Preface

The aim of this book is to provide a systematic survey of the established pathophysiological principles along which patients on dialysis should be treated. For several reasons, these were insufficiently applied in many centers, leading to excessive and at least partly preventable cardiovascular damage. Since the first edition, more reports have appeared supporting the importance of volume control and the concepts are more widely accepted, be it not so quickly as Scribner hoped for in his foreword. There are at least two reasons for this delay. First, due to the extreme difficulty to compare treatment strategies according to the rules of 'evidence based medicine', randomized controlled studies are still lacking. Second, because of understandable preference of investigators to publish new findings instead of 'old truths', attention has shifted to a variety of 'risk factors'. Although some interesting aspects have emerged, none of these have yet opened effective ways of treatment, let alone contested the above-mentioned principles. We would like to acknowledge the support of Prof. Jörg Vienken and Dr. Peter Wabel in preparing the book.

Consequently, although we give due attention to these developments, the basic message of this second edition remains unchanged. For this second edition, we have joined forces, resulting in an updated and strongly edited version of this book.

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Foreword to the first edition „Cardiovascular aspects of dialysis treatment“

I have just re-read the last chapter of this excellent book, which may well become a kind of bible guiding us toward the optimal care of the chronic dialysis patient. Furthermore, writing this foreword provides me with the opportunity of putting into words something that I have wanted to articulate for a long time but never quite got it right. MDs who are destined to care for chronic dialysis patients should receive special training in the care of chronic disease. A Nephrology fellowship seldom if ever provides any training in this discipline. Furthermore, young physicians who choose Nephrology usually are not interested in the chronically ill. Yet, as clearly pointed out in this book, physicians caring for dialysis patients need the same dedication and the same skills that are required for those who are willing to care for other chronic illnesses. This volume describes in a clear concise manner the critical knowledge needed to achieve and maintain life-preserving normotension in the dialysis patient. However, application of this knowledge to successfully control blood pressure in the dialysis patient demands that sufficient time and careful attention be paid to each individual patient's continually changing fluid balance status. Dry weight, and the normal blood pressure that goes with it, is a constantly changing value that must be re-determined with each dialysis. Since it is easier to give a pill and pretend that one is treating hypertension in the dialysis patient, hypertension is so poorly controlled worldwide that an epidemic of its numerous complications is now present in the world's dialysis population. One hopes that, with this book now available, this epidemic will gradually be reversed in the decades ahead.

Belding H. Scribner († 2003)
Seattle/ Washington
January 2000

Preface to the first edition „Cardiovascular aspects of dialysis treatment“ by Evert J. Dorhout-Mees

Many excellent textbooks on chronic dialysis treatment exist, concise as well as comprehensive. Why than yet another book and even one that addresses only part of the problems encountered during this treatment?

Cardiovascular complications are not only responsible for more than half of our patients' mortality; they also represent the bulk of everyday problems in a dialysis unit. Yet the space allotted to them in the textbooks covers only 2-8 % of their total content. Moreover they are often not presented in such a way that the treating physician and nurse can easily translate this knowledge to the individual patient. This is one of the reasons why over-all results of dialysis treatment have not improved as they could have, despite increasingly more sophisticated machines, biocompatible membranes and formula's to calculate 'adequacy of dialysis.

The plan to write this book originated during the 8 years that I had the opportunity to work at the Ege University in Izmir, Turkey. For the second time in my career I engaged in the daily care of dialysis patients. It gradually became clear that systematic application of well-known pathophysiological principles could improve their condition even beyond my expectations. More importantly, it appeared that world literature was mainly concerned with evaluating risk factors and that efforts to improve prognosis were concentrated on urea removal. It is symptomatic that 'volume control', which will be the central issue of this book is not incorporated into the 'adequacy' concept.

Some experienced nephrologists have warned against the negligence of these principles, but their voices are like 'calling in the desert' of modern technological, commercialized medicine. Implication of these simple concepts has

been proven difficult in practice (fig I). Both patients and treating staff may become discouraged when instant success is not apparent. As a result, publications casting doubt on 'old truths' and suggesting new 'factors' prevail during the past years. This inevitably creates a bias by mass effect. It is the aim of this book to restore the balance.

