneous contractions observed in peripheral afferent lymphatics to popliteal lymph nodes in the unmanipulated extremities of rats, mice, and guinea pigs may be described under three headings: first, the contraction of a single segment or that portion of the lymphatic between two valves, second, the progression of segmental contractions along the vessel, and last, the activity of the hilar segment of the efferent lymphatic.

Immediately after dissection the newly exposed lymphatic vessel appeared as an immobile, double-walled, translucent structure, containing small irregularly spaced sacular dilatations delimited by valves. Contractile movement of a segment was initiated by a sudden slight dilatation followed immediately by contraction. In contrast to this sudden narrowing of the lumen the return to normal caliber was slow and deliberate. Forceful contractions almost entirely obliterated the lumen of the vessel, but all movements were not of equal intensity. The segmental contractions were independent of respiration and the pulsations of adjacent arteries.

Examination of the entire dissected portion of the lymphatic vessel revealed rapid wave-like contractions spreading along the vessel toward the node. The phenomenon frequently occurred with such rapidity that it was evident only as a general constriction of the vessel, but occasionally it could be identified as a propagated spread from one contracting segment to another. In addition to narrowing the lumen the more forceful waves of contraction caused a definite foreshortening of the vessel. That this intrinsic lymphatic motility resulted in transport of lymph was clearly demonstrated by the injection of a minute amount of trypan blue into the intradermal tissue of the foot-pad. With each contractile wave the dye flowed rapidly through several segments, paused during the phase of relaxation, and again flowed swiftly along with the next contraction. Occasionally several segments could be seen contracting asynchronously, in which case the dye moved only within the same segment and did not flow on until a normally propagated wave of contraction was initiated.

At the hilar area of the popliteal node the efferent lymphatic appears as an irregular cystic structure funnelling down to form one or two large vessels. Although contractility of the efferent vessels progressed as described, it was initiated by a peculiar, diaphragm-like, pumping movement of the enlarged hilar portion of the vessel. At times this pumping action was evident without concomitant spread of the contraction to the efferent vessels. There was no synchrony between contractions of afferent and efferent lymphatics.

During dissection the effect of minimal trauma to lymphatic vessels was well

demonstrated. Direct injury by probe or forceps was manifested, first, by constriction of the involved segment, and later by a non-contractile phase of dilatation. At times dilatation was irreversible, in which case the injection of a small amount of trypan blue demonstrated increased permeability of the vessel wall. This marked alteration in lymphatic permeability as a result of minimal trauma has been well described by Hudack and McMaster (12). Chilling or drying of the dissected area likewise produced both spasm and increased permeability of the vessels.

The intrinsic nature of the lymphatic contractions was demonstrated by the fact that when an animal died during an experiment, the lymphatic vessels remained actively contractile for 30 to 45 minutes after death.

(b) *The Initiation of Lymphatic Contraction.*—The observation that contraction of a lymphatic vessel was preceded by a momentary dilatation suggested that changes in intraluminal pressure were responsible for initiating the contractile mechanism. The following experiments were performed to test this hypothesis.

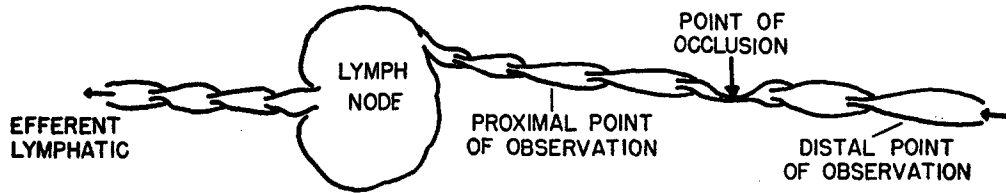
A section of the afferent lymphatic to the popliteal node was exposed in the usual manner. The flow of lymph was interrupted by section or by occlusion of the vessel by pressure. Observations of the lymphatic were then made both proximal and distal to the point of manipulation (Text-fig. 1). Reproducible results and clear cut observation of contractions were facilitated by intradermal injection into the foot pad of 0.05 ml. of 0.1 per cent trypan blue in Locke's solution.

