killing of tumor cells is brought about by macrophages and, most efficiently, by sensitized, cytotoxic lymphocytes. Sensitization of lymphocytes, induceable *in vitro (C. F. McKhann)* and demonstrable *in vivo (J. Stjernswärd* and *F. Vanky),* however, is not sufficient for protection: under certain conditions sensitized lymphoblasts, for reasons unknown, appear to be unable to leave the site of their production (regional lymph node). The role of humoral antibody, known to inhibit lymphocyte cytotoxicity *in vitro,* has not been elucidated in this respect.

At the end of the conference, it was decided to hold the next meeting in Yugoslavia in 1972; by acclamation, the organization was put in the hands of *B. J. Jankovic* and his collaborators.

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Lymph and Plasma Proteins: Barriers to their Movement throughout the Extracellular Fluid*

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During the development of the mammalian organism two vascular systems are formed in most tissues. The fluid they contain, blood plasma and lymph, together with that in the intervening connective tissue, comprises the extracellular fluid or the "milieu intérieur" of *Cl. Bernard* (5). Each system is lined by endothelium which is supported in the larger vessels by layers of connective tissue and smooth muscle cells: in the smallest vessels, however, the endothelium usually has little support except a basement membrane, and even this may sometimes be absent. It is, therefore, mainly by exchanges through the thin walls of these small vessels that the cells of the body maintain their normal metabolism. Substances of small molecular size very rapidly exchange by diffusion; the macromolecules such as the proteins and lipoproteins move much more slowly from compartment to compartment throughout the extracellular phase.

Towards the end of the last century, the mechanisms concerned in the formation of lymph were critically debated (40). However, there has evolved over the years a concept which has been fairly generally accepted. It embraces the view that lymph from any tissue contains all the proteins that can be detected in plasma and that lymphatic vessels are, in general, essential for the continual movement of these proteins in one direction throughout the extracellular fluid of the body – from plasma to tissue fluid to lymph and back to the plasma. In the course of a day in man, protein equivalent to about 25 per cent or more of the total extracellular fluid proteins leaves the blood vascular compartment and an equivalent amount is returned to the plasma in the lymph; in some

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mammals, especially in ruminants, this rate is somewhat greater. Any proteins entering the tissue fluid other than from the plasma also take part in this movement by first gaining access to the lymph, as depicted in Fig. 1.

In recent years with the introduction of new techniques, some aspects of this concept have again been challenged. I should, therefore, like to thank the Organizing Committee of the 3rd International Congress of Lymphology for inviting me to give this lecture in which I thought it would be appropriate if I confined my remarks to a brief consideration of the barriers or partial barriers to the movement of proteins throughout the extracellular fluid.

