THE PLASMA PROTEINS IN RELATION TO BLOOD HYDRATION

VIII. Serum Proteins in Heart Disease

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In uncomplicated heart disease the proteins of the serum appear to be little disturbed. In patients with heart failure, on the other hand, they may be considerably reduced at the expense of the albumin fraction (1, 2, 3). Attempts to relate these reductions to the incidence of edema or the state of the water balance have not been successful. The protein concentration may fall during diuresis or rise during the development of edema. In some cases, however, changes in the opposite direction have been observed.

In the hope that more extensive studies might throw some light on the nature of these apparently paradoxical phenomena, 53 determinations of the serum proteins were made on 24 patients with heart disease in various stages of decompensation. In 49 instances albumin and globulin fractions were determined separately. Efforts were made to estimate the nutritional state of each subject. In 2 cases nitrogen metabolism was determined while the subjects were recovering from cardiac decompensation. The nature of the cases included in the series is tabulated briefly below. In none was renal function seriously impaired. The concentrations of

TABLE 1

Classification of patients

Nature of disease	Number of cases			
	Total	Improved	Unimproved	Died
Arteriosclerotic without hypertension	8	5	1	2
Arteriosclerotic with hypertension	6	5	0	1
Rheumatic	6	2	1	3
Syphilitic	3	1	0	2
Acute endocarditis	1	1	0	0

[1] The data in this paper are taken from the thesis of Dr. Sheldon A. Payne, done in partial fulfilment of the requirement for the degree of Doctor of Medicine at Yale University School of Medicine.

protein and protein fractions of the serum bore no relation to the fundamental nature of the heart disease; but seemed to be related only to functional disturbances connected with heart disease in general.

All the data are presented in Figure 1, which is designed to show the relation of both decompensation and edema to the concentration of total

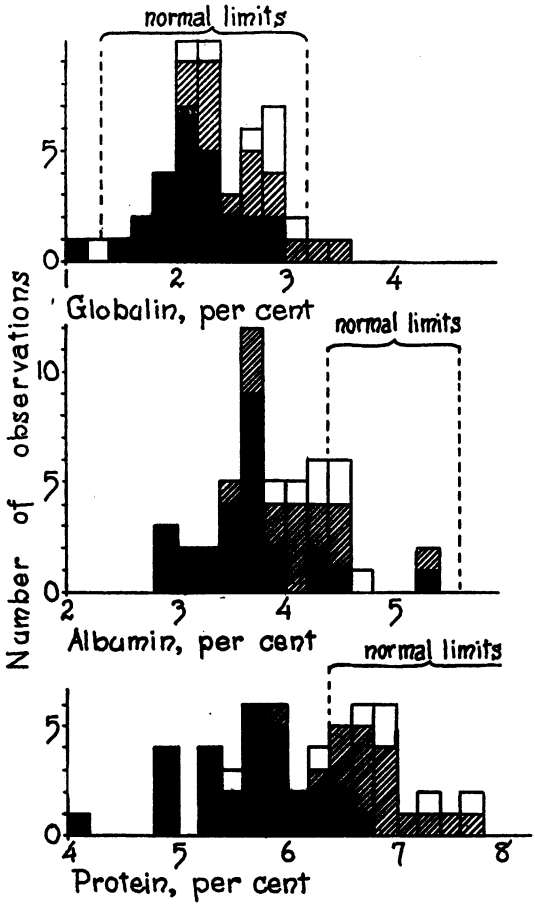

FIG. 1. RELATION OF SERUM PROTEINS TO EDEMA AND TO HEART FAILURE

Solid squares indicate heart failure with edema; diagonally lined squares, heart failure without edema; open squares, no heart failure nor edema.

protein and of the protein fractions of the serum. The presence of decompensation and edema is indicated by the solid squares, decompensation without edema by diagonal lines. The criteria by which decompensation has been distinguished in these cases are quite arbitrary. Patients have been considered as compensated only when they were sufficiently well to be discharged from the hospital.

If all observations are considered, total proteins and albumin are found to be reduced in the majority of instances, while globulin does not depart appreciably from the normal range. The proteins in compensated cases were, with one exception, within, or not more than 0.2 per cent below, the limits of normal variation. This exception had only 5.55 per cent protein. However, albumin accounted for 4.24 per cent of this, the protein reduction being due merely to an unusually low globulin, only 1.31 per cent. Albumin also lay within or near the normal limits when compensation had been established.