When the flow of lymph was halted by pressure on the vessel, that portion of the lymphatic proximal to the point of occlusion immediately ceased contracting and the size of the lumen remained unchanged throughout the period of interrupted flow. However, after release of the occlusion, contractions were resumed at a rate more rapid than normal (Text-fig. 2). In contrast, that portion of the vessel distal to the point of occlusion continued to contract at a faster rate, but eventually stopped moving in a state of marked dilatation (Text-fig. 3). Contractility of the distal segment was resumed at a rapid rate upon release of the block unless extreme dilatation had ensued, in which case a slight delay resulted before contraction was initiated. When the vessel was severed, the proximal portion remained unchanged (valves prevented backflow), the lumen of the distal segment almost entirely disappeared, and no further contractions were seen throughout the period of observation.

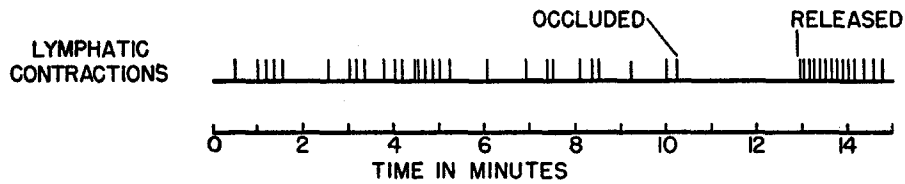
It is concluded from these findings that changes in intraluminal pressure are responsible for initiating lymphatic contractility. Cessation of motility on the other hand, may result either from overdistention of the vessel, or from a subthreshold or decreased intraluminal pressure.

(c) *The Effect of Increased Lymph Formation on the Rate of Lymphatic Contraction.*—Prolonged observation of single afferent lymphatics revealed that

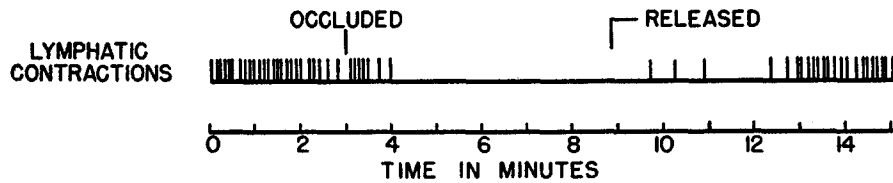
TEXT-FIG. 1



TEXT-FIG. 2



TEXT-FIG. 3



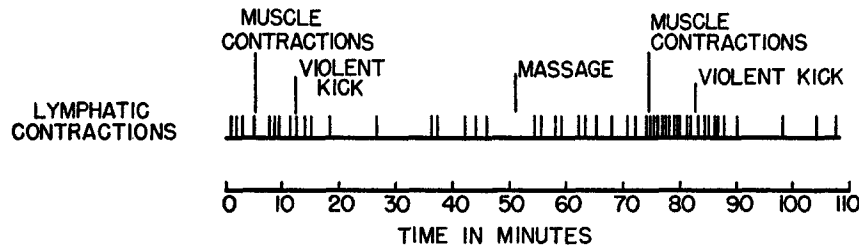
TEXT-FIG. 1. Schematic diagram of lymph node and afferent lymphatic to indicate areas of occlusion and observation as described in the preceding experiment.

TEXT-FIG. 2. Record of the changes in contractile rate of that portion of an afferent lymphatic proximal to the point of occlusion.

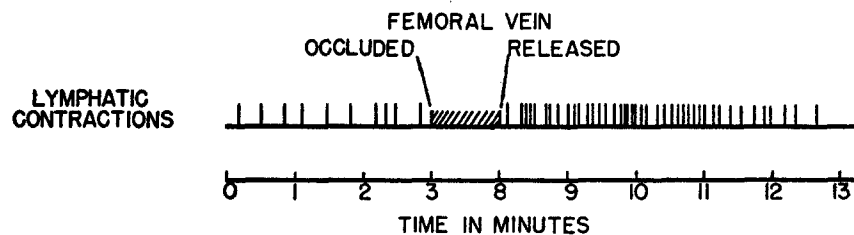
TEXT-FIG. 3. Record of the changes in contractile rate of that portion of an afferent lymphatic distal to the point of occlusion.

the initial rate of contraction (one or two peristaltic-like waves per minute) gradually became irregular and decreased to a rate of one contraction every

