CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Mar. 2000, p. 131–140 Vol. 7, No. 2
1071-412X/00/$04.00+0

MINIREVIEW

Immunoglobulin D: Properties, Measurement, and Clinical Relevance

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INTRODUCTION

Discovered in 1965 (134), immunoglobulin D (IgD) is a unique immunoglobulin with a concentration in serum far below those of IgG, IgA, and IgM but much higher than that of IgE. Despite studies extending for more than 4 decades, a specific role for serum IgD has not been defined while for IgD bound to the membrane of many B lymphocytes, several functions have been proposed (15). The amount of serum IgD is measured routinely in some clinical laboratories, almost always together with the concentrations of IgG, IgA, and IgM, although the clinical relevance of increased or decreased serum IgD values (in comparison to the reference interval or so-called normal range) has not been proven. The serendipitous discovery of an increased serum IgD concentration during attacks of some patients with periodic episodes of fever (156) led to a renewed search for a specific role of serum IgD. Hence, I assessed again the clinical relevance of measuring serum IgD concentration (161). This minireview summarizes the properties of human IgD and focuses more on techniques for its measurement in serum and other body fluids and its concentration in the serum of healthy individuals, as well as in that of subjects with various diseases. Because IgD was first found in a patient with multiple myeloma (134), monoclonal IgD is also briefly discussed. Hyperimmunoglobulinemia D syndrome (HIDS), the only entity for which the measurement of polyclonal IgD is necessary for diagnosis, is also very succinctly reviewed. Recent advances focus on genes for IgD, membrane-bound IgD on B cells, signal transduction via the IgD receptor, secretion of IgD by plasma cells, and the role of IgD in T-B-cell interactions; most of the information on secreted (serum) IgD came from older studies.

PROPERTIES OF IGD AND ITS ROLE IN THE IMMUNE RESPONSE

IgD represents about 0.25% of the total serum immunoglobulins and has an M_r of 185,000 and a half-life of 2.8 days (131), similar to that of IgE (162). Its synthesis rate is at least 10 times lower than that of IgA, IgM, and IgG. The turnover rate is 37% of the intravascular pool per day, much higher than that of IgG, IgA, and IgM (131) but less than that of IgE (162). The catabolism of IgD is decreased at high concentrations in serum. Initially, it was considered that about 75% of IgD was intravascular (131) but more recently it was shown in two patients with IgD myeloma that only 31.5% of IgD was intravascular (3).

The IgD molecule has a long "hinge" region (between Fab and Fc) that appears to render the molecule very susceptible to proteolytic degradation with production of Fab and Fc fragments (53) and also renders the molecule flexible, thus enhancing antigen binding. The human IgD molecule has three constant-region domains. The amino acid sequence of a monoclonal IgD was reported in 1982 (148), and the genomic sequence of human δ chain was reported in 1985 (167).

During storage, plasma proteases, especially plasmin, fragment the IgD molecule; the cleavage is initiated near the carboxy terminus and later in the inter-Fd-Fc area (54). The increased sensitivity to "spontaneous" fragmentation is considered to be also due to the Fc fragment, which is less compact for IgD than for other immunoglobulins (55).

IgD does not induce passive cutaneous anaphylaxis in the guinea pig (61, 118); does not bind to normal lymphocytes, neutrophils, or monocytes (80); and does not cross the placenta (84). Aggregated monoclonal IgD consumed C3 to C9 without loss of the early components of the complement cascade (63), whereas native IgD has very little, if any, activating activity on the components of the alternative pathway of complement (145). IgD binds bacteria nonspecifically through the Fc fragment; for example, it binds strongly to *Neisseria catarrhalis* and *Haemophilus influenzae* and weakly to streptococcal groups A, C, and G (48). IgD has antibody activity to specific antigens (34, 53, 60, 109, 110); individuals with high levels of IgD can produce specific IgD antibodies after antigenic challenge (62). Among 66 selected patients, 3 had IgD antibodies to cow's milk (against bovine gamma globulin), 2 of them had antibodies to bovine serum albumin, 1 had antibodies against diphtheria toxoid, and all 4 also had antibodies of other classes and had evidence of vigorous immunologic responsiveness (60). Specific IgD antibodies were also described against thyroglobulin (71), insulin in individuals with diabetes (34, 83), wheat in patients with celiac disease (6), tartrazine in certain patients with chemical hypersensitivity (165), and hepatitis B core antigen (19).