Once on dialysis, the patient will not die from 'uremia', as used to be his fate before the advent of this treatment. Consequently, the dialysis doctor needs not be a nephrologist. He becomes a 'meta-nephrologist' and should specialize in circulatory and cardiac pathophysiology. However, the events leading to cardiac problems are quite different from these, which the cardiologist usually encounters.

While the purpose of this book is to give advise which is directly applicable, it is my conviction that understanding of the physiological background is indispensable. Thus the first chapter deals with some well-known physiologi-

Figure 1: *The problem that presents itself to all debutant metanephrologists. (Adapted from (Shaldon and Koch, 1985) (Reference see chapter 2)).*

cal principles, as experience shows that some misconceptions start here. Then the pathophysiological results of salt and volume retention leading to cardiac disease and death are described, as systematically as possible, in the following chapters. Yet it was necessary to discuss the most important but complicated relationships between volume and blood pressure and the effects of dialysis upon it on several occasions. All other factors, well known as well as speculative, will be mentioned only briefly. I do not intend to deny their potential importance, but modifying them has not (yet) been shown to feasible in practice. A selected list of references is given at the end of each chapter in alphabetical order. As the titles are most of the time self-explanatory, they will be specifically referred to in the text only occasionally.

In dialysis treatment, teamwork is indispensable. All the members of this team, which includes doctor, nurse, patient, often a dietician and family members should be familiar with the simple rules of 'salt and water'. While primarily intended to dialysis doctors, I sincerely hope that dialysis nurse's will also read this book. After all, they are the ones who do nearly all the work and carry (willing or not) a great responsibility.

1. Synopsis of the physiological regulation of extracellular fluid volume and blood pressure

1.1 Water, salt and body fluid volumes

Definitions and normal values. The body of a normal healthy adult consists for 50-60% of water. The greater part of this is *intracellular* fluid, the rest extracellular fluid. The *extracellular* fluid volume (ECV) consists of a blood compartment containing the *plasma volume* (PV) and interstitial fluid volume. Please note that cerebrospinal fluid is part of the extracellular fluid volume. The blood comprises erythrocytes (red blood cells), other circulating cells and the plasma. Strictly speaking, the plasma is part of the ECV and the blood cell water part of the intracellular fluid volume (ICV). The proportion of the blood taken up by erythrocytes is called hematocrit. Men have slightly higher total body water than women.

A healthy non-obese man of 70 kg, has approximately[1] an ICV of 26 L, an ECV of 16 L, a PV volume of 3L and an erythrocyte volume of 2 L: and as a consequence a hematocrit of 0.40 (40%), (Figure 1.1). If we subtract the plasma volume from the ECV, the resulting volume represents the *interstitial volume*, which is in this case 14 L. We should realize that if a patient is anemic (as often occurs in terminal renal failure) his 'normal' plasma volume at a hematocrit of 20% is 4 L and his ECV 18L.

[1] These values depend on the methods used. Some authors give lower values for ECV and higher for ICV

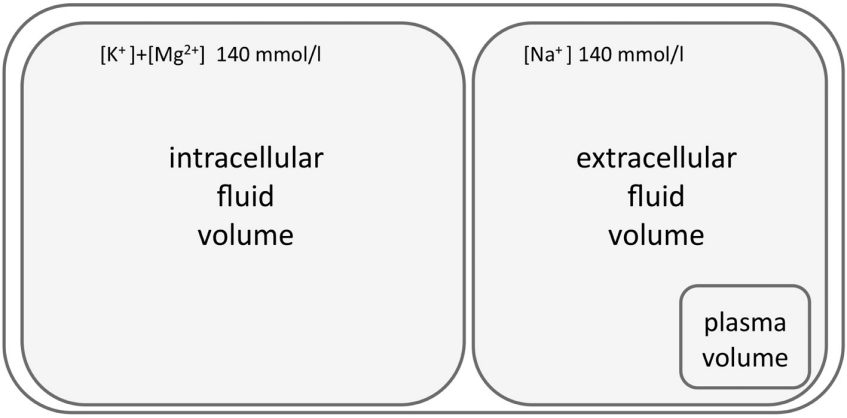

Figure 1.1: *Schematic representation of the body fluid compartments.*

	BW	TBW		ICV		ECV	
		L	%	L	%	L	%
Male	70	42	60	26	37	16	23
Female	65	32.5	50	18.5	28	14	22