The incidence of edema becomes greater as protein and albumin fall. However, it can not be inferred that the two are related, because it has already been shown that the serum proteins return to the normal level with the establishment of compensation, whether there has been edema or not. There is, however, other evidence that edema is more frequent in patients with hypoalbuminemia. Seven of the patients were admitted with all signs of heart failure except edema. In this group total protein lay always above the lower normal limit, albumin in only two instances below 4.00 per cent, 3.61 and 3.83.

Reduction of the serum proteins may be referable to any one or all of a variety of functional disturbances which are known to occur in heart disease. The ones which appear most worthy of consideration are albuminuria, hydremia, filtration of protein through the capillary walls into the edema fluid, and malnutrition. Of these albuminuria seems to play a relatively unimportant rôle. None of the cases studied had profuse albuminuria, and in only 5 did the urine contain more than a faint trace of albumin.

If hydremia were responsible for the protein reductions, both protein fractions, and not albumin alone, should suffer. That alterations of blood volume are encountered in heart failure and that such alterations do affect the blood proteins is apparent in some of the cases which will be discussed in greater detail below. They are not, however, a frequent cause of hypoproteinemia.

Analyses of serous effusions from patients with heart failure have revealed the fact that such fluids contain more protein than comparable effusions from patients with nephrosis (4, 5). This suggests that capillary permeability is somewhat increased in heart failure, presumably as a result of blood stagnation and anoxemia. If, from the same analyses, the total amounts of protein which may pass from the blood stream into the edema fluids are estimated, the quantities seem hardly sufficient to strain the regenerative powers of a normal individual. Iversen and Johansen (5) found in the early stages of heart failure about 0.6 per cent of protein in pleural fluid. Subsequently the protein may rise considerably, as fluid is reabsorbed more rapidly than protein is removed. If 0.6 per cent represents the average concentration of protein in cardiac edema fluid,

the development of as much as 10 kilos of edema would remove from the serum only 60 grams of protein. An equal amount may be excreted in the urine of a nephrotic patient in the course of only 3 or 4 days. Removal of comparable quantities from dogs by plasmapheresis produces only transient serum protein deficiency (6, 7).

TABLE 2

Serum data, edema and weight

Case number	Serum			Edema	Weight			Remarks
	Protein	Albumin	Globulin		Actual	Before illness	Without edema	
	per cent	*per cent*	*per cent*		*kilos*	*kilos*	*kilos*	
80788	7.72	5.35	2.37	0	53.6			Patient noted as slightly obese
48764	7.40	4.38	3.02	0	43.7	43–48		
6099	7.30	3.88	3.42	0	64.8	73–77		
80853	7.01	5.30	1.71	+	88.0	84–86	85.1	
73410	6.92	4.08	2.87	0	82.4	82		Weight reported normal by patient
60084	6.91	4.05	2.86	0	41.6			Vomiting and dehydrated
4607	6.85	3.61	3.24	0	50.2	59–64		
87471	6.65	4.44	2.21	0	47.0	55		Had lost 8 kilos during preceding year. Study made after improvement
73840	6.50	3.62	2.88	+	58.8	73	52.2	
85828	6.45	3.93	2.52	3+	76.8	73	63.8	
82039	6.40	3.73	2.67	0	64.0	68		
79555	6.16	3.46	2.70	2+	70.2	70	60.4	
80060	6.05	3.72	2.33	3+	66.9	73	54.0	
85900	5.83	3.63	2.20	+	69.5	70–77	66.8	
76591	5.83	2.89	2.94	2+				Just before admission patient had noted 22 kilos loss of weight. He was evidently emaciated
87704	5.76	4.59	1.17	+	68.2		63.9	Patient a woman of medium height, well nourished even after elimination of edema
73795	5.75	3.75	2.00	4+	86.3+*	75	71.3	
82756	5.63	3.55	2.08	2+	55.4	59–64		
81512	5.51	3.16	1.90	2+				Emaciated and unable to take food or fluids
24341	5.34	2.96	2.38	3+	59.9	64–68	52.6	
56404	5.30			3+				Emaciation marked
54174	4.97			3+	62.8	69	50.4	
82465	4.97	3.42	1.55	2+				Patient stated he had lost weight
63611	4.96	2.92	2.04	2+	57.4	64	54.0	

* Patient could not be weighed until two days after this determination.

