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STARLING'S HYPOTHESIS IN THE FORMATION OF EDEMA*

The Seventieth Wesley M. Carpenter Lecture

FRANCIS P. CHINARD

Associate Professor of Medicine and of Physiological Chemistry,
The Johns Hopkins University School of Medicine; Acting Physician-in-Chief,
Baltimore City Hospitals, Baltimore, Maryland

THE term edema, in accord with its derivation from the Greek οιδημα, was used until about the middle of the 17th century to denote almost any type of swelling in the body. Since then, its meaning has become more restricted. Now, when we speak of edema, we generally refer to abnormal accumulations of fluid, detectable on physical examination, and involving only the interstitial compartment of the body.

These accumulations can occur in patients with disease of the heart, of the liver or of the kidneys and in the victims of malnutrition. As physicians, we recognize that edema is but a manifestation of an underlying disease process and that two facts link nearly all patients with

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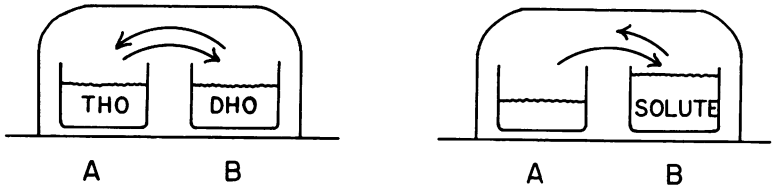

Fig. 1. Two-compartment system with gas phase as ideal semi-permeable barrier. In the diagram on the left the two beakers contain pure water. A contains a tracer amount of tritium oxide (THO) while B contains a tracer amount of deuterium oxide (DHO). There is no net or bulk transfer of water from one beaker to the other. However, molecular exchanges of water take place at substantial but equal rates (equal arrows) as indicated by the transfer of THO from A to B and by the transfer of DHO from B to A. In the diagram on the right, a solute has been added to B and there is net transfer of water from A to B. As indicated by the arrows, the rate of molecular transfer from A to B remains unchanged but the rate from B to A is decreased. See text for details.

clinically significant edema. The first fact is that there is localized or generalized excess of water and salt in roughly the same proportions that obtain in normal plasma. The second fact is that this excess or positive balance of salt and water has been achieved not so much by an excessive intake but rather by a decreased excretion by the kidneys in the face of a normal intake.

It is to Starling that we owe our understanding not only of the distribution of these excesses but also of the factors determining the rate of the initial formation of urine in the glomeruli of the kidneys. Starling's contribution in these fields may be epitomized as follows. *Only physical and physico-chemical factors are involved in the passage of water and solutes across capillary walls; these barriers are inert.* This is the essence of Starling's hypothesis. The hypothesis can be shown to be a special case of membrane equilibria.

The purpose of this communication is to present an elementary review of certain concepts of membrane equilibria, to describe the application of the concepts and of Starling's hypothesis to some clinical situations in which edema is manifest, and finally, to examine briefly some of the hypotheses and facts about the structure and permeability characteristics of certain capillary barriers.

Membrane equilibria in vitro. Consider first two beakers, each containing ordinary water, and confined by a bell jar as shown in Figure 1. Provided the whole system is kept at a uniform temperature, no detectable change will occur in the amounts of water in each beaker

with the passage of time. It will appear that nothing is happening. However, if we place a small amount of tritium oxide (THO) into beaker A and a small amount of heavy water (D_2O) into beaker B, we find that tritium oxide passes from beaker A to beaker B while deuterium oxide passes in the reverse direction. The rates are measurable and significant. Water passes as a gas from one container to the other. This is molecular exchange at rates equal in the two directions. There is still no net change in amounts of water in the two beakers. We say that the escaping tendencies or, more formally, that the chemical potentials* of water in the two compartments are identical.

