CURRENT PLASMAPHERESIS PRACTICE IN THE UNITED STATES

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It has been 30 years since plasmapheresis was first demonstrated at Laboratories Grifols as a practical system for increased plasma procurement⁵. Shortly afterwards, Pyle in our laboratory at Protein Foundation and later SMOLENS and STOKES¹³ published the first reports on plasmapheresis as part of a continuous flow mechanical system in which the donor remained attached to the centrifuge equipment, thus precluding bacteriologic and mismatch errors. During the subsequent three decades there has been a rapid growth in the application of plasmapheresis techniques. They have proved themselves to be the only systems able to produce adequate plasma to supply the world's needs at minimum cost, maximal efficiency and in a fresh enough state to protect the labile coagulation components.

I have been asked to address the distinctive aspects of plasmapheresis as practiced in the USA and to compare it to the pattern of most European countries and the rest of the world. In part, this desire to focus on American plasma production may relate to the fact that between 70 and 90% of the world's supply comes from the USA, but part of it also may reflect a disquietude and concern on the part of numerous critics outside of our country who instinctively are suspicious of the three characteristics of our American system: 1. it is largely commercially controlled rather than operated by the government or an eleemosynary institution; 2. it remunerates its donors rather than relying on volunteerism alone; this is of course in sharp contrast to our American program for whole blood which is entirely a voluntary non-remunerated system; 3. it permits the drawing of much larger volumes of plasma than is practiced in most other countries. Let us, therefore, look critically at these issues in an unbiased and pragmatic manner and see if the facts support the fear that the health of the donors is impaired or their human rights are exploited.

Key-words: Albumin synthesis; Donor profiles; Hyperimmune globulin; Plasmapheresis; Protein balance.

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An estimated 5.4 million l of source plasma are collected by plasmapheresis centers each year. Of this amount, 4.5 million l come from USA commercial sources. It is drawn from approximately 300,000 donors who average 30 plasmaphereses per year. In the beginning of the plasmapheresis industry, some 20-30 years ago, many of the commercial donors were drifters, alcoholics, prisoners and economically deprived individuals. Minimal control was exerted over their pre-existing health or nutritional status. This occurred both within the USA and the neighboring Caribbean islands where intensive plasmapheresis threatened further to aggravate pre-existing malnutrition of the underdeveloped populations. This excessive entrepreneurism appears to have been brought under firm control, however, within a short span of a few years through the combined efforts of the regulatory agencies in Washington (Food and Drug Administration: FDA) and an equally rigid and self-imposed set of standards by the industry itself. A careful contemporary search reveals no evidence of residual abuse. Rigid standards of good health, good weight, normal nutrition and freedom from disease now must be met before acceptance of individuals into the role of compensated donors suitable for plasmapheresis. As a result, the source of the donors, although still derived from lower economic groups, nonetheless represents a relative cross-section of standard American life and includes housewives, students and stable members of the community. How frequently do they donate? A study by REASOR¹¹ (tab. 1) of 25 representative plasmapheresis centers around the USA showed that during a 16-week observation period 90% of the donors appeared only once a week. Less than 10% appeared twice weekly as permitted by regulations. The reason most of the donors did not appear twice weekly as permitted appears unrelated either to their state of health, changes in laboratory findings before the donation or failure to conform to laboratory standards. When questioned about their absence, the replies represented a cross-section of sociologic factors such as hours missed from work, duration and difficulty of travel to the center, discomfort from being stuck by a needle, etc.

What about the question of compensation? Would the donors come at all if not remunerated? Obviously, some are motivated by altruism, but this is a small group. A group of compensated donors (tab. 2) was asked by REASOR¹¹ if they intended to enter a plasmapheresis program again. Eighty-two replied 'yes' under the following circumstances: about a third would do so if they felt they needed extra money; slightly more than 10% were apparently altruistically motivated; another 25% said they would do so if it could

	no. of people visiting	%
1-15 times	5,722	91.3
16-32 times	549	8.7
total	6,271	100.0

Tab. 1 - Number and % distribution of donors visiting a plasmapheresis center during a 16-week period.

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- 30: if I need the money/I need the money
 - 11: because it helps others
 - 10: it depends on job/time available
 - 10: if open later, or more convenient location
 - 7: plan to continue/begin again. When football season is over, school starts, etc.
 - 6: all other reasons
 - 8: no reason
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Tab. 2 · Intend to donate plasma again (82 total).