Table 2 gives the protein values in each case at the time of the first observation when there was obvious heart failure. The presence and degree of edema are also noted. Finally an attempt has been made to estimate the nutritional state of each patient. These estimations are

based on comparisons between the weights of the patients before they became ill, while they were suffering from heart failure with edema, and, in those that improved, after edema had disappeared. The data are arranged according to the serum protein values. General inspection of the weight records and remarks shows quite conclusively that the first patients, those with high proteins, are normally or well nourished, while those with low proteins are distinctly malnourished. Either their weights with edema are little in excess of the normal or else the weights after diuresis give evidence of considerable emaciation.

Certain exceptions to the rule deserve especial consideration. Number 60084, with a weight of 41.6 kilos, was obviously emaciated. His serum proteins, however, were quite normal, 6.91 per cent, and albumin was 4.05 per cent. The patient was desperately ill and vomiting so continuously that he was unable to take food or fluids and had become dehydrated. The high protein and albumin figures are probably the result of hemoconcentration. The relatively high globulin value, 2.86 per cent, supports this explanation. Numbers 6099 and 4607 have high proteins in spite of weight losses of 10 or more kilos. In these cases, however, albumin is distinctly reduced, 3.88 and 3.61 per cent, the protein concentration being maintained by abnormally high globulin, 3.42 and 3.24 per cent. Number 87471 again had normal proteins, although he was 8 kilos below normal weight. Strictly speaking this case should be omitted from the table because the determination was not made until two weeks after hospital admission, during which there had been steady clinical improvement and return of compensation. Number 87704 represents an exception of the opposite nature. In this case the proteins were low without evidence of malnutrition. Albumin, however, is quite normal; the protein deficiency is entirely referable to reduction of globulin.

The effect of malnutrition on serum proteins appears to be confined entirely to the albumin fraction (8). For this reason better correlation is found, in accordance with expectation, between the state of nutrition and the concentration of serum albumin. In the 11 observations with albumin below 4 per cent, when normal weight could be compared with edema-free weight, there was found to have been a weight loss of from 3 to 21 kilos. With the two exceptions noted above, 60084 and 87471, patients with albumin greater than 4 per cent had suffered no loss of weight.

Such consistent correlation seems sufficient proof that the serum albumin deficits of heart failure are due to malnutrition. The histories leave no doubt that anorexia is the chief cause of the malnutrition, with nausea and vomiting frequently acting as contributory factors.

The nature of the protein fluctuations in heart failure is further elucidated by certain individual cases in which repeated observations were made.

Number 82039 (see Figure 2), a male, 60 years old, with syphilitic heart disease and aortic insufficiency, was admitted to the hospital January 4, 1930, without edema, but suffering from severe dyspnea and orthopnea which had developed progressively during the preceding four weeks. His weight, which had previously been 68 kilos, was only 64. Serum albumin was only 3.73 per cent, although total protein was within normal limits. He responded well to treatment and was discharged from the hospital, without symptoms or signs of heart failure, January 29, 1930. At home his condition rapidly deteriorated again. February 18, he was readmitted with the previous symptoms and, in addition, extensive subcutaneous edema. In spite of the edema he weighed only 67.5 kilos.

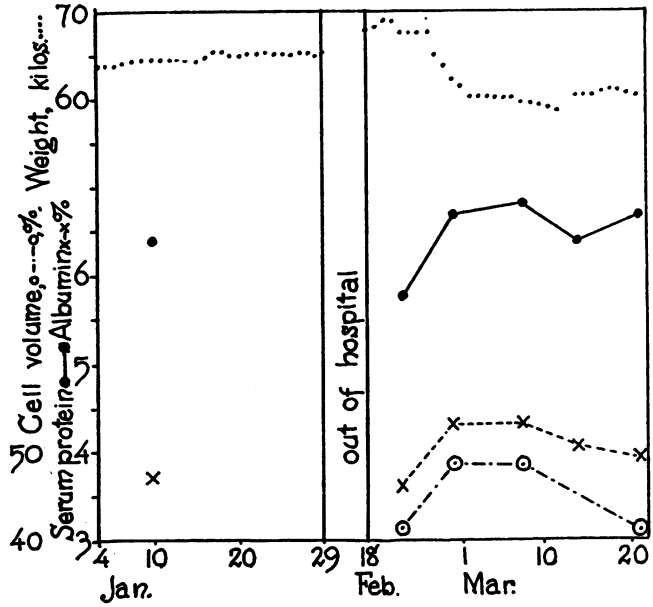

FIG. 2. CASE NUMBER 82039. COURSE OF SERUM PROTEINS DURING RECOVERY FROM HEART FAILURE.