If we now introduce a solute, either a salt or a protein in very high concentration, into beaker B, we will find that there is a continued increase of the amount of water in B and a decrease of the amount of water in A: there is net passage of water from A to B. There is, however, no passage of the solute. The gas phase is an ideal semipermeable barrier allowing free passage of solvent but effectively completely barring passage of solute. Is this net passage of water the result of an *increased* rate of passage of water molecules from A to B or the result of a *decreased* rate of passage of water molecules from B to A? Experiments with labeled water show that there is no change in the rate of passage of water molecules from A to B but that the rate of passage of water molecules from B to A has been decreased. The tendency of water molecules to escape from B (the chemical potential of water in B) has been decreased by the addition of a solute to that container. We can say that the average energy of the water molecules in B is less than the average energy of the water molecules in A.

We can prevent this net passage of water molecules from A to B by adding the same solute to A to the same molecular concentration as in B, or by the addition of *other* solutes, in appropriate concentrations to A. In this instance, the molecular exchanges will again be equal but will be less than if neither beaker contained any solute.

There is another way in which the net passage from one container to another can be prevented, but to illustrate this we must turn to another system of the type illustrated in Figure 2. Here (Fig. 2a), there is a single container divided into two compartments by a barrier

* An introductory discussion of chemical potentials, a concept brought to thermodynamics by Willard Gibbs, will be found in W. Mansfield Clark's *Topics in Physical Chemistry* (Williams and Wilkins, Baltimore, 2nd ed., 1952). I have attempted elsewhere[1] an elementary treatment of the concept in terms of average energy per molecule. In those terms and in the simple systems of concern here, addition of a solute to water decreases the average energy of the water molecules while an increase of pressure increases the average energy of the water molecules.

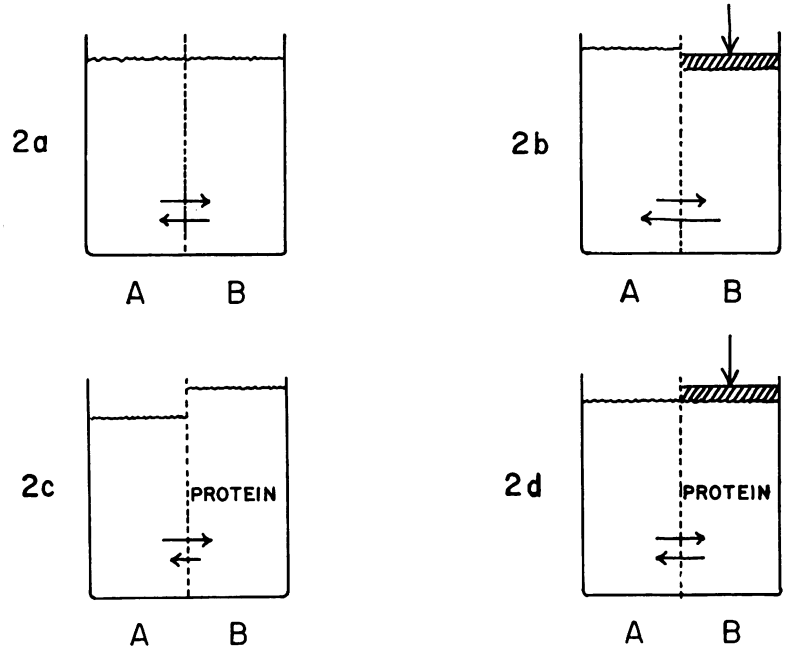

Fig. 2. Two-compartment system with semi-permeable membrane as barrier. In Fig. 2a, with water in both compartments of the container, there is no net transfer and the molecular exchanges (arrows) are equal in the two directions. In Fig. 2b, a pressure is imposed on B. There is net transfer of water from B to A. It is assumed that the molecular transfers from A to B are unaffected while those from B to A are increased. In Fig. 2c, protein has been added to compartment B. Net transfer of water occurs from A to B, assumed to be result of a decreased molecular transfer from B to A and of an unchanged molecular transfer from A to B. In Fig. 2d, equilibrium is established and net transfers of water are prevented by the imposition of a pressure on B. The magnitude of the pressure differential necessary is related to the protein concentration. See text for further details.