In 1972, IgD was discovered on the surface of many B cells (155); in humans and other species, IgD is the major antigen receptor isotype on the surface of most peripheral B cells, where it is coexpressed with IgM. Few plasma cells that contain only IgD could be found in lymphoid tissues (136); adenoids had greater numbers of IgD-containing plasma cells than did human spleen, lymph nodes, or intestinal lymphoid tissue (122, 136). There is spontaneous synthesis and secretion of IgD from the tonsil lymphocytes in culture (90). The heavy chains of IgD from the surface of B cells are covalently linked by only one disulfide bridge, close to the carboxy terminus. This allows a

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higher degree of freedom of the antigen-binding sites than for the other immunoglobulin isotypes (15). Serum IgD and membrane-bound IgD are antigenically similar, but they differ in susceptibility to proteolysis by plasmin. Also, the δ chains from membrane-bound IgD have slightly slower electrophoretic mobility than serum monoclonal δ chains in sodium dodecyl sulfate-polyacrylamide gel electrophoresis, suggesting a larger molecular weight for the former (146).

The signals transduced by IgM or IgD receptors on B lymphocytes are the same but with different kinetics. Signals transmitted through surface IgD caused induction of up to 80 different somatic mutations (95). The majority of the cell-bound IgDs are of the κ type (140), while 90% of the monoclonal IgDs in serum are of the λ type. The so-called IgD paradox is the preferential association between δ heavy chains and λ light chains in IgD-secreting cells (91). This association is expressed in vitro and in vivo, is a property of normal human IgD-secreting cells, and is closely related to the secreted form of IgD. Explanations given for the preferential association are that physical constraints favor secretory δ-λ-chain association during intracellular chain assembly, IgD immune response is highly restricted, and there is a high degree of selectivity and unorthodox regulation of IgD light-chain expression (91). Human neoplastic B cells that expressed surface immunoglobulins of the λ type frequently exported IgD, whereas B cells that expressed immunoglobulins of the κ type did not export IgD (but inserted IgD into their surface membrane). This implies that possession of a λ chain facilitates the IgD secretory pathway.

IgD production is influenced by two major factors: an independent mechanism (only for IgD), which may be genetically determined, and also the same factors that control the production of the other immunoglobulin isotypes (94). The genes for the C region of μ and δ (C_μ and C_δ) are transcribed in the same RNA (a common transcription unit) and can be expressed simultaneously. IgM and IgD molecules present on individual B cells have identical V regions and antigen-binding sites and are coexpressed by differential (alternate) splicing of a common *VDJ* exon to either C_μ or C_δ region exons to produce separate μ and δ RNAs. Allelic exclusion exists for IgD, as for the other immunoglobulin classes (160). After the antigen binds to the B-cell receptor, the secreted form of δ chain is shut off instead of being secreted in large amounts, as is the case with IgM. The cells enter the pathways of plasma cells (which do not have IgD except for IgD-secreting plasma cells, where the μ gene is deleted) or of memory cells in secondary lymphoid organs, cells in which IgD expression is lost (12, 111). Both IgD and IgM receptors can transduce signals by the same mechanism; however, signals mediated by engagement of surface IgD may differ from those mediated by surface IgM—e.g., only the latter cause death of cells by apoptosis (152).

After exposure to aggregated oligomeric or antigen-cross-linked monomeric secreted IgD, 10 to 15% of human peripheral blood T cells (Tδ cells) exhibit receptors for IgD and form rosettes with IgD-coated erythrocytes (26, 27). These receptors are upregulated by interleukin-2 (IL-2), IL-4, and gamma interferon on the Tδ cells. Both human $CD4^+$ and $CD8^+$ T cells can express IgD receptors (28), which can ligate membrane IgD during antigen presentation by B cells to facilitate the responses of antigen-specific T and B cells (168).