Albumin had fallen to 3.63 per cent. Under treatment with rest, digitalis and restricted fluids edema diminished rapidly. By February 28 there was only slight pitting of the ankles, and by March 7 all edema had disappeared. The weight, meanwhile, had fallen, first to 62, finally to 60.5 kilos. Although there is little indication in these weights that nutrition had improved, albumin had risen to 6.40 per cent. At first sight this would seem to refute the theory that the albumin deficiency is connected with the state of nutrition. In this case blood cell volumes were determined by means of the hematocrit. If the cell volumes are compared with the protein values, it will be seen that albumin and cell volume rise together during the period of digitalis diuresis and fluid restriction, to

fall again when edema has been eliminated and more liberal amounts of fluid are given. The natural deduction is that the albumin increase is due to temporary hemocentration. This inference appears the more probable, because globulin and albumin rise together.

Similar evidences of temporary hemoconcentration are seen in other cases, especially when fluids are restricted during periods of diuresis. The kidneys in these cases appear to excrete fluid from the serum more rapidly than it is withdrawn from the tissues. During this period of blood concentration, in the case under discussion, blood nonprotein nitrogen rose from 23 to 50 mgm. per 100 cc. in spite of clinical improvement, to fall subsequently, even when the dietary protein was increased. This phenomenon of dehydration azotemia is well recognized.

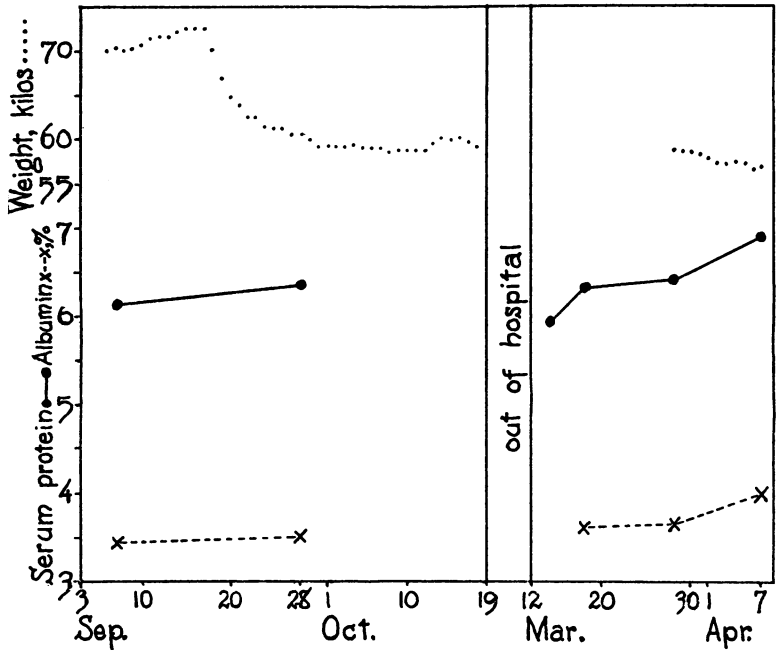

FIG. 3. CASE NUMBER 79555. COURSE OF SERUM PROTEINS DURING RECOVERY FROM HEART FAILURE.

Number 79555 (see Figure 3), a male, 80 years old, with arteriosclerotic heart disease and slight hypertension, was admitted to the hospital September 3, 1929, with severe dyspnea, orthopnea, cyanosis, enlargement of the liver, pulmonary congestion and massive edema of the lower extremities and the lower part of the trunk. On September 7, when his condition was little altered, serum protein was 6.16 per cent, with albumin 3.46. With all his edema he weighed at this time no more than he had weighed before his illness. Under treatment he improved rapidly, and was dis-

charged on October 19, free from edema. September 28, at the end of his diuresis, his weight had fallen to 60.5 kilos, 10 kilos below his normal weight. The serum albumin had not changed appreciably. March 14, he was readmitted with all his previous symptoms and signs and, in addition, ascites. He was too ill to be weighed. The serum protein had fallen still further. In view of his record of weight loss he was given, from the first, a diet containing 80 grams of protein and 2500 calories. With this and other therapeutic measures he had a rapid and profuse diuresis. During the diuresis the proteins rose somewhat in spite of the extreme loss of weight.