Table 1.1: *Approximate percentages of body weight (BW) forming the intracellular fluid volume (ICV), the extracellular fluid volume (ECV), the latter being the interstitial fluid volume and the plasma volume. Values for the reference man / woman. (TBW: Total Body Water).*

Rules of distribution

> ***Rule 1:*** *A change in extracellular osmolality will immediately be followed by a similar change in intracellular osmolality.*

Cell membranes separate ICV from ECV and are freely permeable to water. How do these compartments keep their normal relationship? The answer is that they are impermeable to 'osmotic solutes'. *Despite a completely different composition of their solutes, the osmolality*[2] *of intra and extra cellular fluid is always the same.* Thus their *'water content'* (which is the reverse of osmolali-

[2] The term 'osmolarity' indicates the number of osmotic particles in a liter of the solution, while 'osmolality' is that number expressed per kg of water. Because blood serum and plasma contain +7% (lipo) proteins there is a 7% difference between these two measures.

ty) is also the same. This is the first 'rule of the body fluids'. Because water can pass through the membranes it will equally distribute over all compartments. Therefore, any change in *extracellular* osmolality will immediately be followed by a similar change in *intracellular* osmolality by shifts of water. Thus if pure water is added to the ECV, more than half of it will go to the ICV because this is larger. Conversely, water withdrawal will mainly cause decrease of the ICV. This is one of the reasons why water restriction is relatively ineffective in decreasing the ECV. Similarly, adding salt to the ECV will (apart from causing thirst) increase the ECV by attracting water from the cells. The consequences of adding isotonic saline, pure water and pure salt for the intracellular and extracellular fluid volumes are illustrated in figure 1.2.

Although a very large number of different molecules are present in the ECV (and plasma) the only quantitatively important solute is the Na^+ ion and its accompanying anions (Cl^- and HCO_3^-). As the sum of the latter (because of electric equilibrium) is always equal to Na, we can for all practical purposes estimate the osmolality of plasma by determine the sodium concentration. Indeed the normal osmolality 280 mosm/L, exactly twice the normal Na^+ concentration (140 mosm/L). The reason that all the other solutes (including K, Ca, glucose etc) do not seem to contribute is that 'effective osmotic activity' is less than the calculated number of particles.

> ***Rule 2:*** *In a normo-osmotic state, the extracellular fluid volume is defined by osmotically active body sodium*

Because the 'osmoregulation' is very strict, the extracellular volume is usually defined by total body Na^+: ECV (liter) = osmotically active total body sodium /140. This is the second rule of body fluids. Accordingly, when the ECV is expanded, large excesses in sodium are also present. Determination of Na^+ concentration in the blood does not give information on the Na^+ content of the body. In fact, a decreased sodium concentration is often accompanied by hypervolemia. If one tries to correct hyponatremia by adding a hypertonic NaCl solution, this will mainly serve to increase the ECV further, as shown in figure 1.2D. The challenging concept of osmotically-inactive sodium is further discussed in chapter 10.

