Henry Ford Hospital Medical Journal

Volume 7 | Number 3 Article 8

9-1959

Analbuminemia With The Nephrotic Syndrome

Gerald T. Havey

C. E. Rupe

Robert I. McClaughry

ANALBUMINEMIA WITH THE NEPHROTIC SYNDROME

GERALD T. HAVEY, M.D.,* C. E. RUPE, M.D.*
AND ROBERT I. MCCLAUGHRY, M.D.**

INTRODUCTION

Extreme hypoalbuminemia was described as far back as 1924, when Kollert[1] studied a patient with "chronic nephrosis" whose serum albumen was less than one gram. More recently, Hardwicke and Squire in 1955[2] described a 37 year old white female with the nephrotic syndrome whose serum albumin was 1.8 grams and a 14 year old white female whose serum albumin was 1.6 grams. Gitlin and Janeway[3] also in 1955 studied three children with the full-blown nephrotic syndrome whose serum albumin was 0.58 grams, 0.40 grams and 0.61 grams respectively. In 1957, Rytand[4] in commenting on the polycyclic nephrotic syndrome mentioned a 52 year old white male with recurrent edema and anasarca whose serum albumin was 1.8 grams.

One other case of analbuminemia has been reported in the literature Bennold[5] reported the absence of serum albumin in a woman with edema and menstrual irregularities at Tuebingen, Germany in 1954. One other case of analbuminimia (serum electrophoresis) in a 55 year old white male with generalized anasarca, pleural effusions and thrombophlebitis has been studied at this hospital.[6] This patient, unfortunately, was lost to followup in December 1957.

CASE REPORT

A 46 year old white housewife was first seen in June 1957, complaining of a productive cough, dyspnea on slight exertion and pronounced ankle edema. The patient dated her symptoms back to age 21 when she first knew of bronchiectasis associated with frequent upper respiratory infections. Seven years later, during her first pregnancy the patient developed dyspnea and ankle edema and heart disease was suspected. In the subsequent 5 years the patient developed more dyspnea and ankle edema during her pregnancies and during the menses.

In January of 1957 the patient was admitted to another hospital for the treatment of pneumonia. During the course of hospitalization bronchiectasis was found in seven pulmonary segments. At this time, however, congestive heart failure was thought to be present and surgery was indefinitely postponed. After a good response to digitalis and diuretics, the patient was discharged the latter part of January.

Approximately 3 months later the patient was re-admitted because of progressive ankle edema. Proteinuria (1 plus) was present. The patient responded well to diuretics. After a four pound weight loss in four days and less noticeable edema there was no further diuresis with mercurials. Two weeks after admission a four plus albuminuria was found. The albuminuria persisted for about 11 days. The

*Department of Medicine.
**National Research Council, Washington, D.C.

possibility of a salt losing nephritis was considered but there was no response to hypertonic saline solution.

The non-protein nitrogen on admission was 40 mg. % and gradually rose to 95 mg. % over the six week period of hospitalization. The lack of response of the patient to diuretics posed the question of electrolyte imbalance. The electrolytes, however, were close to normal values (sodium — 130 MEQ, potassium 5.1 MEQ., CO_2 25.4 MEQ., Chloride 90 MEQ.) The serum proteins were measured during the third week of hospitalization and a marked hypoporteinemia was found (total protein 4.7 Gm. %, albumin 0.9 Grm. %, globulin 3.8 Gm. %). Liver function tests were completely normal except for a serum cholesterol of 970 mg. % with 60% esterified. Considering the possibility of amyloidosis, a Congo red test was done and found to be normal. Kidney biopsy was done for further verification and again no

