THE PATHOLOGIC PHYSIOLOGY OF PELLAGRA: *II. The Serum Albumin and Globulin*

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THE PATHOLOGIC PHYSIOLOGY OF PELLAGRA

II. The Serum Albumin and Globulin

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The only determinations of serum protein in pellagra previously reported are those of Ballif, Rennescu and Reznic (1). They used the combined refractometric and viscometric methods in the study of 60 pellagrins. They report only the average and range of their results. The average total serum protein was 7.3 per cent, and the range from 9.3 per cent to 5 per cent. They noted a tendency to abnormally low albumin globulin ratio.

METHODS

Blood for analysis was drawn after an over night fast. It was collected under oil without stasis or exposure to air and without anticoagulant, and time was allowed for clotting and retraction of clot. After centrifugation the serum was pipetted off. Serum albumin and globulin were determined by Greenberg's method (2). This method employs Howe's procedure for separation of the fractions by precipitation of globulin with sodium sulphate and Wu's (3) method of colorimetric estimation. The phenol reagent of Folin and Ciocalteu (4) was used. Values obtained by this colorimetric method agree closely with those obtained by the Kjeldahl method.

The patients were kept throughout on a daily diet described elsewhere (5) containing more than 100 grams of protein of good biological quality and rich in vitamins.

