THE PLASMA PROTEINS IN RELATION TO BLOOD HYDRATION

V. Serum Proteins and Malnutritional or Cachectic Edema

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That extreme restriction of dietary protein results in reduction of serum proteins in rats has been demonstrated by Frisch, Mendel and Peters (1). In the preceding article of this series (2) it has been shown that a serum protein deficiency, in which the albumin fraction alone suffers, is regularly found in patients who have, as the result of disease, become seriously malnourished. Presumably, wastage of tissue proteins is the most important feature of such malnutrition. The appearance of edema in protein-starved rats was first observed by Kohman (3) and Maver (4), whose observations were confirmed by Frisch, Mendel and Peters (1). Furthermore, the occurrence of edema in famine areas has been noted repeatedly, especially during the world war, and has been ascribed by some to the effects of protein starvation (5, 6). It is also frequently observed in patients with wasting diseases. The discovery that malnutrition is regularly attended by serum albumin deficiency seems to afford a rational explanation of the development of edema.

Starling (7) was the first to point out that the exchange of fluids between tissue spaces and the circulating blood was determined by the relative magnitude of two forces: 1. the hydrostatic pressure (blood pressure) which tended to drive fluid out of the blood vessels into the tissues; 2. the osmotic pressure exerted by the proteins of the plasma, which tended to draw fluids into the blood. The theory was given practical clinical application by Epstein (8, 9) in explanation of the

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edema of nephrosis, in which he found serum proteins low. Schade and Claussen (10) and Govaerts (11) have shown by direct measurement that the colloid osmotic pressure of the plasma (conveniently termed "oncotic" pressure by Schade and Claussen) is directly related to the concentration of the plasma proteins and can be closely correlated with the development of edema in nephritis. Landis (15) has found that the rate and direction of the fluid exchange between the circulating blood and the tissue spaces in the mesentery of the frog is related quantitatively to the difference between the blood pressure and the oncotic pressure in the mesenteric capillaries and that the walls of these vessels are ordinarily impervious to protein. The flow of fluid from the vessels may be greatly increased if the endothelium is rendered more permeable by asphyxia, but is still determined by the relative magnitudes of hydrostatic and oncotic pressures. As might be anticipated from its lesser molecular weight albumin exerts a far greater osmotic pressure per gram than globulin does. It follows that a given deficiency of serum albumin is more likely to produce edema than an equal deficiency of globulin. By comparison of chemical analysis and oncotic pressure measurements Govaerts (11) has estimated that the osmotic pressure of 1 gram per cent of albumin is 7.54 cm. of water, that of 1 gram per cent of globulin is 1.95 cm. of water. Perhaps the most unequivocal evidence of the influence of serum proteins on edema production is found in recent experiments of Leiter (12) which have been confirmed by Darrow and Hopper (13). By repeated plasmapharesis they were able to reduce greatly the serum proteins of dogs. When the proteins had fallen below a level of about 3 per cent the dogs became edematous.

Schittenhelm and Schlect (5) reported serum refractive indices low in certain patients with famine edema during the world war. Jansen (6), using the Kjeldahl method, found serum proteins greatly reduced, and by comparison with studies of hemoglobin, concluded that undernutrition caused a specific reduction of proteins due, perhaps, to failure of regenerative processes.

In figure 1 of the preceding article (2), are presented serum protein values from normal persons and from patients with various diseases in whom no obvious affection of kidney or circulatory system could be discovered. The incidence of edema among these patients was indicated in the figure. Edema was observed on 36 occasions in malnourished patients and in only one of the 36 instances were serum proteins above the average normal level. A large variety of disease conditions was studied; but non-inflammatory edema which could not be ascribed to cardiac or renal disorders was found only when there was obvious malnutrition.

In figure 1 the incidence of edema is compared with the concentration of total serum proteins, albumin and globulin in the mal-