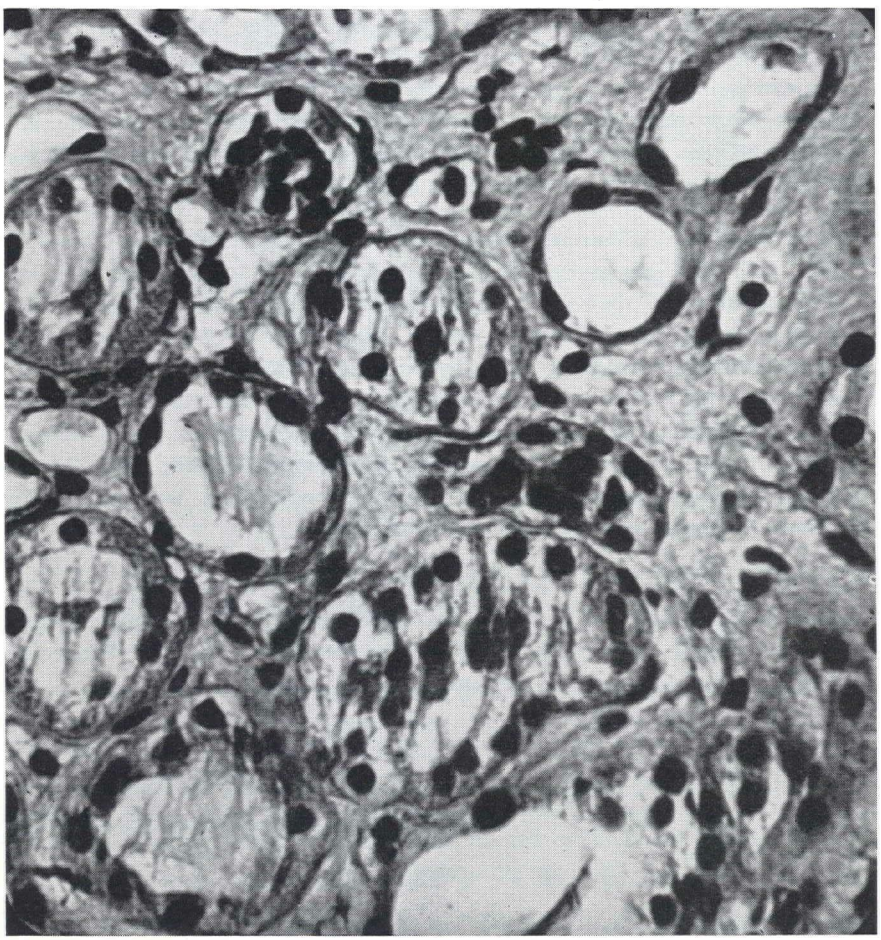

Figure 1
Needle Punch Biopsy.

amyloid was found. (Fig. 1) The biopsy was not adequate for glomerular changes but mild interstitial nephritis was reported. An intravenous pyelogram showed poor renal function but no structural abnormality was present.

A course of ACTH was started approximately 4 weeks after admission according to the following schedule: 25 U. ACTH i.v. slowly over 8 hours for 3 days, 50 U. ACTH gel i.m. for 5 days, followed by a good eosinophil response but no definite diuresis. Within 48 hours there was subjective improvement in the patient and some degree of drop in the proteinuria. The azotemia showed improvement in that the NPN dropped to 55. Eight days after the corticosteroid therapy was given the patient was transferred to the Henry Ford Hospital on June 6, 1957.

On admission the physical examination showed an emaciated 46 year old white female with evidence of anasarca and avitaminosis. The thyroid was small. There was no lymphadenopathy. Dullness was present over the right base and bronchial breathing was present. Inspiratory rales were present over both bases. The heart was not enlarged. The heart tones were of good quality. No murmurs were present. The apical rate was 25/4 and blood pressure was 110/75. The liver was percussed 2 centimeters below the right costal margin and a fluid wave was present. A four plus ankle edema was present with 3 plus pretibial edema and 3 plus sacral edema. The abdominal wall contained subcutaneous edema.

