THE LYMPHATICS AND LYMPH FLOW IN THE EDEMATOUS SKIN OF HUMAN BEINGS WITH CARDIAC AND RENAL DISEASE

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Lymph flow in human skin, even in a resting limb, is far more rapid than has been generally supposed (1, 2). The fact has led us to investigate the share taken by the lymphatics in the removal of fluid from the skin of patients suffering from the edema of cardiac and renal disorder. It seemed reasonable to assume that lymph flow in patients with long standing edema from circulatory failure might differ radically from that of individuals afflicted with renal disorder and edema but without any circulatory failure. For the purposes of the present study patients of the two classes were selected. They will be referred to as cardiac or nephritic respectively. Those of the latter sort were all individuals under 30 years of age, with acute or chronic hemorrhagic nephritis. All had marked or moderate hypoproteinemia, and at some time during our studies edema and pronounced albuminuria. No nephritic patients were included who showed any evidence of cardiac decompensation. The patients with cardiac edema on the other hand were mostly over 60 years of age, and had suffered repeatedly from cardiac incompetence with edema of the lower limbs and other classical symptoms of circulatory failure. Patients yielding any signs of renal disease were excluded from the group. We are well aware that some renal disorder must inevitably follow in the train of cardiac disease, but it was too slight to merit consideration in the patients selected for this study.

Method

The technique described in an accompanying paper (1) was utilized to demonstrate changes in the lymphatics and in the lymph flow.

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The method depends upon the intradermal injection of a vital dye, patent blue V, which renders the lymphatic capillaries visible (1–5). The sequence of events following such an injection in normal skin has already been recorded (2). The injected dye enters the rich cutaneous network of lymphatics and spreading through them appears as a highly colored net; but some remains as a bleb in the interstitial tissue. After the removal of the injecting needle the dye continues to spread through the minute lymphatics, increasing the area in which they are visible. Diffusion from the channels takes place rapidly. Within a few minutes it is noticeable that one or several extensions of dye have taken place, for a coloration of some of the larger draining lymphatics attests to the movement of fluid along them. When this occurs these deeper channels appear like colored streamers through the skin.

To render the findings comparable with those presented in the previous paper (1) the same dye solution was used and in the same concentration, the amounts varying from 0.02 to 0.04 cc. as the experiments required. The smallest volume was employed whenever a patient was injected for the first time. In nearly all instances larger amounts of dye were given in subsequent tests.

In addition to the elderly patients above mentioned, with cardiac disease and various stages of edema, and the young patients with nephritis, a few persons living under the same hospital conditions and suffering from diseases not characterized by edema or circulatory disturbance were utilized. Normal individuals, young and old, served as controls. During the observations and for half an hour prior to the first dye injection, the normal subjects were kept at rest in a position similar to that of the patients. Save where especially mentioned the patients had been confined to their beds and during the observations they remained semi-recumbent, with both legs horizontal. They were usually injected intradermally on the anterior surface of the ankle at the level of the malleoli of the tibia, where edema is usually intense, but the injection site was shifted a little when this was necessary to avoid varicosities, dilated venules or other skin lesions. When possible, tests were repeatedly made upon the same patients in different stages of the disorders studied—during the formation of edema, while it remained stationary and during its disappearance, as will be described below.

Changes in lymph flow during the increase or decrease of transient edema were studied in ambulatory patients who acquired the edema upon standing and lost it when reclining. These patients were injected in one ankle and observed for half an hour while the legs remained horizontal. They were then allowed to stand or sit, with the feet down, and injected again as the edema appeared. When obvious edema had developed they were put to bed and 10 minutes later were injected while the edematous leg rested in a horizontal position.

The tests were made as in the preceding paper, the binocular microscope, camera and lighting device extending over the bed on an adjustable metal stand. Thus there was no need for the patients to move. At intervals for 3 to 5 hours after the injections the sites were examined to observe the colored streamers and the interstitial spread of the dye bleb.
Findings under Normal Conditions

It is necessary to consider first the state of affairs following the introduction of dye into the skin of the ankle of normal individuals. Scores of tests on 10 normal volunteers have shown that injections of 0.02 to 0.04 cc. of patent blue V yield information on the rate of lymph flow in the skin of the ankle and leg. Colored streamers develop in the deeper lymphatics which are long or short, pale or deep colored, under conditions which are known to increase or decrease lymph flow respectively. Some of the observations have been described in the preceding paper.

Figs. 1 a to i show the typical findings after dye injection into the skin of the ankle of a normal individual with the leg horizontal and at rest for 3/4 hour. The pictures were taken 10, 16, 25, 40 seconds, 1 minute and 1 second, 1 minute and 50 seconds, 2 minutes 45 seconds, 3 1/2 minutes and 20 minutes, respectively, after the beginning of an injection which extended over a period of 62 seconds. All but the last picture are reproduced in natural size, and they show the bleb of dye at the point of the needle, the extent to which dye entered the lymphatic capillaries and the later spread within them. Dye escape from the channels appears as a fuzzing or blurring of their borders (Figs. 1 f, g and h). The last photograph, taken 20 minutes after the injection, shows 2 small streamers which extended up the leg for a distance of about 10 cm. In this connection it should be noted that streamer formation is less in the normal skin of the leg than in that of the arm, and the lymphatic capillaries are narrower.