CASE I
SERUM PROTEINS PER CENT
N
ŒDEMA
SKIN STATE
DIARRHŒA
TRANS-FUSION
TRANSFUSION

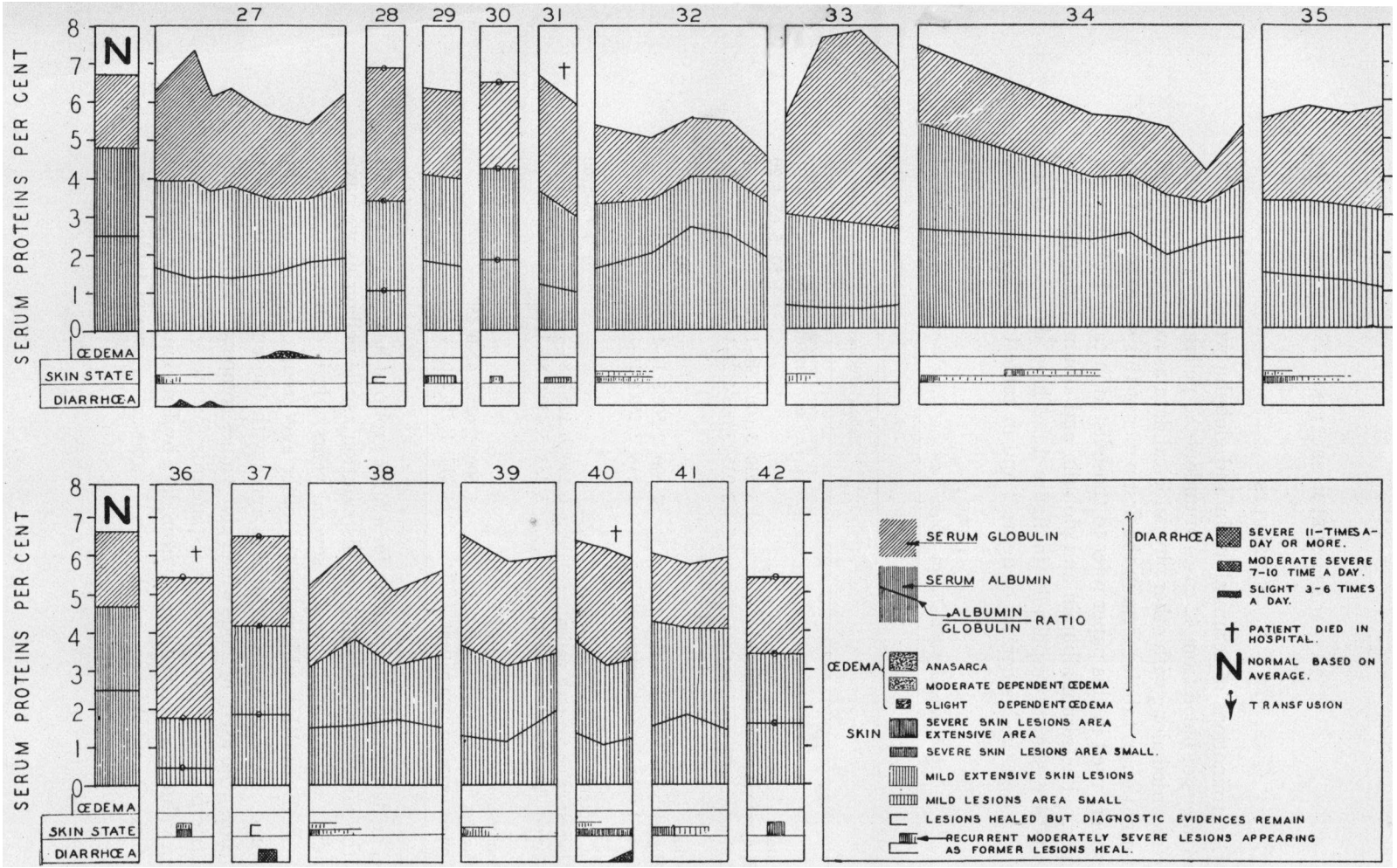
SERUM PROTEINS PER CENT
N
27
28
29
30
31
32
33
34
35
ŒDEMA
SKIN STATE
DIARRHŒA
36
37
38
39
40
41
42
SERUM GLOBULIN
SERUM ALBUMIN
ALBUMIN / GLOBULIN RATIO
ŒDEMA
ANASARCA
MODERATE DEPENDENT ŒDEMA
SLIGHT DEPENDENT ŒDEMA
SKIN
SEVERE SKIN LESIONS AREA EXTENSIVE AREA
SEVERE SKIN LESIONS AREA SMALL.
MILD EXTENSIVE SKIN LESIONS
MILD LESIONS AREA SMALL
LESIONS HEALED BUT DIAGNOSTIC EVIDENCES REMAIN
RECURRENT MODERATELY SEVERE LESIONS APPEARING AS FORMER LESIONS HEAL.
DIARRHŒA
SEVERE 11-TIMES A-DAY OR MORE.
MODERATE SEVERE 7-10 TIME A DAY.
SLIGHT 3-6 TIMES A DAY.
PATIENT DIED IN HOSPITAL.
NORMAL BASED ON AVERAGE.
TRANSFUSION

FIG. 1

RESULTS

Determinations of serum albumin and globulin were made on 129 specimens of blood from 42 cases of undoubted pellagra. The results are recorded along with other physiological data as well as the clinical information in tabular form in the first paper of this series (5). Case numbers used in this paper refer to those listed in table 1 of the first paper. The serum albumin and globulin and albumin-globulin quotients are shown graphically in figure 1. These data are further analyzed in the histograms of figure 2 and in table 1 of this paper.

TABLE 1

Summary of the serum albumin and globulin values

	Pellagrins			Normal standards	
	Average	Median	Range	Average	Range
	gms. per 100 cc.	*gms. per 100 cc.*	*gms. per 100 cc.*	*gms. per 100 cc.*	*gms. per 100 cc.*
Albumin				4.80	5.65–4.20
Highest value for each patient	3.530	3.600	5.46–1.71		
Lowest value for each patient	3.035	3.093	4.22–1.64		
Globulin				1.90	2.91–1.32
Highest value for each patient	2.690	2.500	5.11–1.19		
Lowest value for each patient	2.348	2.250	4.18–1.19		
Total protein				6.70	7.65–5.60
Highest value for each patient	6.140	6.125	7.84–4.19		
Lowest value for each patient	5.433	5.430	6.85–3.42		
Albumin-globulin quotient				3.19	4.20–2.20
Highest figure for each patient	1.509	1.625	2.62–0.45		
Lowest figure for each patient	1.277	1.316	2.62–0.45		

The determination of values for a large group of healthy individuals of the same race, age, and sex distribution as the pellagrins we have studied will probably require several years. It is difficult to secure for study healthy subjects in the older age groups, particularly the colored. The values we now have agree with those reported by other authors who used methods which give values comparable to the colorimetric method. Our tentative standards for the normal serum protein values are derived largely from data by Bruckman, D'Esopo, and Peters (6) and Wiener and Wiener (7) and are shown in table 1.

