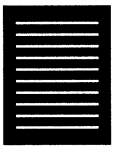

IN 1914, JOHN J. ABEL, OF THE Pharmacological Laboratory of The Johns Hopkins University, demonstrated the feasibility of removing large quantities of plasma from dogs by a process he called "plasmapheresis" (apheresis from the Greek *apairesos* or Latin *aphairesis*, meaning "to take away by force"). Subsequent use of plasmapheresis as a therapeutic modality was predicated on assumptions that a disease state is causally related to a substance found in the plasma, and that the pathogenic substance can be removed via the plasma efficiently enough to permit resolution of the illness. Therapeutic plasma exchange (TPE), as defined by the American Society for Apheresis (ASFA) *Journal of Clinical Apheresis* (JCA) Special Issue Writing Committee, is the specific procedure where blood is passed through a medical device that separates out the plasma component and replaces it with a solution (albumin or plasma). The earliest application of TPE in clinical medicine was the treatment of hyperviscosity syndrome in Waldenström macroglobulinemia during the 1950s. The offending immunoglobulin in this disease, IgM, is known to be predominantly intravascular and therefore can be readily removed from the plasma. Subsequent development of the automated blood processor broadened the potential applicability of therapeutic apheresis to other disease states that fit the fundamental assumptions stated above, as well as to other procedures, including therapeutic removal of cellular elements from the blood. In addition, it brought into focus the need to assess more clearly the dynamics of changes in blood composition brought about by these therapies.

Modeling the Effects of Plasma Exchange

Normally, TPE removes 40 to 60 mL of plasma/kg over 2 to 3 hours, which is typically replaced with albumin or plasma. The replacement of removed plasma solutes is dependent on several factors, and a number of mathematical models have been developed over the years to predict these hemodynamic changes. Synthesis of a plasma protein can be assumed to proceed at a relatively consistent synthetic rate (S), which is equal to the rate of the protein's degradation and/or excretion from the plasma (the fractional catabolic rate, or {CR}). Because S and {CR} preferentially affect the intravascular mass of the protein and are balanced, the intravascular mass is in a steady state, in equilibrium with the proportion of the protein that resides in the extravascular compartment and thus can be considered as an isolated space for the purpose of a "one-compartment" model for TPE. Therefore, the effectiveness of TPE depends on the volume of plasma removed relative to the patient's total plasma volume, the distribution between the intravascular and extravascular compartments of the pathogenic substance to be removed with the plasma, the degree of binding to albumin or red cells, and the rapidity with which that substance equilibrates between compartments.

The Isolated Intravascular Compartment: The "One-Compartment" Model

Mathematical models used to predict the efficiency of TPE assume the intravascular plasma volume is a closed compartment and that the intravascular mass of the substance to be removed is *isolated* from the extravascular compartment of the body. In this situation, removal of a substance by TPE proceeds rapidly and efficiently so as not to be affected by the transfer of the substance between the intravascular and extravascular compartments. However, it is known this is not always true in vivo, as the fluid balance in living beings is a constantly changing dynamic process. The isolated compartment model also assumes that the steady state between endogenous synthesis and catabolism is not effectively altered during the TPE procedure. In clinical practice, these assump-

tions apply fairly well to immune complexes (whether endogenous or iatrogenically administered) in addition to large intravascular molecules such as low-density lipoprotein (LDL) or fibrinogen. The changing hemodynamic balance that occurs with in-vivo fluid shifts means that the extent to which TPE depletes a substance from the whole body is a function not only of the substance's intravascular mass but also of its distribution between intravascular and extravascular compartments. Proteins located predominantly in the *intra*vascular compartment (IgM) are more completely removed than proteins with an extravascular component of distribution (IgG), in a predictable fashion (Table 3-1).

Protein Transfer between Intravascular and Extravascular Compartments

Transfer of the protein from the intravascular compartment to the extravascular compartment proceeds mainly by diffusion down a concentration gradient in accordance with Fick's Law, in addition to convective transport across biologic membranes (Fig 3-1). The predominant transfer of extravascular protein back to the intravascular compartment proceeds via the lymphatic system. The major barrier to the movement of large molecules from the intravascular to the extravascular compartment is the vascular capillary wall, with the permeability of large molecules being a function of both molecular weight and the Stokes-Einstein radius. Small molecules and solutes are transferred in equilibrium between the two compartments largely via diffusion, with the other two mechanisms playing a lesser role. Although they are unable to pass across the capillary endothelium, larger molecules (>3 nm) approach their steady-state lymphatic concentrations faster than smaller ones because of "gel column" exclusion effects in the interstitial space.

The transfer of proteins such as IgG from the intravascular compartment to the extravascular compartment can be quantified as the fraction of the intravascular compartment transferred per unit of time, and this can be expressed as a clearance (the volume of plasma completely stripped of the substance of interest per unit of time, quantified in mL/hour). Such clearances, on the order of 5 to 20 mL per hour, are slow compared to plasma flow rates of 15 to 40 mL/minute typically achieved during TPE procedures. Hence, the decrement in plasma IgG achieved by TPE can be predicted by the one-compartment model, which considers only the physical removal of plasma and its solubilized immunoglobulins from the intravascular compartment during the TPE procedure.

Patterns of Protein Catabolism

The plasma survival time, {CR}, and response of {CR} to changes in the concentration of serum proteins will all factor into the effectiveness with which a TPE will deplete the body of these soluble substances. Serum immunoglobulins are catabolized in a compartment that is in rapid equilibrium with the intravascular mass of the protein and at a rate that depends, in part, on the metabolic rate and thyroid function.

