PLASMA VOLUME AND THIOCYANATE SPACE IN NUTRITIONAL OEDEMA

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Received June 25; read October 9, 1953)

Oedema is a common feature observed in patients exposed to malnutrition or suffering from conditioned nutritional deficiency. The distribution of body water over the various fluid compartments in such oedematous patients has been studied by a number of workers (Perera, 1946; Mollison, 1946; Beattie *et al.*, 1948; Walters *et al.*, 1947; and Keys *et al.*, 1950). As regards the extracellular space, all the investigators agree upon its increase which even outlasts the disappearance of the clinically recognisable oedema during the recovery period. The plasma volume per kg. of body weight of such patients is reported either within the normal range given by Gibson and Evans (1937) or increased. Some of these investigations were carried out in patients with hypoproteinemia, others in persons having a more or less normal serum protein concentration. Well controlled animal experiments (Metcoff *et al.*, 1945; Weech *et al.*, 1937) have shown a contraction of circulating plasma volume as a result of dietary protein deficiency which has caused hypoproteinemia.

To clarify the situation it appears appropriate to consider the cases with hypoproteinemia separate from those having normal serum proteins. Such a distinction permits correlation of clinical observations on hypoproteinemic patients with the condition in experimental animals mentioned above. The investigations reported here are therefore restricted to such cases having lowered serum proteins.

There is another point which deserves consideration: it is common experience with patients suffering from nutritional oedema that they very often lose their swelling within a short time after admission to the hospital by diuresis. It is obvious that the relative size of the fluid compartments undergoes considerable changes during this period so that the plasma volume will alter in relation to the time of measurement. The significance of this point will be illustrated by the results of repeated estimations of the plasma volume in each individual patient in different stages of the disease as reported in this paper.

MATERIALS AND METHODS

Eighty-three patients were subjected to the investigations. The diagnosis was arrived at by considering the following points:—

(1) History of poor dietary intake or conditioned nutritional deficiency.
(2) Presence of oedema, being generalised from the start or starting from the lower extremeties.
(3) Absence of signs of portal obstruction, cardiac failure or albuminuria.
(4) Absence of marked anaemia.
(5) Absence of any congenital abnormalities like Milroy's disease, etc.

Cases in which malnutrition was secondary to other diseases like tuberculosis, malignant tumour, etc., were not included.

After admission to hospital, the patients were simply put under observation, the daily weight (under standard conditions) and urinary output charted. If

* Indian Council of Medical Research Fellow: May and Baker Fellow from 2-4-1953.

during a period of two days following admission to the hospital, the weight remained steady or was on the increase and the urinary output was less than 500 ml. on an unrestricted fluid intake, the patients were placed under group A. Out of the 83 patients investigated 25 belonged to this group according to the criteria given. If, however, they manifested diminution of weight, decrease of oedema and polyuria they were placed under group B which consisted of the remaining 58 patients. On the third day after admission the plasma volume, thiocyanate space, total serum protein, albumin and globulin were estimated. The tests were repeated at an interval of 1-2 weeks.

The plasma volume and thiocyanate space (C.N.S.) were determined simultaneously by the method of Gregersen and Stewart (1939). The total serum proteins, albumin and globulin, were estimated by the microkjeldahl technique and later on in the course of the investigations by the method of Greenberg (1929).

The following results were obtained in the first series of estimations following admission (mean and standard deviations are given in each case):—

No. of cases.	Plasma vol. (ml.)	Plasma vol. (ml./kg.)	Cell vol. (%)	C.N.S. space (ml./kg.)	Total serum protein. (g.%)	Serum albumin. (g.%)
	GROUP A:					
25	1849 ± 266	43·7 ± 2·2	28 ± 1·0	398 ± 18	4·8 ± 0·3	1·9 ± 0·4
	GROUP B:					
58	2876 ± 216	71·9 ± 4·4	22·5 ± 1·3	376 ± 44	4·9 ± 0·2	1·7 ± 0·8
	Normal controls (figs. taken from Chaudhuri *et al.* (1951 *a*, *b*.)					
	1591 ± 180	47·7 ± 8·1		236·3 ± 30·8		

It is obvious that the mean plasma vol./kg. in the patients in group A is much less than that in group B, the difference being statistically significant at 0·01% level; it is even lower than that in the average normal persons found by Chaudhuri *et al.* (1951*a*) for Indians and as also found in our normal controls. So long as the patients in group A did not develop diuresis and lose weight, their plasma vol./kg. did not show any significant change as found by repeated estimations. When as a result of treatment (high caloric protein rich diet, plasma infusion, amino acid administrations and supplements of vitamin concentrates *) these patients developed diuresis and started losing weight and oedema, their plasma volume became markedly increased. It is interesting to note here that not only the relative plasma volume (per kg. body weight) was increased but there was an increase of absolute plasma volume as well which means that the loss of weight could not simply account for the relative increase of plasma volume/kg. The average values shown by these patients during the period of recovery were as follows:—

No. of cases	Plasma vol. (ml.)	Plasma vol. (ml./kg.)	Cell vol. (%)	C.N.S. space (ml./kg.)	Total serum protein (g.%)	Serum Albumin (g.%)
	GROUP A:					
25	2808 ± 358	70·7 ± 4·4	23·5 ± 1·2	336 ± 26	4·9 ± 0·2	1·8 ± 0·5

* Litrison, Hoffmann La Roche.

