Fluid Physiology

Fluid Physiology:

A Handbook for Anaesthesia and Critical Care Practice

By

Thomas Woodcock

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FOREWORD BY WILLIAM W. MUIR

Like many, I was introduced to Dr. Thomas Woodcock, "Tom", by reading his publication of the Revised Starling equation and the glycocalyx model of transvascular fluid exchange. Shortly thereafter I learned of Toms website *FluidPhysiology*[1] and watched the video of his lecture at The Physiological Society, London[2] wherein he wittily and persuasively enlightens his audience on plasma - interstitial - lymphatic fluid dynamics. Shortly thereafter I had the opportunity to invite Tom to the 23rd International Veterinary Emergency and Critical Care Symposium (IVECCS) held at the Gaylord Opryland Resort in Nashville TN, September 2017. This was without question one of the most enlightening and all-too brief encounters I have enjoyed with Tom other than our ongoing email exchanges pondering vascular physiology, fluid physiology, fluid balance and fluid therapy. In my opinion Tom is one of a handful of clinical scientists that is able to conceptualize and translate complex, and at times, vague and ambiguous physiologic processes into transparent scenarios that explain their clinical relevance and therapeutic implications. Tom's writings, lectures, and website posts have enlightened and modernized our understanding of vascular and fluid physiology and highlight uncertainties that a new generation of fluid therapy enthusiasts can investigate. Tom's teaching and clinical experiences in conjunction with his keen interest in fluid flux, fluid filtration, and fluid balance encompass modern day evidence-based discoveries ever advancing his promotion of the "revised Starling principle". This revision challenges historical interpretations and encourages the development of a new paradigm for fluid selection and administration, especially regarding the administration of biophysical therapies. Most notably, and contrary to many textbooks, this paradigm predicts that at subnormal arterial and capillary pressure the infusion of an isotonic crystalloid solution efficaciously increases intravascular volume and that transvascular fluid flux remains close to zero and, contrary to most textbooks, the administration of a colloid solution provides little to no significant long-

[1] https://fluidphysiology.org/
[2] https://www.youtube.com/watch?v=oIvEvFYtukA,

term therapeutic advantages. Readers will enjoy a clear, concise, and comprehensible description of body fluid compartments, the key role of the endothelial surface layer (i.e. glycocalyx) and the vital importance of interstitial fluid and lymph flow in determining transvascular fluid flux in both the pulmonary and systemic circulations. They will also enjoy his discussion of why venous excess and not venous return is the primary determinant of cardiac output. These discussions apply to all mammals and will capture the interest of anyone interested in fluid balance and fluid therapy. Tom's writing style combined with his lucid evidence-based discussions encourages readers to rethink many historic fluid physiology precepts and their implications for fluid therapy. Importantly this text provides a more physiologic based understanding of body fluid kinetics and transvascular fluid flux that conforms to clinical observations and directs readers towards improved therapeutic approaches of context specific fluid balance disorders. This text is a must read for all medical professionals (human and veterinary) interested in advancing their knowledge and understanding of the physiologic processes that dictate safe and effective fluid therapy practices.

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PREFACE

I believe that understanding fluid physiology is critical to the practice of medicine. For many years, I gave lectures on intravenous fluid therapy to Final Fellowship examination candidates at the Royal College of Anaesthetists in London. The physiological principles I taught were essentially those described by Alison Twigley and Ken Hillman back in 1986 [1]. It was their claim that if you wanted to expand the plasma volume, you should administer an albumin solution or a synthetic colloid solution. If your aim was to expand the extracellular fluid volume, give an isotonic salt solution like Normal Saline or Hartmann's Solution. A free water (or non-electrolyte) solution, such as 5% Dextrose, would distribute itself throughout the total body water. They concluded that this revelation marked "the end of the crystalloid era" and that more focus on preserving plasma colloid osmotic pressure could reduce the total volume of fluid prescribed. Knowing that the Twigley-Hillman paradigm did not explain clinical experience or published data, I read widely on fluid therapy, but it was not until 2010 that I came across a review article [2] that led me to realise a whole new paradigm for fluid prescribers who wanted to be physiologically rational. Experiments had confirmed the role of the endothelial glycocalyx in capillary filtration and permeability by 2004. Charles Michel (London) and Sheldon Weinbaum (New York) had been jointly credited with solving the puzzle of filtration and absorption of fluid by capillaries. J. Rodney Levick explained;