The hemoglobin concentration was 13.4 gm/100 ml. The white blood count was 21,950, with 82% polymorphonuclear leucocytes, 7% lymphocytes, 5% eosinophils, 2% basophils, 4% monocytes. The platelets were slightly increased. The red cells were normocytic. The urine was weakly acidic (pH 6, pH 5), specific gravity 1.016, 4 plus albumen, contained many hyaline casts with waxy lipoids, without red blood cells. The LE cell preparation was negative. The anti-streptolysin titer was 12 units per cc. Blood chemistries were: Fasting blood 94 mg %, NPN 72 mg. %, total lipids 2070 mg. %, calcium 5.3 mg. %, phosphorus 11.6 mg. %. The kidney function was decreased markedly as the phenolsulfonphthalein was found only in trace amount. The urea clearance, standard, was 14 ml.

Chest fluoroscopy showed a honeycomb pattern in each base suggesting bilateral lower lobe bronchiectasis. The heart was small and pulsation was adequate to exclude constrictive pericarditis. The diaphragmatic excursions were adequate. Electrocardiogram showed small complexes and inverted T waves in all leads.

During the next twelve days the edema remained unchanged and weight showed no downward trend. Retrograde pyelograms were negative. On June 18, 1957, the patient was given two units of salt-free albumin after a 24 hour urine was collected for albumin and the blood taken for an electrophoretic pattern. The electrophoretic patterns of the blood and urine are illustrated in Fig. 2.*

The forty-eight hours following the albumin administration a weight drop from 127 to 124 pounds was noted. The NPN rose to 80 mg. %. On June 26, 1957, the

*Immuno-chemical determination of serum at Detroit Cancer Institute showed 0.628 mcg. of albumen.

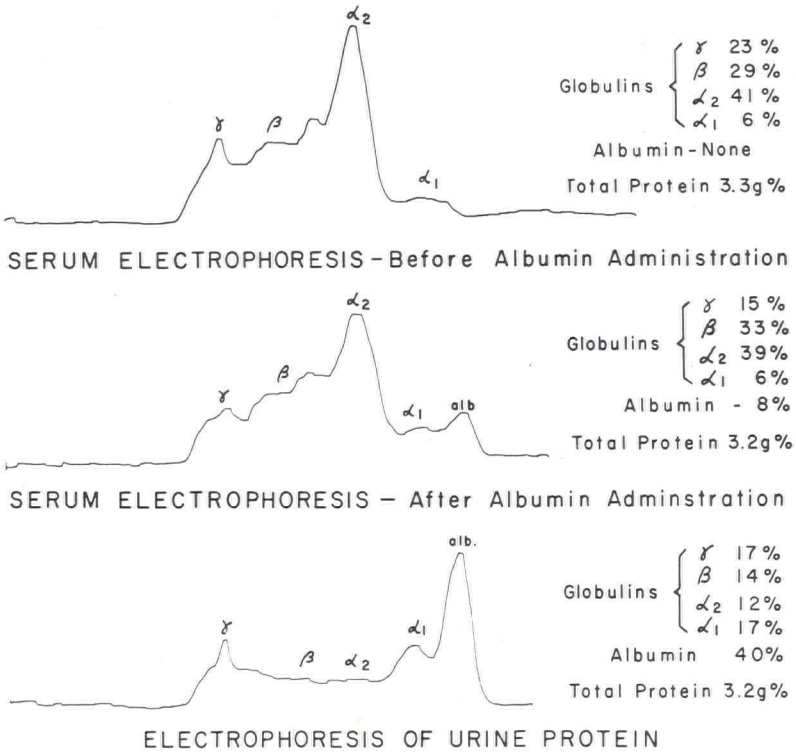

Figure 2

patient was again started on aqueous ACTH (75 U.) without any noticeable effect. One month after admission the patient became extremely restless and then quickly expired. Autopsy permission was not granted.

DISCUSSION

This patient showed all the clinical features of hypoproteinemia, advanced renal disease and bronchiectasis. This case illustrates the complete depletion of the body pool of serum albumen.

