Lymphology 6 (1973) 69-79

Lymphatic and Venous Transport of Colloids from the Tissues

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Summary

Colloid molecules injected into the tissues are absorbed both by lymphatic and blood capillaries. In dogs with cannulated thoracic duct, 94% of I^{131}-albumin injected into the renal cortex was recovered within 1 min in renal venous blood, after 5 min, 90% of Cr^{51} labelled blood corpuscles was found in circulating blood. In 6 hours, 5.4 ± 1.7% of albumin and 11.1 ± 1.5 of Au^{198}-colloid (diam. 300-700 Å) injected into the myocardium is transported by the lymphatics, 35% of the albumin was found in circulating plasma and 8.6 ± 1.2 of the gold colloid was recovered in plasma and liver. From the pancreas, 7.2 ± 2.0% of the albumin and 7.0 ± 0.5% of the gold colloid was transported by the lymphatics, and 12.3% (albumin) and 1.2 ± 0.4% (Au^{198}-coll.) by blood capillaries. Lymphatic transport of the gold colloid from the intestinal wall was 15.9 ± 1.9% recovery in liver and plasma 1.4 ± 0.8%. From contracting skeletal muscle, lymphatic transport of albumin was 40.1 ± 3.5% and of gold colloid 4.6 ± 0.72%. Recovery of albumin in circulating plasma was 3.7% of gold colloid in plasma and liver 0.5 ± 0.1%. From the subcutis, 21.6 ± 6.2% of albumin is transported by lymphatics, 11% by blood capillaries. Tissue pressure increased during injection but preinjection values were reestablished within 2 to 5 minutes. Accordingly, tissue pressure changes do not play a dominant role in colloid absorption.

Plasma proteins are present in the tissue fluids and it was shown that there is a constant interchange of these substances across the capillary walls (6, 11, 25). This process is comparatively slow, nonetheless the estimated turnover time for the total circulating plasma albumin is in the order of magnitude of 24 hours (24). The calculation is based on the assumption that the colloids are returned from the interstitial space only by the lymphatic vessels. This view, which seems to be almost generally accepted (4, 14) is supported only by a few observations made on the absorption of subcutaneously or intraperitoneally injected colloids (5, 7, 10).

The large regional differences in the protein content of the lymph were already known to *Starling* (19) and he postulated corresponding differences in the permeability of capillary walls. Regional differences in the permeability to large molecules were demonstrated also with artificial or labelled colloids (9, 15, 18) and electronmicroscopic studies supplied to these observation a morphological explanation (1). It is now held that there are almost as many different capillaries as there are organs and tissues (13). The subcutaneous or peritoneal capillaries are obviously not representative for all capillaries of the body. If there are regional differences in the protein leakage from the capillaries there may be also differences in the movement in the opposite direction, in the absorption of colloids from the tissue spaces.

Actually colloids and even small particles injected into the spleen or bone marrow are rapidly carried into the circulation by the venous blood flowing from these tissues.

In an attempt to visualize the lymphatics of the renal capsule, we injected Evans blue dye and India ink into the renal cortex. The injected substances did not stain the

lymph vessels, nonetheless they disappeared from the site of injection within a couple of minutes. It was concluded, that colloids and particles are removed from the renal tissue by blood vessels and not by the lymphatics. This observation led to the systematic study of the colloid transport, first from the renal cortex and later from other tissues.

Material and Methods

The experiments were done on mongrel dogs under sodium pentobarbital anesthesia (30 mg/kg). The intestines, pancreas or the right kidney were exposed by a midline incision of the abdominal wall. The heart was exposed by a left side thoracostomy in the 4th intercostal space. These animals were artificially ventilated with an Electrospirator positive-negative pressure pump.