> "The new paradigm… renders untenable the popular argument that sustained venular absorption accounts largely for tissue fluid balance. During fluid absorption the subglycocalyx colloid osmotic pressure will increase quickly, due to reverse ultrafiltration, and thus prevent sustained absorption… To explain tissue fluid balance we must now focus increasingly on lymphatic function." [3]

The *British Journal of Anaesthesia* published The Revised Starling Equation and Glycocalyx Model Paradigm for Rational Fluid Prescribing in 2012 [4]. My son and I argued that consideration of Starling forces enables us to understand why biophysical colloid osmotic pressure

therapy is much less effective than Twigley and Hillman claimed. The Twigley-Hillman representation of the interstitial fluid as a homogenous isotonic aqueous solution also has to be revised. The interstitium is structurally diverse and biologically active. One major discovery has been the phenomenon of excess sodium storage. Excess sodium storage is linked to interstitial volume homeostasis, and these may be important players in the pathophysiology of oedema, haemorrhagic shock, burns, and sepsis.

What is rational prescribing? For most patients the maintenance of arterial blood pressure and heart rate within a normal range is an adequate haemodynamic goal, and the fluid prescriber's main consideration will be the avoidance of fluid and plasma electrolyte imbalance. If we choose instead the restoration or maintenance of oxygen delivery as our clinical goal, a rational approach is to prescribe enough fluid to "optimise" the cardiac preload and stroke volume without overly diluting the oxygen-carrying red cells. If we choose the minimisation of interstitial fluid volume accumulation as our clinical goal, a rational approach is to reduce the rate at which extracellular fluid enters the interstitium and to facilitate its return from the interstitium to the plasma. An observational study revealed why doctors in one Australian Emergency Department gave immediate intravenous fluid boluses in 500 cases [5]. Not all of them were self-evidently rational and included headache, nausea, and something called deconditioning.

At the time of writing, the revision of the original Starling principle to the steady-state Starling principle is increasingly accepted by physicians. Clinical journals are publishing review articles explaining the new physiology and the implications for rational therapy. A few experts remain unaware of, or unconvinced by, the twenty-first century steady-state Starling principle and prefer to focus on the volume of distribution of blood constituents such as albumin, presuming that they are estimating the plasma volume. Some have used normal plasma volume as their clinical goal for rational fluid therapy, in particular for treatment with albumin or a synthetic colloid solution. They teach (wrongly) that albumin is constrained within the circulating blood volume, ignoring the fact that most of the total body albumin is at any one time within the interstitium. They teach (again wrongly) that albumin determines plasma volume. Around 5% of plasma albumin normally escapes the circulation every hour and is balanced by albumin

returning to the bloodstream *via* the lymphatic system. In many of our patients the transcapillary escape rate for albumin is up to around 15%. To pursue a normal plasma volume of distribution of albumin as a therapeutic goal in patients with no haemodynamic signs of intravascular volume depletion is not rational.

Sir Karl Popper taught in his '*Introduction to Scientific Method*' lectures that knowledge grows from problems (P1) that we observe with the prevailing paradigms and theories. We gather relevant information and construct a tentative theory (TT) that explains what we have observed. We then subject TT to criticism - Popper suggested Eliminate Errors (EE), which brings us to the next problem P2. Popper's thesis is summarised as P1 -> TT -> EE -> P2. The problems we address in this monograph are the failings of traditional Starling physiology to explain or predict the consequences of intravenous fluid infusions. The solution lies in accepting the steady-state Starling principle and using it to re-interpret past clinical trial data and to interpret future findings.