It can be further observed that these changes in body fluid distribution are not accompanied by any significant change in total serum protein concentration. It is only some time after the patients lost their oedema, that the serum protein level went up.

Seven seriously ill patients, on admission belonging to group A, had moderate to severe oedema, profuse diarrhoea and very low blood pressure. They were particularly interesting because they had clinical signs of dehydration, i.e., a dry tongue, pinched features and circles around the eyes in spite of their oedema. Their weight remained steady, urine varied from 180–240 ml./24 hours, their anaemia was not marked, cell volume was about normal, erythrocyte sedimentation rate (E.S.R.) was 1–4 mm. with the Westergren scale; plasma volume was between 41–44 ml./kg., C.N.S. space was 398–422 ml./kg. They remained like this, critically ill, with the signs of dehydration persisting so long as the diarrhoea continued. When the number of stools became reduced and they started to improve, the signs of dehydration cleared up. But the weight increased and oliguria persisted. The haemoglobin concentration (per 100 c.c. blood) now was about half of that observed on admission, cell volume decreased, E.S.R. rose markedly (60–110 on the Westergren scale) and plasma volume became increased. Strikingly enough, the thiocyanate space at this period showed diminution to the extent of 2–4 litres though there was no diuresis and loss of weight. Shortly afterwards these patients developed increased urinary output and followed the usual pattern of recovery as in the other patients belonging to group A.

The further course undergone by the patients in group A, once the diuresis started, followed closely the pattern in group B. Gradually the patients lost weight and oedema, the plasma volume remained high for some time and then started to return to normal. But though the oedema could no longer be detected clinically, the thiocyanate space was still high. There was a lag period when, although there was no gain or loss of weight and the patients were not clinically oedematous, the thiocyanate space became progressively reduced and it is only after that, that the serum proteins increased.

Two patients belonging to group A deserve special mention because they redeveloped oedema during the progress of the investigation. On admission they had reduced plasma volume, increased C.N.S. space and normal E.S.R.; however after a few weeks' stay they started diuresis, lost weight and their oedema subsided. During this recovery period the same change in the body fluid distribution occurred as mentioned before, i.e., the plasma volume increased, C.N.S. space diminished, there was hemodilution and increased sedimentation rate. Then, for no apparent reason, the patients suddenly gained weight and became oedematous. At that stage, the plasma volume again diminished, C.N.S. space slightly increased and there was the same diminution of sedimentation rate as originally.

In six patients belonging to group A mercurial diuretics were administered intramuscularly being preceded by ammonium chloride. There was diuresis during the next 24 hours. The plasma volume, however, showed no significant change.

Discussion

From these investigations it becomes clear that two phases can be distinguished in the course of the nutritional oedema. As the oedema develops the plasma volume becomes reduced on a weight basis as well as on an absolute scale, whereas it appears increased during the recovery phase. The question now arises whether the initial reduction of the circulation plasma volume can be regarded simply as one of the features of the disease or whether it is a primary event in the course of the disease leading to a reduced glomerular filtration rate (Cort, 1952) and 'glomerulo-tubular imbalance'—a condition, which, under appropriate circumstances, will lead to sodium retention. In any case, this initial phase of the disease is markedly different

from the oedema due to cardiac failure or hepatic cirrhosis, since in both cases an increased plasma volume has been repeatedly observed (Gibson and Evans, 1937; Perera, 1946). The suggestion that the reduction of serum albumen gives rise to the decrease of plasma volume (Weech, 1938) is not supported by the observations of Mollison (1946) and Beattie *et al.* (1948) and by our own data, since we regularly observed that the return of the body fluid distribution to normal is not linked up with a concomitant alteration of the serum protein concentration.

Although there is oedema and expansion of the thiocyanate space, the patients appear dehydrated considering their reduced plasma volume—a fact which is even confirmed by the presence of clinical signs of dehydration in some of them; an excess production of antidiuretic hormone could, therefore, be assumed. Gopalan (1950) seemed to have succeeded to demonstrate an increased amount of antidiuretic substances in the urine of such patients, but other workers (Saha and Sengupta, 1952), have failed to confirm it.