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- 4: damage to veins/veins too small/scars
 - 3: not worth the trouble/do not need the money
 - 3: moving/no convenient center, etc.
 - 2: not good for you/health reasons
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Tab. 3 · Do not intend to donate plasma again (12 total).

be fitted into their regular work schedule or if the time and location of the center were more convenient; and a small number indicated they would become active donors again after the football season, or school schedule permitted more time off for such activities. Twelve donors from the same group indicated they would not enter a plasmapheresis program again. The reasons for this (tab. 3) were damage to veins on the part of 4, too much trouble on the part of 3, moving to a new residence on the part of 3, and worry over health implications on the part of 2.

Let us turn then to the important consideration of whether the American standards for plasmapheresis permit the loss of sufficient volume of plasma and its content of albumin, fibrinogen, γ -globulin and coagulation components to constitute an immediate or long-range hazard to the donor. For the past decade, this has been debated heatedly. Unfortunately, the discussions have been fraught more with socio-political polemics than scientific data or facts. Before we examine new data of MCAULEY¹⁰ which I would like to present, or the previously accumulated data of others, it would be worthwhile to review the basic physiology and chemistry of plasma protein production.

An important and often overlooked fact is that each plasma protein has its own homeostatic level and its own individual stimulus for production, circulation, destruction and resynthesis again. The overall protein anabolism and catabolism of a healthy human is summarized schematically on scheme 1. The total body breakdown of a normal adult is 200 g of protein/day. This bulk of structural and functional body components is degraded to amino acids and then resynthesized back into new protein again. An additional 50 or 60 g is lost to the body each day through excretion, urea formation and CO₂ loss. This is of course balanced by the intake of a comparable amount of protein in the diet so that the system as a whole is in balance with neither loss nor gain. It should be noted that even the increased protein re-

quirement of infancy and adolescence has minor effect on this large daily protein turnover. During the maximal growth period of infancy, the added requirement is only 0.2 g/kg or less than 10% of the overall turnover of 3 g/kg/day.

On tab. 4 we can see from data of BISTRAN¹ the division of the total body protein into its several component parts. Fifty percent is in the form of structural proteins and only 1 or 2% in the form of secretory protein which is lost through the salivary glands, gastrointestinal tract and similar secretions. However, the percentage of total body turnover in reference to the 200 g noted on the previous table, comes primarily from the secretory proteins, rapidly growing cells such as bone marrow and skin and the non-structural proteins such as albumin.

If now one examines the effect of plasmapheresis at the maximally permitted 4 U of plasma per week, or 1,200 total, it can be seen (tab. 5) that there is a 15% increase in the total protein mass which is turned over each week.

Let us next look at what happens to albumin alone. In normal adults this protein turns over at a rate of 3-5%/day¹². The factors which regulate its concentration in the plasma are only partly known; but they appear to be distinct. For one thing, albumin has no specific consumptive role in which the body utilizes it for a unique process that results in its own destruction, as occurs in the case of fibrinogen when it converts to fibrin in the clotting system or γ -globulin when it combines with a specific antigen in an immunologic reaction. Next, albumin has a precise and relatively narrow range of normality. Excesses of albumin concentration are never seen. The administration of a foreign oncotic substance like dextran, for example, immediately shuts off albumin synthesis by a delicately controlled set of osmolar receptors in the hepatic cells. Thirdly, no initial stimulus is needed in a neonate to get albumin production started. This again is in contrast to other plasma proteins; γ -globulin, for example, would not exist at all if an infant were not exposed to antigenic stimuli. Another important characteristic of albumin is the ease with which its rate of production can be markedly increased above the estimated normal range of 17 to 23 g/day if the oral intake of protein or amino acids is adequate. Evidence shows that only about 20% of the hepatocytes are actually involved in albumin production at any given time, thus

Scheme 1 - Overall protein anabolism and catabolism of a healthy human.

classification	% total body protein	% total body protein turnover
structural protein	50	14
protein associated with proliferating cells	12	25
secretory proteins	1.2	44
non-structural proteins from non-proliferating cells and body fluids	36	17

Tab. 4 - Percentage of total body protein and turnover for different types of tissue. [Adapted from: WANNEMACHER R. W. Jr.: Protein metabolism (applied biochemistry). In: GHADIMI H. (Ed.): Total parenteral nutrition: premises and promises. John Wiley and Sons, New York, 1975; p. 85].

	bed rest	standard activity	plasmapheresis
daily	100 g 1.5 g/kg/day	200 g 3 g/kg/day	236 g 3.54 g/kg/day
weekly	0.7 kg 11.5 g/kg	1.4 kg 21.5 g/kg	1.47 kg 22.08 g/kg

Tab. 5 - Protein synthesis (66.66 kg male).

reflecting at least a potential 5-fold increase on demand¹⁴. Thus, a theoretical 10- to 20-fold excess production capacity exists to balance the protein loss from two plasmaphereses per week, about half of which would be in the form of albumin.