> ***Rule 3:*** *Blood sodium concentration is a reliable estimate of cellular hydration*

In contrast, blood sodium concentration is a reliable estimate of cellular hydration. When the sodium concentration changes, body weight changes are

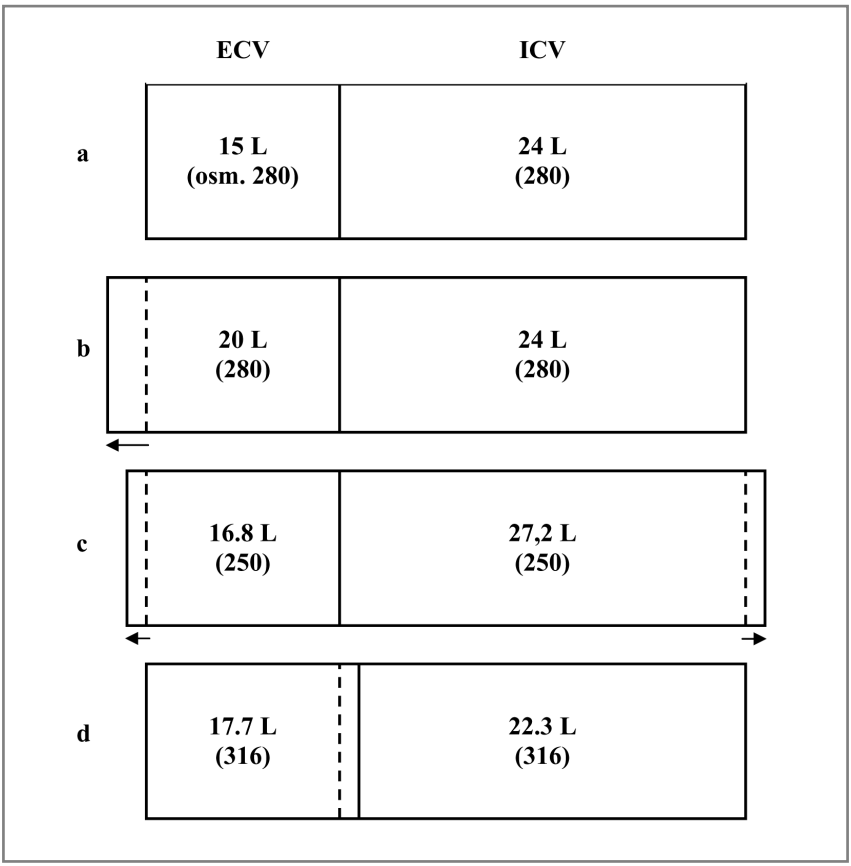

Figure 1.2: *Changes in ECV and ICV in a hypothetical subject. Osmolality in brackets. (a) normal condition; (b) addition of 5l isotonic saline (1400 mmol $Na^+ + Cl^-$); (c) addition of 5 l water; (d) addition of 1400 m mol ($Na^+ + Cl^-$) without water.*

no longer reliable estimates of ECV changes, because they are accompanied by a relatively large shift of water to or from the cells. For example, a 10% decrease in Na^+ concentration in a 'standard person' means an excess of 2.6L (Kg) of intracellular water.

Although we know the amount of (osmotically active) particles in the intracellular fluid (which is the same as in the ECV) its composition is completely

different (the main cations being K^+ and Mg^{2+}, see figure 1.1). Intracellular ion concentrations cannot be measured easily in clinical practice. However, we may safely assume that their total amount does not change acutely.

How disturbances in urea, glucose and alcohols affect fluid distribution

Urea is a small molecule that, like water, easily crosses the cell membranes. Thus the urea concentration in the cells follows urea concentration in the blood. This means that urea is 'not osmotically active'. In uremic patients osmolality as determined by the freezing-point method will be elevated and should be corrected by subtracting the urea level (60 mg urea = 1mmol) from the measured value to know 'effective' osmolality. However, when urea level is rapidly lowered during dialysis, urea diffusion out of the cells lags behind and thereby becomes temporary osmotically active, causing a disequilibrium (See Chapter 6).

Glucose is osmotically active and when present in the extracellular fluid volume will attract fluid from the cells. It can thereby 'dilute' the extracellular fluid . For instance, in uncontrolled diabetes, a glucose level of 35 mmol/L (30 mmol above normal) will lead to a water flux from the cells to increase the ECV by 10% and decrease Na^+ level to the same extent. After normalization the reverse process takes place.