Albumin

When only the highest albumin value for each pellagrin was considered, 4, or 10 per cent, fell within the range for normals, while 38 or 90 per cent were below the lower limit for normals. When the lowest value for each case was considered all were below the normal range, and 18 or 43 per cent were less than 3 per cent, a decidedly low value.

Changes in serum albumin content while the patient was under observation seem of particular interest. Wiener and Wiener considered 10 per cent change in an individual's serum protein level as the limit of physiologic variation. I have considered changes of greater than 12 per cent as being of possible pathologic significance. Thirty of the patients were studied more than once; 11 of these, or 27 per cent, showed no significant change in serum albumin concentration, while 14, or 47 per cent, showed decrease of more than 20 per cent, and 3, decrease of at least 40 per cent. Five patients showed definite increase in serum albumin while under study. In one (case 17) the change was undoubtedly due to dehydration from diarrhea and vomiting. For two (cases 19 and 24) the period between studies was short and the results could be partially explained by changes in plasma volume. Due to the fact that the patients left the hospital before other studies could be made, it is not known whether the gains were more than temporary. However, there was some indication of a return to normal. In another patient of this group (case 32), after a month of gradual gain in serum albumin, there was a definite loss. In only one patient (case 20) was there a return to approximately normal serum albumin values in association with striking clinical improvement.

The graph in figure 3 represents an effort to investigate correlation between the state of nutrition and the serum albumin concentration. For each patient the percentage deviation from ideal body weight is plotted against the percentage deviation from average normal serum albumin values. The lowest weight and the lowest figure for albumin for the period the patient was being studied were used. Serum albumin concentration was not always lowest for a given patient when the body weight was at its lowest. The appearance of edema sometimes caused body weight to rise even though serum albumin fell. The in-

terval between the time of lowest body weight and the time of lowest serum albumin concentration was never more than three weeks and usually only a few days. Standard for ideal weights were those of Tables IV and IX of "Medico Actuary Mortality Investigations" according to sex, age, and height. These tables, of course, give average weights, but may be used satisfactorily for determining for a given patient the ideal weight. Inspection of the spot graph shows for the whole group doubtful correlation between serum albumin and fall of weight. However, for a considerable number of the patients there appears to be correlation of some importance; the exceptions fall into interesting groups. Of those whose body weights were higher in proportion to serum albumin level, three (cases 38, 39, and 14) were characterized by the absence or mildness of gastro-intestinal symptoms. One (case 10) had ascites due to tuberculous peritonitis and edema of the extremities associated with severe anemia. In three (cases 40, 11, 36) the disease was fulminating and rapidly fatal. These instances suggest that fall in serum albumin may be a more sensitive index of disturbed nutrition in pellagra than is loss of body weight. Two (cases 9, 33) showed high globulin concentrations. There were fewer patients whose body weights were proportionately lower than their serum albumin levels. One (case 4) had syphilis; another (case 25) was not studied until after all major symptoms of pellagra had disappeared. When these eleven exceptions are excluded from the group, those remaining are too few to justify statistical analysis. For the whole group the coefficient of regression of weight on serum albumin was 0.26 ± 0.16.