The studied substances were injected in 0.06-0.08 ml of physiological saline solution with a No. 30 needle into the submucosa of the jejunal wall, the head of the pancreas, the renal cortex, biceps femoris muscle, the myocardium of the left ventricle, or the subcutaneous tissue of the shank. To promote lymph flow in the extremity, the leg of these animals was passively moved with a frequency of 60/min by a motor driven eccentric wheel. In the experiments on muscular absorption, active muscular contractions were elicited by direct electric stimulation with a square wave impulse generator. The electrodes were applied to the biceps femoris, gracilis and semitendinosus muscles. The frequency was again 60 imp./min.

The tissue pressure during and after the injection was measured with a double lumen needle. Actually, two No. 30 needles were welded together. Through one lumen 0.1 ml of 2% albumin in saline solution was injected and the other needle was connected to a Statham strain gauge.

In all animals the thoracic duct was exposed and cannulated in the left supraclavicular fossa, and all secondary branches communicating with the veins were ligated. In the experiments on myocardial absorption, the cardiac lymph vessel was cannulated. A femoral artery was exposed for the collection of blood samples. Lymph was collected for 6 hours in 30 or 60 minute periods. Arterial blood samples were removed at the end of each collection period. In the animals where absorption from the renal cortex was studied, a cannula was introduced into the renal vein and the blood flowing from the kidney was shunted through silastic tubes into the jugular vein. The tubes were disconnected immediately after the injection of the labelled substances and blood was allowed to flow freely for 1 minute into a measuring cylinder.

The injected substances were I^{131}-human albumin, Au^{198}-colloid (particle size 300-700 Å) and Cr^{51}-labelled canine red blood corpuscles.

I^{131}-albumin was tested for the presence of uncoupled label by dialysis and by plasma clearance studies after intravenous injections in dogs. The material usually contained less than 2% free iodine. If this limit was exceeded, the material was dialysed before use. A lead shielded scintillation probe was placed immediately after the introduction of the labelled substances above the site of injection, at a distance of 10 cm. The diameter of the visual field of the probe was about 8 cm. The decrease of local radioactivity was recorded continuously with a linear ratemeter during 6 hours. Blood samples were taken at 15, 30, and 60 minutes and thereafter at hourly intervals for 6 hours.

At the conclusion of the experiments the tissues at and around the site of injection were excised. In the animals receiving Au^{198}-colloid, the liver and the regional lymph nodes were removed and weighed. Aliquots of the removed tissues were digested in 20% sodium hydroxide. Lymph and plasma samples were checked for the presence of free label by dialysis and trichloroacetic acid precipitation. The radioactivity of the samples was measured in a well-crystal gamma counter. There was generally good agreement between the absorption measured by external counting and the values calculated from the recovery of the introduced material from the tissue removed at the site of injection.

Circulating plasma volume was measured twice, at the beginning and at the end of the experiment, with the Evans blue dilution method. The values for the intermediate periods were interpolated between the two extremes.

The results are expressed as per cent of the injected activity. The amounts of labelled substances in circulating plasma were calculated from the plasma concentration and the volume of circulating plasma. In the experiments where labelled blood corpuscles were injected the activity was measured in whole blood and this value was multiplied by the circulating blood volume, calculated from plasma volume and hematocrit.

During the experiments there is a constant secondary loss of the absorbed albumin from the circulation into the interstitial space. In 12 dogs with thoracic duct fistulas, 47,3 ± 2,5% of the intravenously injected I^{131}-albumin was lost in 6 hours from the plasma. The constant of the loss of label from the circulation (k') was found to be 0.00218 ± 0.0006. Accordingly, the total absorption via the blood capillaries was calculated from the relationships:

$$f_1 = Ae^{-kt};\ f_2 = Be^{-k't};\ f_3 = \frac{Ak_1}{k'-K}(e^{-Kt} - e^{-k't})$$

where

A = is the amount of the labelled protein injected into the tissues,
B = the amount of protein present in circulating plasma,
K = the constant of the disappearance of the labelled substance from the site of injection,
k_1 = the constant of the increase of plasma concentration.

The lymphatic transport could be also characterized by an exponential constant (k_2).