At the heart of this vital debate are the new fields of glycocalyx and interstitial matrix biology. One august Professor of Clinical Physiology told me it was B******t Bingo. A Professor of Intensive Care Medicine who once wrote that the glycocalyx was too fragile to be of relevance to clinical care went on the write a Review Article about its importance in a major international Journal. I hope that this book will be an essential resource for those who care for patients and who want to understand and apply the science of fluid physiology. It has been Charles Michel's life work to investigate and understand the science of fluid and solute circulation from plasma to interstitium and back again, and Charles has been most patient and generous with his time and support for my own efforts to translate that knowledge into a clinically useful explanatory paradigm. Geraldine Clough gave me inspiration and encouragement at The University of Southampton, and convened the H3 Symposium *Microvascular physiology - implications for understanding intravenous fluid therapy* on 28 November 2014 at The Physiological Society, Hodgkin Huxley House, London. Kenton Arkill convened a one-day Workshop for researchers with an interest in the endothelial glycocalyx at the British Microcirculation Society meeting in Nottingham in 2017. Last but not least I thank my son, the molecular biologist, who answered my clinician's questions about basic sciences. These scientists unwittingly inspired me to write this book for other non-scientist clinical practitioners.

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CHAPTER 1

STARLING'S FLUID PHYSIOLOGY: HISTORIC PERSPECTIVE

Chapter summary

I present a historical narrative of the evolution of the Starling principle in physiological sciences. We can credit Starling with the proof that solvent and solutes of plasma are mostly filtered to the interstitium through an endothelial filtration barrier. We meet Eugene Landis and John Pappenheimer who developed the understanding of Starling forces in fluid physiology. Pappenheimer is perhaps best remembered for his compelling theory, still alluded to today, that there must be small pores and large pores perforating the endothelial filtration barrier. A full understanding of the processes that mimic large pores remains elusive to this day, but the small pore effect is now explained by Curry and Michel's fibre matrix theory which emerged from the discovery of an endothelial layer only detectable by electron microscopy. Charles Michel in London, and Sheldon Weinbaum in New York independently proposed what we now call the Michel-Weinbaum Hypothesis, or the Glycocalyx Model, which explains why microvascular filtration - absorption is not a two-way process. The asymmetry of the endothelial filtration barrier facilitates filtration but severely restricts fluid reabsorption of interstitial fluid to the plasma. I present how the Glycocalyx Model operates in narrative form, keeping mathematical accounts to a minimum. A critical learning point is that the Starling forces of fluid physiology are normally in a steady-state. Acute disturbance to one or more of the forces (disequilibrium) starts a sequence of events that eventually restores a new steady-state filtration equilibrium. The preferred term for the revised Starling principle is the steady-state Starling principle. It makes us acknowledge the existence and importance of an interstitial fluid and lymph circulation running in parallel with the circulation of blood.

The original Starling principle

Ernest Henry Starling was born in London on 17th April 1866. At the age of 16 years he entered the Medical School of Guy's Hospital and took his Bachelor of Medicine degree in 1889, soon followed by his Doctorate in 1890. Starling had an early interest in lymph formation, and in 1892 he spent several months working with Rudolf Heidenhain in Breslauer (now the Polish city of Wroclaw) familiarising himself with Heidenhain's experiments and methods. The great debate of that time was whether lymph was formed by capillary secretion or filtration. Discovering that there are lymphagogue substances that increase lymph flow, Starling was initially attracted to the secretion viewpoint. Starling returned to London intending to confirm Heidenhain's view that interstitial fluid was formed by secretion and that the secreted fluid was returned to the bloodstream as lymph. In his canine experiment collaboration with William Bayliss, Starling soon made the discovery that immortalised his name. In 1896 Starling published "On the absorption of fluid from connective tissue spaces" in which he demonstrated that connective tissue fluid is formed by capillary filtration. He said:

> "the osmotic attraction of the serum for the extravascular fluid will be proportional to the force expended in the production of this latter so that at any given time there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids."
>
> "Here then we have the balance of forces necessary to explain the accurate and speedy regulation of the circulating fluid." [2]

The forces that Starling identified became known as the Starling forces, and to this day they are recognised as major determinants of the transcapillary solvent filtration rate J_v. Unfortunately, misinterpretations of Starling's Principle relegated lymph to the role of a buffer system returning to the bloodstream just the small excess of filtered over reabsorbed fluid. It was later asserted (incorrectly, as we now know) that "Starling verified all Heidenhain's experiments and disproved all his conclusions." It has taken more than a century to reconcile Starling's hypothesis that interstitial fluid is formed by capillary filtration with Heidenhain's hypothesis that interstitial fluid is predominantly returned to the bloodstream as lymph. We may now call this the **revised Starling principle** or the **steady-state Starling principle**:

perhaps there is a case for calling it the Starling-Heidenhain principle!