The relationship of serum protein concentration to edema in the group of pellagrins was not clear. One patient (case 3) developed slight generalized edema when the serum proteins fell to very low levels and another (case 2), with almost equally low serum proteins, showed only slight dependent edema. The latter suffered from diarrhea. Three patients (cases 21, 23, 11) showed no edema in spite of low serum proteins. Four patients (cases 9, 15, 18, 22) who had no edema had serum albumin values of less than 3 per cent, but total proteins were above 5 per cent. One patient (case 10) with ascites and tuberculous peritonitis showed marked edema when the serum albumin was between 2.50 per cent and 3 per cent and the total proteins

5 per cent or 6 per cent. In this case there was an extremely high plasma volume and a very low hematocrit reading. The patient suffered from dyspnea on slight exertion. Three patients (cases 16, 17, 20) showed edema when the serum proteins were practically normal. Two of these (cases 16, 17) showed marked oliguria due to diarrhea and vomiting, and edema appeared a short time before death. One patient (case 26) was so edematous five days before our study that unwarranted diagnosis of congestive heart failure was made although edema had disappeared at the time of our study. Her serum albumin was 3.16 per cent and total proteins 4.75 per cent.

Diarrhea

For 26 patients (cases 1 to 26) diarrhea was a symptom of considerable importance, while in the remaining 16 (cases 27 to 42) there was no diarrhea or it was either mild or of brief duration. Considering only the lowest serum albumin value for each patient, the average for the group with diarrhea was 5 per cent lower, and the average for the group without diarrhea 8.1 per cent higher, than the corresponding general average for the whole group of 42 pellagrins. When only high albumin values were considered the differences between averages was in the same direction but of less magnitude.

The value of serum albumin concentration as an index of severity of pellagra may be judged by examining the values for the fatal cases. Considering those who died within three weeks after study, and were not known to suffer from heart disease and were not dehydrated, there were 9 cases. The average for their lowest serum albumin was 2.20 per cent as compared to 3.03 per cent, the corresponding figure for the group as a whole.

Globulin

The histogram in figure 1 shows the tendency to high serum globulin values in our group of pellagrins. When only the highest value for serum globulin for each patient was considered, only three, 7 per cent, were less than 1.90 per cent, which is an average value for normal globulin; and when the lowest value for each patient was considered, there were only 9, 21 per cent, with figures 1.90 per cent or less.

There were 13 patients in the group whose highest globulin values

were greater than 3 per cent. Two had luetic heart disease (cases 18 and 31) another (case 4) a positive Wassermann reaction without clinical evidence of syphilis, four (cases 2, 24, 28, 32) had stricture of