How then can one explain the hypoalbuminemia and hypoproteinemia which has been reported after prolonged and intensive plasmapheresis? Apparently, it is on the basis of inadequate protein intake. An old study with which I am sure you are familiar shows that twice-weekly plasmapheresis can become excessive if the donors are on a restricted protein intake. This study, conducted in a Louisiana prison, showed that after one year of twice-weekly plasmapheresis of 1,500 ml in prisoners on a borderline diet in a range of 50 g of protein daily, hypoalbuminemia developed in a number of the donors. A separate study by KLIMAN et al.⁹ of persons on *ad libitum* protein intake showed that hypoproteinemia did not occur until 5 l of blood per week were withdrawn, and in this study it was principally the γ -globulin which was decreased. A study by CRISPEN³ showed that hyperimmunized housewives participating in a Rho-gam program showed no evidence of hypoalbuminemia after intensive plasmapheresis of many years duration. An equally intensive plasmapheresis study reported many years ago by GREENWALT⁵ with Rh-immunized donors showed that one donor who donated 918 U of plasmapheresis in an 8-year period and an additional 4 U/week for a subsequent 3-year period showed no fluctuation of serum protein concentration out of the range of 6.3-6.7 from the beginning to end of the program.

A study not yet published, by MCAULEY et al.¹⁰, evaluates intensive plasmapheresis on 96 long-term donors. I have been given permission to repro-

duce their data. The length of individual donor participation ranged from 2 to 7 years. Nine percent had been regular donors for greater than 6 years and 50% for more than 4 years. All of the serum proteins were evaluated and then compared to a comparable group of 94 one-time-only donors in the same plasmapheresis centers. The latter controls were felt to be a better frame of reference for comparison than healthy laboratory personnel, who are commonly used and who do not truly reflect the same ethnic and sociologic group. On tab. 6 it can be seen that albumin levels were 4.19 ± 0.32 in the long-term donors and 4.27 ± 0.33 in the one-time-only donors. Although this represents a decrease in albumin, it is still within normal limits. Indeed, the variations in weight, hematocrit, total solids as measured by refractometer and total serum protein as measured by the biuret determination were all within 1 standard deviation of the mean. On tab. 7 one can see the variation in globulins in the same group. Here again, no valid differences are evident in α_1 , α_2 , β -globulin or γ -globulins. Admittedly, these donors did not all donate to the maximal extent permissible, but they averaged 40 donations per year over the length of the study, which is about 25% above the plasmapheresis average for the country as a whole. The most intensively plasmapheresed subjects ever studied were those reported by DAWSON et al.⁴ and presented as a preliminary report in 1979. A final publication is not yet out, but I am told no significant changes were seen.

variable	mean $\pm$ standard deviation	
	one-time-only no. = 94	long-term no. = 96
age	24.39 $\pm$ 8.30	26.62 $\pm$ 8.48
weight	166.25 $\pm$ 28.60	164.63 $\pm$ 27.38
hematocrit	44.96 $\pm$ 2.80	44.94 $\pm$ 2.73
refractometer (T/S meter) reading of total protein in g/dl	7.75 $\pm$ 0.50	7.87 $\pm$ 0.48
total serum protein	7.28 $\pm$ 0.44	7.21 $\pm$ 0.40
albumin	4.27 $\pm$ 0.33	4.19 $\pm$ 0.32

Tab. 6 - Comparison of long-term and one-time-only plasmapheresis donors.

variable	mean $\pm$ standard deviation	
	one-time-only no. = 94	long-term no. = 96
α_1 -globulin	0.21 $\pm$ 0.05	0.22 $\pm$ 0.05
α_2 -globulin	0.81 $\pm$ 0.11	0.79 $\pm$ 0.14
β -globulin	0.89 $\pm$ 0.11	0.88 $\pm$ 0.11
γ -globulins	1.10 $\pm$ 0.20	1.14 $\pm$ 0.24

Tab. 7 - Comparison of long-term and one-time-only plasmapheresis donors.