We should also note that a speculation by Ernest Starling in his 1896 paper anticipates this century's steady-state Starling principle:

> "With diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid, until this becomes richer in proteids; and the difference between its proteid osmotic pressure and that of the intravascular plasma is equal to the diminished capillary pressure."

After 1896 Starling turned his published experimental efforts to other aspects of physiology, but he continued to teach in his lectures and textbooks what we came to learn as the original Starling principle. In 1922, August Krogh declared in his Lectures that nothing new had been contributed to capillary exchange physiology since Starling's paper on the subject. This comment may have inspired a University of Pittsburgh medical student by the name of Eugene Landis to develop a technique for the direct measurement of capillary pressure in the mesentery of a frog. With an ingenious approach to estimating the rates of filtration and absorption across the wall of the capillary, Landis found a strong positive correlation between capillary pressure and the transcapillary flow rate, whether positive (filtration at higher pressures) or negative (reabsorption at lower pressures). It was Landis who proposed that his findings could be expressed by a mathematical equation that has evolved into the Starling equation.

The science of Starling forces

Starling died of sepsis on a Caribbean banana boat in 1927 and was buried in Kingston, Jamaica. A year later, Eugene Landis achieved his degree in Medicine and crossed the Atlantic to London, where he spent the winter of 1928-9 working in the laboratory of the great Clinical Scientist Sir Thomas Lewis at University College Hospital. There he developed a technique for the direct measurement of capillary pressure in the fingernail beds of human subjects. With the hand rested at the level of the heart, he determined the capillary filling pressure to be around 32 mmHg, the lowest capillary pressure (venular filling pressure) to be about 12 mmHg, and the pressure at the apex of the capillary loop in the fingernail bed to be around 25 mmHg. With plasma oncotic pressure measured to be around 25 mmHg, such observations

strongly supported Starling's speculation. Landis then moved on to work in August Krogh's laboratory in Copenhagen where he returned to his frog model and added proof to Starling's conjecture that plasma loses fluid by filtration to the tissues as it flows through the upstream (arterial) half of the capillary, then regains fluid by absorption as it flows downstream in the venous half. This idea is encapsulated in the familiar diagram of filtration declining with pressure as plasma moves along a hypothetical capillary, becoming zero when hydrostatic pressure is equal to the oncotic pressure of plasma, and then absorption increasing with continually falling hydrostatic pressure. In later years Charles Michel has called this "the diagram to forget", because this linear relationship only occurs transiently after acute disequilibrium of the Starling forces. (Figure 1.1)

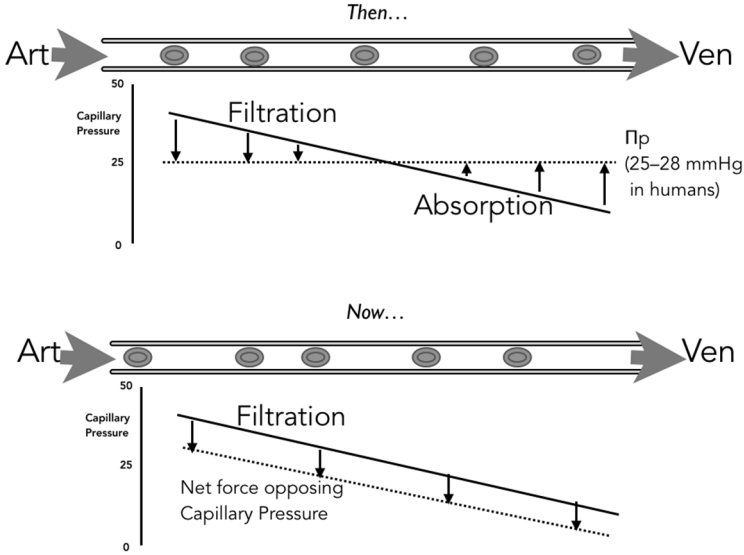

Figure 1.1

While in Krogh's laboratory Landis developed a plethysmographic technique for estimating the transcapillary solvent filtration rate in the forearm of human volunteers, and he continued this work on his return to the United States. In 1933 he published, with E.M. Gibbon, "The effects of temperature and tissue pressure on the movement of fluid through the human capillary wall."