With use of sensitive assays, IgD has been found in all of the mammalian and avian species tested and is conserved across species (89), which suggests an evolutionary advantage (15). The role of IgD (especially the secreted form) is not fully understood; it has even been thought sometime that IgD might have no function (15). This was investigated in animals treated with anti-IgD and, more recently, in IgD-deficient mice. In one model of IgD knockout mice, there was only a slight decrease in the number of B cells in the periphery and immunoglobulin isotypes were almost normal (112). In another model, there was a delayed affinity maturation during T-cell-dependent antigen response (130); hence, surface-bound IgD may serve as an accelerator of affinity maturation in the primary B-cell response (125). In IgM-deficient mice, B-cell development and maturation were normal and IgD replaced membrane-bound and secretory IgM (99). It appears that, with regard to B-cell development, IgD can largely substitute for IgM in many respects; i.e., there is redundancy between these two isotypes (99).

Serum IgD was considered an early marker of B-cell activation (107). IgD can have a regulatory role, e.g., to enhance a protective antibody response of the IgM, IgG, or IgA isotype, or to interfere with viral replication (110). IgD can also participate in the generation and maintenance of B-cell memory and might have an important role in the transition from a stage of susceptibility to induction of B-cell tolerance to one of responsiveness (22, 142). Finally, IgD is a potent inducer of tumor necrosis factor alpha (TNF-α), IL-1β, and IL-1 receptor antagonist (38). IgD also induces release of IL-6, IL-10, and leukemia inhibitory factor from peripheral blood mononuclear cells. Monocytes seem to be the main producers of cytokines in vitro in the presence of IgD (38).

MEASUREMENT OF IgD

The techniques used to measure IgD became more sensitive with time, and this had a bearing on the detection of low levels of IgD, e.g., in serum of children, as well as in other body fluids of adults. With sensitive assays, e.g., radioimmunoassay (RIA) and enzyme immunoassay (EIA), IgD was detected in the serum of all individuals tested whereas with the less sensitive radial immunodiffusion (RID) assay, IgD was not detected in some sera and in several other body fluids.

Among the techniques used to measure IgD, the first and still the most commonly used method in clinical laboratories is RID. Commercial reagents for measuring IgD by RID are readily available from several companies (e.g., Beckman, Binding Site, and Behring). From an analysis of the survey (proficiency testing) for serum IgD provided by the College of American Pathologists, it appears that the so-called Mancini RID assay ("endpoint") technique is now used much more often than the "timed" (Fahey and McKelvey) method (24). The former technique has a lower coefficient of variation (CV) than the latter. In one study, RID had a sensitivity of 10 mg/liter (68) but a significant number of individuals had undetectable amounts of serum IgD when tested with this method. Others reported 3 mg/liter as the limit of detection, but the precision for the range between 3 and 14 mg/liter was poor (77). It is well known that gel techniques such as RID are particularly affected by the variability in the molecular size of the antigens because of alterations in the rate of diffusion through the gel when the size is heterogeneous (166). Therefore, IgD measurement by RID should be influenced by the high sensitivity of IgD to proteolysis, which gives rise to faster-diffusing fragments of IgD that retain their antigenic reactivity. This means that the concentration of IgD in old serum specimens would be overestimated by RID, not underestimated as was recently claimed (40). Inhibitors of proteolysis, e.g., ε-aminocaproic acid (final concentration, 10 nM or 0.1%), aprotinin (1,000 kU/ml), or 0.01% benzamidine should be added to serum to minimize the degradation of IgD before measurement. Another disadvantage of RID is that the ring of diffusion

may pass across adjoining areas of the plate, depletes them of antibodies, and gives incorrect results for other samples on the same plate (166). Surprisingly, specimens stored at 37°C for either 6 or 12 months had lost 10% of their antigenic reactivity when assayed by RID (137). When stored at −20°C, the rate of IgD degradation was so low as to be negligible for 10 to 20 years (137). However, it was claimed that, despite its fragmentation, the IgD molecule could be quantitated by RID in blood stains (for forensic purposes) even after several weeks (72).