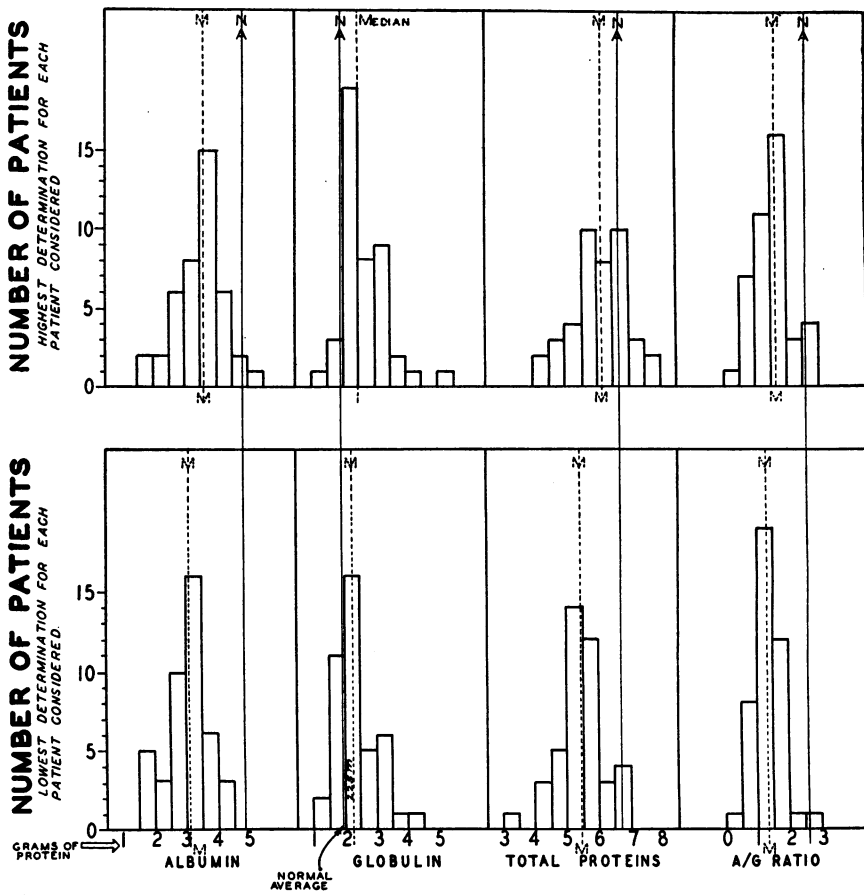

FIG. 2. HISTOGRAMS SHOWING DISTRIBUTION OF VALUES FOR SERUM ALBUMIN; SERUM GLOBULIN AND ALBUMIN-GLOBULIN RATIO

the rectum. One patient of the 13 suffered from intestinal tuberculosis (case 10), and another had active gonorrhea (case 9). Four of the 13 patients (cases 15, 36, 48, and 22) had no complications, but had such severe skin damage as to involve tissue necrosis. When one

excludes the globulin values for the above mentioned 9 patients with syphilis, tuberculosis, gonorrhea and stricture of the rectum, and the values for two other cases of syphilis, the tendency toward high globulin values becomes much less pronounced. The average of the highest values for the 31 uncomplicated cases was 2.415 as compared to 2.690 for the entire group of 42. The median was 2.324 as compared with 2.500.

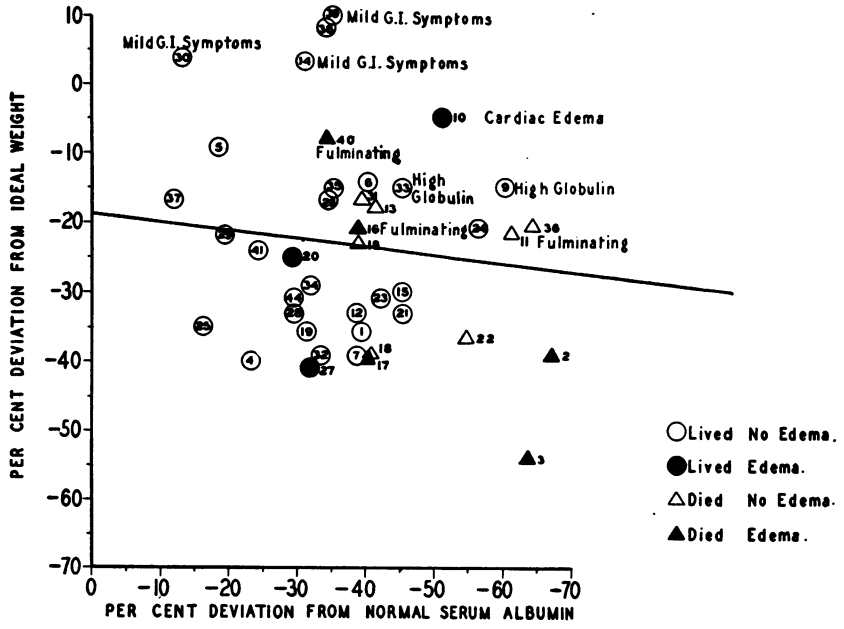

FIG. 3. SPOT GRAPH SHOWING RELATIONSHIP BETWEEN UNDERWEIGHT AND CONCENTRATION OF SERUM ALBUMIN, BASED ON LOWEST SINGLE WEIGHT AND LOWEST SERUM ALBUMIN VALUE FOR EACH PATIENT
Line shows regression of weight on serum albumin

The concentration of serum globulin in a given individual tended to be much more constant from week to week than that of albumin. Three patients (cases 28, 32, 34) showed irregular fluctuation in globulin concentration. It may be of some interest that they suffered from neuritis. Two patients (cases 33, 35) improved clinically as serum albumin values gradually fell and the globulin concentration

increased. One patient (case 17) died soon after a definite drop in globulin. Another patient (case 2) began a steady decline clinically and in serum albumin concentration immediately after a brief period of decreased globulin concentration.