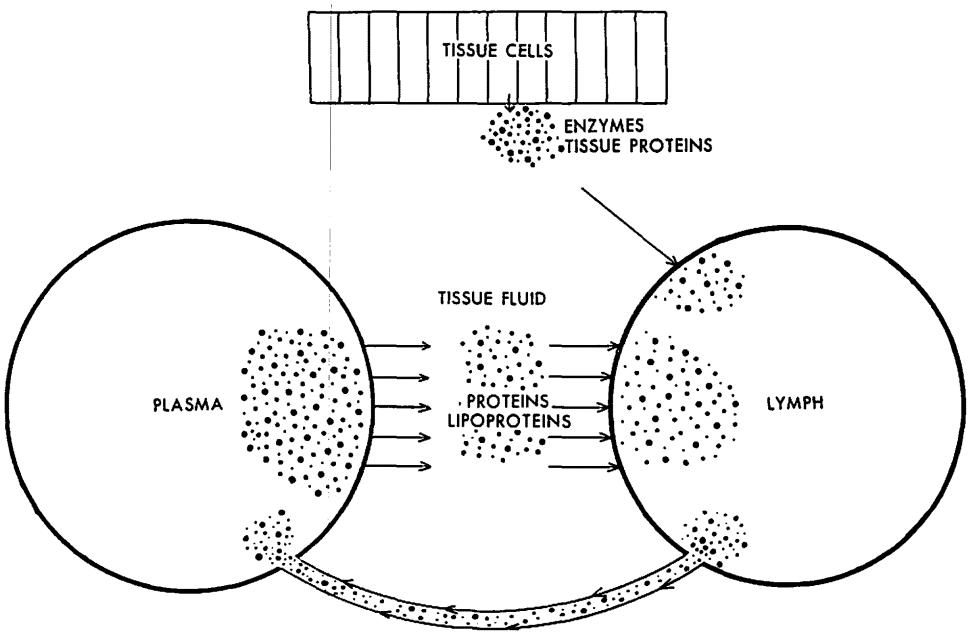

Fig. 1 Diagrammatic representation of the movement of proteins throughout the extracellular fluid. In a man of 70 kg body weight the blood plasma contains ~ 220 g protein and the tissue fluid and lymph ~ 250 g protein. During the course of a day ~ 100 g protein escapes from the plasma and an equivalent amount is returned to the plasma in the lymph. Proteins entering the tissue fluid from the cells also enter the lymph.

1. The walls of the blood vessels

Movement of protein from plasma to tissue fluid

The most significant of these barriers resides in the walls of the blood vessels, the overall effectiveness of which is of the utmost importance in maintaining the plasma volume and, therefore, the circulation of the blood to the various tissues of the body. This effectiveness, however, varies in different tissues with the fine structure of the small blood vessels; it also depends to some extent on the size of the macromolecules concerned and on the haemodynamics in the tissue at the time.

The outward movement of plasma proteins through the small blood vessels has been clearly shown by many investigators who have injected labelled protein into the blood stream and observed its appearance in the lymph. Ultimately the specific activities in plasma and in lymph come into equilibrium suggesting that under normal circumstances most, if not all, of the protein in the lymph is derived from the plasma (68).

In those tissues with "continuous" capillaries, such as muscle and skin, the turnover of labelled protein from plasma to lymph is relatively slow. The weight of electron-microscopic evidence suggests that the transport of the protein is mainly by way of the vesicles (8) although this is still controversial (37, 38). An increase in filtration pressure in such a tissue leads to an increase in lymph flow and a fall in protein concentration in the lymph, so that the total amount of protein leakage is not very greatly increased. This is characteristic of the exchange that occurs in tissues with "continuous" capillaries: the principles involved were clearly enunciated by *Starling* (57, 58) towards the end of the last century and have been confirmed by many investigators since.

Although markers used by electron microscopists appear to pass rapidly through the fenestrae of "fenestrated" capillaries (10, 33) physiological experiments suggest that the leakage of protein from these vessels behaves in a somewhat similar way to that from "continuous" capillaries. In the gastrointestinal tract, for example, an increase in filtration pressure leads to an increase in lymph flow with a considerable fall in the concentration but little increase in total amount of protein in the lymph (66, 67).

In tissues with "discontinuous" capillaries such as the liver or an injured tissue, on the other hand, the leakage of protein is high and an increase in filtration pressure leads not only to an increase in lymph flow but also to a very considerable increase in protein turnover from plasma to lymph: often the actual concentration of protein in the lymph is increased (14, 15, 16, 17, 64, 67).

Experimental evidence leaves no doubt, therefore, that proteins are continually moving from the plasma to the tissue fluid through the small blood vessels at rates which vary considerably in different tissues. In comparison, there is probably extremely little escape of protein across the endothelium of the larger transporting vessels. In the arteries where the pressure is very high, proteins and lipoproteins do pass to some extent across the endothelium (22, 23, 24, 25, 26) as do the markers horseradish peroxidase and ferritin used in electronmicroscopy (28); injury of the endothelium increases this movement (13, 18). As far as I am aware, there is no evidence to show the extent of protein movement across the endothelium of the low pressure venules and veins.