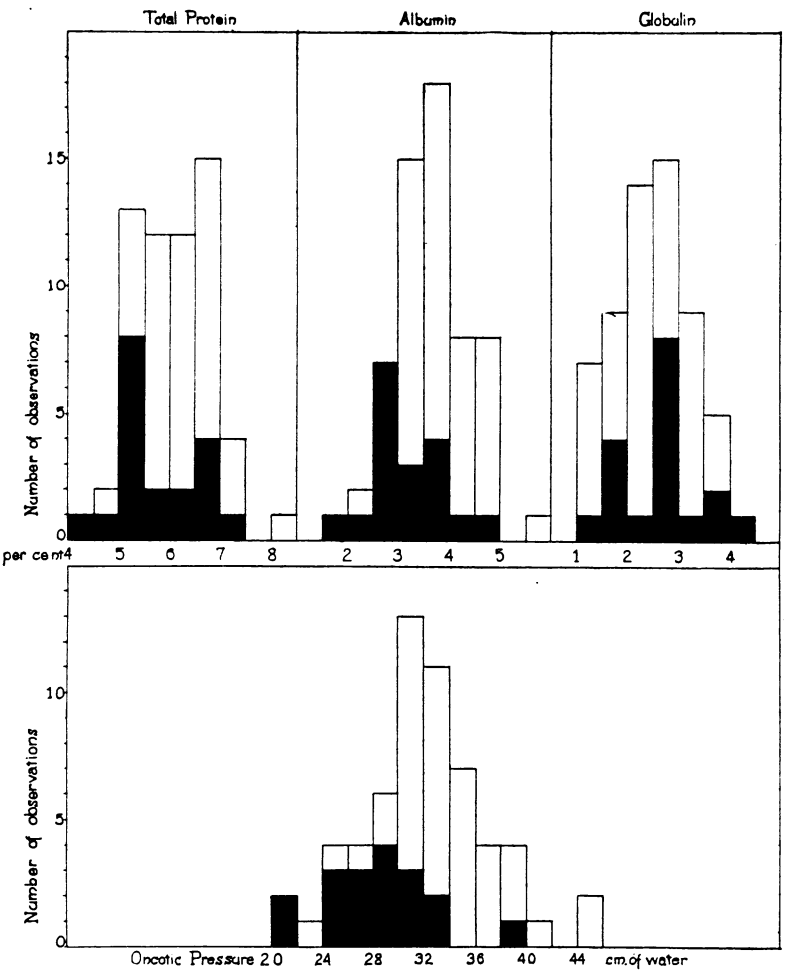

FIG. 1. THE RELATION OF SERUM PROTEINS AND SERUM PROTEIN FRACTIONS IN MALNUTRITION TO EDEMA

In the lower half of the figure comparison is made with the serum "oncotic" pressure calculated by means of Govaerts' factors. The solid blocks indicate that edema was present.

nourished patients whose serum proteins were fractionated. From this figure it becomes at once apparent that there is no correlation between occurrence of edema and globulin concentration. In fact, among the edematous cases globulin is more often high than low. The

correlation with albumin is somewhat better than with total protein. This is to be expected if the appearance of edema depends upon the osmotic pressure exerted by the serum proteins, because this is influenced far more by albumin than by globulin. If attention is centered upon albumin alone, edema is found in every instance but one when albumin is below 3 per cent and on only two occasions when albumin exceeds 4 per cent. In the two last exceptions the edema was minimal, described as slight pitting of the ankles and feet. In some of the patients with extremely low albumin massive general anasarca was seen.

In the lower part of the figure the incidence of edema is compared with the oncotic pressure of the serum, calculated by means of Govaerts' factors (see above). Correlation is not improved, probably because in this series variations of globulin never attained sufficient magnitude to influence the oncotic pressure greatly. It is conceivable that, with extremely high globulin, edema might fail to occur even in the presence of albumin deficiency. Salvesen (14) has reported a case of nephrosis without edema in which an albumin which varied from 1.69 to 2.56 per cent was balanced by a globulin varying from 7.10 to 8.08 per cent so that the oncotic pressure of the serum remained relatively high in spite of a considerable albumin deficiency.

In certain patients observations were made when edema was present and after it had been eliminated by dietetic measures alone. The data from such a case are given in the table in the previous article. In such cases disappearance of edema was attended by increase of serum albumin.

On the whole, although the occurrence of edema can not be correlated exactly with the level of serum albumin or the oncotic pressure, the correlation is quite as satisfactory as could be expected from the nature of the material investigated. It is recognized in the theory of Starling that plasma oncotic pressure is only one of the two forces that determines the direction of fluid exchange between the circulating blood and the lymph or interstitial fluids of the body. The other, the hydrostatic pressure in the capillaries, can not, as yet, be measured.

CONCLUSIONS

Edema has been observed in patients with malnutrition only when serum albumin is below the normal level. It almost invariably

develops when serum albumin falls below 3 per cent, is seldom found when albumin exceeds 4 per cent. Malnutritional edema appears to be referable to a serum albumin deficiency brought about by wastage of body protein, the result of disease or inadequate diet.

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