Total Proteins

As indicated by the histograms in figure 2, total serum proteins, that is albumin plus globulin, tended to be low in our group but less strikingly so than albumin, due to the many high figures for serum globulin. Considering only the highest value for each case, there were 11, 26 per cent, with total serum protein concentration of 6.70 per cent or more while 31, or 74 per cent, were less than this normal average. However, 31, or 74 per cent, of the 42 cases showed total protein values in the normal range, that is 5.60 per cent or greater. When only the lowest value for each case was considered all but two, 95 per cent, were below the normal averages, 15, or 36 per cent, were within the range for normal and 27, or 64 per cent, were below 5.60 per cent, the lower limit for normals.

DISCUSSION

Our knowledge of the physiology of the serum proteins is still extremely meagre, and any explanation given at present for abnormal serum protein levels is based on incomplete evidence. However, the work of Kohman (8), Maver (9), and Frisch, Mendel and Peters (10), on experimental animals has shown that protein starvation produces a reduction in serum proteins. Low serum proteins were found in patients suffering from malnutritional edema by Schittenhelm and Schlecht (11) and by Jansen (12). Bruckman, D'Esopo and Peters (6) studied the serum proteins in poorly nourished patients with diabetes, with obstructions of the gastro-intestinal tract, and with chronic pulmonary infections and found low values. Wiener and Wiener (7) found low albumin values in patients with a variety of infections. Their report does not mention the state of nutrition.

It has now become well known that there exists, in certain types of nephritis, lowering of serum proteins, especially of albumin. This is especially true of those patients who suffer from prolonged, marked albuminuria. Repeated examinations of the urine for albumin in our

cases excluded albuminuria as the mechanism responsible for low serum albumin.

Many observers have been impressed with the faulty or inadequate protein of the pellagrin's dietary. It has been considered by many as the chief factor in the pathogenesis of the disease. If protein starvation were a major cause of the disease, one would expect to find low serum albumin in the early stages of pellagra. The patients who were studied in the very early stages of the first attack showed values nearly normal. This observation in addition to the observed tendency for serum albumin to fall after the diagnostic evidences of pellagra had disappeared, has led me to suspect that the low serum albumin concentration was a result of pellagra, and represents impaired digestion or absorption of protein, and is dependent upon injury to the alimentary tract by pellagra. It is a well known fact that damage to the alimentary tract in pellagra is a frequent if not invariable occurrence. It may involve any portion of the alimentary mucosa from lips to anus, and has been described histologically by Denton (13) as degenerative in character. This injury is manifested clinically by glossitis or stomatitis, by dysphagia and esophageal pain, by vomitus streaked with blood in certain very severe cases, by diarrhea and abdominal discomfort and by injection of the rectal mucosa as viewed through the proctoscope. Many observers have been impressed by the idea that, in a given patient, pellagra may involve, predominantly, only one system, whether this be the skin, alimentary tract or nervous system, and causes little or no damage to the other systems. When the alimentary tract of pellagrins, who died during the earlier stages of the disease, was examined at autopsy the distribution of injury, as indicated by areas of injection, superficial erosion or ulceration, was found to be quite irregular. In one instance the mouth and esophagus and lower colon showed the greatest damage, while in another the upper small intestine was chiefly involved. Even in a given portion of the small intestine itself, the injury seems to involve irregular patches of several square centimeters in area, leaving others apparently undamaged. The value of the available histological studies of the alimentary tract in pellagra is impaired by the possibility of postmortem auto digestion, by an insufficient variety of cases, and by inadequate correlation with clinical study. The pathologist reported extreme

atrophy of the mucosa of the small intestine for the pellagrin, (case 3) who, in spite of taking an excellent diet, was the most striking example of undernutrition.