The gold colloid gaining access to the circulation is taken up almost quantitatively by the Kupffer cells of the liver and from the lymph the particles are filtered by the lymph nodes. In our experiments the thoracic duct lymph and the post-nodal lymph in the intestinal lymph trunk or in the cardiac lymph vessel contained only negligible amounts of the radioactive particles and 6 hours after the introduction of the radioactive material almost no activity was found in the circulating plasma. Accordingly, the activity found in the regional lymph nodes at the end of the experiment plus the activity excreted in 6 hours in the thoracic duct or cardiac lymph was the measure of the lymphatic absorption of Au^{198}-colloid. On the other hand, the absorption by blood capillaries and the venous transport of the gold particles was calculated from the amount recovered in the liver plus the amount found at 6 hours in the circulating blood.

Results

Renal cortex. The clearances of the injected substances (Cr^{51}-rbc, I^{131}-albumin and Xe^{133}-gas) from the renal cortical tissue was studied in 42 dogs, 3 rabbits and 4 cats.

No species differences were detected, therefore only the results of the experiments made on dogs are here reported. The injected material disappeared from the renal cortex with extreme rapidity (Fig. 1). Cr^{51}-labelled homologous red blood corpuscles,

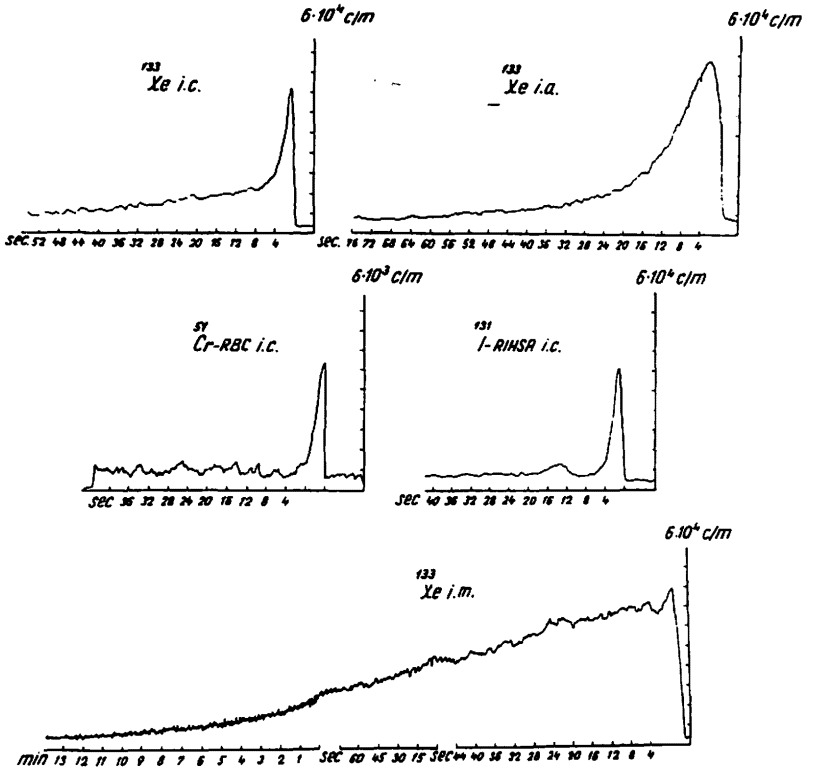

Fig. 1. Clearance of radioactive material from the kidney
i.a. injection made into the renal artery;
i.c. injection into the renal cortex;
i.m. injection into the renal medullary tissue.

I^{131}-labelled human serum albumin and Xe^{133}-gas dissolved in physiological saline were removed at identical rates. T 1/2 for all 3 substances was around 0.06 min.

Within one minute after the injection, 94% of the introduced albumin could be recovered in the renal venous blood and 80% of the albumin and 90% of the blood corpuscles were present after 5 minutes in the circulating blood (Fig. 2). The thoracic duct lymph collected for 30 minutes after the injection contained only 0.6% of the injected radioactive albumin and the lymphatic concentration was usually below the concentration found in blood plasma. This observation indicates that the lymphatic activity originates from the I^{131}-albumin that escaped from the circulation to the extracellular fluid.