Intoxications with small molecular substances like *ethanol, methanol and ethylenglycol* (anti-freeze) will cause measurable increases in blood osmolality and their concentration in the blood in practice can even be estimated by the osmolar gap (measured osmolality minus calculated osmolality). However, ethanol and methanol, like urea, cross the cell membranes and is not osmotically active. In fact ethanol increases water excretion by inhibiting anti-diuretic hormone secretion.

How are volumes measured? Volumes can be determined by injecting a biologically inactive substance, which is known to be distributed only in that compartment and can be measured accurately (usually a radioactive isotope with a short half-life). Dividing the injected amount by the concentration reached after equilibration gives the *distribution volume*. Such *dilution methods* are rather impracticable. A major difficulty is also to establish the normal value for a certain individual. bioimpedance spectroscopy has proven its ability to assess ECV, ICV and TBW as precise as the dilution methods; this tech-

nique is further discussed in chapter 2. Alternatively, plethysmographic methods can be used. Assessment of volume status is further discussed in chapter 2.

1.2 Regulating mechanisms of osmolality and ECV in normal man

Osmoregulation. Keeping the extracellular osmolality (closely related to Na^+ concentration) constant indirectly controls the intracellular volume, which is of paramount importance for cell function. This is accomplished by two separate mechanisms:

The *first* is the ability of the *kidney* to produce hypertonic urine (4 x plasma osmolality) or hypotonic urine (1/4 of plasma osmolality) when hyper-or hypo-osmolality occurs. Osmoregulation works with amazing precision and rapidity. It is so efficient that it is virtually impossible to cause 'water intoxication' by drinking in a person with normal kidneys. If a normal person drinks 1 L of water (less than 0.5% of TBW) the kidney excretes this same water load in less than a few hours. Antidiuretic hormone (ADH, also called vasopressin) is the effector of this regulation and is a polypeptide secreted by the posterior hypophysis, which forces the kidney to produce, concentrated urine. Mechanistically, it increases the number of aquaporin channels (AQP2) in the collecting duct, leading to more water reabsorption. The complex countercurrent mechanism supports this reabsorption of water in states of water depletion by creating an environment in the renal medulla that is highly hyperosmotic, which facilitates water reabsorption via the mentioned channels. This leads to the production of hyperosmolar urine that can contain 1200 mosmol/L. Typically, urine is iso-osmolar when entering the early connecting tubules. In states of water excess, further sodium reabsorption will make the urine hypo-osmolar. In the absence of ADH, no water will be reabsorbed via the aquaporins and the urine will also be hypo-osmolar, in extreme states leading to urine osmolality of 50-100 mosmols/L.

The *second* mechanism is *thirst*, which protects against hyperosmolality. This is such a strong urge that *hyperosmolality almost never occurs unless the patient is unconscious* or prohibited to drink. The opposite-dislike of drinking as a protection against water intoxication-does not exist, because the kidney, as we have seen, under normal conditions provides enough protection to water intoxication. Also, if not under social obligation to drink tea, beer etc. people drink just enough to produce a moderately concentrated urine (particularly in summer since perspiration is hypotonic) because ADH secretion threshold is

below the thirst threshold. In other words, if a minor increase in plasma osmolality occurs, this leads to ADH release and increased water retention. A further increase in osmolality will lead to thirst and increased water intake.

With declining renal function, the ability to dilute the urine (excrete a water load) decreases in parallel and becomes abolished when end stage failure occurs. Thus the advice to renal patients, sometimes erroneously given, to drink a large amount of water 'to protect the kidney' or 'to wash away toxic metabolites' lacks a pathophysiological basis and may be harmful. The origin of this widespread belief is that with normal kidneys the clearance of urea is dependent on urine flow, but only at flow rates below 1 ml/min (which is entirely normal; 1.4 L/day). This is due to urea back diffusion in the distal nephron from the concentrated filtrate. In patients with decreased renal function this phenomenon does not occur because concentrating power is lost and such low flow rates cannot be achieved any more. As a consequence, their obligatory urine volume to excrete the urea is higher, as is minimal fluid intake. On the other hand their diluting capacity becomes also impaired, and consequently the maximal water intake that can be excreted is diminished. Thus high water consumption caused by inappropriate advice may lead to hyponatremia.