or membrane permeable to water and small solutes but not permeable to macromolecules such as proteins. If the pressures on the two sides are equal it appears that nothing happens. There is no net transfer of water and solutes from one compartment to the other. The chemical potentials of water in the two compartments are equal. Again, however, the molecular exchange of water can be demonstrated to be equal in the two directions by suitably labeled water. If now we impose a pressure difference across the barrier (Fig. 2b), such that the pressure on B is greater than the pressure on A, there will be net passage of water from compartment B, where the pressure is greater, to compartment A, where the pressure is smaller. The chemical potential of water in B is

greater than the chemical potential of water in A. If the pressures on the two sides are made equal by increasing the pressure on A, there will be no net passage of water and again the molecular exchanges will be equal. We can consider for present purposes that the imposition of a pressure increases the escaping tendency or chemical potential of the water molecules. If we now add protein to compartment B with the pressures on the two compartments equal (Fig. 2c) we will find a net transfer of water from compartment A to compartment B. The level of the solution in compartment B will rise to a height above A related to the final concentration of the solute. This rise of the level of the solution and hence the net transfer of water can be prevented by the imposition of a pressure on B greater than on A (Fig. 2d). The magnitude of the pressure difference is found experimentally to be related to the concentration of solute B. By analogy with our first system, we can consider that the escaping tendency of the water in B has been decreased by the introduction of solute into that compartment. This decreased escaping tendency has been increased to equal that of the water in compartment A by the imposition of the pressure difference so that equilibrium once again obtains. With a little extrapolation we can consider that similar relationships would obtain if there were some "non-diffusible" solute but in different concentrations in the two compartments. The pressure difference that must be imposed across the barrier in order to establish equilibrium with respect to water when "non-diffusible" solute is present in one compartment but not in the other is what we commonly call the "osmotic pressure".*

Our conditions of equilibrium can now be simply stated as

$$P'' - \pi'' = P' - \pi'$$

or

$$\mu'' = \mu'$$

The P's denote the actual hydrostatic pressures, the π's denote the osmotic pressures as just defined; the μ's are the chemical potentials of water. The double primes indicate values obtaining in the protein-containing compartment and the single primes indicate values obtaining in the protein-free compartment. The resultant of the actual hydrostatic pressure and of the osmotic pressure we call the chemical potential of water in that compartment. Equality of the resultants of $P - \pi$, or more simply, equality of the chemical potentials indicates that equilibrium obtains.

* The concept of "osmotic pressure" has been widely misunderstood and misapplied. For derivations of and comments on osmotic pressures see References (1 and 2).

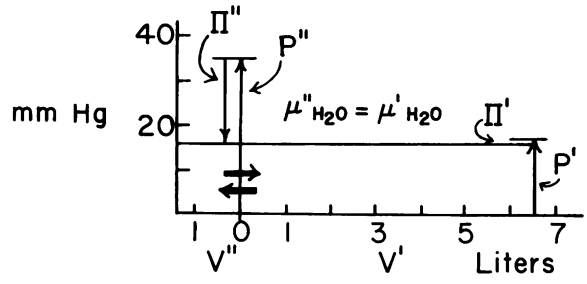

Fig. 3. The Starling factors and the compartment volumes in a patient with the nephrotic syndrome. This patient had been rid of her edema by repeated infusions of concentrated serum albumin. See text for details.

For application to capillaries in the body, the double primes refer to the blood side of the capillaries, and the single primes refer to the interstitial fluid side. P″ is then the capillary hydrostatic pressure, π'' is the osmotic pressure of the plasma protein, P′ is the tissue pressure and π' the osmotic pressure of the proteins of interstitial fluid. Note that the chemical potentials on each side of equality correspond to the difference of P and π.

If equilibrium does not obtain, then the rate of passage of water across the barrier can be shown to be proportional to the algebraic sum of the four factors.

Rate of passage $= k\ (P'' - \pi'' - P' + \pi') = (\mu'' - \mu')$.

This algebraic resultant is generally referred to as the net or effective filtration pressure. This rate of passage is equated with the glomerular filtration rate in the kidney.