New Yorker John Pappenheimer obtained his medical qualifications at Harvard University, Massachusetts in 1936, before travelling to England and obtaining his PhD at Cambridge University in 1940. By 1948 Pappenheimer was working in Landis' new laboratory at Harvard, and there began the work for which he is most renowned. With A. Soto-Rivera he published an important work entitled "Effective osmotic pressure of the plasma proteins and other quantities associated with the capillaries circulation in the hindlimbs of cats and dogs." The experimental protocol they created confirmed most of the predictions made by Starling. They were also able to demonstrate the linear relation between filtration and fluid absorption rates and mean capillary pressure seen by Landis in frog capillaries. Pappenheimer went on to deduce the presence of small pores and large pores penetrating capillary walls from the rates of transendothelial movements of solutes of different sizes – Pappenheimer's pore theory.

The theory of osmotic pressure measurement across semi-permeable membranes was greatly advanced by the published work of A.J. Staverman in the early 1950s and gave us Staverman's Reflection Coefficient (sigma, σ) which we see in the modern Starling Equation and which we may consider an indicator of capillary permeability to larger molecules such as albumin. Kedem and Katchalsky developed Staverman's approach to osmosis to describe membrane transport for binary non-electrolyte solutions, generated by the hydrostatic pressure difference ΔP and the osmotic pressure difference ΔΠ, in the late 1950s. The K-K equations are derived from the principles of linear thermodynamics of irreversible processes. There are two "K-K equations", one of which is the familiar Starling formulation for the movement of the solvent across capillaries which introduces the concept of hydraulic conductance (L_p). The surface area for filtration is S, or alternatively the product of L_p and S gives the filtration coefficient K_{fc}. The other K-K equation describes the movement of a specified solute such as albumin and gives us a definition of capillary permeability. Membrane transport is described by the equations for the solvent flow (volume flow) J_v and the solute flow (mass) J_s.

K-K Equation 1: $J_v = L_p S (\Delta P - \sigma \Delta \Pi)$

K-K Equation 2: $J_s = \omega \Delta \Pi + c(1 - \sigma) J_v$

where c stands for mean concentration, $c \approx (c_1 + c_2)/2$ and (L_p, σ, ω) are coefficients of filtration, reflection and permeation, respectively. These

equations are used in research on substance permeability through artificial and biological membranes and remain valid for the revised (steady-state) Starling principle. As we shall see, the twenty first century revision of K-K Equation 1 for microvascular endothelium recognises that $\Delta\Pi$ depends on J_v.

Up to this point physiologists had largely ignored the hydrostatic pressure of the interstitium, presuming that it would be close to atmospheric pressure. They had ignored the colloid osmotic pressure of interstitial fluid, presuming that it would be negligible. In 1963 Arthur Guyton published his work using an implanted subcutaneous capsule in dogs and cats to measure interstitial pressure. He found substantially sub-atmospheric pressures which seemed to undermine the concept of a tightly regulated balance between the Starling forces. In 1973 Auckland and Fadnes published their work using implanted wicks that revealed interstitial colloid osmotic pressures of the order of 10 mmHg in the subcutaneous tissues of rats and dogs.

Though the symmetric filtration - reabsorption concept was well established at this time, researchers began to realise that all the capillaries they studied were filtering fluid to the interstitium, and they were not finding capillaries that were reabsorbing tissue fluid to the plasma. The linear relationship governing transcapillary fluid movement as postulated by Starling needed to be reconsidered.

Revising the Starling principle

An "endocapillary layer" seen on electron microscopy was described by Luft in 1966. Experiments reported during the 1970's led to Roy Curry and Charles Michel's **Fibre Matrix Model of Capillary Permeability**. They proposed that:

> "the endocapillary layer is a three-dimensional network formed by the fibrous chains of the membrane glycoproteins of the endothelial cell coat reinforced by the absorption of plasma proteins." [5]

This hypothesis gave anatomic asymmetry to the plasma/tissue barrier and made it possible to explain functional asymmetry in the predominance of filtration over reabsorption. In 1984 Michel published his theory of steady-state filtration through capillary walls. Michel and Phillips later reported their experiments which showed that when they dropped arterial pressure, there was a temporary adjustment period

during which reabsorption of fluid from interstitium to plasma occurred. But reabsorption was only transient; within minutes filtration was resumed at the "new" lower capillary pressure with no change to plasma proteins [7]. A major flaw in the design and interpretation of Starling's experiments, and others since, was exposed. Researchers were measuring transient reabsorption as a result of changing experimental conditions, a disequilibrium, without following through to ascertain the consequent steady-state.