The IgG Pattern of Catabolism

The catabolic rates of IgG and albumin are directly proportional to their serum concentrations. IgG molecules have a longer survival and lower {CR} than most other serum proteins. The normal mean survival half-time of IgG is about 21 days (7.5-9 days for IgG_3), and about 6% of the intravascular pool is catabolized daily. In patients with elevations of IgG from inflammation, liver disease, and multiple myeloma, the half-time of survival of IgG may decrease by half, and the {CR} may increase threefold.

Table 3-1. Metabolic Characteristics of Select Plasma Proteins*

Protein	mg/mL†	Molecular Weight (kDa)	% Intravascular	% FCR‡	Δ FCR with ↓Concentration	% TER§
IgG	12.1	150	45	6.7	↓	3
IgA	2.6	(160)n	42	25	constant	
IgM	0.9	950	76	18	constant	1-2
IgD	0.02	175	75	37	↑	
IgE	0.0001	190	41	94	↑	
Albumin	42 ± 3.5	66	40	10	↓	5-6
Fibrinogen	2-4	340	80	25	constant	2-3
C3	1.5	240	53	56		
α_2-macroglobulin	2.6	820	100	8.2	constant	

*Adapted from Chopek M, McCullough J. Protein and biochemical changes during plasma exchange. In: Berkman EM, Umlas J, eds. Therapeutic hemapheresis. Washington, DC: AABB, 1980:13-52.

†Concentration in normal serum or plasma.

‡Fractional catabolic rate: as percentage of intravascular mass per day.

§Transcapillary escape rate: total transfer of protein from intravascular compartment to extravascular compartment as percentage of intravascular mass per hour.

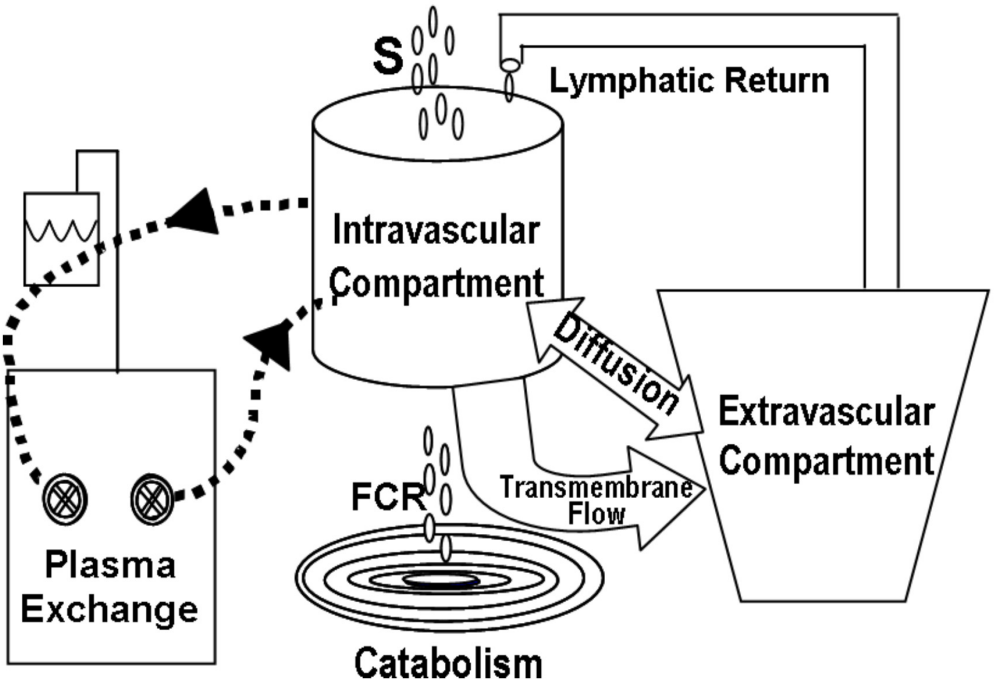

Figure 3-1. A model for the interaction between intravascular and extravascular compartments and the effects of plasma exchange.

A soluble substance enters the body through the intravascular compartment at synthetic rate S and is catabolically removed from the body at its fractional catabolic rate (FCR). Movement from the intravascular compartment to the extravascular compartment takes place primarily by diffusion, whereas a smaller component of transmembrane flow occurs by other mechanisms. Soluble substances return from the extravascular compartment back to the intravascular compartment mainly through the lymphatic system, although a small component of back-diffusion takes place.

Plasma exchange directly removes soluble substances only from the intravascular compartment. S, FCR, and intracompartment movement of solutes are balanced and in a steady state, and they proceed much more slowly than the removal of plasma from the intravascular compartment by plasma exchange. Therefore, for the purpose of therapeutic plasma exchange, the intravascular compartment is considered to be an isolated system that can be depleted of its soluble contents by the exchange of plasma for a replacement fluid.

Conversely, the {CR} decreases in patients with primary IgG deficiency caused by chronic lymphocytic leukemia, hypogammaglobulinemia, or other lymphoproliferative disorders. Patients with secondary IgG deficiency (eg, multiple myeloma with decreased normal IgG, renal homograft, nephrotic syndrome) may demonstrate an increased {CR} and decreased serum half-life of their IgG. These effects on IgG catabolism are related to the serum concentration of IgG and not to the concentrations of other proteins or immunoglobulins. For example, albumin infusion does not affect the catabolism of IgG.