After diuresis was apparently complete albumin rose rapidly from 3.68 to 4.02 per cent, although the weight did not increase. Determinations of the nitrogen metabolism during the period between the last two observations show that the patient was daily storing nitrogen equivalent to a little more than 30 grams of protein. Restoration of the body protein stores was, therefore, proceeding rapidly. In recovery from famine edema Ling's (9) data show that reconstitution of serum albumin occurs rapidly after administration of adequate diets and may be complete before body weight has returned to the normal level. The same course of events, illustrated by this case, and, to a lesser extent by the preceding one, is seen during the recovery period in other patients who were subjected to frequent examinations.

DISCUSSION

According to Starling's (10) theory passage of fluid between the blood stream and the tissue results from the interplay of two forces: the hydrostatic force of the capillary blood pressure, which tends to drive fluid out of the vessels, and the osmotic pressure of the non-diffusible colloids, chiefly serum proteins, which tends to draw fluid back from the tissue spaces into the blood stream. In nephrosis and in malnutrition reduction of the oncotic pressure is chiefly responsible for the production of edema, which has been found to occur only when the serum proteins, especially serum albumin, fall below a certain level (8). In heart failure, presumably, increase of capillary blood pressure, the result of venous congestion, is the main cause of edema. For this reason exact correlation between serum oncotic pressure and edema production is neither to be expected nor found.

Edema may be associated with any protein or albumin concentration. One can conceive of extreme conditions in which hydrostatic pressure became so great that fluid was forced from the vessels until proteins rose far above the normal level and a high grade of hemoconcentration developed in the presence of edema. In a moderate degree such a state is illustrated by the vomiting case, 60084, noted above, and during diuresis and fluid restriction, in 82039 (see Figure 2 and text above). A more

striking instance was observed in a patient with arteriosclerosis involving both heart and kidneys. The subject, a woman of 60, when admitted to the hospital, had general anasarca and was vomiting frequently. The serum protein concentration at this time was 9.13 per cent, the red blood cell volume 33.6 per cent, the oxygen capacity of the blood 17.3 volumes per cent. As she improved under rest and digitalis the proteins fell to 7.90 per cent, the cell volume to 28.9 per cent, and the oxygen capacity to 15.1 volumes per cent. The parallel fall in all 3 functions is almost conclusive evidence that the serum protein changes during this period were due chiefly or only to dilution of the blood to its normal volume by fluids withdrawn from the edematous tissues.

Although edema may, if capillary blood pressure rises significantly, occur at any protein value, its production can proceed only to the point where the mean capillary pressure equals the oncotic pressure. If the latter is reduced by reason of serum protein deficiency the same degree of congestion will produce a greater degree of edema. It is not, therefore, entirely without significance that edema (Figure 1) is more consistently found in patients with low serum proteins. From a therapeutic point of view it would seem reasonable, certainly, to direct some attention to the prevention or correction of serum albumin deficits. As these appear to be referable to malnutrition, the common practice of restricting diet, and especially protein, in heart failure, may represent misdirected effort. By proper choice of foods a diet containing reasonably generous quantities of protein and adequate calories may be given in a form which will not overtax the digestion of even an elderly arteriosclerotic with heart failure. This is well illustrated in case 79555, cited above. Such a diet can also be provided without an excess of salt or fluid. Heart failure is, and should rationally be treated as, a wasting condition, with only the necessary compromises for the digestive disturbances by which it may be accompanied.

How large a part increased capillary permeability may play in the production of cardiac edema it is hard to say. Experiments of Krogh (11), Landis (12) and others have demonstrated that if venous obstruction, with consequent impairment of tissue oxygenation, becomes sufficiently great, the capillary walls will permit protein to escape. Serous effusions from patients with heart failure contain distinctly higher concentrations of protein than do the almost protein free effusions of nephrosis (4, 5). Although loss of serum proteins in this manner is probably a minor cause of serum protein depletion, it may, nevertheless, contribute distinctly to edema formation by reducing the effective oncotic pressure of the serum. This is, of course, measured, not by the actual concentration of protein in the serum, but by the difference between the concentration of protein in the serum and that in the interstitial fluids. Under normal conditions the latter is so small as to be negligible. If it becomes increased the serum protein must rise by an equal increment to balance the same capillary blood pressure.

CONCLUSIONS

1. In patients with heart failure serum albumin is frequently reduced.

2. Although edema of heart failure may occur even when serum protein and serum albumin are at or above the normal level, it is more commonly associated with some degree of albumin deficiency.

3. The albumin deficits appear to be directly referable to malnutrition.

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