On the basis of these observations, it does not seem justified to attribute to the decrease of the serum protein level a primary rôle in the genesis of the oedema as assumed in the Starling hypothesis (Starling, 1908). However, the possibility exists as shown by Ayer, Schiess and Pitts (1947) in experiments on dogs and by Dicker (1948) on rats, that the glomerular filtration rate is decreased in the presence of hypoproteinemia. Besides, the glomerular filtration rate is no longer independent of the rate of urine flow in the presence of hypoproteinemia (Dicker, 1949). It is furthermore known that an artificial alteration of plasma colloid content by means of infusion of albumin (Welt and Orloff, 1949) exerts a considerable influence on the excretion of water and salts, infusion of hyperoncotic solutions causing a reduction of sodium excretion, that of iso-oncotic solutions producing increased excretion of water; but both the hyperoncotic as well as the iso-oncotic infusion cause increase of the circulating blood volume. Rapid administration of albumin causes in addition a marked increase of the total renal plasma flow, possibly by opening previously closed arterio venous anastomosis (Michie *et al.*, 1949; Barker *et al.*, 1949). These facts indicate that the balance of at least two forces, namely the colloid osmotic pressure and the plasma volume, determine in some way the excretory function of the kidney. Possibly the size of the extracellular fluid compartment also influences the urinary output, since in oedematous subjects even hyperoncotic solutions have diuretic effect (Orloff, Welt and Stowe, 1949). If the decrease of the serum protein level is the primary cause at all for the water retention, then it appears to be so because of the colloid osmotic pressure being one of the conditioning factors for water and salt excretion through the kidney and not because of the disturbance of the Starling equilibrium.

During the development and the height of the disease a paradoxical state exists where the plasma volume is reduced but the thiocyanate space is increased. The disturbance of the fluid compartments seems, however, to be even more complicated than already mentioned. During the recovery phase in these patients a stage was observed in which the thiocyanate space became reduced though there was no alteration in weight and urinary output. A transfer of water from extracellular into intracellular space must have taken place as the simultaneous increase of plasma volume cannot account for more than a small fraction of the diminution of the extracellular fluid. We do not know to what extent a potassium depletion arising from the associated diarrhoea contributes to the observed disturbance of the fluid distribution. Eliel *et al.* (1950) have recently shown that, in such a condition, intracellular dehydration can occur concurrently with expansion of the extracellular fluid compartment. Possibly as the patients recover, their tissue protein content increases towards normal thus accounting for a water movement from outside into the intracellular space. Of course, we do not know the degree of protein depletion in the tissues, however, the reduced serum protein level certainly indicates that some degree of tissue protein depletion must be present. Besides there is evidence

that the proportion of osmotically inactive base within the cells may vary under certain circumstances (Elkinton *et al.*, 1948) and malnutrition might represent an instance which alters that proportion.

One particular fact noticed in the patients of group B is the lack of any correlation between the circulating plasma volume with total serum protein concentration. In this respect and in the subsequent course of the disease, they resemble the patients of group A during the recovery period. There is no reason to assume that a basic difference of the pathological process exists between the patients of group A and group B; they simply represent different stages of one and the same disease.

The possible part played by the proteins in the development of the nutritional oedema has been considered before. Unfortunately no data are yet available to ascertain the significance of sodium, the main ionic constituent of the extracellular fluid, in that condition. Based on the well-supported observation that in most instances isotonicity is more carefully guarded by the body than the constancy of the fluid volume (Peters, 1947), we would expect sodium retention at the onset of the oedema; but Schroeder (1949) has demonstrated that oedeme is also compatible with the presence of a 'low salt syndrome'. Particularly the clinical signs of dehydration observed in some patients together with the reduction of the plasma volume at the initial stage of the disease might reflect a chronic sodium depletion (Black, 1953). The constantly observed diarrhoea certainly gives sufficient reason to suspect such a condition. Besides, salt depletion is known to impair the elimination of water through the kidney (McCance and Widdowson, 1937; Baldes and Smirk, 1934) and the existence of such a markedly impaired water excretion was repeatedly demonstrated in our patients of group A by administering a water load by mouth: no significant amount of extra urine was produced in such tests; moreover the urine maintained its hypertonicity with respect to the osmotic pressure of serum. Leaf and Mamby (1952) have recently shown, that conditions exist which cause conservation of water irrespective of serum solute levels; these authors believe that the constancy of the extracellular fluid tonicity is sacrificed in these cases and water is retained to maintain the fluid volume high: low salt intake or salt loss combined with ad libitum water intake seems to trigger this volume conserving antidiuretic mechanism which, together with the hypoproteinemia, appears to determine the symptomatology of nutritional oedema.

Summary

Plasma volume, thiocyanate space, total serum proteins and albumin concentration were determined in 83 patients suffering from nutritional oedema. The patients could be divided into two groups (A and B) according as they were gaining or losing oedema on rest in bed. The plasma volume/kg. in group A (43·7 + 2·2 ml./kg.) was significantly lower than that in group B (71·9 + 4·4 ml./kg.). This lowered plasma volume persisted in the patients in group A till they developed diuresis and commenced losing oedema. They had signs of haemoconcentration as well and seven patients manifested clinical signs of dehydration. When they started to lose the oedema their plasma volume increased (70·7 + 4·4 ml./kg.) and approached that in group B. The thiocyanate space was increased considerably at the start but remained higher than normal, even when there was no clinically detectable oedema in both groups. No correlation was found between the serum protein concentration and the changes in the distribution of the body fluid.

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Issued March 2, 1954.