In general, *solute excretion* either by the normal or the diseased kidney is *independent of water excretion,* while adequate water intake is safeguarded by the thirst feeling: *The body (and in particular the kidney) knows better than the doctor*. We will come back to other misconceptions in discussions on overhydration.

Regulation of extracellular fluid volume. The ECV completely depends on salt (NaCl) balance. As 'natural' food contains little salt, the mammalian kidney is conditioned to preserve it. In normal conditions the volume of the EC fluid is determined by the total amount of sodium in the body, because 'water follows sodium' (see above: the second rule). When the volume is to low, the kidney can do no more than prevent further loss. There is not such a thing as 'salt craving'.

Because a regular Western diet contains more salt than is needed to replace the minute losses by sweat and stools, modern men are constantly threatened by (extracellular) overhydration. The kidneys are thus constantly excreting the excess salt ingested with the food.

The ability of the kidney to excrete salt is limited. Although the upper limit has never been systematically investigated, some of the evidence indicates that

GFR ml/min	Filtered Na^+ mmol/min	Filtered Na^+ mol/day	Max. Excreted NaCl g/day	Max. Excreted Na^+ g/day
120	16.8	24.2	49.1	27.7
90	12.6	18.1	36.8	20.8
60	8.4	12.1	24.5	13.8
45	6.3	9.1	18.4	10.4
30	4.2	6.0	12.3	6.9
15	2.1	3.0	6.1	3.5
10	1.4	2.0	4.1	2.3

Table 1.2: *Illustration of the issue that if one assumes a maximum possible fractional sodium excretion of 5%, a decrease in GFR is accompanied by the retention of sodium, when GFR falls to 15-30% of normal, if sodium intake is not limited.*

salt will be retained if intake exceeds amount to be excreted is more than 5% of the 'filtered load' (see below, about 30 grams). While this still seems consireable, it should be realized that, when GFR of a patient drops below 10 ml/min, 5% of it represents more than the salt content of a normal diet (table 1.2).

The way in which the body regulates ECV is one of the unresolved riddles of physiology. A 'volume center' has not been identified. However it is clear that the mechanisms by which the kidney is informed (afferent pathway) are mediated by changes in *blood volume*, which normally changes in proportion to ECV (Chapter 2). The *efferent pathway* is sodium excretion by the kidney. An important mechanism is *'pressure natriuresis'* (see below). In the isolated kidney, salt excretion is directly dependent on blood pressure. In the intact organism, this phenomenon is often not directly apparent, because many other mechanisms that regulate in an integrated way the vitally important volume homeostasis. Among these the *renin-angiotensin-aldosterone system* (RAAS) is the most important one. This is activated by hypovolemia and is inhibited by hypervolemia.[3]

Angiotensin II has a powerful vasoconstrictive and blood pressure elevating effect and at the same time stimulates sodium retention by the kidney. Aldos-

[3] The antidiuretic hormone (ADH) normally serves osmoregulation and has no function in volume regulation under normal conditions. With extreme hypovolemia it may be activated, but the volume threshold is much higher than the osmotic threshold. This volume stimulus is supposedly mediated by angiotensin II.

terone also forces the kidney to reabsorb sodium and thus increases ECV and blood volume, which raises blood pressure, provided that the function of the diseased kidney in this regard is still intact. According to Guyton, an upward shift of the setpoint for pressure natriuresis is the basic disturbance causing hypertension (Guyton, Coleman et al. 1972). Despite the fact that abnormalities of the RAAS play an important role in different forms of hypertension, phylogenetically this system seems to be primarily related to salt-and volume depletion. This is important because in dialysis patients normal blood pressure can be achieved in the large majority by manipulating their volume state (see next chapters). Indeed normotension can be associated with a broad range of renin-angiotensin levels. However, hypervolemia almost invariably leads to hypertension, even in the absence of renin. It should be noted, however, that in diseased kidneys the relationship between pressure and renin release is disturbed, and renin is inappropriately high for any level of ECV.