Finally, what is the effect of plasmapheresis on the coagulation components which were not measured here or in most other studies?

Total plasma-exchanges which I carried out experimentally 20 years ago and which were reported with HAYNES⁷ showed that plasma-exchange in a 90-min period to 87% of total plasma volume with replacement by albumin results in a fall of all clotting components to about 30% of starting levels. The replacement of clotting components from the extravascular reservoirs and a prompt increase in synthesis is able to maintain the plasma concentrations at about such levels with the sole exception of fibrinogen. Because of its molecular size and shape, fibrinogen is predominantly an intravascular protein and must be replaced after exchanges in excess of 75% in order to maintain hemostasis adequately. A less intensive level of plasma-exchange was recently conducted experimentally in Spain and reported at the Mediterranean Society of Thrombosis and Hemostasis in 1980³. Antithrombin III was found to decrease transiently on each day of intensive plasmapheresis conducted on four consecutive days. The synthesis rate of new antithrombin III, however, was sufficient to correct the deficiency by each following morning. A more recent report by JAFFE and MOSHER⁸ showed that intensive plasmapheresis of 15 prison subjects at a volume of 600 ml of plasma twice-weekly for 52 weeks, with replacement with only normal saline showed no statistical difference between the values of either antithrombin III or plasminogen when compared with the expected normal ranges for these coagulant inhibitors.

So much for the acute changes which may or may not follow plasmapheresis. The only question we have not addressed, and indeed there are few studies that have, is the possible harm which hyperimmunization may cause to that small group of plasma donors who supply high-titer globulins for selected diseases. Among these are the donors who are stimulated to produce Rho-gam for protection against erythroblastosis fetalis, the donors who are immunized with tetanus toxoid, herpes zoster and rabies. The short-term effects of such hyperimmunization appear to be minor but the possible long-term hazards of repeated stimulation of specific clones of plasma cells have not begun to be evaluated. Will the donors who constitute such human factories have an increased incidence of monoclonal gammopathies and other malignant blood dyscrasias three or four decades hence? Equally importantly, are there unknown viral contaminants of the biologic materials which are used as antigens in such programs? Particularly in the case of red cell immunization, what types of slow virus may be transmitted that could give rise to late neurologic sequelae? These are questions to which the present state of the art has no answer. On a cost-benefit basis, the tremendous value which these agents have for the control of various diseases seems to outweigh the hazard, but how does one explain this conclusion to the so-called informed donor who is the one who is at risk? If people wish to continue to express concern about plasmapheresis, perhaps they should address this subject selectively and establish protocols now which will answer these important questions many years hence.

Meantime, and in conclusion, a critical look at all available data shows that the standards of plasmapheresis approved by the FDA and accepted as suitable for American patterns appear reasonable, safe and within totally ac-

ceptable standards of medical prudence. If they are not, or if any data now or subsequently shows them to be of even questionable safety, one can rest assured there would be a prompt restriction and publication of new standards by our Federal regulatory agencies. Their sole purpose is to protect the public against any form of exploitation.

From the standpoint of the ethical issues raised earlier of remuneration of donors in such programs, I am equally reassured after reviewing the data objectively that good controls now exist to assure that this process is not being pressed on disadvantaged or malnourished individuals. All entries into such programs are voluntary and fully protected by codes of human rights. Perhaps it is time for us to stop leveling criticism at commercial plasmapheresis programs and to thank the donors for the fact that their current participation is helping to supply the world's needs for many important therapeutic products.

New scientific methods such as recombinant DNA techniques make it likely albumin will be synthesized in the laboratory within another decade thus lessening significantly the present needs for source plasma. It is unlikely these techniques will be successfully applied to γ -globulin synthesis and to coagulation factor VIII at any time in the foreseeable future because of the size, complexity and diversity of the different globulin moieties. The loss of albumin as a driving force for the plasmapheresis industry may have ripple effects of significant extent particularly economically but such discussions are beyond the scope of the review today.

SUMMARY

The principal differences of the USA plasmapheresis collection system from most other countries are: it is conducted by the pharmaceutical industry rather than government, it uses remunerated donors, and it draws a larger volume of plasma than is permitted elsewhere. The implications of these features are reviewed in terms of the effects on donors and the effects on the plasma supply. Protein metabolism is reviewed, and the effects of plasmapheresis on overall nitrogen balance are presented.

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