Findings in the Edematous Skin of Cardiac Disease

More than 100 tests in 20 individuals with cardiac disease and edema of the lower limbs have all yielded evidence of stagnation of lymph, and incompetence of the lymphatics.

The patients selected for this portion of our study varied in age from 52 to 67 years and were chosen, as already stated, because they showed marked cardiac incompetence with little or no evidence of renal disorder. Tests were usually made shortly after their entrance into the hospital, when the edema was still increasing in the lower legs. Later they were injected while the edema seemed stationary and again while rapidly losing fluid as result of rest or therapeutic measures. The tests were repeated when the patients became edema-free in the
ankles as indicated by the lack of pitting on pressure, and in a few instances were repeated 2 or 3 weeks later while edema was still absent. When possible several tests were carried out in each of these stages.

The results can best be presented by a brief consideration of some typical findings obtained in a single individual in the various stages of edema formation and resolution.

The patient, 63 years of age, had experienced repeated cardiac incompetence in the previous 6 years. For several days before entering the hospital he had been confined to bed. Both legs were congested and dark red, showing many dilated venules and bluish purple varices. In 37 seconds 0.03 to 0.04 cc. of dye solution was injected. It entered the lymphatic capillaries far more readily than in normal persons with result that there remained at the point of the needle only the smallest bleb of interstitial dye. The channels were very wide, and during the injection dye passed much farther along them than in the lymphatic capillaries of normal skin. This is shown in Figs. 2 a, b and c, which, like Figs. 1 a, b and c, of a normal subject, were taken 10, 15 and 25 seconds after beginning the injection. The colored area extended beyond the limits of the photograph of Fig. 2 c, taken after 25 seconds, and 20 seconds later the spread of color had become so great that the position of the camera was shifted and four photographs taken at short intervals to include all the region of the dye-containing lymphatic capillaries. The shifting was done during the period from 3/4 of a minute to 1 minute 15 seconds after the beginning of the injection. The overlapping areas of the four photographs were cut away and the remainders pieced together to furnish Fig. 2 d. Such shifting of the camera was never necessary in tests upon normal individuals.

The photographs show the dilatation of the superficial lymphatics and the plexus richly injected, demonstrating the presence of free intercommunication between the channels even better than in normal skin. Secondary dye escape was more rapid than in normal skin. Furthermore, dye appeared in many channels at a greater or less distance from the stained area, like little disconnected twigs of color. The phenomenon, mentioned here in passing, will receive consideration further on. In Fig. 2 f, the arm and the stained region are shown after 20 minutes. The lymphatic capillaries were now colored over a wide area, yet the same amount of dye had been used as in the tests yielding the photographs of Fig. 1. No colored streamers appeared at any time in the deep draining channels. In other words there was no evidence of lymph flow.

A month later the patient's edema began to decrease rapidly. On the 3rd and 5th days of active diuresis, while fluid loss continued but edema was still present, intradermal dye tests were made again in both legs. The findings in the first of these tests are shown by photographs a to f in Fig. 3, taken at approximately the same intervals as some of those in Figs. 1 and 2, that is to say at 18, 25, 35 seconds, 55 seconds, 2 minutes 20 seconds, and 20 minutes, respectively, after beginning the injection which lasted 50 seconds. The findings were similar to those just de-
scribed. Again there were no streamers of dye, which would have evidenced lymph flow. From the local spread of dye one could not tell whether edema was increasing or decreasing.

A week later, 3 days after the patient had become edema-free, as judged by the absence of pitting on pressure, the tests were repeated. The lymphatic capillaries in both legs appeared just as before, and an exceedingly wide area was colored by the dye. In other respects too the results were similar to the previous ones, save perhaps that dye escaped less rapidly from the channels. Despite the subsidence of the edema the lymphatic capillaries had remained dilated, and no streamers developed to indicate flow in the deeper lymphatics.

In many instances of long standing cardiac edema isolated "islands" of dye-containing superficial lymphatics appeared during the actual course of the intradermal injections, frequently 10 to 12 cm. away from the point of the injecting needle, though more often closer. They were separated from the area of staining by skin of normal hue. These islands were never seen under normal circumstances. It was plain that some of the dye, injected into the superficial plexus of lymphatics, had passed into those of the deeper layer, and spread along them unseen to emerge again at some distance, in the superficial plexus.

The six photographs of Fig. 4 show a typical finding of this sort. They were taken at intervals of 20, 30, 55 seconds, 1½, 3½ and 20 minutes, respectively, after beginning the injection, which required 48 seconds. Photograph b was taken about 10 seconds before the first pair of islands appeared, which are seen in c. To obtain Fig. 4 d the camera was moved slightly to show 2 more islands which had appeared in the interval. This picture was taken 1½ minutes after beginning the injection. The next figure, 4 e, shows the rapid escape of dye from these islands that occurred in a further period of 2 minutes. At the time of the injection itself, or just a few seconds later, several other islands appeared, too far away to be photographed. These are shown in Fig. 4 f as they appeared 20 minutes after the injection. One group, indicated by the arrow at A, appeared 8 cm. away from the original injection site, below and far back at the heel, the distance being diminished by perspective. The other group, shown by the arrow B, was situated 3.5 cm. above the immediate area of injection. The islands of dye appearing in Figs. 4 a to e are easily distinguished in Fig. 4 f. The dark shadows running up the leg above the arrows A and B are merely groups of dilated venules.