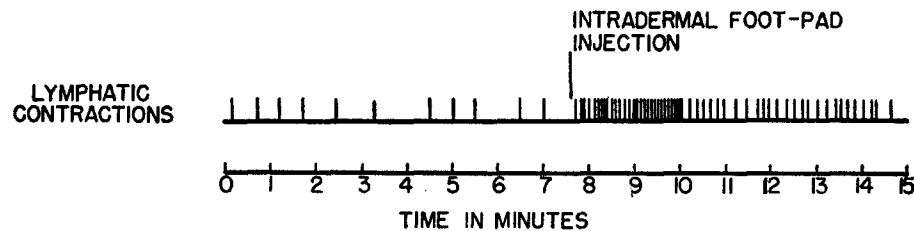
TEXT-FIG. 4



TEXT-FIG. 5



TEXT-FIG. 6



TEXT-FIG. 4. Record of normally occurring contractions of an afferent lymphatic to the popliteal node. The minimal, unsustained effect of spontaneous movement or manipulation of the extremity is well demonstrated.

TEXT-FIG. 5. The effect of venous hyperemia on the contractile rate of an afferent lymphatic to the popliteal node.

TEXT-FIG. 6. The effect of an artificial increase in extracellular fluid on lymphatic contractile rate produced by injection of 0.05 ml. of Locke's solution in the tissues of the foot-pad.

2 to 7 minutes (Text-fig. 4). Progressive vasoconstriction in the dissected extremity, with a resultant decrease in lymph formation (1), was thought to be the factor responsible for the spontaneous change in contractile rate. Momentary jerking movements of the extremity, mild massage, or elevation of the

extremity, all of which temporarily augment lymph flow but not lymph formation (1), caused only transient unsustained increases in the rate of lymphatic contraction (Text-fig. 4). In order to determine whether the rate of lymphatic contraction was directly proportional to the rate of formation of lymph, the following experiments were performed.

The afferent lymphatic was exposed as previously described, and after an initial period of observation the femoral vein was exposed through a small incision in the groin and occluded by pressure. Resultant changes in the rate of lymphatic contraction due to venous occlusion were then noted and recorded. In a second series of experiments the effect of an artificial increase in lymph, produced by injection of 0.05 ml. of Locke's solution intradermally into the foot-pad, was studied in the same manner.

As may be seen from Text-figs. 5 and 6 an increase in lymph formation in the tissues, either artificially induced by injection or resulting from elevated venous pressure, caused an increased rate of lymphatic contractility. On occasion the injection of isotonic fluid into the tissues produced a cessation of lymphatic contractility by overdistingending the vessel. It was interesting to note that such accidental gross dilatation of lymphatic vessels frequently produced incompetency of the valves as evidenced by non-apposition of the valvular cusps.

(d) *The Effect of Drugs on Lymphatic Contractility.*—Previous investigators have described the effect of several drugs on lymphatic motility (19, 21). In an effort to corroborate these findings epinephrine, pituitrin, and novocaine were applied to exposed lymphatics. Acetylcholine and pilocarpine were not used because they have been shown to increase the flow of lymph by their effect on extralymphatic structures (31, 32).

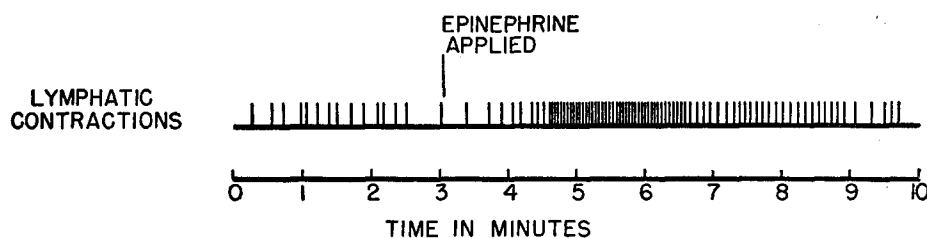
After exposure of the afferent lymphatic to the popliteal node, the vessel was observed for a preliminary period and its normal contractile rate recorded. After an adequate time the drug to be tested was placed on the vessel and the area of dissection was irrigated profusely with Locke's solution. Epinephrine (1:1000 solution) and pituitrin (20 pressor units per ml.) were applied as a drop from a No. 27 gauge needle, whereas a crystal of novocaine was allowed to melt in the area of dissection.

Epinephrine and pituitrin produced either spasm of the lymphatic followed by a markedly increased rate of contraction, or only a change in rate (Text-figs. 7 and 8). Novocaine, on the other hand, caused a cessation of movement and gradual dilatation of the vessel, but after a period of approximately 20 to 30 minutes a normal contractile rate was resumed.