These are the fundamental relationships which are derivative of Starling's concepts and of his conclusions based on his experimental evidence that "so far as experimental evidence goes, the glomerular epithelium may be looked upon as a simple filtering membrane resembling in many particulars a membrane of gelatin".[3] Nowadays, we have accepted the extension of that conclusion to other capillaries.

Membrane equilibria in vivo. The studies of Landis and his collaborators[4] and of Pappenheimer and his associates,[5] among others, have shown that the hypothesis and the conclusions are compatible with the additional experimental data that these investigations have provided. The capillary barriers in muscle can be considered inert. The factors or independent variables that determine the net transfer of water between

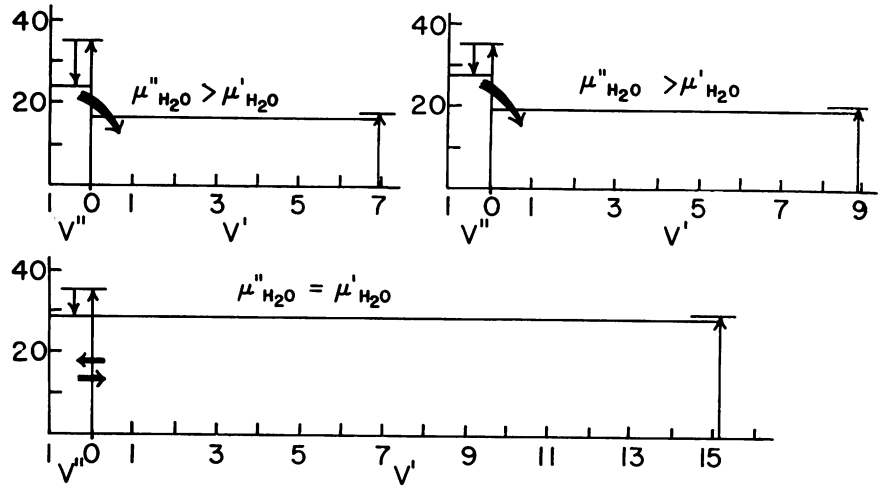

Fig. 4. Changes of the Starling factors and of the compartment volumes following withholding of albumin in the same patient. See text for details.

plasma and interstitial fluid are the capillary and tissue hydrostatic pressures and the nondiffusible solute concentrations in plasma and tissue fluids (i.e., the osmotic pressures).

What are the implications with respect to the development of clinical edema? The relationships can be appreciated most readily by examining a clinical situation: the development of edema in a nephrotic patient.

As a specific example we can consider the case of a 5-year old girl with the nephrotic syndrome who was studied some years ago in Dr. Van Slyke's department at the Rockefeller Institute.[6] The patient had been rid of her edema by repeated infusions of concentrated human serum albumin. Except for pronounced proteinuria, there were no gross abnormalities. The Starling relationships are indicated in Figure 3. The estimates of the plasma volume, v″ (to the left of the zero), and of the interstitial fluid volume, v′ (to the right of the zero), were essentially within normal limits for a patient of this age and height. The value for the capillary pressure indicated by the vertical upward line has been blandly assumed to be normal. The value for the osmotic pressure was calculated from the serum albumin and total protein concentrations. The resultant, indicated by the horizontal line, is a measure in mm. Hg of the chemical potential or escaping tendency of

water in this patient's plasma relative to a solution containing no proteins but all the other solutes of this plasma in the same concentration. The patient was assumed to have reached a state of equilibrium, although transiently. Accordingly, arbitrary but probably reasonable values could be assigned to tissue pressure and tissue fluid osmotic pressure to set the chemical potential of water in this compartment equal to that in plasma.* The two small arrows indicate that the molecular exchanges of water are taking place at equal rates in the two directions.

Further administration of albumin was withheld, the proteinuria continued and the concentration of albumin in the patient's plasma decreased rapidly.

The diagrams in Figure 4 illustrate the volumes of the compartments at three points during the next few weeks.

