In their article Grose et al. provide much needed information on two patients with possible hyperimmunoglobulinemia D and periodic fever syndrome (HIDS). Thus far HIDS has mainly been diagnosed in European patients and no cases from the United States were known. From 1992 onward the International Hyper-IgD study group has maintained a case registry that collects the clinical data on all known HIDS patients to improve awareness of, facilitate diagnosis of and investigate novel therapies for this syndrome. Including the cases presented by Grose we now have accurate clinical data on 74 HIDS patients.

The clinical features of the described patients are characterized by short bouts of periodic fever accompanied by skin lesions and arthralgias which might very well be compatible with HIDS. The diagnosis of HIDS is made on the basis of the clinical history and elevated serum IgD concentrations (>100 units/ml). Although the clinical picture is compatible with HIDS, the reported IgD concentrations of these patients, being 15 mg/dl (106 units/ml) and 9 mg/dl (63 units/ml), are rather low. However, these values may underestimate the true figure because IgD is susceptible to spontaneous fragmentation during storage and shipping which interferes with the single radial immunodiffusion used to measure IgD.

Of special interest is the occurrence of 2 cases in one family. Indeed HIDS appears to be a familial disorder with an autosomal recessive hereditary trait; thus far 12 families with 2 or more affected family members are known to us. Recently we have initiated efforts to localize the gene encoding for HIDS. We were able to exclude the gene causing familial Mediterranean fever (another periodic fever syndrome) as the primary disease locus for HIDS, but more families are needed to identify the HIDS gene.

Grose et al. suggest that the patient described in the initial report of IgG4 deficiency could suffer from HIDS because she had concomitant elevated IgD and IgA concentrations. This patient, a 36-year-old Caucasian woman, suffered from recurrent infections of the upper and lower respiratory tract. In our opinion the diagnosis of HIDS in this patient is unlikely because HIDS patients do not present with recurrent infections and reported serum IgG4 concentrations are normal in these patients. Furthermore the combination of elevated serum IgD and IgA concentrations is not unique for HIDS but is also seen in other patients without HIDS.

IN REPLY:

I have reviewed the letter from Drs. Drenth and Weemaes from the Netherlands about the hyperimmunoglobulinemia D syndrome (HIDS). I concur with their initial remarks about the difficulty with making that diagnosis in the two siblings from Iowa. For that reason I personally followed the index case for 7 years to be assured that the diagnosis of HIDS was reasonable and that all alternative diagnoses had been excluded. Every attempt was made to adhere strictly to the criteria laid out by the European investigators. In that regard I note that Drenth et al. in a 1994 article outlined the following two major criteria for diagnosis of HIDS: "patients were included if they had a history of recurrent fever, defined as an elevation of body temperature above 38.5°C, and had a sustained elevated level of serum IgD above 6 mg/dl measured on two occasions with at least a one month interval." In their definitive review of HIDS in European children and adults, they "could not detect a relationship between the level of the serum IgD (as long as it was elevated) and either the frequency or severity of attacks." We excluded all diseases mentioned in the list of differential diagnoses from the European studies; many of these diseases or conditions are obvious, e.g. leprosy, tuberculosis, Hodgkin's lymphoma, ataxia-telangiectasia, X-linked agammaglobulinemia and recipients of bone marrow transplants. More recently the fourth edition of Immunologic Disorders in Infants and Children has been published, including a section on HIDS. After a perusal of that comprehensive textbook, I found no other known condition that explains the signs and symptoms carefully documented in the two children since 1988.

In our review we included a section on IgD immunology because the functions of this immunoglobulin isotype remain largely unknown. Is it an evolutionary remnant or does it continue to play a role in regulation of human immunoglobulin synthesis? In that regard we consider that our multiyear case analyses are instructive. In addition to an elevated IgD level, our index case had an extraordinarily high serum IgA level at age 3 years (893 mg/dl). Over the next 7 years the IgA level fell to <300 mg/dl. Also at age 3 years he had no detectable IgG4, but by age 9 it was detectable. A symptomatic sibling of the index case had elevated IgD and mildly elevated IgA. As a reminder, normal IgD levels (under 3 mg/dl) are sustained elevated level of serum IgD above 6 mg/dl measured on two occasions with at least a one month interval. In our review we included a section on IgD immunology because the functions of this immunoglobulin isotype remain largely unknown. Is it an evolutionary remnant or does it continue to play a role in regulation of human immunoglobulin synthesis? In that regard we consider that our multiyear case analyses are instructive. In addition to an elevated IgD level, our index case had an extraordinarily high serum IgA level at age 3 years (893 mg/dl). Over the next 7 years the IgA level fell to <300 mg/dl. Also at age 3 years he had no detectable IgG4, but by age 9 it was detectable. A symptomatic sibling of the index case had elevated IgD and mildly elevated IgA. As a reminder, normal IgD levels (under 3 mg/dl) are attained in early childhood. This insight into the natural history of HIDS suggests a broader defect in regulation of immunoglobulin synthesis and switching with variable affects on isotype levels from patient to patient. Indeed elevated serum IgA levels remain an excellent marker for HIDS.

Since publication of the HIDS article in January 1996, I have received telephone consultations from physicians in Lincoln, Nebraska, Wichita, Kansas and Dallas, TX. In each instance the physicians described children with histories and laboratory findings compatible with HIDS. Therefore HIDS

Accepted for publication July 16, 1996.

Key words: Hyperimmunoglobulinemia D, periodic fever syndrome.