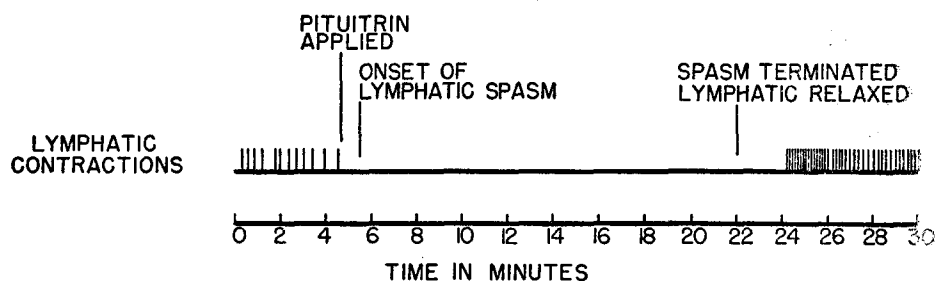
Attempts to evaluate the effect of nerve impulses on lymphatic contractility were unsuccessful. Stimulation or section of sciatic and femoral nerves produced no change that could not be attributed to concomitant vascular or muscular reactions. Several authors (26–29) have reported experiments purporting to show specific effects of stimulation of sympathetic and parasympathetic nerves

to the thoracic duct, cisterna chyli, and lacteals. Their results have not all been consistent, and in view of the present experiments it would appear that no definite conclusions are justified at the present time concerning the effect of either sympathetic or parasympathetic stimuli on peripheral lymphatic vessels.

TEXT- FIG. 7



TEXT- FIG. 8



TEXT-FIG. 7. Effect of topical application of epinephrine (1:1000) on lymphatic contractile rate.

TEXT-FIG. 8. Effect of topical application of pituitrin (20 pressor units per ml.) on lymphatic contractile rate.

Afferent lymphatic vessels to the popliteal lymph node of rabbits and dogs failed to show the spontaneous, brusque, contractile movements described above for rats, mice, and guinea pigs. Although minimal dissections and strict control of environmental conditions during experiments did not alter the results, cold irrigating fluid or direct trauma usually resulted in constriction of the lymphatic vessels. Despite the absence of spontaneous lymphatic contractility in these large animals, it was noteworthy that after intradermal injection of small amounts (0.05 to 0.10 ml.) of fluid into the foot-pad the dilatation of afferent

lymphatics thus produced was followed in 15 to 30 seconds by contraction of the vessel wall and resumption of preinjection caliber. Dilatation of lymphatics produced by massage or passive exercise was likewise followed by a prompt return to normal caliber, but at no time except after chilling or trauma did the lumen appear to be narrowed beyond its normal diameter. When an afferent vessel was severed, the lumen of the distal portion immediately became obliterated, presumably due to the sudden drop in intraluminal pressure. In contrast, the caliber of the proximal portion remained unchanged for several minutes but then gradually diminished in size. Epinephrine, pituitrin, and novocaine produced the same results as previously described, and no effect was noted after section or stimulation of either femoral or sciatic nerves. Therefore, it seems justified to conclude that the peripheral lymphatic vessels of rabbits and dogs possess an intrinsic irritability similar to that observed in rats, guinea pigs, and mice, and that dilatation of these lymphatics by exercise, massage, or injection of fluid is followed by a rapid return of the vessels to their normal caliber.

DISCUSSION

To our knowledge, the foregoing observations regarding spontaneous contractility of peripheral lymphatic vessels of rats, mice, and guinea pigs have not heretofore been described. Pullinger and Florey (11, 22) noted movement of inguinal lymphatics of rats but did not investigate the problem further. The present experiments strongly suggest that in animals displaying spontaneous lymphatic contractility the movement of the vessels is intimately associated with the transport of lymph, *i.e.* the rate of contraction is directly related to the rate of formation of lymph, and contractions are initiated by a change (increase) in intraluminal pressure. Therefore, in some mammals at least, intrinsic as well as extrinsic mechanism would appear to be responsible for the return of lymph to the general circulation.