The situation is entirely different, if the substances are introduced into the medullary tissue. 30 minutes after the injection of labelled albumin into the inner medulla

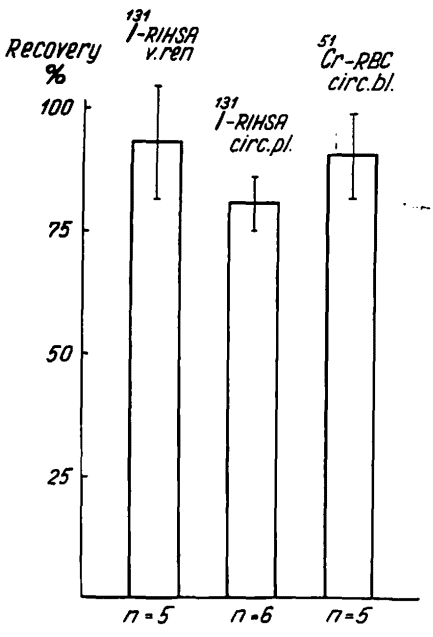

Fig. 2. Recovery of radioactive human albumin (I^{131}-RIHSA) and Cr^{51} labelled canine blood corpuscles in renal venous blood after an injection made into the renal cortical tissue.
v. ren.: recovery in renal venous blood 1 minute after the injection;
circ. pl.: recovery in circulating plasma and
circ. bl.: in circulating blood 5 minutes after the injection.

8.2 ± 1.8% of the substance was recovered in circulating plasma and 4.2 ± 1.4% in thoracic duct lymph (n = 6). The lymphatic concentration was about 35 times higher than plasma concentration.

Myocardium. In the myocardium, as in other tissues which will be subsequently reported, the injected substances were I^{131}-human albumin and Au^{198}-colloid. In 6 hours, about 55% of the albumin and 31% of the gold colloid was cleared from the site of the injection (averages of 11 and 9 experiments). 5.4 ± 1.7% of the albumin was recovered in the cardiac lymph collected in 6 hours and 11.1 ± 1.5% of the gold colloid was found in the regional lymph nodes of the heart. The amount of albumin found in plasma 6 hours after the injection was 23.6 ± 3.1%. With corrections made for the secondary loss of albumin to the extracellular space, this value attained 35%. The respective constants of the accumulation of the label in plasma and lymph were 0.00141 ± 0.00010 and 0.00027 ± 0.00005. This means that the transport of albumin via the blood vessels is more than 5 times as rapid as the lymphatic absorption and transport (Fig. 3). 8.6 ± 1.2% of the injected gold colloid was recovered in the circulating plasma and liver tissue i.e. nearly as many large gold particles are carried away from the myocardium by blood capillaries as by the lymphatics.

Pancreas. In 13 dogs, the 6 hours clearance of I^{131}-albumin from pancreas was 37 ± 4.5% (K = 0.00170 ± 0.00013), the thoracic duct transported in 6 hours 7.2 ± 2.0% of the injected dose (for the lymphatic transport k_2 = 0.00032 ± 0.00004 and during the same period 12.3% (k_1 = 0.00047 ± 0.00005) gained access into the circulation (Fig. 4).

In 10 animals, 20.3 ± 4.1% of the injected Au^{198}-colloid disappeared in 6 hours from the pancreas and 7.0 ± 0.5% was recovered in lymph and lymph nodes. Very little, 1.2 ± 0.4% of this substance gained directly access into the circulation.

Intestinal wall. When albumin was injected into the intestinal wall, the label was rapidly split from the protein. Accordingly, in 11 dogs only Au^{198}-colloid was injected into the muscular layers of the jejunal wall. In 6 hours, 26.0 ± 1.8% of the material was removed from the site of injection and 15.9 ± 1.9% was recovered in the lymphatic system (thoracic duct lymph + regional lymph nodes). The transport via the blood capillaries was again insignificant: 1.4 ± 0.8 was found in blood plasma and liver tissue.