With the decrease of albumin concentration the osmotic pressure of serum decreased, the chemical potential of water in plasma increased and there followed a net transfer of water (and of solutes) from plasma to interstitial fluid. The plasma volume decreased from 1.2 to 1 liter because of this transfer. Such a decrease of plasma volume has been observed during the development of edema in nephrotic patients.[6-8]

Why was the decrease of the plasma volume limited? Why didn't the bottom drop out of the plasma volume? In the system under consideration we have four variables: the chemical potentials of water in the two compartments, μ'' and μ', and the volumes of the two compartments, v'' and v'. The chemical potential differences are determined by differences of hydrostatic pressures (P) and by differences of nondiffusible solute concentrations (π). A volume change in one compartment can be expected to produce a hydrostatic pressure change of the same sign in that compartment and to be closely followed by a change of π of opposite sign. For example, if the blood volume is abruptly decreased as in a blood bank donation, P'', the capillary pressure can be expected to decrease. This change will result in a decrease of the chemical potential of water in blood, μ'', relative to the chemical potential of water in interstitial fluid, μ'. Hence, there will be a transfer of water from interstitial fluid to plasma. Such a shift of water (and of

* The standard of reference for comparisons of chemical potentials of water would ordinarily be "pure" water at the same temperature as the solution and at one atmosphere of pressure. In this discussion we are, in fact, using another standard: water containing all the solutes in plasma (except proteins) at the same concentrations as obtain in plasma within the constraints of the Gibbs-Donnan equilibrium, at the same temperature as plasma, and at a pressure of one atmosphere. Those who would cavil at such a flexible standard are reminded that the purity of water is relative: ordinary water always contains some deuterium oxide.

diffusible solutes) should produce a decrease of P' and an increase of P'' over the decreased value obtaining after the blood-letting.

These changes in and of themselves will serve to moderate the shift of fluid from interstitial spaces to the blood compartment. In addition, as emphasized by Starling,[9] such a shift of water will produce an increase of nondiffusible solute concentration (hence, a further decrease of μ') in the interstitial fluid and a concomitant decrease of nondiffusible solute concentration (and hence, an increase of μ'') in the plasma. Equilibrium can thus be reestablished earlier than would be the case if the moderating effects were not operative.

In this manner, a variation in any one of the four factors μ'', μ', v'' and v' produces a transformation of the blood-interstitial fluid system such that if this transformation had occurred alone the variation of the factor would have been of opposite sign to that imposed. This is simply a statement of the Le Chatelier-Braun principle of moderation. In modern jargon, we can call this a feed-back effect.

It is obvious that such transfer of water as does occur cannot in a period of a few hours produce significant edema. For edema to accumulate, there must be a decreased excretion by the kidneys of salt and water if the intake remains constant.

Such a retention occurred in this patient and in her subsequent course she developed massive edema once again. Here, with the moderating effects of a sustained increase of tissue pressure "supporting the plasma volume", a new quasi-equilibrium state occurred, with the patient swollen, with skin tense, with a very low serum albumin and a low osmotic pressure.

Similar considerations apply to the changes of plasma volume occurring in the 24-hour period immediately following the infusion of concentrated human albumin solutions.[8]

Generalized edema and more localized accumulations of fluid occurring in other disease states can be considered from the same viewpoint. For example, in right-sided heart failure, the increased venous pressure implies that the capillary pressure must also be increased. The chemical potential of water in plasma becomes greater than the chemical potential of water in interstitial fluid, and there follows a net transfer of water from the vascular compartment to interstitial space. Beginning with swelling of the ankles, the edema increases at a rate and reaches an extent determined by the imbalance between the intakes of salt and

water and the outputs of these same substances by the kidneys. The rate of transfer and the net transfer of water will be moderated by the increase of tissue pressure attendant on the increase of the interstitial fluid volume and possibly by the reciprocal changes of protein concentration occurring in the two compartments as the transfer of water takes place.

In the ascites of liver disease, the experimental evidence indicates that a combination of increased capillary pressure in the portal system and of decreased plasma albumin concentration is necessary for its development. Increased intra-abdominal pressure may become manifest and limit the extent of water transfer. Conversely, an increased concentration of protein in ascitic fluid, such as occurs quite frequently, will serve to increase the transfer of water into the abdominal cavity.