McMaster and coworkers (33), in a series of experiments designed to study the rate of uptake of fluid by capillary lymphatics, injected the ears of mice intradermally and noted that the absorption of lymph was intermittent. The periods of more rapid uptake corresponded well to the rate of contractions shown in Text-fig. 2, and although these authors concluded from subsequent experiments that the intermittency of absorption was dependent on arterial pulsations (34) it would seem more likely from the present experiments that intermittent lymphatic contractility was responsible for the results recorded. The danger of applying observations, such as those made by McMaster using mice (33) to mammals in general is at once obvious when it is realized that in dogs and rabbits no such spontaneous, periodic contractility can be demonstrated.

Although no spontaneous contractile movement occurs in the peripheral

lymphatic vessels of rabbits and dogs, it was observed in both these animals that if a lymphatic becomes dilated by intradermal injection of fluid, massage, or passive movement, the vessel rapidly returns to its normal caliber. It is obvious that in valved vessels such maintenance of a constant intraluminal volume in itself gives rise to directional movement of fluid in the vessel. Without this intrinsic mechanism of propulsion, lymph pushed cephalad upon movement of the foot would merely remain pooled in the proximal, freely distensible lymphatics of the leg and thigh. During studies of thoracic duct pressure Lee (35) noted that if maximum pressure was attained and lymph was then allowed to flow from the manometer, the interval of time necessary to obtain a second pressure reading was much shorter than the time required to obtain the first reading. Lee attributed this finding to distention of lymphatics, but failed to emphasize that for the effect to occur with such rapidity in an animal at rest some dynamic change must have occurred in the lymphatic vascular bed. This phenomenon probably represents the rapid resumption of normal caliber of the larger lymphatic vessels of the trunk and limbs with the result that contained lymph is forced ahead into the manometer. The ability of the lymphatic vascular bed to perform the increased work necessary to move a large volume of fluid is well provided for by the increased muscular development of the vessels from the periphery cephalad.

Drinker (1) remarks of some experiments performed in human beings by Hudack and McMaster (36), that "While we are ready to believe there may be some flow of lymph from collecting trunks in a quiescent limb, we do not believe that the flow is ever the profuse one implied by Hudack and McMaster. With the volume of capillary lymph flow that their descriptions indicate, there would result a steady flow from draining trunks; and this does not occur." However, even such slight increases in extravascular fluid and lymph as produced by Hudack and McMaster (36) would seem sufficient to dilate the smaller lymphatic vessels and by this means initiate the intrinsic mechanism necessary to move lymph a significant distance. Lymph flow, as observed by Hudack and McMaster (36) in the intact human skin, cannot be compared with the flow observed by Drinker and coworkers (37, 38) after section and cannulation of a lymphatic, for removal of intraluminal pressure appears to alter the fluid dynamics which are necessary for normal transport of lymph.

As previously emphasized, the rôle of extrinsic mechanisms in the transport of lymph has been well studied. Intrinsic mechanisms, on the other hand, have been largely disregarded. The concept of lymph transport presented in this report, embodies but three characteristics of the lymphatic vessel, all of which have been shown to be present; (1) frequent valves so that the amount of fluid contained between segments does not, due to hydrostatic pressure alone, maintain the vessels at their maximum distensibility, (2) elasticity of the vessel wall, and (3) the ability of the vessel to return to normal caliber against an increased

gradient of pressure. These three factors allow extrinsic and intrinsic mechanisms to act synergistically in maintaining the flow of lymph.

SUMMARY

The most peripheral lymphatic vessels of rats, mice, and guinea pigs were found to possess a spontaneous intermittent contractility. (a) The rate of contraction was shown to be directly proportional to the rate of formation of lymph and contractions were apparently initiated by an increase in intraluminal pressure. (b) Epinephrine and pituitrin caused an increased contractile rate, or lymphatic spasm, whereas novocaine caused cessation of movement and lymphatic dilatation. (c) Section or electric stimulation of femoral and sciatic nerves did not alter the contractile rate of popliteal lymphatics.

This spontaneous lymphatic contractility was not observed in rabbits and dogs although the lymphatic vessels did contract when irritated. Epinephrine, pituitrin, and novocaine produced the same effects as observed in the smaller mammals. Dilatation of lymphatic vessels produced by intradermal injection of fluid, massage, or passive motion was followed by a rapid return of the vessel to normal caliber.

The frequency of valves in lymphatic vessels, the distensibility of the lymphatics, and their ability to return to normal caliber against an increased gradient of pressure are considered to be the essential elements of an intrinsic mechanism contributing to the transport of lymph.

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