In its steady state the rate of synthesis of any constituent in the body pool must equal the rate of dissipation or utilization. In other words, the total body pool of serum protein in its state of dynamic equilibrium is dependent upon its volume, its concentration and the rate at which the input, output and interconversion of the individual components occur.[7]

The total exchangeable pool is equal to the total amount of substance in the body which is available for exchange with additional or newly synthesized molecules of that specific protein.[3] Citrin et al., by tagging albumin molecules with 1131 found that the total albumin pool was 360 Gms. with a daily turnover of about 17.7 Gms. per day.[8]

On the other hand, the turnover time of albumin is the amount of time required for half of the body pool of that protein to be lost. In normal adults the turnover time for albumin is about 11 days.[9] This reduction in the body pool is a stimulus for the hepatic cells to synthesize more albumen.[10]

Kerr, Hurwitz and Whipple presented the first experimental evidence that diet influenced favorably the regeneration of depleted plasma protein. Beef serum was found to favor production of three times as much plasma protein by the hepatic cells as beef heart and more than five times that of beef stomach after plasmaphoresis of dogs to 4 grams of plasma protein. On the other hand, they noted a definite lag in regeneration of serum protein of Eck fistula dogs following acute plasma depletion. Thus, the liver was singled out as the main synthesizing compartment.[11]

As to the increased rate of catabolism in the nephrotic syndrome, albuminuria seems to be of greater magnitude than synthesis of the protein molecule. The exact mechanism of proteinuria in this syndrome is controversial. Hasson and Berkman,[12] emphasize that the tubular reabsorptive mechanism was of greater importance than the glomerular factor. They stressed the tubular atrophy and interstitial atrophy seen in nephrotics secondary to renal vein thrombosis as the most probable lesion responsible for impaired reabsorption. Contrary, to this Chinard,[13] postulated increased glomerular permeability due to increased glomerular capillary pressure and Allen,[14] attributed the changes in the glomerular basement membrane as the responsible lesion in the extensive proteinuria seen the nephrotic syndrome.

The electrolyte disturbance associated with increased renal vein pressure points strongly to the tubules as a major source of dysfunction. Using inflatable balloons Farber, et al.[15] produced elevated pressures at various levels of the inferior vena cava and found a depression of salt and water excretion whether the balloon was above or below the renal vein. Sirota and Nabotoff,[16] postulated a specific tubular effect of venous congestion to account for the depressed salt and water excretion after salt loading on a unilateral renal vein hypertension secondary to a spleno-renal vein anastomosis. Blake and his associates,[17] found that after raising the pressure in the left renal vein for 20 to 30 minutes by means of a clamp in dogs, the water and sodium excretion was depressed but glomerular filtration rate and renal plasma flow remained constant. Talbott,[18] postulated that the loss of oncotic materials from the vascular system leads to a hypovolemic state. This in turn stimulates the neuro-hypophyseal system to retain water and the adrenal to secrete more aldosterone to conserve sodium at the tubular level.

Kark in 1956,[19] reported five patients ranging from 15 to 82 with a gradual onset of edema. All had massive proteinuria, hypoalbuminemia, hypercholesterolemia, casts and oval bodies in the urine. Renal biopsy specimens showed severe tubular degeneration with much interstitial edema. Absence of changes in the glomerular basement membrane contrasted with the findings of autopsy studies of adults dying with the nephrotic syndrome. Kark compares these cases to lipoid nephrosis in children, Kaplan et al.,[20] reported dilated renal tubules with alteration in the tubular

epithelium on renal biopsy in patients with the nephrotic syndrome. Paper chromatography showed increased amino-aciduria.

The case which is presented suggests a tubular basis for the excessive proteinuria, viz. loss of concentrating power in face of low intake, acidosis in the face of alkaline urines, low urinary sodium output in the face of edema.

Since this patient presented an overwhelming hyperlipemia comment should be made on the relationship between this state and the disturbed protein metabolism in this patient.

Four fractions, free cholesterol, cholesterol esters, phospholipids, and the neutral fats comprise the serum lipids.[21] Boyd,[22] in 1937 and Ahrens in 1947, [23] found that the clear sera found in some cases of hyperlipemia was due to the phospholipids' strong surface action preventing coalescence to visible sized particles, whereas neutral fats made up a large portion of the lipemic sera.

Corazzo[24] describes essential hyperlipemia as a clinical state due to the increase in the neutral fat fraction of the blood lipids. He cites the experimental work of Thannhauser and Stanley with I131 labeled fat in which a defective fat clearing mechanism was present.