Movement of protein from tissue fluid to plasma

Except in certain special instances, such as the absorption of protein from the cerebrospinal fluid through the arachnoidal granulations (61, 62) and the direct entry of proteins synthesized in the liver into the hepatic sinusoids, it seems that protein in the tissue fluid is returned to the blood stream only, or at least very largely, by way of the lymphatic vessels. This aspect of our concept of the movement of macromolecules is at present being challenged. It has been reported for example, that proteins may re-enter "continuous" capillaries in the lung (42) and skin (32) and "fenestrated" capillaries of the gut (47) and kidney (59) and later in this conference Dr. *Szabo* will support the view that proteins

injected into muscle are to a considerable extent absorbed into the blood capillaries. However, before we change our present concept, we should weigh these findings against fairly substantial evidence to the contrary.

In trying to solve the problem of whether or not labelled protein injected into a tissue can pass from tissue fluid to blood plasma directly through the walls of the blood capillaries, we are faced with a major technical difficulty – the trauma caused when injections are made. I well remember, for example, some of the first experiments we did on lymph from the lactating mammary gland of the sheep. We had injected a small amount of dye into the gland to delineate the lymphatic ducts into which the lymph drained. On cannulating the duct we were astounded to see that the lymph was quite milky in appearance; when, however, the duct was cannulated without any injections being made into the gland, the lymph was quite clear. Injections into such tissues as skin or muscle are also likely to cause trauma to some of the small vessels and to affect the pressure relationships that normally exist. To overcome difficulties such as these, Dr. *Steinbeck* and I some years ago studied the removal of labelled protein injected into the peritoneal cavity. This protein is absorbed mainly through the undamaged diaphragm. When we collected the lymph from the right lymph duct and thoracic duct, about 95 per cent of the absorbed protein entered the lymph, but we did find about 5 per cent in the blood; we thought that this might have entered by small lymphatic vessels that were not ligated or cannulated (19). When we ligated both right lymph duct and thoracic duct and stripped the veins at the base of the neck thus ligating or severing any small branches of these ducts, we could find no labelled protein in the blood stream after intraperitoneal injection (20).

In certain circumstances proteins in addition to those from the plasma may enter the tissue fluid naturally without the necessity of injection. For example, the γ-globulins of colostrum are absorbed intact through the intestinal mucosa of ruminants (ox, sheep and goat), horse and pig during the first 24 to 48 hours after birth or if introduced into the intestinal tract of the foetus. Although the blood capillaries are closer to the base of the mucosal cells than are the lymphatics this protein enters the lacteals (3, 12, 55). In adult dogs, ingested egg albumin has been detected in the thoracic duct lymph but not in the portal blood (2). Certain enzymes are transported to the blood stream from the intestine, to a large extent at least, by the lymph; for example, alkaline phosphatase during fat absorption (6, 27) and the lysosomal enzymes during shock (21). During fat absorption the large lipoproteins formed in the intestinal mucosa enter the lymphatics and not the blood capillaries (68). When the skin is injured by a thermal burn "tissue" proteins and enzymes are released into the tissue fluid and then enter the lymphatic vessels (35, 46, 48).

These experiments concern "continuous" capillaries in the diaphragm, "fenestrated" capillaries in the intestine and "discontinuous" capillaries in the injured skin. The results suggest that at most, very little tissue fluid protein re-enters the blood capillaries. This view is further supported by the effects of lymphatic obstruction, whether this is produced experimentally or occurs naturally in clinical disorders in man. Lymphoedema of limbs in such circumstances is well known. In the gastrointestinal tract, obstruction or hypoplasia of lymphatic vessels leads to chylous ascites or loss of protein into the intestinal lumen (68).

This is but some of the considerable body of evidence which supports the view that, in the mammal, tissue fluid protein does not, to any significant extent at least, enter the blood stream directly through the walls of the blood capillaries, whatever their ultrastructure.