Islands such as are here described often appeared below, that is to say distal, to the site of injection in cardiac patients, as well as toward the trunk or at the sides. A valvular incompetence of the deeper lymphatics, due to widening of them, will explain them all.
Fig. 5 shows the phenomena to better advantage. The injection was made into the ankle of a patient with marked edema which was rapidly decreasing through profuse diuresis. The photograph was taken half an hour after beginning the injection, which required less than a minute. The arrow A shows the point at which the needle entered. Dye escape from the channels and its interstitial spread has obscured the lymphatics but several more or less confluent islands of color can be made out. A semilunar strip of more lightly colored lymphatics indicated by the arrow B was originally completely separated from the main coloration. Above this, as seen in the photograph, there remains a small isolated patch of color. The large continent of dye indicated by arrow C was originally made up of fine islands now joined owing to diffusion of dye. The figure is shown at this stage to illustrate the fact that even half an hour after an injection in a cardiac patient with marked edema that was rapidly disappearing no evidence was obtained of lymphatic drainage. At the upper part of the stained area some deep lymphatic channels are seen containing colored fluid, but these had filled during the injection, and the dye did not pass further along them.

The findings in our other tests bear out those just described. When dye was injected into the skin of the ankle of a patient with cardiac edema the material entered the superficial lymphatics much more readily than in normal skin. The lymphatic capillaries were seen to be widely distended and apparently filled with fluid, for at the periphery of the injected regions there often appeared an abrupt paling of dye within the distended lymphatic capillaries themselves, as if from dilution with a copious fluid already present in the vessels. Almost all of the injected dye entered the lymphatics directly, the interstitial bleb at the point of injection being negligible. As result dye extended much farther and colored a wider area than in the normal individual, the intercommunications between the channels being, to all appearance, freely open and the injection of the superficial network in consequence very complete. Furthermore dye escaped from the channels with far greater rapidity than from those in normal skin. In patients with slight or moderate edema the changes were less marked. The studies as a whole disclosed every gradation from the normal to a state even more changed than that described, depending upon the condition of the patients.

We have never observed the formation of colored streamers in the edematous skin of horizontally resting legs of patients with cardiac edema, despite the distention of the lymphatic channels. In other words there is none of the evidence of lymph flow seen in the normal
limb. Dye merely diffuses from the lymphatic capillaries into the tissues and colors a widespread area which loses its blue hue gradually within the next 24 hours. The failure of streamers to appear is not due simply to the passage of the dye into great reservoirs of tissue fluid in which it is retained or dispersed. In the skin of patients with cardiac disease almost all the dye entered the lymphatic capillaries directly and, as the photographs show, remained within them long enough to indicate movement of the lymph had it occurred. (Compare Figs. 2 and 3 with Fig. 6, of the edematous skin of a nephritic individual.) After a few minutes most of the dye had escaped into the edema fluid, to be sure, but it remained in a localized area and in such tinctorial concentration that lymph draining from the region could not but have shown the color too. This happened indeed after intradermal injections of dye in the edematous skin of nephritic patients, a fact which will be brought out further on.

That the deep lymphatics were patent in the edematous skin of cardiac disease could easily be demonstrated. When a region of edematous skin stained by an intradermal injection was rubbed soon afterwards with the thumb, colored streamers promptly appeared. If the rubbing had been strong, these deep streamers looked like those appearing spontaneously in a normal leg, save for the fact that they were longer and darker.

When a stained area of skin of a patient with outspoken long standing edema was stroked slowly and firmly from the injection site toward the periphery, a retrograde passage of dye took place along the superficial lymphatics. For 10 to 12 cm. dye could be seen through the epidermis running ahead of the moving finger. In some of these instances it has also been seen in the deeper channels, forming a retrograde colored streamer. We have never been able to elicit this phenomenon in normal man, either by pressure or massage, nor for that matter in the patients themselves a few days after the edema has been done away with by therapeutic measures. It seems as if extreme dilatation of the lymphatics had rendered the valves functionless or partly so, which would account for the islands of dye described above.

In the preceding paper we have reported the formation of retrograde streamers in normal skin during the reactive hyperemia that followed
20 to 25 minutes of complete circulatory obstruction in the arms of normal subjects. We are unable to give a satisfactory explanation of the phenomenon. To test for the presence of valvular incompetence in the skin lymphatics of the patients with cardiac edema we have repeatedly produced artificial streamers by immediately massaging an injected area, and have then attempted to carry out upon the lymphatics Harvey's classical experiment which demonstrated the valvular action in veins.

The first fingers of both hands, held closely together, were pressed upon the skin at the lower end of a dye streamer artificially produced by actively rubbing a region of skin just injected. At once the first finger of the hand nearest the knee was moved upward for about 10 cm., pressing upon the skin directly over the streamer. Continuous pressure was maintained by the first fingers of both hands. In this way the colored fluid within the lymphatic was squeezed along the channel in the direction of normal lymph flow while the entrance of more colored lymph from below was prevented by the pressure of the lower hand. Unfortunately by the time these manipulations were finished enough dye had escaped from the streamers in the lymphatics to color the surrounding tissues slightly. As result the segment of skin above the lymphatic and lying between the fingers of the upper and lower hands,—which still maintained pressure,—showed some color because of the extravascular dye. While pressure was maintained over the lower end of the streamer the upper finger was removed from the skin to allow the stained lymph to return in a retrograde direction into the vessel from which it had just been squeezed. There appeared to be an increase in the color of the previously pale colored strip of skin, indicating a retrograde flow of colored lymph into the previously empty lymphatic. However owing to the obscuring presence of extravascular dye, as above mentioned, one cannot be wholly certain that a retrograde flow of the colored lymph actually occurred, though the observations strongly suggested it.