In the formation of pulmonary edema, it has been shown by Guyton and his associates[10] that the factors of Starling's law also apply. An increase in the osmotic pressure of plasma requires that a higher pulmonary capillary pressure obtain in order to produce pulmonary edema. There is no evidence that the barrier participates in any but a passive way to the molecular exchanges and to the net transfer of water and perhaps of solutes. The experimental data and Starling's concepts form a concordant assembly.

It is important to note here the implicit assumption made, that in the normal individual there is equilibrium, or at least a close approach to equilibrium, with respect to water between the vascular and interstitial compartments. This may be a close approximation to the facts in a recumbent individual; but in an individual standing erect a steady state rather than equilibrium may obtain in, for example, the lower limbs. Lymphatic drainage may be very important here and in other regions of the body as well.

Capillary permeability. It is appropriate at this point to turn briefly to a consideration of the possible ways in which water and solutes, such as sodium ion and urea, may cross these barriers. There are two conflicting views of the manner in which this passage is achieved. The view held most widely is that passage or net transfer of water and solutes occurs in bulk without separation through discrete pores, the dimensions of which have been calculated from the experimental data. This is the filtration or pore hypothesis.[5] The minority view is that molecular exchanges are taking place across the major portion of the surface of

the barrier and that net transfers are the resultant of small differences of the large molecular and ionic exchange rates in the two directions. This is the diffusion hypothesis.[11, 12] Evidence for the pores has not been found on electron microscopy. There are substantial objections on physicochemical and thermodynamic grounds to pore hypothesis.[11, 12] Objections to the diffusion hypothesis have also been raised.[13, 14] Both hypotheses, however, in one fashion or another incorporate the basic tenets of Starling's hypothesis.

These uncertainties as to the mechanism of passage are in part a reflection of the experimental difficulties involved in studying capillary permeability. The two sides of the barrier are not generally accessible to examination. It is tempting to conclude that passage occurs in bulk because the composition of the solution on one side is similar, within the constraints of the Gibbs-Donnan relationships, to the composition of the solution on the other side. For example, the results of the micropipetting experiments of glomerular fluid[15-17] can be most simply interpreted as indicative of bulk filtration. However, the samples of fluid were obtained under steady-state conditions, conditions not designed to demonstrate diffusion effects. These experiments do not in fact exclude diffusion as the mechanism of passage of water and solutes across this barrier.

The alveolar-capillary barrier. That the properties of barriers may not be quite what they seem at first sight is shown by some experiments that I have been carrying out with Dr. Theodore Enns and Miss Mary Nolan on the lungs of dogs in order to obtain information on the properties of the alveolar-capillary barrier. The experimental technique used is an extension of the indicator-dilution procedure devised by Hamilton and Stewart. The test solutions contain T-1824 and labeled sodium ion, urea, or water. Injection is made by means of a catheter into the right side of the heart. Serial samples are collected from an artery during the minute or so following the injection. The usual corrections are made for recirculation. The percentage recovery of each substance injected in each arterial sample is calculated on the basis of the assumption that none of the T-1824 leaves the circulation in passage through the lungs. The results of a representative experiment in which T-1824, Na^{22} and labeled water were injected is shown in Figure 5.