J. Rodney Levick of St George's Hospital in London proposed a significant reconsideration of the extravascular factors affecting capillary filtration - reabsorption balance in 1991 [8]. He collated published data for the interstitial hydrostatic and colloid osmotic pressures that had been determined in many different tissues and estimated the mean microvascular pressure $P_{cap(0)}$ that would balance the difference between plasma osmotic pressure and the interstitial pressure of that tissue. A plot of measured venular pressure P_{ven} against the calculated $P_{cap(0)}$ distinguished those tissues in which fluid filtration predominates (venous pressure $P_{ven} > P_{cap(0)}$) from a few where absorption is favoured ($P_{ven} < P_{cap(0)}$). His examples of absorbing capillaries included renal peritubular capillaries and afferent vasa recta in the kidney, tissues whose purpose is fluid absorption from the interstitium. Intestinal mucosal capillaries could either absorb mucosal interstitial fluid when there was intestinal fluid available or filter plasma solvent during fluid deprivation. For capillaries with reported values for their normal hydraulic conductance L_p (which is the reciprocal of resistance to flow) it was possible to use the pressure data to estimate the expected rate of filtration. Calculations suggested filtration rates substantially in excess of measured lymph flow rate in these tissues, which is clearly impossible. The search for a new hypothesis for the role of Starling forces to resolve this large discrepancy began, and experimental designs by which to test the hypothesis were devised.

In 1977 and 1978 Charles Michel of Imperial College, London and Sheldon Weinbaum of City University New York had independently advanced similar hypotheses for a revised Starling principle. Roy Curry of the University of California at Davis proposed experiments that were then conducted by Roger Adamson and colleagues; the results were published in 2000 [9] and 2004 [10]. In the Abstract of the 2004 report, Adamson writes:

> "We hypothesized that ultrafiltrate crossing the luminal endothelial glycocalyx through infrequent discontinuities (gaps) in the tight junction (TJ) strand of endothelial clefts reduces albumin diffusive flux from tissue into the 'protected region' of the cleft on the luminal side of the TJ."
>
> "our three-dimensional hydro-dynamic model confirmed that fluid velocity was high at gaps in the TJ strand so that even at relatively low hydraulic pressures the albumin concentration on the tissue side of the glycocalyx was significantly lower than in the interstitium. The results conform to the hypothesis that colloid osmotic forces opposing filtration across non-fenestrated continuous capillaries are developed across the endothelial glycocalyx and that the oncotic pressure of interstitial fluid does not directly determine fluid balance across microvascular endothelium."

Figure 1.2 is a redrawing of the Cartoon Adamson used to illustrate the microanatomy of an interendothelial cleft, the paracellular pathway for filtration. I have added the more recently discovered extension of the endothelial surface layer beyond the membrane-bound glycocalyx molecules. Adamson refers to the subglycocalyx space as the **protected region**.