Nephelometry has also been used for IgD quantitation, but specific reagents for IgD are not readily available. From experience gained with quantitation of other serum proteins, it appears that the nephelometric method is more precise, as well as more sensitive, than RID. The means of CVs obtained after the measurement by nephelometry of several serum proteins were significantly lower than the means obtained when RID was used for measurement (126). The sensitivity of a nephelometric assay for IgD was 3 mg/liter (11). Results obtained with laser nephelometry apparently were not influenced by the molecular size of the protein assayed (159). Hence, the likely fragmentation of IgD during prolonged storage is not important for its quantitation by nephelometry. Discrepancies between the results obtained for the same specimens by different investigators with either RID or nephelometry occur when the unknown and standard samples differ in molecular size or antigenic valence (52). It is noteworthy that in a study of 12 analytes measured by RID, electroimmunodiffusion ("rocket assay"), rate nephelometry, endpoint nephelometry, immunofluorometric assay, and EIA, no method-associated bias was observed and the results were in close agreement (126). In another experiment, a freshly drawn sample of serum was divided into nine aliquots and each was subjected to a different treatment (e.g., incubation at 37°C for up to 5 h and exposure to up to 10 cycles of freezing and thawing). None of these treatments significantly altered the concentration of IgD (43).

RIA is 1,000-fold more sensitive than RID (150), and sensitivities for IgD of 10 to 50 μg/liter were reported (43, 69). After modifications, the sensitivity could be extended to 0.0008 U/ml (43). When measured by RIA, IgD appears to be stable during prolonged storage in frozen plasma; a frozen serum sample assayed repeatedly over 2.5 years did not change in any consistent manner (44). An RIA that used paper disks had a range of measurable IgD concentrations of 2.5 to 250,000 μg/liter (8), and the sensitivity of the assay was 10 μg/liter (7). Another RIA, with the use of two antibodies, had CVs of <8% within the assay and 12% between assays (45).

EIAs for measuring serum IgD were also reported (121). Monoclonal anti-IgD antibodies were not as good as polyclonal antibodies (gave a lower optical density); and the sensitivity of the test was 4 μg/liter (121). A sandwich EIA that utilized microtiter plates and affinity-purified goat anti-human IgD was used to report results as optical densities at 405 nm without the need for standards (169). Another EIA used avidin and biotin. Antibody-coated plates could be stored at 4°C for up to 1 week without loss of sensitivity, and the test showed linearity for serum dilutions of 1/200 to 1/12,800. The CVs between and within assays were <10% (123). EIA and RIA have also been used to measure specific IgD (53, 93, 109). Other methods used for quantitation of IgD were particle counting immunoassay (100) and inhibition of hemagglutination (23).

As for other serum proteins, the standards (calibrators) are crucial to accurate measurement of IgD (166). Although several reference materials are available for the three most abundant immunoglobulins (reviewed in reference 166), there is a dearth of international reference preparations (IRP) for IgD. International units have been allocated to several international calibrants of proteins, and collaborative efforts were undertaken to ascribe mass values to them. Some of these values were "far from the truth" (166). An IRP with the declaration of a single protein, IgD, lot 67/37 (1967), has 100 U per ampoule, and the weight of lyophilized material is 81.88 mg (1-ml ampoule) (10). This is, in fact, British Research Standard 67/37, the most commonly used primary standard (World Health Organization standard) for IgD. However, reference to the World Health Organization standard is rarely reported and most studies have relied on a secondary reference source. The commercially available reagents at the present time are calibrated with a reference standard from Kallestadt (now Beckman) or Behring. Differences between reference preparations could be due to the freeze-drying procedure (10), which increases the turbidity because of an alteration in the low-density lipoprotein structure, which is best stabilized by a high percentage of water. The use of an IgD-myeloma protein as a reference protein reduces the reliability of the estimate (137).

The weight of IgD corresponding to 1 U of activity was calculated to be 1.41 μg. The conversion factor from grams per liter to units per milliliter was obtained with the use of RID (10). This value provides only an approximate indication of the IgD content of a research standard. It was said that a "true value" is not near to being achieved by using grams per liter instead of units per milliliter and that a "consensus value" (in grams per liter) invalidates the general standardization (10). However, for many investigators, there is poor acceptance of a change in the association from grams per liter to the abstraction of units per milliliter (10).

