Hereditary Disorders of Albumin Synthesis

BRUCE A. BUEHLER, M.D.

Department of Pediatrics,
Division of Metabolism,
University of Utah College of Medicine,
Salt Lake City, UT 84132

ABSTRACT

Albumin, the major serum protein, is considered to be responsible for maintenance of normal serum colloid osmotic pressure, transport of certain hormones and maintaining an endogenous source of amino acids. The acute loss of albumin in the nephrotic syndrome leads to severe generalized peripheral edema and difficulties in maintenance of normal blood pressure as well as hypocalcemia. Yet, there are now 14 reported cases of congenital analbuminemia in which serum albumin is absent or greatly reduced without clinical evidence of edema, decreased hormone levels or abnormal amino acid requirements. These “experiments of nature” are reviewed in detail comparing clinical and laboratory findings in these patients with the postulated effects of a low serum albumin level.

Albumin Synthesis and Function

Albumin is the major protein component in human plasma. It has a molecular weight of approximately 69,000 and is essentially free of carbohydrate. Approximately 40 percent of albumin is in the intravascular pool, and approximately 40 percent of the total extravascular albumin is contained in the skin. The majority of intravascular and extravascular albumin pools are readily exchangeable, but Owen et al showed that as much as 2.8 mg of albumin per g of bone is tightly bound into calcified matrix in the rabbit and possibly in man.

Albumin in man is composed of a single polypeptide chain with an “N-Terminal” residue of aspartic acid. The preceding amino acid is alanine and the “C-Terminal” amino acid is leucine. This structure varies among animal species with the “C-Terminal” amino acid being leucine in man, dog, and rabbit; alanine in horse, donkey, mule, pig, cow, sheep, goat, duck and chicken; and valine in the turkey.

The postulated functions of albumin in man are the establishment of colloidal osmotic pressure; the transport of long-chain fatty acids, bilirubin, serum hormones (corticosteroids, estrogen and thyroxine), calcium, and vitamins; the protection of thrombin from inactivation; and the provision of a constant source of endogenous amino acids. Albumin normally constitutes approximately 80 percent of the intravascular colloid oncotic pressure; however, in the absence of al-
bumin, interstitial fluid concentrations can be effectively controlled by regulation of intravascular and extravascular sodium concentration.¹⁷

The site of production of albumin is still unclear. However, Lin and Chang⁶ have provided evidence that liver cells, aortic endothelium, lymphatic endothelium, Bowman's capsular endothelium, and proximal convoluted tubular epithelium may produce albumin. In the liver, it appears that the light hepatocytes, lipocytes, endothelial sinusoids and hepatocytes synthesize albumin. Intracellularly, the polysomes on the nuclear membrane and rough endoplasmic reticulum produce albumin which is discharged directly into the cytosol and then released extracellularly.

The normal mean for adult human serum albumin level is 4.2 g per dl with a range of 3.5 to 5.0 g per dl. Mean serum albumin concentration is elevated in males by approximately 0.2 g per dl as compared with females between the ages of 20 and 50.¹⁸ In humans, the normal rate of albumin synthesis has been calculated at 150 and 250 mg per kg per day.¹⁹ The rate of albumin synthesis is markedly decreased in starvation states or with chronic alcohol ingestion. During chronic alcohol ingestion, there is disaggregation of the intrahepaticcyte polysomes associated with albumin synthesis.¹ The decreased rate of albumin synthesis and polysome disaggregation can be rapidly reversed by the intravenous infusion of tryptophan, ornithine, spermine and arginine.⁸ Another factor involved in albumin synthesis rate is the level of intravascular albumin; low levels cause mild increases in synthesis rates.¹⁵ High levels of thyroid hormone increase the rate of albumin synthesis with concomitant increased degradation of albumin.⁵ Therefore, no change in the size of the albumin pool occurs. In the absence of thyroid hormone, decreased synthesis and decreased degradation occur with a shift of albumin to the extravascular space contributing to myxedema. Growth hormone, insulin, testosterone and corticosteroids increase albumin synthesis rates.⁵

In spite of all these factors which change the synthesis rate of albumin, the most common cause of acquired hypoalbuminemia is severe damage to liver cells. Only 10 percent of the normal liver cell number is required to maintain adequate serum levels of albumin. Therefore, generalized hepatic cell necrosis must occur before hypoalbuminemia is evident.¹⁴