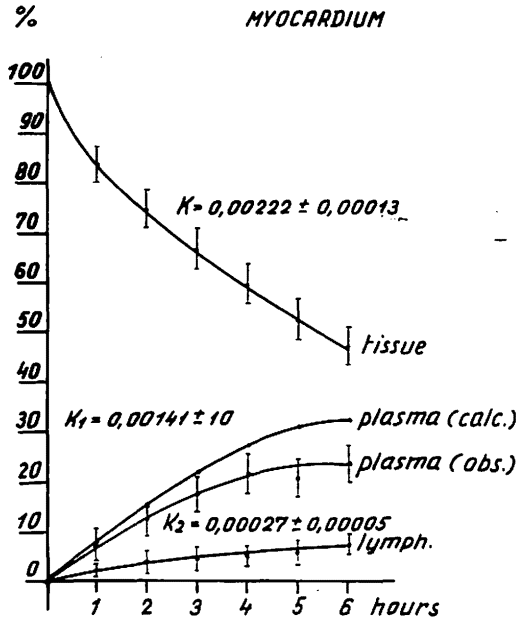

Fig. 3. Disappearance from the site of injection, transport by the lymphatics and recovery in circulating plasma of I^{131}-human albumin injected into the myocardium.

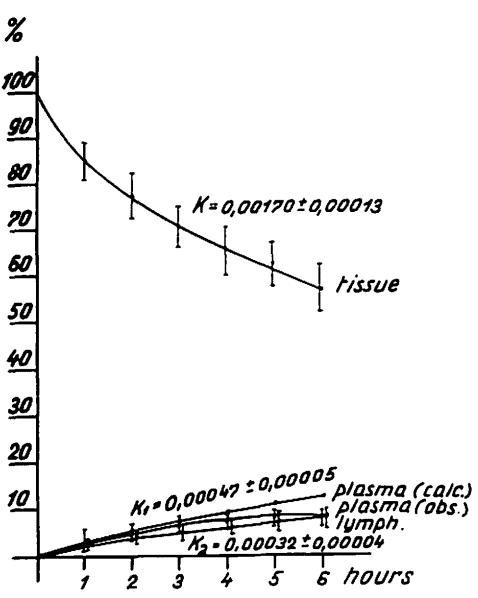

Fig. 4. Tissue clearance, lymphatic transport and recovery in bl. plasma of I^{131}-albumin injected into the pancreas

Skeletal muscle. Colloid absorption from inactive muscle is a very slow process. The 6 hour-clearance of albumin was only 14.8 ± 2.2% (K = 0.00055 ± 0.00003) (average of 9 animals). The total amount gaining access to the blood stream was 3.1% (k_i = 0.00017 ± 0.000003) and the lymphatic transport was absolutely negligible (6 hours transport 0.76 ± 0.29%, k_2 = 0.000008 ± 0.000002).

When the muscle was actively contracting with a frequency of 60/min, in 8 experiments the 6 hour-clearance increased to 57.5 ± 5.3% (K = 0.00365 ± 0.00025) This amount was mostly (40.1 ± 3.5%, k_2 = 0.00232 ± 0.00015) absorbed by the lymphatics. The amount absorbed by blood capillaries (3.7% k_1 = 0.00018 ± 0.00003) remained practically the same as in the inactive muscle (Fig. 5).