2. *The walls of the lymphatic vessels*

Tissue fluid and lymph

Other possible barriers of the movement of protein are the walls of the lymphatic vessels. Firstly, let us consider the wall of the lymphatic capillary which is of the utmost importance in the formation of lymph. Because it is not possible to collect normal tissue fluid, the relationship between the composition of tissue fluid and that of lymph cannot be directly measured. This relationship has consequently become controversial. Some investigators hold the view that the composition of lymph reflects that of the tissue fluid from which it is derived. That this is not too far from the truth is evident from measurements of the volume of extravascular fluid (tissue fluid and lymph) and of the total amount of protein in this fluid. For example, experiments have shown that a man of 70 kg body weight has on the average about 10.5 litres of extravascular fluid and that this contains about 250 g protein. Calculations show that the extravascular fluid in the viscera – liver, gastrointestinal tract, kidneys, lungs and heart – amounts to about 1.5 litres and, if we assume that the concentrations of protein in the tissue fluid in these organs are the same as in the lymph draining them, this fluid will contain 60 g protein. Thus the head and neck, limbs and trunk, the bulk of the tissues of the body, will contain 9 litres of extravascular fluid containing 190 g protein or 2.1 g/100 ml. This is fairly near the values obtained for lymph from these regions. Other investigators, however, do not accept this view (29, 49, 50, 51). In general, they feel that the proteins are in a much higher concentration in lymph than in tissue fluid and during this conference Dr. *Casley-Smith* will give papers in support of this.

It seems, however, in my opinion at least, that the weight of experimental evidence at present favors the concept that the composition of lymph reflects that of the tissue fluid from which it is derived. A mammalian preparation where this problem can readily be studied in individual vessels is the bat wing. In this animal the lymphatic capillaries are large, bulbous structures. Dr. *Nicoll* and his colleagues have shown that Berlin blue injected by micro-techniques just outside such a capillary readily enters the vessel; when injected into the lymphatic capillary, the Berlin blue was shown to escape at various points, but once it passed further on into the collecting duct, little or no escape was seen. Electronmicroscopy showed that the points where dye escaped were at endothelial junctions which were open (11, 43). As in other animals the walls of the lymphatic capillaries often have little or no basement membrane and the junctions may readily separate in places to allow the passage of large molecules or particles.

If, therefore, we accept the view that the movement of tissue fluid and of lymph in the lymphatic capillaries is mainly through intercellular gaps, and can be in either direction depending on the pressures prevailing, then it would seem that the composition inside a lymphatic capillary would in general be the same as that of the tissue fluid just

outside the capillary. In any tissue the composition of tissue fluid would no doubt vary at any one time from point to point, but the mean composition of tissue fluid just outside lymphatic capillaries should be about the same as that inside.

Passage of lymph along collecting ducts

After it leaves the lymphatic capillaries the lymph is transported by the larger collecting ducts. The endothelium here contains mainly closed or tight junctions and is supported by a basement membrane and by varying thicknesses of connective tissue and smooth muscle cells. During its passage along these ducts lymph usually passes through one or more lymph nodes where once more the lymph in the network of lymphatic sinuses comes into close association with a network of blood capillaries.

The balance of evidence suggests that proteins do not normally escape from these lymph channels during their passage from capillaries to the lymphatico-venous communications at the base of the neck. For example, the volume and protein composition of lymph in the afferent and efferent vessels to the popliteal node are approximately the same (45). Other experiments show that labelled proteins infused in the direction of lymph flow into an afferent vessel of the popliteal node or into a mesenteric vessel may be recovered almost entirely in the efferent vessel of the popliteal node or in the thoracic duct respectively (31, 41, 60). When a lymph node is challenged with an antigen and the efferent lymph from that node collected, the immune response can be confined to the node (30, 56). Proteins of small molecular weight may, however, escape to some extent and enter the blood stream, presumably in the lymph nodes (9).

It seems, therefore, that during the passage of lymph from the capillaries to the veins at the base of the neck, all or almost all the protein remains in the vessels. Although the use of isotopes shows that there is an exchange of small molecules between lymph and blood, probably in the lymph nodes, there will normally be little net flux since the concentrations of these molecules throughout the extracellular fluid are very similar. Even the pO_2 in central lymph reflects the pO_2 in the tissues from which the lymph drains (4, 52, 63, 65). Under normal conditions, therefore, it seems that the concentration of proteins will not change appreciably during the passage of lymph along the larger vessels.