When similar tests were made on normal subjects the skin above the compressed lymphatic also became slightly tinged with blue by the time the first manipulations could be made. But when the upper finger was raised there was no observable increase in color in the previously compressed segment, that is to say no apparent retrograde flow.

In both normal subjects and cardiac patients tests were made like those just described save that pressure was maintained by the finger at the upper end of the streamer and released by that at the lower end. When, now, the injected area was rubbed, the color of the streamer returned as far as the upper finger, showing that the dye-stained lymph readily entered the lymphatics in the normal direction of lymph flow.
Postural Effects on Lymph Drainage from Edematous Skin

According to our observations therapeutic measures which relieve the edema of patients with cardiac incompetency do not notably increase the lymph flow while so doing. What are the effects of massage, mild exercise or change of posture upon the rate of flow or drainage of edema fluid by way of the lymphatics in these patients? That these procedures increase lymph flow in normal individuals (1, 6) and in animals (6-10) is well known. The preceding paper has shown too that dye streamers in normal limbs increased under these circumstances. Experiments on cardiac patients showed that slight drainage by way of the lymphatics could be obtained by active local manipulation.

We have already described the effect on dye spread of rubbing the recently injected normal skin. Dye is forced farther than usual through the minute lymphatics and soon one sees the development of colored streamers, darker and longer than normal ones. This is the case also in edematous skin. The edematous ankles of 4 patients were massaged for a few minutes after making the usual dye injection and in consequence dye was forced into the draining subcutaneous lymphatics and long streamers promptly appeared. The phenomenon will be discussed below. As our previous work has shown, such streamers of dye result from exercise of the normal leg. Five trials of the sort were made with 3 ambulatory cardiac patients having mild edema of the legs. In each, slight streamer formation took place, far less than that seen in normal limbs under the same circumstances. The patients were then allowed to rest on a high chair, feet hanging down. Almost at once the short dye streamers paled and in two instances disappeared, leaving only faint, almost invisible streaks where color had escaped from the draining lymphatics into the surrounding tissue. In normal individuals the streamers remained. It seemed as if the colored fluid which had risen in the draining lymphatics, forced up by the muscular movement, had fallen back to a lower level when this movement ceased and the limb hung vertically, the lymphatic valves then failing in their function.

As is well known, the edema of the legs occurring in cardiac disease may shift upon change in posture. Under such circumstances is there any fluid drainage by way of the lymphatics? In 2 of our cases we elevated an edematous leg while the patient remained semirecumbent in bed and then injected dye into it. In these instances colored streamers had appeared within 6 and 10 minutes respectively after the dye injection and within 20 minutes they had extended 10
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cm. or more toward the trunk, showing that lymph flow had followed upon the postural change.

Tests were made upon 3 patients who showed transitory edema of the foot and ankle, which became evident in an hour or two on standing and disappeared within about the same period of time when the leg was once more horizontal.

Each of the patients was injected in one ankle before rising in the morning. For half an hour the behavior of the dye was studied, and as usual no streamers appeared. The patients then sat in a chair, with both feet on the floor, for an hour, after which the same ankle was again injected, and again no streamers appeared. The subjects remained thus until both ankles pitted on pressure, after which they returned to bed, with legs horizontal. After another 15 or 20 minutes, the second ankle of each was injected in the usual way.

In each instance within 20 minutes short streamers developed 5 to 7 cm. long. In length and intensity they were similar to the streamers seen in the normal, resting, horizontally placed leg at equal intervals of time and after the injection of similar amounts of dye. That is to say lymph flow, as judged by streamer formation, had been induced in the edematous legs of patients with cardiac edema. The posture would undoubtedly aid in removing the collected edema fluid.

Cutaneous Lymph Flow in Patients with Nephritic Edema

In contrast to the stagnation of lymph in the edematous skin of patients suffering from cardiac disorder, there exists a greatly increased cutaneous lymph flow in patients with nephritic edema. More than 70 tests similar to those just reported were carried out on 14 nephritic individuals varying in age from 3 to 35 years. In most the edema had been preceded or attended by a lowering of the plasma proteins. Intradermal dye injections were made in the usual manner into the skin of the ankle and occasionally on the volar surface of the forearm, 6 of the patients being injected repeatedly during the different stages of the disease, that is to say while edema was increasing, while it seemed to be stationary and during marked diuresis. In all the lymph flow was increased as judged by the rapidity and intensity of streamer formation. The lymphatic capillaries were wider than the normal but much narrower than in advanced cardiac edema. Dye entered the channels more easily, was carried further to color a wider area,
and escaped more rapidly too, but all these changes were less pronounced than in the skin of the cardiac patients.

The characteristics of the lymphatics and of the lymph flow differed much in the same individual during the various stages of his disease. The findings can best be presented by a description of typical tests upon a patient during the periods of edema increase, of fluid equilibrium and of diuresis and edema loss.