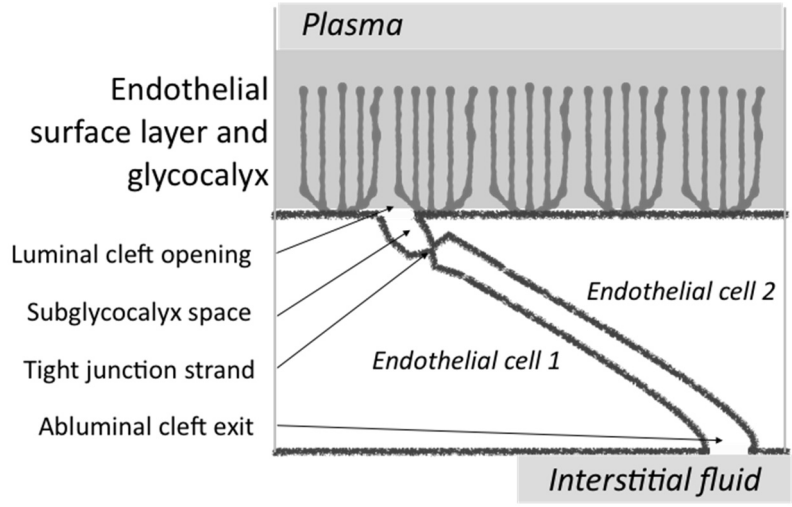

Figure 1.2

This confirmation of the Michel-Weinbaum hypothesis was a watershed moment in fluid physiology. The Michel-Weinbaum model was launched. An accompanying *Perspective* by J Rodney Levick welcomed the new paradigm and pointed out three important implications for fluid balance and oedema formation [11].

1. The Michel-Weinbaum model rendered untenable the argument that sustained venular absorption accounts for tissue fluid balance. To explain tissue fluid balance the focus must turn to lymphatic function.
2. The Michel-Weinbaum model helped to resolve the low lymph flow paradox (that net capillary filtration rate calculated from tissue-averaged Starling forces is much greater than the tissue lymph production).
3. The reduction of bulk interstitial colloid osmotic pressure π_i had been considered a major part of the 'safety margin' against oedema formation. This was now shown to be untrue at higher filtration rates.

Large pores

This work established the physical nature of small pores, but the roles and the significance of transcellular large-pore systems for transport of proteins from plasma to the interstitial fluid in systemic inflammation remains unclear. We discuss greater detail in Chapter 4. Protein flux can, of course, be increased by paracellular hyperfiltration, especially when the reflection co-efficient for the membrane to the protein is reduced. If they exist, their effective pore size is about 50 nm. An increase in large pore numbers is a concept to raise the general interstitial protein concentration, supporting the observed increase in J_v during inflammation.

The revised or steady-state Starling principle

We have already met the Kedem-Katchalsky Equation for volume flow J_v, adopted by biologists as the Starling equation even though Starling had died many years before it was formulated!

Equation (1): $J_v = S\, L_p\, (\Delta P - \sigma\, \Delta \Pi)$

In plain English it tells us that the volume flow of the aqueous solvent J_v across a semi-permeable membrane is proportional to the difference between the hydrostatic pressure difference ΔP and the effective colloid osmotic pressure gradient σ ΔΠ. Note that the actual osmotic pressure gradient ΔΠ may be greater, but has to be modified by Staverman's reflection coefficient σ to account for the fact that the colloid molecule has some ability to move through the membrane. The proportionality constant is traditionally called the hydraulic conductance L_p. It should be self-evident that the greater the surface area S for filtration or absorption of solvent, the greater J_v will be.

Plasma and interstitial fluid contain many solutes, and to fully describe fluid movement across the intervening capillary wall we ought to take them all into account. But, in most microvascular beds, only the macromolecular solutes are present at significantly different concentrations on either side of the membrane, and for the small solutes, σ has a value of 0.1 or less, so they can be ignored. Under these conditions, J_v can for our purposes be described approximately by the formula above, where the value for σ is an average value for the biological macromolecules rather than specifically for, say, albumin. We can see all the Starling forces at play if we express ΔP as capillary pressure (P_c) - interstitial pressure (P_i), and ΔΠ as plasma oncotic pressure (π_p) - interstitial oncotic pressure (π_i);

Equation (2) $$J_v / S = L_p ((P_c - P_i) - \sigma (\pi_p - \pi_i))$$

If σ is presumed close to 1, and both P_i and π_i are presumed close to 0, the classic experiments of Landis and Pappenheimer mentioned above lend credence to the simple Starling hypothesis of fluid exchange symmetry. Landis was able to demonstrate a linear relation between J_v and P_c for a population of frog mesentery vessels. Pappenheimer and Soto-Rivera confirmed Landis' results using isolated perfused cat and dog hind limbs, ingeniously estimating the mean tissue P_c from the arterial and venous pressures and vascular resistances and J_v from rate of change in weight of the limb. Sad to say, much current clinical practice is still claimed by "experts" to be justified by this original Starling principle.