Manufacturers have to check the conversion factor from time to time and correct the value if unstable proteins have changed their structure. The change of a batch can cause the assignment of a new value for the conversion factor (10). The former conversion factor obtained by RID could no longer be confirmed, so that the IRP is not suitable in some new immunoassays. Dunnette et al. (43) found that three commercial companies had reference standards with various ratios of mass units to units of activity (1.41, 0.77, and 0.83). Yet, when their RIA for IgD measurement was compared to the RID kits from three companies, the values obtained with the two methods were comparable, with a CV of <16%.

The College of American Pathologists, to my knowledge, is the only organization that offers proficiency testing for serum IgD. However, of more than 3,500 laboratories that usually participate in surveys by this organization, a little more than 100 (range, >100 in 1982 to 6 in 1992) participated in the survey for IgD. According to Cheek and Papadea (24), in 1995 only 35 laboratories participated in this survey and all of the laboratories used RID to measure serum IgD.

I reviewed the results of the surveys for IgD from 1980 to the present and noted that until 1989 the RID timed method was used by more laboratories than the RID endpoint method. After 1989, the latter method was more often used; reagents obtained from only one manufacturer were used by most of the laboratories. Only one specimen is sent to laboratories for the measurement of serum IgD, in contrast to the two to four specimens sent for other determinations (e.g., for IgG). The survey specimen was sent four times per year until 1993 and thereafter only three times per year. The low number of laboratories that participate in the survey for IgD precludes a meaningful statistical analysis of the results. It has been noted, however, that the CV for the results obtained by all participants in the survey for IgD that used the RID timed method was mostly 20% or above while for the endpoint method it was slightly lower.

Some investigators (39) implied that laboratories that measure IgD in fewer than 20 specimens weekly do not have enough volume to maintain testing proficiency. This seems not to be the case, since the techniques for IgD measurement are not more difficult than similar techniques routinely used in clinical laboratories to measure other proteins. Also, it seems that only a very large reference laboratory, if any, measures IgD in more than 20 specimens per week, since there is not much need for this testing.

IgD IN BLOOD AND OTHER BODY FLUIDS OF NORMAL INDIVIDUALS

There is no single method used universally for IgD measurement, nor is there, to my knowledge, a preferred method recommended by a professional organization or a scientific forum. Therefore, in this section, values reported for IgD were obtained with the use of several techniques. The reported concentrations of IgD in serum and other body fluids depended on the techniques used for measurement when low levels of IgD were present. For example, with the use of RID, IgD was found in serum of children only after they had reached 12 months of age (66) and was unmeasurable in cord blood (84). In an older study, IgD was found by RID in only 2 of 83 cord blood samples and in 4 of 90 newborn serum samples (86). However, with use of an RIA, IgD was found in cord sera of 38 of 39 newborn infants. There was no relationship between the concentrations of IgD in cord blood and maternal serum, and although this suggests a fetal origin of IgD, it does not reflect the synthesis of a specific antibody but rather it may be a developmental phenomenon (23). In newborns, the concentration of IgD in blood was about 0.08 mg/liter (81).

The concentration of IgD in sera of infants and adults was age dependent (94) and showed considerable biological variation, even in people of the same age, from undetectable to 400 mg/liter (43, 136). Some investigators found a linear increase of IgD until the age of 10 (66), followed by a gradual decrease until the age of 14 (50). Others showed that age was not a factor in IgD levels after 6 years of age (44); indeed, there was no difference in serum IgD concentration from 19 to 59 years of age (43). Another study also showed that the serum IgD level of adults is attained in early childhood and persists throughout life (69). Levels of IgD were reported by some investigators to be stable in healthy adults over 1.5- and 3.5-year periods (136), but two- to threefold variations in the same individuals were seen by others when the subjects were monitored for weeks or months (81).