The absorption of the intramusculary injected Au^{198}-colloid was studied in 10 dogs. The 6 hour-clearance from the

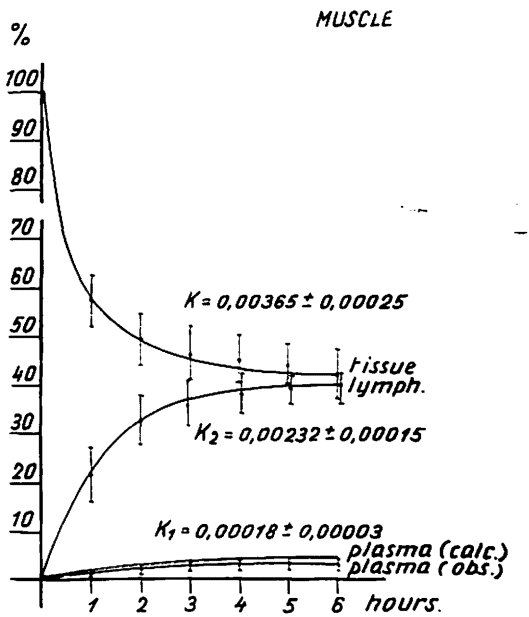

Fig. 5. Tissue clearance, lymphatic transport and recovery in bl. plasma of I^{131}-albumin injected into active sceletal muscle.

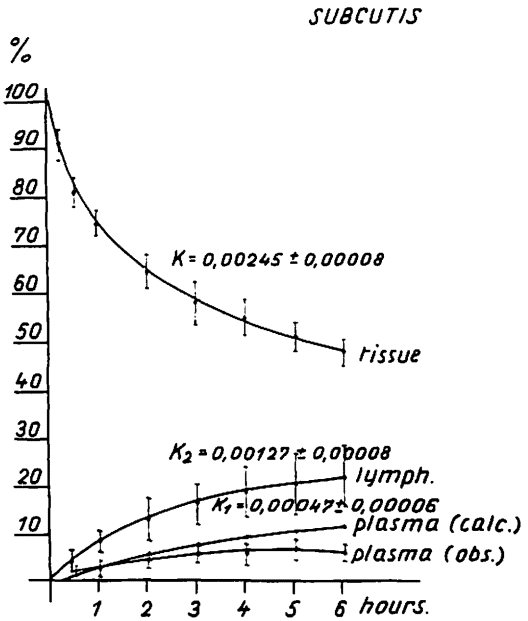

Fig. 6. Tissue clearance, lymphatic transport and recovery in bl. plasma of subcutaneously injected I^{131}-albumin.

actively contracting skeletal muscle was 10.1 ± 3.4%, lymphatic transport 4.6 ± 0.7% and the amount found in the liver and circulation 0.5 ± 0.1%.

Subcutis. At the conclusion of the experiments (n = 10) 52.7 ± 2.2% was absorbed from the subcutaneously injected albumin (K = 0.00245 ± 0.00008). Six hour-lymphatic transport was 21.6 ± 6.2 (k_2 = 0.00127 ± 0.00008) and during the same time 11.0% (k_1 = 0.00047 ± 0.00006) gained access into the blood capillaries (Fig. 6).

Tissue pressure changes. During the injection there was a sharp rise of the needle pressure: in the myocardium to 48.6 ± 6.1, in the skeletal muscle to 33.7 ± 2.1 and in the pancreas to 19.6 ± 0.8 mmHg. The pressure, however, dropped rapidly. 30 sec from the beginning of the injection it was in the myocardium 11.5 ± 2.3, in the muscle 7.2 ± 2.0 and 7.0 ± 0.9 in the pancreas. Base line pressure (-3 to + 1 mm Hg) were attained in the heart muscle in 4.8 ± 0,9, in the skeletal muscle in 4.1 ± 0.9 and in the pancreas in 2.1 ± 0.6 minutes (Fig. 7).

