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*240500 HYPOGAMMAGLOBULINEMIA, ACQUIRED [IMMUNOGLOBULIN DEFICIENCY, LATE-ONSET; COMMON VARIABLE HYPOGAMMAGLOBULINEMIA; COMMON VARIABLE IMMUNODEFICIENCY; CVID; CVI]

Wollheim (1961) described 2 females with 'acquired' hypogammaglobulinemia who came from different parts of Sweden but were remotely related. He suggested that a recessive genetic factor may be involved in 'acquired' hypogammaglobulinemia. Kamin et al. (1968) found that phytohemagglutinin-induced incorporation of labelled precursors into DNA and RNA by lymphocytes is significantly diminished in cells of adults with so-called 'acquired' agammaglobulinemia. The difference was independent of the characteristics of the culture-medium, indicating a cellular abnormality. Cooper et al. (1971) found normal numbers of B lymphocytes bearing membrane-bound immunoglobulins; germinal centers were normally formed in antigen-stimulated lymph nodes. They postulated that although the B lymphocytes in such patients have surface recognition antigens, they lack the mechanism for plasma cell differentiation. In a provocative, although not thoroughly convincing report of the family of a patient with hypogammaglobulinemia of the common variable hypogammaglobulinemia type associated with deficiency of alpha-1-antitrypsin, Phung et al. (1983) suggested genetic linkage of the PI locus (107400) and a locus exercising a regulatory role in immunoglobulin synthesis. Two members of the kindred were thought to be recombinants; they had hypogammaglobulinemia with normal PI MM phenotype. Because of the relatively close situation (on the distal end of 14q) on the PI locus and the loci for immunoglobulin heavy chains, the observation is of considerable interest. Phung et al. (1982) had concluded that a serum suppressive factor, which prevented pokeweed mitogen-induced differentiation of B lymphocytes both in the proband and in normal subjects, was present in the proband. Heterogeneity in this disorder was emphasized by Geha et al. (1974). Kirkpatrick and Schimke (1967) focused on low IgM as a 'marker' in familial hypogammaglobulinemia. Litwin and Fudenberg (1972) reported quantitative deficiency in the expression of the Gm gene in families with primary antibody deficiency. Molecular mapping of the immunoglobulin genes in these families may lead to elucidation of the nature of the abnormality which may bear similarities to the thalassemias.

With a prevalence of about 1 in 800 Caucasians, selective IgA deficiency (137100) is the most frequently recognized primary immunodeficiency. The clinical consequences are highly variable. Many of the affected persons have no obvious health problems, while others may have recurrent infections, gastrointestinal disorders, autoimmune diseases, allergies, or malignancies. A central feature in pathogenesis is an arrest of B-cell differentiation. Affected individuals have a normal number of IgA-bearing B-cell precursors but a profound deficit in IgA-producing plasma cells. Although common variable immunodeficiency (CVID), defined by panhypogammaglobulinemia, has long been considered a 'wastebasket' category that includes a number of immune disorders, most individuals with CVID show a distinctive phenotype characterized by normal numbers of immunoglobulin-bearing B-cell precursors and a broad deficiency of immunoglobulin isotypes. Schaffer et al. (1989) proposed that CVID of this particular subset and selective IgA deficiency may represent polar ends of a spectrum reflecting a common underlying genetic defect. The proposal was supported by findings that persons with these immunodeficiencies have in common a high frequency of C4A (120810) gene deletions and C2 (217000) rare gene alleles. In an analysis of the MHC haplotypes of 12 IgA-deficient persons and 19 CVID persons from 21 families and of 79 of their immediate relatives, Volanakis et al. (1992) found that a small number of MHC haplotypes were shared by the majority of immunodeficient persons. Five of the families contained more than one immunodeficient individual and all of these 5 families included both IgA-deficient and CVID members. At least 1 of 2 MHC haplotypes was present in 24 of the 31 (77%) immunodeficient persons. No differences in the distribution of these haplotypes were observed between IgA-deficient and CVID persons. The analysis suggested that a susceptibility gene (or genes) for both immunodeficiencies is located within the class III region of MHC, possibly between the C4B and C2 genes.

Common variable immunodeficiency is a heterogeneous group of disorders characterized by hypogammaglobulinemia, antibody deficiency, and recurrent bacterial infections. Most CVID patients have normal numbers of circulating T cells and surface immunoglobulin-positive B cells; however, CVID B cells fail to differentiate into immunoglobulin-secreting plasma cells in vivo. Consequently, CVID patients have reduced levels of serum immunoglobulin and respond abnormally to immunization with protein and polysaccharide antigens. Various defects, including an intrinsic B-cell defect, excessive T-suppressor activity, and defective T/B-cell interaction, have been postulated as responsible for the failure of CVID B-cell differentiation. Farrington et al. (1994) found that 23 of 31 patients (74%) exhibited a T-cell defect, whereas the remaining 8 patients did not. Patients with T-cell dysfunction could be further subdivided into those with a broader defect (n = 11) resulting in depressed expression of gp39 (CD40 ligand; CD40LG; 308230) and variable lymphokine deficiency; others had a more selective defect of either CD40 ligand expression (n = 2) or deficiency of 1 particular lymphokine (n = 10). Thus, CVI may arise from a number of different molecular aberrations. Inefficient signaling via CD40 may be responsible, in part, for failure of B-cell differentiation in these patients.

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#240600 HYPOGLYCEMIA WITH DEFICIENCY OF GLYCOGEN SYNTHETASE IN THE LIVER; GSD-0 [GLYCOGEN STORAGE DISEASE-ZERO]

A number sign (#) is used with this entry because of the presumption that the defect resides in liver glycogen synthase, or glycogen synthase-2 (138571).

In a well-studied family, Lewis et al. (1963) demonstrated that infantile hypoglycemia was due to a deficiency of glycogen synthetase in the liver. The cases were probably of the same type as those reported by Broberger and Zetterstrom (1961) because urinary excretion of catecholamines was not influenced by hypoglycemia. The observations of Lewis et al. (1963) are particularly convincing evidence for autosomal recessive inheritance of this one form, although iron-clad proof awaits demonstration of a partial deficiency in both parents. See hepatic deficiency of fructose-1,6-phosphatase (229700), another cause of hypoglycemia. Howell (1972) doubted that the deficiency of glycogen synthetase is primary. He suggested that the low level of glycogen synthetase is due to low levels of insulin, which normally stimulates the enzyme. He pointed out that, with feeding, glycogen is synthesized and glucagon is effective. The exact defect remains unknown but presumably concerns gluconeogenesis. Dykes and Spenc-

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