The total recoveries of Na^{22} and of the labeled water were slightly

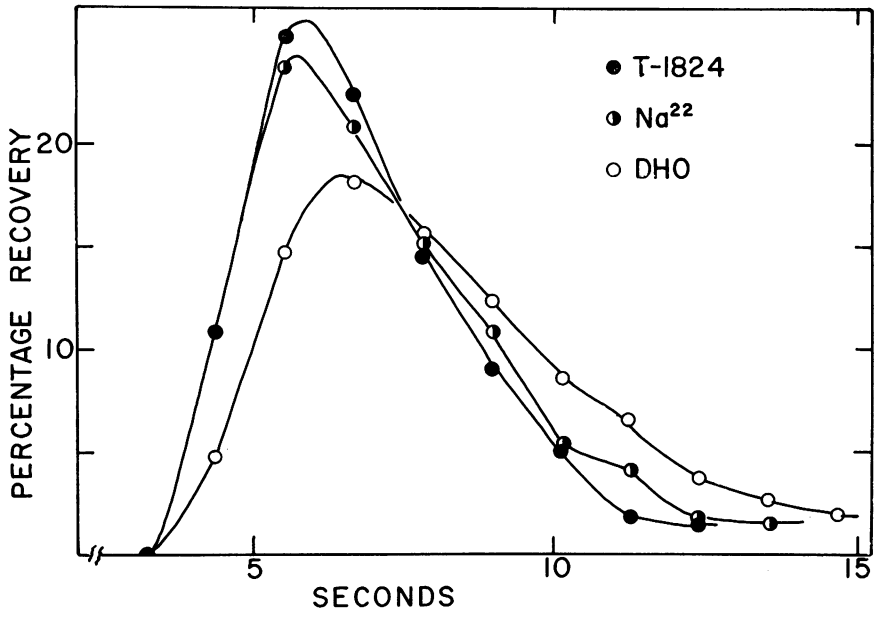

Fig. 5. Percentage recovery-time relationships of T-1824, Na^{22} and labeled water in arterial blood following a quasi-instantaneous injection into the right ventricle.

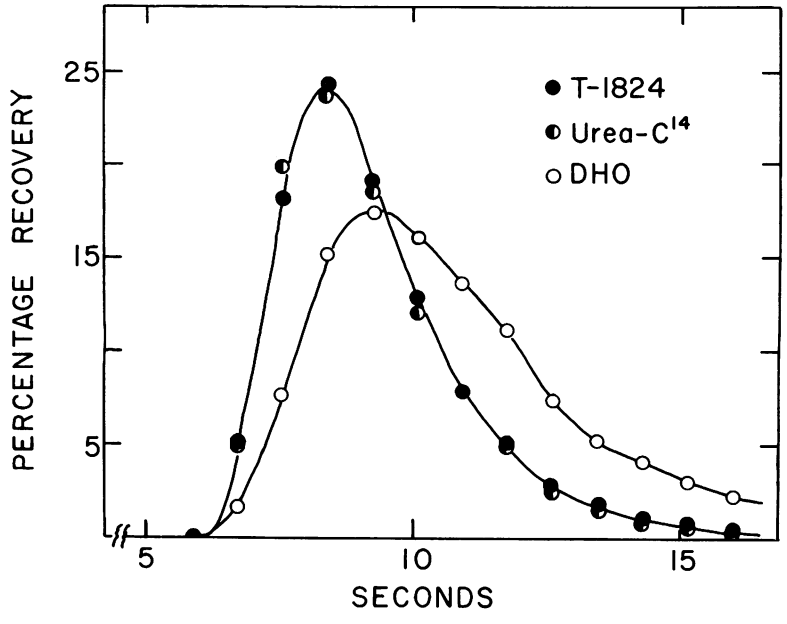

Fig. 6. Percentage recovery-time relationships of T-1824, urea-C^{14} and labeled water in arterial blood following a quasi-instantaneous injection into the right ventricle.

less than that of T-1824, in keeping with the results of a series of such experiments where the labeled sodium and water recoveries averaged about 95 per cent of the T-1824 recoveries.[18] The displacement of the curve for water relative to the curves for T-1824 and for Na^{22} indicates that the volume of distribution of water in the lungs is substantially greater than the volumes of distribution of the other two indicators. This excess volume of distribution of water amounts to approximately two-thirds of the water content of the lungs. The restriction of Na^{22} to a volume of distribution only slightly greater than that available to T-1824, the indicator restricted to the vascular compartment, could be the result of impermeability of the walls of the capillaries to that ion or the result of a vanishingly small interstitial fluid space in this capillary system as would be expected from the Starling relationships.

In similar experiments in which urea replaced sodium quite similar results were obtained: urea appears to be restricted in its distribution to a volume but slightly greater than that available to T-1824 (Figure 6). And yet, urea would be expected to go where water goes.