It is evident from the work of others, already cited, that low serum albumin is to be found in many conditions. I have studied a variety of gastro-intestinal conditions, especially those with diarrhea as a chief symptom, and have found low serum albumin in a number. Serum albumin may fall rapidly in acute bacillary dysentery, but it is striking how rapidly it may return to normal with termination of the disease. In acute dysentery it is easy to imagine that there is a considerable loss of serum protein from the intestinal mucosa as a part of the exudative inflammatory processes. This may also happen in pellagra during the stage of acute damage to the alimentary tract. Three cases of chronic moderately severe diarrhea, apparently non-pellagrous, were found in which there were normal serum proteins.

It is possible that injury to the pancreas may occur in pellagra resulting in deficient secretion of the proteolytic enzymes. In another article of this series (14), evidence is presented to show that in pellagra serum electrolytes are frequently diminished. This probably represents excessive loss of electrolytes in the feces. Excessive secretion of pancreatic juice may be involved, followed by a period of hypofunction.

These data suggest that, in many instances, the dependent edema of pellagra is due to decreased colloid osmotic pressure of the blood plasma. Goldberger and his co-workers (15) considered the edema in their group of pellagrins, in the Georgia Insane Hospital, as evidence of beriberi. The edema of beriberi is not well understood and may itself be due partly to low serum proteins. Most of our patients had been taking abundant antineuritic vitamin. Why some pellagrins did not develop edema in spite of low serum albumin is not known. Low hydrostatic pressure in the capillaries is one possible explanation, since there was definite arterial hypotension in these particular patients as well as in nearly all the other pellagrins. Another possible factor is the ease with which water escapes from the serum into the lumen of the gut in association with diarrhea. Low electrolyte content of the tissues may be of importance.

The very low serum albumin in the patients who died of pellagra,

and the relatively normal values in those with mild pellagra indicate that determinations of serum albumin are of importance as furnishing an index of severity of the disease, and as a basis for prognosis.

Is one justified in demanding that serum albumin return to normal before classifying the patient as cured? If my suggestion that the pellagrin's inability to build up serum albumin to a normal level is due to damaged digestion, is supported by further work, then the situation of a pellagrin suffering from malnutrition, in spite of adequate diet, will be similar to that of a patient who has passed through one attack of acute nephritis and then suffers from impaired kidney function.

SUMMARY

Determinations of serum albumin and globulin are reported for 129 specimens of blood from 42 pellagrins and the results analyzed in table, graph and histograms.

Every patient, at some time during the period of study, had a serum albumin value below 4.20 per cent, and 95 per cent of the patients had at least one value less than 3 per cent.

There was little tendency for serum albumin concentration to return to normal, and frequently there was a considerable decrease during the consumption of a diet adequate in protein and vitamins.

Two patients died long after characteristic evidences of pellagra had disappeared, and in spite of taking an excellent diet, with a serum protein content similar to that seen in protein starvation. The mechanical effects of diarrhea on digestion did not seem to constitute a major factor in the chronic malnutrition observed.

For part of the group, the decrease in concentration of serum albumin seemed to be proportional to the degree of undernutrition as indicated by body weight. Exceptions were chiefly individuals whose body weights were higher for their serum albumin values than the remainder of the group and who had very mild gastro-intestinal symptoms or fulminating rapidly fatal pellagra or edema, or whose serum globulin values were high.

Serum globulin concentration tended to be slightly increased in the patients with uncomplicated pellagra, except in the patients with skin necrosis, certain chronic infections and stricture of the rectum, who showed moderate increase.

Total serum protein concentration tended to be low but not as low, relatively, as serum albumin.

CONCLUSIONS

In pellagrins there is a tendency toward low serum albumin concentration, which seems to develop after the disease is manifest and frequently remains long after the diagnostic evidences of the disease have disappeared and in spite of adequate diet.

It is suggested that the abnormality is one of disturbed digestion, causing difficulty in the absorption of proteins, dependent upon injury of the digestive system by pellagra.

Serum protein determinations are of value in estimating the severity of pellagra and in furnishing one criterion of cure.

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