_The Flow during the Stage of Marked Edema with Diuresis._—Fig. 6 (a to i) shows the result of dye injection into the ankle of an edematous, nephritic patient 2 days after diuresis had begun. For comparison with the previous figures, photographs are shown which were taken at intervals of 17, 30 and 51 seconds, 1½, 2, 5, 18, 20 and 25 minutes respectively after the beginning of the injection, which took 55 seconds.

The patient had been in the hospital for 4 weeks. He was a man 27 years old, with chronic hemorrhagic nephritis. Although confined to bed there had been a daily gain in weight with increasing ascites and edema of the legs during the first part of the hospitalization; then a period of equilibrium, and finally one of rapid loss of weight owing to profuse diuresis. On 12 occasions dye tests were made, the first 4 of them while edema was increasing and the next 3 while it seemed stationary. By good fortune the 8th injection was done just before diuresis became clinically evident, the 9th a day later when diuresis was well under way. The 10th test, now to be described, was done the following day and yielded results similar to those of the 9th test. In the 2 preceding days the patient had lost nearly 2 kilos in weight, the total plasma proteins were 3.83 per cent and the urea clearance only 14 per cent. The skin of the ankles and legs was soft and moderately edematous, pitting on pressure. The plicae, however, were far from obliterated.

On injection the lymphatic capillaries proved to be moderately widened and broader than in normal skin, yet narrower than in that of the patients with cardiac edema. The dye entered the channels readily and extended further primarily, coloring a wider area than in normal skin. These facts are shown in Figs. 6 a to e, which should be compared with Figs. 7 a to d, depicting the results of injection into the same patient when relatively edema-free about a month earlier. It will be seen that much of the dye entered the lymphatic channels directly and the interstitial bleb of colored fluid forming at the needle point was small. The staining of the superficialplexus was richer than usual, denoting free communications between the channels. Dye escaped from these channels secondarily with more rapidity than from those of normal skin, a circumstance not evident in the photographs.

Dye could be seen entering the deeper draining channels (Figs. 6 d and e) within 1/2 minute after withdrawing the needle and approximately 1½ minutes
after beginning the injection. A few minutes later streamers had formed and
grew rapidly in length and intensity, showing a far more active lymph flow
than had ever been seen in normal persons or indeed in this patient prior to the
onset of diuresis. The finding was characteristic of all patients injected while in
the stage of diuresis. Within less than 5 minutes after beginning the injection
pale streamers 6 to 7 cm. long became visible (Fig. 6f). By the 6th or 7th minute
these joined apparently into one band extending 4 cm. further. By the 10th
minute the streamers had extended another 6 cm., forking and travelling upward
yet another 3 cm. by the 13th minute, a total of 20 cm. from the center of the
injection site. By the 15th minute the 2 streamers had progressed 7 cm. further
up the leg and by the 18th minute had joined and had reached the knee at the
level of the patella, 31 cm. from the point at which dye entered the skin (Fig. 6 g).
Two other photographs are reproduced to show the intensity of the streamers after
20 and 25 minutes respectively. By the 28th minute the streamer could be seen
at the level of Poupart's ligament, 70 cm. from the injection site.

Dye that had escaped from the lymphatics filled at the original injection spread
more rapidly through the tissues than usual during the period of streamer exten-
sion. A comparison of the photographs of the normal ankle, Fig. 1 i, taken 20
minutes after an injection, with Figs. 6 f and g, taken at 5 and 18 minute intervals
respectively, brings this point out. During this period and indeed for an hour
the streamers deepened in color and broadened, owing to escape of dye from the
lymphatic trunks. Thereafter they gradually paled though they were still present
3 hours later as continuous colored bands. By the 5th hour only segments of
them remained visible. The dye at the injection site had spread still further
interstitially and had paled greatly. The rate of disappearance of dye seemed
much more rapid than in the normal subject.

It is obvious from the findings that lymph flow was far more rapid
than usual. The course of events after dye injection into the other
patients tested under the same conditions was the same, colored
streamers extending from the ankle to Poupart's ligament with equal
or greater rapidity. Indeed in one nephritic patient streamer forma-
tion was so rapid in the horizontal resting leg that a test was made
forthwith to determine whether lymph flow might occur in the
other leg after it had been allowed to hang vertically over the edge
of the bed for 12 minutes and while still in this position. Within
15 minutes after injecting dye in the skin of the ankle streamers had
extended against gravity from the ankle to the knee,—a phenomenon
never seen in normal individuals with the leg hanging down. The
islands of dye observed in the cardiac cases were not seen nor were
other signs of lymphatic incompetence met with in any of the stages
of nephritis. The color phenomena showed a great exaggeration of
the general features of the normal.

Lympb Flow during the Formation of Edema and in the Periods of
Relative Equilibrium of the Fluids.—When edema was in process of
forming or while it remained stationary the differences from the
normal were less apparent. Tests made upon the patient who fur-
nished the data just given showed these points typically.

One month prior to the experiment now to be described edema of the ankles
was just detectable by pressure of the thumb. The skin was soft and pale, and
the plicae not obliterated. Nevertheless edema was increasing, for the patient
gained 1/4 kilo each day. The plasma contained but 1.00 per cent albumin and
2.08 per cent globulin, yielding an A/G ratio of only 0.48.

