AGAMMAGLOBULINEMIA and extreme hypogammaglobulinemia occur as concomitants of several human diseases. Depression of the serum gamma globulin concentration may occur because of loss of protein from the body, generalized failure of protein fabrication, inordinately rapid destruction of serum protein, or because of an isolated deficit in gamma globulin synthesis.

In the nephrotic syndrome, for example, hypogammaglobulinemia and hypoalbuminemia occur reflecting the loss of these two protein components in the urine. Patients with nephrosis are not lacking in capacity to synthesize protein. Instead, Kelley and associates showed that increased rather than decreased protein fabrication characterizes patients with this disease. These findings are in substantial agreement with the conclusions of Kunkel and Ward and others, that patients with nephrosis are producing more than normal amounts of serum albumin in an attempt to keep up with the urinary losses. That the same conclusions hold for the gamma globulin metabolism in these patients has recently received experimental support.

Hypogammaglobulinemia and perhaps even agammaglobulinemia occur also as part of a disease featured by failure of protein production originally observed by McQuarrie and associates. Similar patients have since been studied and reported by others. In the original patient studied by McQuarrie, the patient's disease was featured by generalized edema, very low total serum proteins, especially low serum globulins, and inordinate susceptibility to infection. Fried and Henley studied a similar case and emphasized the deficiency of circulating gamma globulin in these patients. In this disorder, the albumin and globulin deficiency was attributed to failure of fabrication of serum proteins by the liver. Occasionally, as pointed out by Krebs, nutritional deficiency may result in hypogammaglobulinemia associated with generalized hypoproteinemia. Hypogammaglobulinemia along with generalized hypoproteinemia may also be a function of excessively rapid destruction or utilization of serum protein as in a patient intensively studied by Dixon. Recently Ulstrom and associates described an infant suffering from hypoproteinemia, edema, anemia, and agammaglobulinemia in whom all the abnormalities were self limited.

In each of the above disorders of protein metabolism, depression of gamma globulin concentration occurs in the plasma or serum, but in each instance it is associated with a disturbance in the metabolism of other serum protein components.

In 1952, Bruton and associates, described a disease entity expressed clinically as an inordinate susceptibility to bacterial infection. Electrophoretic studies revealed that this disease was featured by complete absence of gamma globulin from the serum. Bruton's patient, an 11-year-old boy, was shown to be lacking in circulating antibodies and to be unable to produce antibodies in response to antigenic stimulation. Unlike the instances of agammaglobulinemia previously described, electrophoretic analysis of the plasma or serum from this patient revealed a protein partition essentially normal except for the absence of gamma globulin. Following Bruton's case report, Janeway and Gitlin gathered together 9 such cases. Each of the latter group exhibited the cardinal features described by Bruton, namely: (1) increased susceptibility to bacterial disease, (2) absence of gamma globulin in the serum, (3) absence of antibody in the blood and tissues, and (4) failure of antibody production in response to antigenic stimulation.

These studies of the Boston group established that agammaglobulinemia is due to failure of synthesis of this particular electrophoretic component of the serum proteins and is not a function of generalized protein dysmetabolism. Further, it was established that this type of agammaglobulinemia is not due to inordinately rapid decay of gamma globulin. For example, parenterally administered gamma globulin had, in these patients, a half life essentially the same or somewhat longer than that described by others for normal human subjects.