Discussion

Surveying our results it can be stated, that blood capillaries in almost all examined tissues are permeable to colloids in the inverse direction. Their behavior corresponds roughly to the expectations derived from electronmicroscopic studies. There are, however, some discrepancies which are difficult to explain. In the kidney the peritubular capillaries are fenestrated (17) but the diameter of the intracellular openings is below 0.1 μ and they are usually

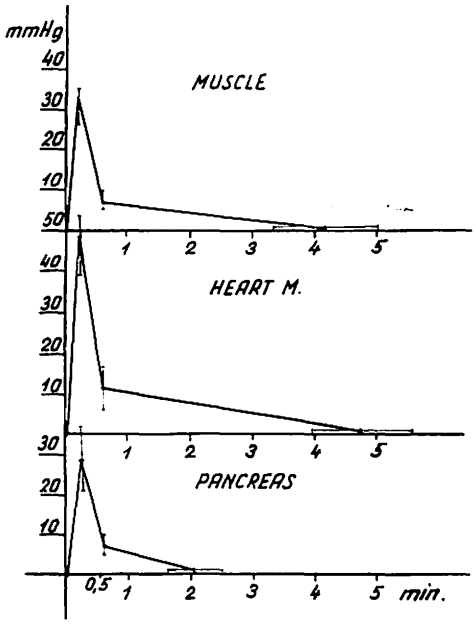

Fig. 7. Tissue pressure changes after the injection of 0.1 ml albumin solution.

closed by a diaphragm. Moreover, the capillaries are surrounded by continuous basal membrane. There are, however, observations pointing to an extremely high capillary permeability in the kidney. The equilibration of the renal extravascular albumin pool with plasma albumin is very rapid (8, 12) and if it is assumed that the lymphatics are instrumental in this process this would imply in the dog a renal lymph flow of 0.25 ml/min/kg (23), i.e. about 5 times the amount flowing from the thoracic duct. In the other hand, if the kidney is removed and the blood dripping from the renal vein collected, it can be observed, that the blood is diluted by a fluid with high protein content. It was concluded, that this protein is of extravascular origin and that it gains access rapidly to the renal venous blood (20).

Table 1. Tissue clearance, transport by the lymphatic system and by the blood stream of Au^{198}-colloid injected into the tissues

	Tissue clearance	Lymphatic system	Bl.plasma + liver
1. Heart muscle	31.0 ± 10.6	11.1 ± 1.5	8,6 ± 1.2
2. Intestinal wall	26.0 ± 1.8	15.9 ± 1.9	1.4 ± 0.8
3. Pancreas	20.3 ± 4.1	7.0 ± 0.5	1.2 ± 0.4
4. Skeletal muscle	10.1 ± 3.4	4.6 ± 0.7	0.5 ± 0.1

The observations made in the present experiments point to the possibility that capillary permeability in the renal cortex is similar to that in spleen and bone marrow. Nothing is known, however, about the presence of sinusoids with discontinuous wall structure in the kidney. As long as there is no appropriate morphologic explanation for the observed phenomena, the possibility cannot be excluded, that in the renal cortex the injected material is forced into the severed blood vessels by the injection pressure.

In the myocardium, even if allowance is made for the direct entry of the injected material into severed blood vessels, the present observations suggest that there are capil-

laries, probably fenestrated ones, allowing the retrograde passage of particles over 300 Å in diameter.

More generally, it can be concluded, that the importance of the venous and lymphatic channels in the transport of colloid molecules is different in the individual tissues. In the tissues with discontinuous or fenestrated capillaries (kidney, pancreas, intestinal wall and probably also the myocardium) at least from the smaller colloid molecules (e.g. albumin), more is transported by blood capillaries than by lymphatics. Myocardial, and especially renal capillaries are permeable also to larger particles. In the other tissues the dimensions of intracellular gaps in the blood capillary wall are such that they practically do not allow the passage of gold particles (diameter 300-700 Å).

Continuous blood capillaries e.g. in skin and skeletal muscle can absorb much less colloid from the tissues than the fenestrated ones. In these tissues lymphatic transport of albumin exceeds several times the transport by blood stream.

The absolute amount of the transported colloid and the ratio of lymphatic versus venous transport depends also from the size of the particles. The movement of larger particles into the blood capillaries is more restricted than their entry into the lymphatics. The greater permeability of the lymphatic capillaries has been repeatedly observed in morphologic and physiologic studies.