In an attempt to resolve these problems, we have approached the alveolar-capillary barrier from the other side by way of the trachea. In these experiments, 5 ml. of deuterium oxide-containing tracer amounts of Na^{22} and of urea-C^{14} are introduced suddenly into the lungs by way of catheter in one of the bronchi. At the same time, T-1824 is injected into the jugular vein. Serial samples of arterial blood are collected as in the preceding type of experiment. The results of a representative experiment are shown in Figure 7.

The alveolar-capillary barrier does not appear to offer much hindrance to the passage of water. The relationships of the curve for water to the curve for T-1824 are similar to the relationships obtaining in the preceding type of experiment in which both the labeled water and the T-1824 were injected into the right ventricle.

But with respect to both urea and Na^{22}, it is evident that the rates of transfer are much smaller than the rate for water. A rough calculation suggests that the rate of molecular exchange of water is at least one order of magnitude greater than the molecular exchange rates for urea and for sodium.

The net passage of water across the endothelium of the barrier appears to follow the dictates of Starling's hypothesis. But the barrier itself has remarkably greater permeability to water and to "gases" than

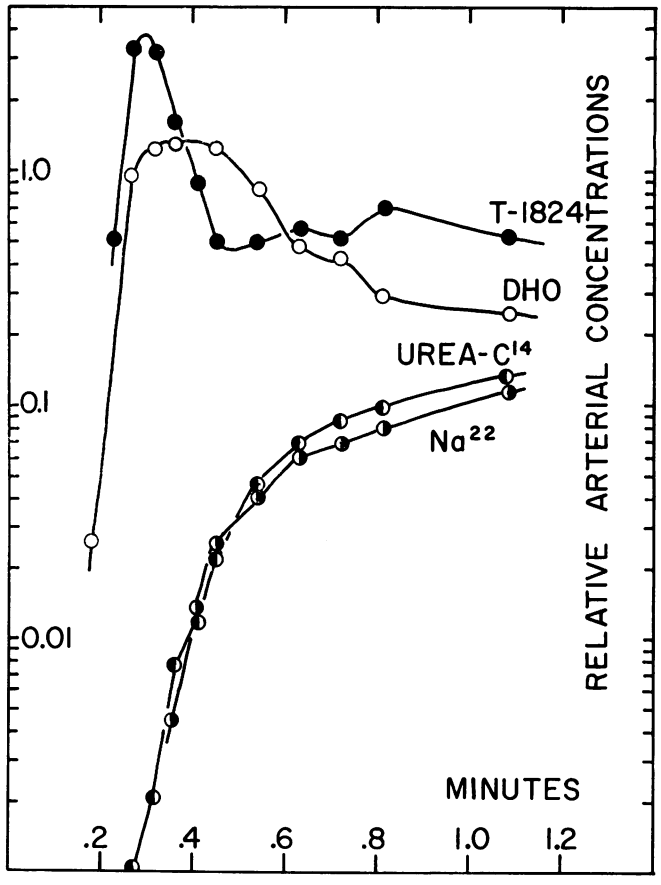

Fig. 7. Percentage recovery-time relationships in arterial blood following the introduction into a bronchus of 5 ml. of deuterium oxide-containing tracer amounts of Na^{22} and of urea-C^{14} and the simultaneous injection of T-1824 into the right jugular vein.

it has to ions and even to urea. Thus, the alveolar-capillary barrier has peculiar properties. It does not have the properties that would be expected of a lipid barrier in view of its permeability to water. The exchanges of gases in the lungs appear to take place across an aqueous barrier rather than across a lipid barrier.

Conclusions

1. Starling's concepts and hypotheses are applicable, with appropriate modifications, to a wide variety of clinical situations in which edema develops.

2. There is still much to be learned concerning the properties and characteristics of the capillary barriers in various parts of the body across which net transfers of water and solutes occur in the development of edema as the result of unequal rates of molecular exchanges.

3. When clinically evident edema develops, we must recognize the significance of the kidneys as the peccant organs that have permitted the body to accumulate the excesses of water and of salt.

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