Dye injection showed the lymphatic capillaries to be less dilated than during
the period already dealt with; the superficial plexus was far less extensively in-
jected; and the interstitial bleb at the end of the needle was larger and more like
that formed in normal skin. Nonetheless the dye passed with unusual rapidity
into the draining trunks. In Figs. 7 b, c and d, taken 30, 40 and 51 seconds after
the beginning of an injection, which required 1 minute to complete, faint cloudy
extensions of dye can be seen in the deeper draining channels, becoming much more
obvious in e and f, which were taken 1¾ and 3 minutes respectively after beginning
the injection. Dye escape from the small lymphatic capillaries was rapid, their
individual outlines soon becoming merged in a blur of color. In Fig. 7 g, the arrow
at the left in the photograph marks the upper extremity of the dye streamer 20
minutes after beginning the injection. It was easily visible to the eye and longer
than the average colored streamer found in normal ankles at rest, but streamers of
like dimensions have been seen from time to time in tests upon normal individuals.
The second arrow indicates the course of the streamer. 2 other injections in the
same patient 2 and 3 days later yielded similar results. The difference between
this result and that obtained during diuresis, as already described, was pronounced.

For more than a week after this test the patient's edema increased and then
became approximately constant for another week. At this time the legs were
markedly edematous, the skin soft and the plicae partially obliterated. Deep
pitting showed itself on pressure. Dye injection into the skin of the anterior
surface of the ankle at the level usually selected for such injections showed the
lymphatic capillaries more dilated than in the period of edema increase just de-
scribed. The findings were similar to those shown in Figs. 6 a and b. Dye escaped
from the superficial lymphatics more rapidly than from those of normal skin but
one cannot say that escape was more or less rapid than in other tests upon this
patient. As in the test first described (Fig. 6), the lymphatic capillaries took up
the dye readily and it colored a wider area than that shown in Fig. 7. As result
the dye bleb at the needle point was not as large as that seen when normal skin
is injected. During the injection itself, which lasted but 3/4 minute, dye passed
into several draining trunks, and within 2½ minutes streamer formation began, becoming pronounced within 3 minutes. The streamers darkened faster than under normal conditions and by the 8th minute extended 10 cm. up the leg. By the 15th minute they had outstripped the streamer shown in Fig. 7, being 18 to 20 cm. long. After 20 minutes they were easily detectable about 25 cm. above the site of injection, that is to say about 12 cm. below the patella. The streamer formation was more rapid and apparent than in the previous week when edema was increasing, but not as great as in the period of diuresis.

Other studies on nephritic patients have given similar results. The variations from the normal were evidently determined by the stage or severity of the disease process.

A few atypical findings deserve notice.

A dye injection was made as usual into the ankle of an obese woman of 25 years with generalized edema of face, trunk and extremities and tense ascites. The patient had pronounced glycosuria and mild nephrosis, with the plasma proteins reduced but moderately, to 4.5 per cent. Her feet and legs were fat and enormously swollen, the skin, glistening and soft, pitted easily on pressure. The pliaceae were obliterated. There was no evidence of cardiac decompensation. On test the lymphatics were found widely dilated, and the injected dye entered them with great ease. The resulting picture was in one respect similar to that seen in the edema of long standing cardiac disorder, islands of dye appearing, but streamer formation occurred. A pale extension of dye running up the leg for 6 to 7 cm., and requiring nearly half an hour to form, yielded evidence of a little lymph flow, far less than the normal. During the test the patient remained semirecumbent in bed, the abdomen pressing upon the skin of the upper legs. The test was repeated 2 days later with the patient lying flat on the back to avoid pressure upon the legs. Streamer formation was much more active, 2 streamers 20 cm. long developing in 20 minutes. The new posture presumably relieved lymphatic obstruction.

Sometimes the test has yielded unexpected results that were highly informative. One case should be cited but without undue emphasis.

For a week the nephritic patient, C, whose tests have already been described, had been in a stage of unchanging edema. One more test in this period was desired for purposes of comparison. Shortly after the injection streamers developed which lengthened and darkened with unexpected rapidity, resembling those appearing in other nephritic patients during periods of diuresis. The urine collections of the next 12 hours showed that diuresis actually had set in. 24 and 48 hours later, while diuresis was at its maximum, the 9th and 10th tests were made (Fig. 6), which produced long dye streamers that have already been described.
One is tempted to infer from this case that the method used is sufficiently delicate to elicit evidence of fluid movement through the lymphatics at the onset of diuresis before the latter becomes certain from urinary measurement. We feel, however, that individual differences are too large for such findings to be reliable. Recently Aldrich and McClure (11) have studied the rate of disappearance of saline blebs injected subcutaneously in patients with edema and they have reported that, in these cases, just prior to the onset of diuresis, the bleb fluid is removed more rapidly than during periods of stationary edema; and still more rapidly when diuresis is established. No doubt the two phenomena have something in common.

DISCUSSION

Before discussing the results it may be well to appraise the method employed. The evidence that the length and intensity of the colored streamers can be interpreted in terms of lymph flow has already been given (1). However, intradermal injections of vital dyes are subject to many influences, and these must be reckoned with. A faulty insertion of the needle, so that it goes too deep in the skin, or on the other hand an especially fortunate injection, whereby all the dye is introduced directly into the lymphatics, may prove misleading. To avoid these sources of error we have injected the patients 2 or 4 times upon each occasion, and in studying changes in lymph flow at the various stages of a disease have injected the patients upon several occasions during each stage. For example the nephritic patient yielding the results already described received 2 to 4 injections on each of 12 occasions,—3 or 4 of these in each stage of his disease. The tests yielded notably concordant results. In all instances the injections were made on the anterior surface of the ankle at approximately the level of the malleoli of the tibia, as close to the midline as possible. Slight variations in the level of the injection site to avoid recently injected areas or skin blemishes have yielded no significant differences in the tests upon either normal subjects or patients.