The *sensitivity* of volume regulation (read: salt regulation) is much less than that of osmoregulation. Roughly speaking an increase of 1 to 1.5 L (8%) is needed to keep the required balance, as shown by the fact that a normal person looses 1 to 1.5 kg when put on a salt free diet. Volume adjustments are much slower than osmotic adjustments and generally take more than 24 hours. It is not clear whether the ECV under conditions of the low sodium intake or the higher sodium intake should be considered 'normal' and how the 'set point' is determined.

Taken together, body fluid volumes are controlled by a perfect interaction of osmo-and volume- regulation. Because the former is more rapid and sensitive, it takes priority in conditions of 'conflict of interest' as stated already by John Peters more than 50 years ago (Peters 1948). The seeming paradox: 'Sodium concentration (osmolality) is determined by water balance and volume regulation by salt balance', has extremely important clinical consequences. We will come back on this issue in the following chapters.

1.3 The relationship between extracellular fluid volume, blood volume and blood pressure

Terminology: Because blood volume (BV) and extracellular volume (ECV) are closely related, the terms fluid retention, overfilling and hypervolemia are not sharply defined and are often used interchangeably. We will use 'fluid retention' and overhydration for an increase in ECV and 'hypervolemia' for an increase in BV, while avoiding the word 'overfilling'.

Relation between ECV and BV: As the blood plasma is a part of the extracellular volume, plasma volume and therefore blood-volume (BV) change concomitantly with the ECV. For every liter ECV excess, BV would increase 180 ml (Figure 1.3). Because the 'Starling forces' which govern the partition between BV and interstitial volume may change, this relationship is not the same in all circumstances. For instance, in patients with low plasma colloid osmotic pressure (like in patient with the nephrotic syndrome) BV hardly increases despite the large increase in interstitial volume.

A very important fact about the ECV-BV relationship is that it is not linear. This is also illustrated in Figure 1.3, which shows BV and ECV measured in patients with renal failure at different levels of fluid retention. BV increases only slowly when ECV expansion exceeds 5 L, which is the threshold for edema to appear. It is evident that the volume of blood within the vascular system cannot increase indefinitely, while there is no apparent limit to expansion of the ECV.

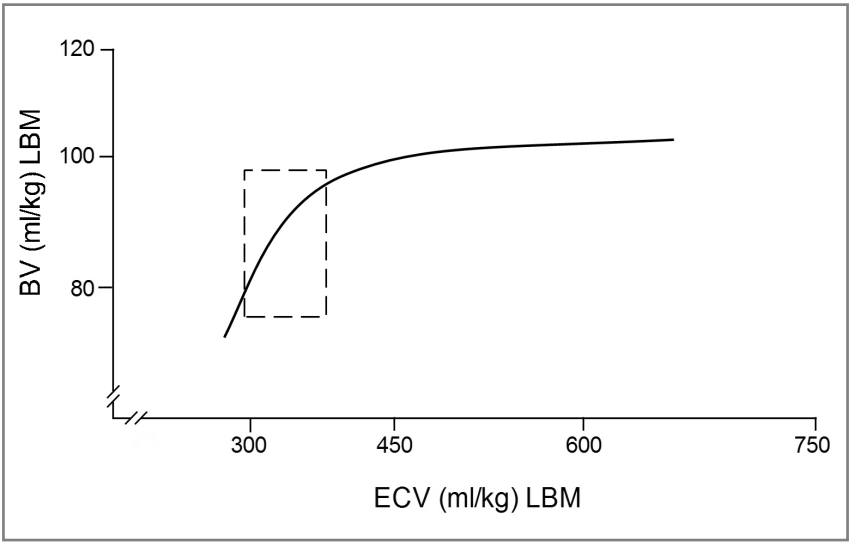

Figure 1.3: *Relationship between extracellular volume and blood volume in patients with chronic renal failure. (Adapted from (Koomans, Braam et al. 1986)).*