In contradistinction, alimentary hyperlipemia is a physiologic state in which the neutral fats are normally increased 4-6 hours post-prandially without a rise in the phospholipid fraction. Secondary hyperlipemia is associated with diabetes mellitus, the nephrotic stage of chronic glomerulonephritis, pancreatitis, myxedema, starvation, Nieman-Pick's disease and various lipoidoses, amyloidosis, renal vein thrombosis, the toxic hepatoses and the so-called "pericholangiolitic" hepatitis.

Leiter in 1931,[25] writing on the "lipoid nephrosis" pointed out a disturbed humoral clearing mechanism for the hyperlipemia rather than a disturbance in the actual oxidation and combustion of fat.

It is now generally agreed that essentially all of the cholesterol and phospholipid in human plasma is associated with polypeptides in lipid peptide complexes classified as lipoproteins (alpha or beta). The hypercholesterolemia in adults with the nephrotic syndrome is due to an increase in the plasma concentration of low density lipoproteins (sf 200-300),[26] in association with a decrease in the conversion of the low density lipoprotein to a lipoprotein of a greater density (sf 3-9). This has been attributed to either an increased concentration of the plasma with the low density lipoproteins so that there is a saturation of the normal conversion system, or there is a depression in one or more factors necessary for the conversion or clearing process.[27]

In the transfer of lipid from the blood to the tissue the lipolytic reaction acts as a transport mechanism. In this way the blood stream is cleared of lipid fractions. (Fig. 3) The triglyceride substrate (chylomicra, lipoproteins, artificial oil emulsion)

combines with the fatty acid acceptor, which is the serum albumin and calcium and is transported to the tissue depots as a fatty acid acceptor complex with the formation of glycerol as a by-product.[28] Lipoprotein lipase which is abundant in cardiac muscle and presumably activated by heparin has an enzymatic role in this hydrolysis. As such, an absence of albumin or a deficiency of lipoprotein lipase causes a decrease in the hydrolysis and a defective clearing of hyperlipemia.[29]

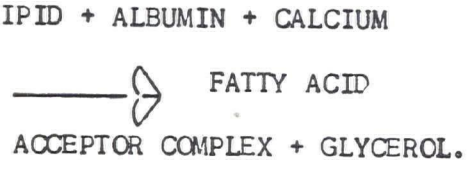

Figure 3

SUMMARY

1. A patient with the nephrotic syndrome is presented with a complete absence of serum albumin.

2. The literature is reviewed on the mechanism of proteinuria. The evidence for suggesting a tubular source of proteinuria in our case was advanced.

3. Hyperlipemia and its basis for existence in the nephrotic syndrome was discussed.

4. A plausible explanation has been offered for the observed clearing of the serum cholesterol which follows repeated infusions of serum albumin.

REFERENCES

1. Kollert, E.: Albuminuria and blood proteins, Zeitschr. f. klin. Med. 99:426, 1924.

2. Hardwicke, J., and Squire, J. R.: Relationship between plasma albumin concentration and protein excretion in patients with proteinuria, Clin. Sc. 14:509, 1955.

3. Gitlin, D., Janeway, C. A., and Farr, L. E.: Studies on metabolism of plasma proteins in nephrotic syndrome. Albumin, gamma-globulin and iron-binding globulin, J. Clin. Invest. 35:44, 1956.

4. Rytand, D. A., and Cox, A. J., Jr.: Polycyclic nephrotic syndrome, Am. J. Med. 22:297, 1957.

5. Bennold, cited by Grassman, W.: General methods of paper electrophoresis with examples of its use in medical and biochemical problems, In Ciba Foundation Symposium on Paper Electrophoresis, Boston, Little, Brown, 1956, p. 2.

6. Wilt, E. F., and Brady, N. C.: Protein electrophoresis, Henry Ford Hosp. M. Bull. 6:196, 1958.

7. Leroy, G. V.: Clinical research using compounds labelled with radioactive carbon and hydrogen as tracers, Ann. Int. Med. 42:239, 1955.