The previous activity and posture of the limb have much to do with the formation of streamers, as shown in the preceding paper. One cannot state categorically that lymph flow in the edematous skin of the leg of nephritic patients is greater than the normal at all times.
Such a statement might prove erroneous if lymph flow of the bedridden patient was compared with that of a normal individual during periods of muscular activity or with that in the skin of a normal limb recently elevated from a dependent position and in which in consequence lymph drainage was taking place with unusual rapidity. Yet when such a comparison is made lymph flow in the edematous skin of the resting nephritic patient usually proves the greater. We can state with assurance, however, that there is no sign of subnormal lymph flow during the building up of edema in the nephritic patient, while there is clear evidence of an increase in flow during the periods of edema equilibrium or subsidence. In the edematous skin of the horizontally resting legs of the cardiac patients on the other hand lymph flow is negligible.

The lymphatics in edematous skin are open. Even during the tense edema of cardiac disease they are found to be wide and full of fluid. We have already shown that such is their condition in the ear of the mouse (5) rendered edematous by paintings of xylol; and more recently Pullinger and Florey (12), using the same organ, have shown that local edema following injection of saline or 1 to 1,000 histamine solution into the tissues leads to dilatation of the lymph channels. Clark and Clark (13) have shown that lymphatics in edematous tadpoles are dilated and filled with fluid, and Drinker and Field (6) report that swelling of the tissues after complete venous blockage does not shut off large collecting lymphatics. Why, then, do the lymphatics function so well in edematous skin of nephritic edema and scarcely at all in that of cardiac patients?

In the nephritics tested the blood pressure was normal or only slightly raised; hypertension cases were avoided. There were no obvious signs of cardiac weakness, and the concentration of plasma proteins was much decreased. It follows that there was an increased escape of fluid from the blood capillaries of these patients, together with a more active circulation than obtained in the cardiac patients. This difference readily explains the increased fluid turnover by way of the lymphatics. In advanced cases of nephritis, in which the colloid osmotic pressure of the blood might on occasion be lower than the capillary hydrostatic pressure, we would expect to find even more of the fluid, normally returned by the blood, taken away by the lymphatics.
The stagnation of lymph in the edematous skin of the cardiac patients is not easily explained. In cardiac incompetence the venous pressure is generally greater than normal. Can the higher pressure in the veins at the point where thoracic duct lymph enters the blood be transmitted to the peripheral lymphatics and account for the stasis of lymph? 4 tests were made on this point. Patients with cardiac failure and edema of the ankles and legs but none of the arms were so placed in bed that the wrists and ankles lay at the same level. In this position any back pressure existing must have been the same in the lymphatics draining the upper and lower limbs. Yet while dye injections in the arms resulted in the development of colored streamers with the rapidity and intensity seen in normal subjects (as described in the preceding paper), that introduced into the skin of the ankles gave rise to no streamers. Lymph flow in the arms appeared to be normal whereas in the legs it was absent, a finding which would appear to rule out decisively the influence of back pressure to account for the stasis of lymph.

A partial failure in the circulation of blood cannot explain the complete cessation of lymph flow in the cardiac cases, though it might account for a decrease in lymph formation. Both the cardiac and nephritic patients showed dilatation of the lymphatic capillaries, the former far more than the latter. In both more dye entered the lymphatics directly during the injection than was the case in normal skin. Yet in the cardiac patients it was not drained away. Stagnation of lymph might be accounted for by a change in the permeability of the lymphatics so great that fluid within these vessels might pass without resistance into the large reservoir of edema fluid; but a change of this magnitude is not indicated by our findings. To be sure, the lymphatic capillaries of both cardiac and nephritic patients were more permeable than normal, but the observed differences in permeability were quite similar in both, judging from the rapidity of dye escape, and surely they were not great enough to account for the absence of streamer formation in the edematous legs of the cardiac patients through the escape of dye from the channels before the current of lymph had swept it along. Nor can it be assumed that streamers failed to develop in the legs of these patients because the dye was diluted to invisibility by the great amount of fluid present. For in the edematous skin of nephritic patients dye escaped with approxi-
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mately equal speed into the tissue fluid, yet streamers of color developed in the deeper lymphatics which were longer and more deeply colored than in normal limbs, the increased amount of fluid present having no evident effect to prevent their formation.

The presence of retrograde streamers in the edematous skin of the cardiac patients and their absence from that of the nephritics constitutes evidence for the existence of a valvular incompetence of the lymphatics in the patients of the sort first mentioned. The presence of such a valvular incompetence would explain the lack of lymph flow, but, as already described, complete proof of its existence is lacking.

SUMMARY

Local intradermal injections of dye have disclosed the fact that the skin lymphatics in regions of cardiac edema are patent, full of fluid and much widened. Intercommunication between them is ready and dye escapes from them more rapidly than from the vessels of normal skin. A retrograde distribution of dye by way of the lymphatics often occurs and it may pass unseen along the deeper channels to emerge in the skin at unexpected, distant situations. A valvular incompetence of the lymphatics consequent on dilatation would appear to be the cause of these phenomena. In regions of cardiac edema lymph stagnates, despite the fact that the channels are open.