When we take into account measured values of P_i and π_i, whether in humans or in animals, several problems arise:

- In real microcirculations both P_i and π_i change with changing J_v. As noted above, Starling himself had addressed this in his 1896 paper.
- The interstitial fluid immediately downstream of the semipermeable membrane (fluid on the abluminal side of the endothelial glycocalyx) has a markedly different composition to the general interstitial fluid average, particularly at higher volume flow rates.
- "Sum of Starling forces" evidence does not support the simple Starling hypothesis of fluid exchange symmetry.
- As first reported by Michel and Phillips in 1987, absorption is observed transiently but not in the steady state at capillary pressures below plasma colloid osmotic pressure [7].

Michel and Phillips conducted their classic experiments using perfused single capillaries in frog mesentery in two distinct ways. In their "transient state" set of experiments they raised or lowered P_c abruptly and measured the immediate change in J_v. Their findings were similar to those of many previous investigators. But in their "steady-state" set of experiments P_c was changed and then held at the new value for two minutes or more before the resultant J_v was measured. The steady-state results were markedly different. If P_c was greater than $\sigma \Delta\Pi$, raising or lowering P_c increased or reduced J_v. But when P_c was less than $\sigma \Delta\Pi$ there was no absorption (no negative J_v), contrary to the transient state results and the expectations of the traditional downstream absorption model.

We can now state with confidence that capillaries with a low blood pressure can absorb fluid transiently, but not in the steady-state. The lungs, which normally function at a low blood pressure, are an important example. There is an additional principle operating in steady-state Starling physiology, and this is the coupling of extravascular plasma protein concentration (which determines π_i) to capillary filtration rate J_v. Furthermore, P_i increases non-linearly with increases in volume that follow increases in J_v in some tissues, such as subcutaneous and lung.

The inverse dependence of pericapillary π_i on J_v restricts absorption to a transient phenomenon in most tissues

At steady-state the interstitial concentration of proteins c_i, and hence π_i, is not fixed, but is inversely related to the capillary filtration rate J_v. Their relationship can be represented by an **extravascular dilution curve**. At zero filtration protein concentration is the same on either side of the glycocalyx. As the transendothelial pressure difference rises, filtration of (low protein) solvent increases, and the sub-glycocalyx protein concentration (or the interstitial colloid osmotic pressure as shown here) decreases.

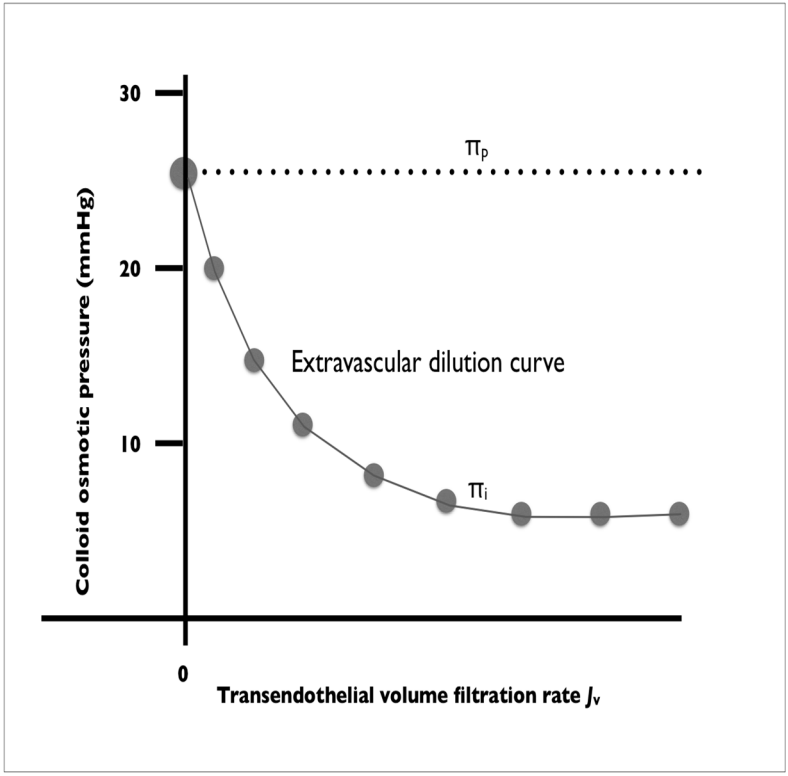

Figure 1.3