If the intralymphatic pressure is considerably raised, however, protein may leave the transporting vessels. In our studies on the lymph drainage of the peritoneal cavity, for example, we ligated the parasternal vessels and observed the movement of protein labelled with the dye T 1824 from the peritoneal cavity (20). This protein was absorbed through the diaphragmatic lymphatics and could be observed in the intercostal branches of the parasternal vessels when the valves of these vessels became incompetent. Ultimately the dye-labelled plasma appeared in the pleural cavity and it seemed, although not proved definitely, that it had escaped through the terminal capillaries of the intercostal vessels rather than the larger ducts. This confirmed the view that proteins can pass either way through the walls of the lymphatic capillaries, depending on the pressures inside and outside. In conditions of high intralymphatic pressure, proteins may also escape through the sinuses of the lymph node (31). It is also well known that an injury to the walls of a collecting duct will cause protein to escape (39). In all these conditions it seems that lymph as a whole escapes to be returned to the blood stream ultimately

by other lymphatic vessels. It is not known to what extent raised intralymphatic pressure will cause filtration through the walls of the collecting ducts resulting in an increased protein concentration in the lymph.

3. Barriers within the tissue fluid compartment

It is possible that the structure of the tissue fluid compartment may affect the movement of proteins in some tissues. I shall consider briefly only two such cases, cellular membranes and lobular organs.

Cellular membranes

Mesothelial membranes which line the serous cavities may vary in their structure in different parts of each cavity. As we have seen, proteins in the peritoneal fluid are mainly absorbed through the lymphatic vessels of the diaphragm. The mesothelial cells overlying the lymphatic lacunae of the diaphragm are smaller than elsewhere and relatively large gaps or stomata are present which vary in diameter with respiratory movement (68). The effectiveness of the mesothelial lining of the serous cavities as a barrier to the movement of protein varies greatly therefore, from one situation to another depending on its fine structure.

Recent experiments have shown that the alveolar membrane in the lungs is normally very impermeable to protein, a factor which no doubt accounts for the almost absence of protein from the fluid in the lungs of the foetus and for the relatively slow removal of protein introduced into the alveolar sacs (1, 44, 54).

In the choroid plexuses, the fenestrated capillaries are covered with a layer of cuboidal cells joined by "tight" junctions (7). This cellular layer probably reduces the amount of protein entering the cerebrospinal fluid in the ventricles.

Lobular organs

To what extent fibrous connective tissue forms a barrier to the movement of proteins in the tissue fluid is difficult to assess. *Rodbard* (49, 50) puts forward a view that such a barrier exists between the tissue fluid bathing the parenchymal cells and the tissue fluid which is the source of the lymph.

In some tissues such as lobular organs, e.g. the lactating mammary gland and liver, the tissue fluid formed inside the lobule has to move to the periphery of the lobule before entering lymphatic capillaries. Lymph in these small lymphatic vessels on the periphery of the lobule should have the same composition as the tissue fluid in their immediate environment. This will to some extent reflect the exchanges occurring across the walls of the blood capillaries in the connective tissue in this area; it would seem, however, that it would to a far greater extent reflect the transcapillary exchanges occurring within the lobule, since most of the blood flow to such an organ would pass through the lobules. In the lactating mammary gland where the blood flow and filtration pressure are increased compared with the non-lactating gland, the lymph flow is increased but the protein concentration in the lymph falls considerably (34, 36). In this respect the mammary gland behaves in the same way as non-lobular tissues with "continuous" capillaries such as the skin (14, 17) and uterus (53). In the liver with "discontinuous" capillaries we have seen that an increase in filtration pressure causes an increase in the lymph flow

and also in the escape of protein from the blood stream often with an increase in the concentration of protein in the lymph. A non-lobular tissue with "discontinuous" capillaries, such as injured skin, responds in the same way (14, 17). It seems, therefore, that in lobular tissues there is no effective barrier to the movement of tissue fluid from the centre to the periphery of the lobules.

In summary I feel that the weight of experimental evidence strongly supports the concept that the lymphatic vessels are, in most tissues of the mammalian organism, essential for the continual movement of proteins in one direction throughout the extracellular fluid. The rate of this movement is related to the existing pressures and the fine structure of certain barriers that exist in this fluid phase. I hope that my remarks will help to stimulate discussion of some of the papers that will be given during the course of this Conference.

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