In nephritic edema the lymphatic capillaries are wider than normal but not as wide as in cardiac edema. No sign of incompetency of the valves is to be observed. Instead lymph flow is considerably greater than normal, even when edema fluid is accumulating. It was noted to be greater in the periods of fluid equilibrium also and extraordinarily rapid in periods of diuresis.

We wish to express grateful appreciation to Dr. Alfred E. Cohn, Dr. Irvine H. Page and Dr. J. Murray Steele for the opportunity to study the cardiac and nephritic patients at the Hospital of The Rockefeller Institute and for clinical data and chemical findings concerning them. The observations on changes in lymph flow during the various stages of edema would have been impossible without the generous cooperation of the physicians mentioned.
BIBLIOGRAPHY


EXPLANATION OF PLATES

PLATE 14

Figs. 1 a to h. Photographs of the intradermal spread of dye in the skin of a normal ankle, natural size. They were taken at intervals of 10, 15, 25, 40 seconds, 1 minute and 1 second, 1 minute 50 seconds, 2 minutes 45 seconds, and 3½ minutes respectively after beginning the injection, which lasted 62 seconds. The interstitial bleb of dye which formed at the point of the needle is of about the size usually seen. Dye escape from the lymphatic capillaries colored with the dye appears as a fuzzing at their borders. Fig. e is the last picture to show the injecting needle.

Fig. 1 i. Taken 20 minutes after making the injection. 2 pale streamers of dye approximately 10 cm. long had developed in this period. Reduced to 1/7 natural size.

Fig. 2. Spread of dye in the edematous skin of the ankle of a patient suffering from cardiac insufficiency. The natural size photographs were taken at 10, 15, 25 seconds respectively after beginning the injection, which lasted only 37 seconds. Fig. 2 d, composed of parts of four overlapping photographs taken at 10 second intervals from 3/4 of a minute to 1½ minutes after beginning the injection, shows the size of the injected area. The lymphatic capillaries are seen to be widely dilated and dye escape from them has been rapid. Compare with Fig. 1. Fig. 2 f, taken 20 minutes later, and reduced to 1/7 natural size, shows the large area covered by the injection and the absence of deep streamers of dye.

PLATE 15

Fig. 3. Results of a dye injection into the skin of the same patient, who was now rapidly losing edema. The photographs were taken after intervals of 18, 25, 35 and 55 seconds, 2 minutes 20 seconds and 20 minutes from the beginning of the
injection, which lasted 50 seconds. Note that almost all the dye is within lymphatic capillaries: there is almost no interstitial bleb. Again no deep, colored streamers can be seen. Magnifications similar to those of Fig. 2. The central pale areas in these and other photographs are high lights caused by dye solution that had escaped on the surface of the skin.

Fig. 4. Results of an intradermal dye injection into the edematous skin of another patient with cardiac edema. Photographs a to e inclusive (natural size) were taken at intervals of 20, 30, 55 seconds, 1½ and 3½ minutes respectively after beginning the injection, which required 48 seconds. Photograph f, reduced to 1/7 natural size, was taken 20 minutes after beginning the injection. Islands of dye are shown, as described in the text. Again no streamers were visible. In photographs c, d and e the shiny, white marks in the center are due to high lights caused by dye solution on the surface of the skin.

Fig. 5. The same phenomenon as Fig. 4, but as it appeared half an hour after beginning the injection, which lasted less than a minute. The figure, described fully in the text, is about 1/2 natural size.

Plate 16

Fig. 6. Results of an intradermal dye injection in an edematous, nephritic patient during a period of flood diuresis. The injection required 55 seconds. The photographs were taken at intervals of 17, 30, 51 seconds, 1½, 2, 5, 18, 20 and 25 minutes respectively after beginning the injection. The first five are natural size. Fig. 6 f is reduced to 1/7, Fig. g to 1/11, Figs. h and i to 1/5. The lymphatic capillaries are wider than in normal skin but less so than in the skin of cardiac edema; the injected area is large, dye escape rapid (Figs. 6 a to d) and the interstitial bleb of dye small. Beginning streamers appeared early, after 1½ to 2 minutes (Figs. 6 d and e) and streamers 6 to 7 cm. long developed in less than 5 minutes (Fig. 6 f). Note the strong bands of color showing at the level of the knee (Fig. 6 g), in the photograph of the same leg taken after 18 minutes but reduced to 1/11 of the natural size. The leg was rotated slightly to show the intensification of the lower streamer. The two larger pictures are reproduced to show the remarkable streamers.

Fig. 7. Results of an injection of dye like that of Fig. 6 and made in the same patient during a period in which edema was increasing. The photographs were taken 18, 30, 40, 51 seconds, 1½, 3 and 20 minutes after beginning the injection, which required 1 minute to complete. The first five photographs are natural size; the last is reduced to 1/7. The lymphatic capillaries are much more normal in appearance than in Fig. 6, but streamers soon began to appear. In 20 minutes the streamer flowing from the injected area reached the point indicated by the upper arrow. The tip of the streamer was too faint to be discernible in the photograph.
(McMaster: Lymphatics and lymph flow in edematous skin)
FIG. 3

FIG. 4

FIG. 5

(McMaster: Lymphatics and lymph flow in edematous skin)
FIG. 7

(McMaster: Lymphatics and lymph flow in edematous skin)