Against the method applied in this study the objection can be raised that the fluid injected into the tissues might be driven through the junctions in the capillary wall or even through the gaps in the severed vessels purely by the force of injection. If the colloids are forced into the capillaries by increased tissue hydrostatic pressure a relationship should exist between tissue pressure and colloid absorption. Tissue injections of small volumes of fluid produced, however, only transient changes in interstitial hydrostatic pressure. This increase of pressure, lasting only a couple of minutes, cannot play a determinant role in protein absorption, because the latter process takes several hours. There is probably only a single exception from this rule, i.e. the renal cortex. Material injected into this tissue disappears with extreme rapidity, before tissue pressure has returned to normal.

On the other hand, in experiments not involving an injection of the colloid into the tissues, it was shown that protein molecules of cellular origin (LDH liberated from the cells in consequence of ischaemia or muscle activity) are also transported by blood capillaries (21, 22). These observations make it improbable, that increased tissue fluid hydrostatic pressure is necessary for the movement of colloid molecules into the blood capillaries. However, in the experiments the labelled albumin or the cellular enzyme is present in high concentration in the interstitial spaces. This inverse concentration gradient could account for the movement of the protein molecules from the tissue fluid into the blood plasma. There might be, however, an other mechanism promoting the flow of protein into the capillary lumen (3). If fenestrae are present at the venous limb of the capillaries and if much fluid passes through them, the protein can be carried with it against the concentration gradient into the lumen of the capillary. Outward diffusion is prevented by the valve-like action of the diaphragms across the fenestrae. This makes protein movement largely dependent on bulk flow of fluid. Finally, there is also the possibility of cytopempsis or pinocytosis, i.e. of an active transfer of particles and colloid molecules by vesicles (16). In the lymphatic capillaries endothelial vesicles can take up foreign materials from the lumen as well as from the

tissue spaces (4). For the blood capillaries there seems to be no definite proof for a vesicular transport in the inverse direction. There is, however, evidence suggesting, that the present concept concerning the movement of protein molecules from the interstitial space into the circulation is untenable. Protein molecules gaining access to the interstitial space from the blood plasma or from the cells, as a result of cellular activity or cleavage, are constantly removed by the blood and lymph capillaries. It seems that this process renders meaningless permeability measurements based on the determination of the lymphatic transport of the respective protein molecule (3). A revision of the present views concerning the extravascular circulation of protein seems also to be warranted.

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Lymphology 6 (1973) 79-90

Ultrastructural Evidence for the Lymph Node-Venous Transport of Carbon Particles*

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Summary

The primary response of the lymph node sinus endothelial cells to increased intrasinusoidal pressure appears to be an opening of overlap junctions between adjacent endothelial cells. When colloidal carbon particles are injected via an afferent lymphatic, the tracer is found within the patent overlap junctions, the sinus endothelial cells, and the interstitial tissue that separates lymphatic sinuses and nearby capillaries. Carbon particles generally are confined to capillary lumens when injected via the communicating vein that joins the lymph node and the adjacent internal jugular vein. The long-term removal of carbon particles appears to be via an endocytic process, primarily by sinus endothelial cells and sinus macrophages with secondary uptake by fixed parenchymal macrophages. Minimal uptake of the tracer by capillary endothelial cells precludes the capillaries as a major site of removal of tracers from lymph node sinuses.

Introduction

Experiments suggest that radioactive tracers and bacteria are transferred from lymph nodes directly into the circulatory system in response to increased intranodal pressures that occur when these tracers are injected into either the laryngeal submucosa or a lymph node afferent channel (1, 2, 3). Increase in recovery of the radioactive tracer coincides with the increased pressures of injection and subsides upon cessation of injection (1, 2). Since colloidal carbon particles have been utilized successfully as electron

*This work was supported by Public Health Service Research Grant No. CA-10923 from the National Cancer Institute, Training Grant No. NS-5295 from the Neurological Diseases and Stroke Institute, and the California Institute for Cancer Research.