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The Serum Protein Complex as a Factor in Regulating Blood Volume.*

DANIEL MELNICK AND GEORGE R. COWGILL.

From the Laboratory of Physiological Chemistry, Yale University, New Haven, Conn.

The most important function of serum protein resides in its osmotic attraction for water.¹ This complex is the most effective agent in maintaining the fluid balance between the blood and the intercellular tissue spaces and serous cavities. Thus, Whipple and his associates² have reported that intensive and prolonged plasmapheresis results in symptoms resembling those of shock. For the most part, blood volume determinations were not attempted, but the probable explanation of these observed shock reactions is that the reduction of the serum protein concentration prevents the retention of fluid in the vessels in the face of a normal blood pressure. The importance of the colloidal osmotic pressure of the plasma in maintaining a normal blood volume has been emphasized by Stanbury and coworkers.³ They have demonstrated that the substitution of gum acacia for the serum protein complex results in no obvious disturbances of water balance in the mammalian body. The present communication is intended to throw additional light upon factors regulating blood volume.

In our investigations^{4, 5, 6} of the influence of various dietary factors upon the regeneration of serum protein, plasmapheresis was performed quantitatively. Accordingly, the blood volume of the experimental animal was determined periodically as a prerequisite to the calculation of the amount of blood to be withdrawn at each plasmapheresis. The frequency and size of the bleedings were also dependent upon the level of the serum protein concentration, as

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¹ Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry, I. Interpretations*, Baltimore, Md., Williams and Wilkins Co., 1932.

² Smith, H. P., Belt, A. E., and Whipple, G. H., *Am. J. Physiol.*, 1920, **52**, 54.

³ Stanbury, J. B., Warweg, E., and Amberson, W. R., *Am. J. Physiol.*, 1936, **117**, 230.

⁴ Melnick, D., and Cowgill, G. R., *J. Exp. Med.*, 1936, **64**, 865.

⁵ Melnick, D., Cowgill, G. R., and Burack, E., *J. Exp. Med.*, 1936, **64**, 877.

⁶ Melnick, D., Cowgill, G. R., and Burack, E., *J. Exp. Med.*, 1936, **64**, 897.

determined daily. In our study, 55 blood volume estimations were carried out on 3 dogs. On these same days the serum protein concentrations, plasma volumes and cell volumes were also recorded. The methods employed have been described elsewhere.⁴

A consideration of some representative values obtained with Dog No. 3 will serve to illustrate the interrelationship observed between serum protein concentration and the blood, cell and plasma volumes.

TABLE I.
Representative Values Obtained with Dog No. 3 During Plasmapheresis Experiments.

Date 1935	Serum Pro- tein Con- centration %	Blood Volume cc.	Hemato- crit %	Cell Volume cc.	Plasma Volume cc.
3/5	6.82	1335	51.3	684	651
3/21	3.94	1170	44.5	520	650
5/18	3.51	1105	41.3	456	649
5/25	4.47	1242	41.3	513	729
10/18	6.60	1315	44.8	590	725

On 3/5/35 this animal had a normal blood volume of 1335 cc. with a serum protein concentration of 6.82%. A reduction in the serum protein concentration by the technic of plasmapheresis is associated with a drop in the blood volume, as exemplified by the values on 3/21, 5/18 and 5/25/35. In the course of repeated, prolonged plasmapheresis the hematocrit tends to approach anemia levels unless donors' blood cells are injected periodically.^{5, 7, 8} It is for this reason that these values show such wide fluctuations which are in no way correlated with the serum protein concentrations. A drop in the cell volume also tends to reduce passively the blood volume. However, when there is a significant reduction in the hematocrit, then the lowered osmotic effect due to a reduced serum protein concentration appears to be negligible in affecting a further reduction in the blood volume, as is evidenced by the constant value for the plasma volumes on 3/5, 3/21 and 5/18/35. Indeed, in some cases where there is a concomitant low serum protein concentration, value of 5/25/35, and a cell volume decidedly less than normal, the plasma volume may actually be greater than the normal. However, with an increase in the serum protein concentration, but with the cell volume constant (determinations of

⁷ Holman, R. L., Mahoney, E. B., and Whipple, G. H., *J. Exp. Med.*, 1934, **59**, 251.

⁸ McNaught, J. B., Scott, V. C., Woods, F. M., and Whipple, G. H., *J. Exp. Med.*, 1936, **63**, 277.

3/21 and 5/25/35), there is a corresponding increase in the plasma volume. Furthermore, with a normal serum protein concentration and a normal blood volume (value of 10/18/35) but with a significant decrease in the cell volume, the plasma volume was found to be somewhat greater than the initial normal value. In other words, *the plasma volume appears to be regulated by the serum protein concentration only insofar as the cell volume is constant. With a significant decrease in the hematocrit resulting in a passive reduction of the blood volume, a lowered serum protein concentration seems to be negligible as a regulatory factor.* This is another example of homeostasis, the ability of the body to resist changes beyond a critical level.

Numerous examples similar to these are recorded elsewhere.⁹ These observations should not be confused with those recorded by others¹⁰ with respect to plasma replacement in conditions of primary and chronic secondary anemia. In these pathological conditions, characterized by reductions in both blood and cell volumes, the serum protein concentrations are *normal*.

In searching for some explanation of the maintenance of the plasma volume in the face of a lowered serum protein concentration, the reader is referred to the interesting study conducted by Keys and Adelson.¹¹ They report that under certain conditions which tend to distort the blood volume, the walls of the capillaries may become impermeable to the so-called "diffusible" calcium ions in the plasma so that an osmotic force is set up in opposition. They suggest that under similar conditions of stress other substances in the plasma may also act as "osmotic buffers."

⁹ Melnick, D., "Influence of Diet upon the Regeneration of Serum Protein," Dissertation, Yale University, New Haven, Conn., 1936.

¹⁰ Rowntree, L. G., Brown, G. E., and Roth, G. M., "The Volume of the Blood and Plasma," Philadelphia, Pa., W. B. Saunders Co., 1929.

¹¹ Keys, A., and Adelson, L., *Am. J. Physiol.*, 1936, **115**, 539.