8. Citrin, Y., Sterling, K., and Halstead, J. A.: Mechanism of hypoproteinemia associated with giant hypertrophy of the gastric mucosa, New England J. Med. 257:906, 1957.

9. Sterling, K.: Turnover rate of serum albumen using I^{131}, J. Clin. Invest. 29:238, 1951.

10. Pollak, V. E., Kark, R. M., Pirani, C. L., Shafter, H. A., and Meehrcke, R. C.: Renal vein throbosis and the nephrotic syndrome, Am. J. Med. 21:496, 1956.

11. Madden, S. C., and Whipple, G. H.: Plasma proteins: their source, production and utilization, Physiol. Rev. 20:194, 1940.

12. Hasson, J., Berkman, J. I., Parker, J. G., and Rifkin, H.: Clinicopathologic study of chronic renal vein thrombosis in adults, Ann. Int. Med. 47:493, 1957.

13. Chinard, F. P., Lauson, H. D., Eder, H. A., Greif, R. L., and Hiller, A.: Study of the mechanism of proteinuria in patients with the nephrotic syndrome, J. Clin. Invest. 33:621, 1954.

14. Allen, A. C.: Clinicopathologic meaning of the nephrotic syndrome, Am. J. Med. 18:277, 1955.

15. Farber, S. J., Becker, W. H., and Eichna, L. W.: Electrolyte and water excretions and renal hemodynamics during induced congestion of superior and inferior vena cava of man, J. Clin. Invest. 32:1145, 1953.

16. Sirota, J. H., and Nabatoff, R. A.: Effects of unilateral renal vein hypertension secondary to splenorenal vein anastomosis on individual kidney function, Am. J. Med. 13:242, 1952.

17. Blake, W. D., Wegria, R., Keating, R. P., and Ward, H. P.: Effect of increased renal venous pressure on renal function, Am. J. Physiol. 157:1, 1949.

18. Talbot, N. B., Crawford, J. D., and Cook, C. D.: Application of homeostatic principles to the management of nephrotic patients, New England J. Med. 256:1080, 1957.

19. Kark, R.: New pathologic state associated with the nephrotic syndrome, Clin. Res. Proc. 4:, 1956.

20. Kaplan, B. M., Newman, J. S., Kaplan, E., Baker, L. A., and Lee, J. M.: Bilateral renal vein thrombosis and the nephrotic syndrome, Ann. Int. Med. 45:505, 1956.

21. Franklin, E. C., and Weissman, M.: Serum lipids in lipemia retinalis; report of a case, Ann. Int. Med. 40:413, 1957.

22. Boyd, E. M.: Lipid composition of milky blood serum, Tr. Roy. Soc. Canada, 31:11, 1937.

23. Ahrens, E. H., Jr.: Lipid disturbance in biliary obstruction and its relationship to the genesis of arteriosclerosis, Bull. New York Acad. Med. 26:151, 1950.

24. Corazza, L. J., and Myerson, R. M.: Essential hyperlipemia; report of 4 cases, with special reference to abdominal crises, Am. J. Med. 22:258, 1957.

25. Leiter, L.: Nephrosis, Medicine, 10:135, 1931.

26. Furman, R. H., and Howard, R. P.: Influence of gonadal hormones on serum lipids and lipoproteins: studies in normal and hypogonadal subjects, Ann. Int. Med. 47:969, 1957.

27. Gitlin, D., Cornwell, D. G., Nakasato, D., Oncley, J. L., Hughes, W. L., Jr., and Janeway, C. A.: Studies on the metabolism of plasma proteins in the nephrotic syndrome. II. The lipoproteins, J. Clin. Invest. 37:172, 1958.

28. Gordon, R. S., Jr.: Interaction between oleate and lipoprotein of human serum, J. Clin. Invest. 34:477, 1955.

29. Korn, E. D.: Clearing factor, a heparin-activated lipoprotein lipase. II. Substrate specificity and activation of coconut oil, J. Biol. Chem. 215:14, 1955.