Degradation of albumin probably occurs in every organ of the body serving as a source of amino acids. The intestinal loss of albumin accounts for six percent of the total albumin catabolism while the kidney accounts for approximately 15 percent of the loss. In most instances, changes in albumin synthesis are paralleled by changes in albumin degradation leaving the total albumin pool unchanged.¹¹

Analbuminemia

In 1954, Bennhold and associates reported two siblings with virtual absence of serum albumin owing to decreased synthesis. Since then, 12 more cases of “analbuminemia” have been reported. The 14 patients have ranged in age from one month to 49 years. The 13th patient was reported in 1975 by Cormode et al³ and in 1976, Bowman et al² reported the 14th case. A review of these 14 cases provides a better understanding of the functions of serum albumin and the compensatory mechanisms occurring in the absence of circulating albumin.

Normally, albumin accounts for 80 percent of the colloidal osmotic pressure in serum. In Crohn's disease, thermal burns, or nephrotic syndrome where albumin is “lost”, peripheral edema and symptomatic hypocalcemia occur.¹⁵ Normal serum colloid osmotic pressure is 38 ± 3 cm of water. If the colloid osmotic pressure falls below 24 to 27, oncotic edema will usually occur. Normal serum albumin con-
centration is 4.2 g per dl; yet, the 14 reported patients had serum levels of albumin from unmeasurable to 24 mg per dl without evidence of oncotic edema. In two asymptomatic analbuminemic patients, the measured colloid osmotic pressures were 20 and 16 cm of water, respectively. These values are approximately 50 percent of normal osmotic pressures in spite of the markedly reduced albumin concentration.

A possible mechanism for the maintenance of colloidal osmotic pressure in the absence of albumin is the elevation of other protein fractions found in these patients. The fractions most consistently elevated in all patients were ceruloplasmin, fibrinogen and transferrin. These fractions returned to normal levels where the albumin concentration was raised to normal by infusion.9

None of the patients with analbuminemia, including the neonatal patient described by Cormode et al,3 showed any evidence of jaundice, kernicterus or neonatal respiratory distress from the low plasma oncotic pressure. Blood pressures ranged from 80/50 to 110/70 at rest.

Although albumin is considered the major transport system for calcium, none of the patients showed evidence of tetany. In four patients, the calcium levels were below 9 mg per dl; however, no symptoms of hypocalcemia could be observed. This may be due to the fact that lowered albumin should increase the ionized calcium fraction while lowering the bound fraction.

Elevated serum cholesterol was found in five patients. In one patient, this may have contributed to a premature cerebrovascular stroke.7 Ott9 demonstrated lipodystrophy in two female patients with analbuminemia. No mechanism for the lipid abnormalities has yet been elicited.

None of the patients has exhibited evidence of abnormal platelet or blood clotting function. As noted previously, fibrinogen levels were elevated.

Other findings that have been reported include atopic dermatitis in two patients, epilepsy with abnormal EEG’s in two patients, fainting spells without hypocalcemia or hypotension in three patients, and fatigue in five patients. Owing to the prevalence of these symptoms in the general public, it is difficult to evaluate these findings.

The inheritance of analbuminemia appears to be a simple Mendelian autosomal recessive trait. Eight of the 14 patients in the literature were products of consanguineous matings.

**Bisalbuminemia**

Eleven families have been reported to have two bands instead of the normal, single, albumin band on paper electrophoresis. The sum of the two bands is equal to the normal concentration of a single albumin band. The bisalbuminemia fractions have the same molecular weight and immunological characteristics as normal albumin. It has been postulated that these fractions differ from “normal” albumin by a single amino acid substitution. No clinical abnormalities of hypoalbuminemia have been noted in these patients.4

**Summary**

In diseases where albumin is lost, there is secondary peripheral edema. Hypocalcemia, hypotension and aberrations of hormone levels have also been attributed to loss of albumin. Yet in patients with virtually no circulating albumin secondary to an inherited synthesis defect, there is a paucity of clinical features and most are
"clinically normal". In fact, the only consistent findings in the patients studied were hypercholesterolemia and decreased plasma colloidal oncotic pressure without edema. This suggests that the increases in other serum protein fractions found in these patients compensate for the absent albumin or that the functions attributed to albumin may be provided by another serum protein component. Further investigations of the "compensatory" mechanisms in analbuminemia may help to understand better the true functions of albumin in man.

References