IgD has a remarkably wide normal range in serum, probably because of striking differences in its rate of synthesis (131). A study of 200 sera showed that the range was wider (4 logs) than for any other immunoglobulin (150). The median concentration of serum IgD was 30 mg/liter when determined by RID (135). The serum IgD levels (measured by RIA) for 85 normal adults ranged between 0.2 and 121 mg/liter, with an arithmetic mean of 25 mg/liter (17.7 U/ml) (45) and apparently had a trimodal distribution, with modes at about 0.25, 5.1, and 35 U/ml (43). Others could not find a trimodal distribution (69). Many reference intervals ("normal ranges") for IgD concentration in serum have been reported, e.g., 14 to 85 mg/liter (144), 10 to 112 mg/liter (21), and 5 to 240 mg/liter (97). Averages were also scattered, e.g., 50 mg/liter (77), 40 mg/liter (76), 35 mg/liter (97), and 25 mg/liter (45). Since the values for serum IgD did not follow a Gaussian distribution (43), it was common to transform the results into square roots (78) or a natural logarithmic scale for statistical analysis (78, 114, 121).

Individuals can be high or low producers of (serum) IgD (94). Early studies have suggested that about 10 to 14% of individuals had very low concentrations of serum IgD, i.e., <3 mg/liter (43, 81) and that about 10% have high concentrations (>100 mg/liter). It was hypothesized, but not proven (94), that low producers can convert to high producers because of infections and immune activation. Low serum IgD was not dependent on age and was not related to sex (44). It has also been suggested that the low IgD level is genetically determined, with autosomal recessive inheritance (44). However, low serum IgD was seen in 44% of children of parents with high IgD, making autosomal inheritance unlikely (44). No inheritance pattern was observed for high levels of IgD (44). Dunnette et al. (43) proposed, on the basis of mathematical analysis (Hardy-Weinberg equation), that levels of IgD in normal individuals are strongly influenced by inheritance through a monogenic mechanism. Twin studies also supported an influence of inheritance on the serum IgD concentration (1, 81) but there are also environmental influences (100). It was reported that Gm allotype (163) and histocompatibility antigens (44, 49) can influence IgD levels.

There was a positive correlation among serum IgD concentration, the number of IgD-positive plasma cells in bone marrow (62), and spontaneous in vitro IgD secretion by B lymphocytes (92). However, there was no correlation between the amount of IgD in serum and the amount expressed by lymphocytes (69). A positive correlation was found between serum IgD level and serum IgA and IgE levels (69), white blood cell count, and number of $CD4^+$ and $CD25^+$ lymphocytes but not with other immunoglobulin isotypes or markers of immune activation (94). Although the amount of IgD usually paralleled the amount of other immunoglobulins in serum (45), the values of IgG and IgM did not always correlate with the presence or absence of IgD, as detected by double-diffusion-in-gel assay (120).

It has been proposed that the female sex hormone influences IgD synthesis (76), although values for serum IgD in males and females were similar in many studies (43, 44, 135). In another study, females 1 through 5 years of age had higher serum IgD concentrations than males (86). The concentration of IgD was also elevated in pregnant women (76) and increased throughout gestation (85), also suggesting that hormonal factors influence IgD metabolism (76). A highly significant exponential correlation was reported between maternal IgD levels and gestational age (78). IgD was also elevated in maternal sera at term, but the influence of labor (76, 85) and delivery was not clear (58, 76, 85). Increased IgD levels in maternal sera at term may represent antibodies directed to either leukocytes or trophoblastic antigens (76). HLA-A2 and HLA-A13 in the mother was correlated with IgD concentration at delivery (78). Sera of women with premature delivery had a significantly lower mean concentration of IgD than other groups (78). A correlation between parity and IgD level was also reported (85).

IgD was not detected by RID in 10-fold-concentrated saliva, bile, highly concentrated urine, concentrated tears, and unconcentrated cerebrospinal fluid (136). Isoelectric focusing of unconcentrated cerebrospinal fluid showed oligoclonal and polyclonal IgD patterns (102). Human colostrum (8) and milk contain considerable quantities of IgD (43, 93); IgD was found in all 11 specimens of milk tested, with an arithmetic mean of 1,150 U/liter, a geometric mean of 161 U/liter, and a median of 137 U/liter (range, 8 to 8,600 U/liter) (43). Values of IgD in nasal washings ranged from 11 to 503 U/g of protein; the values were higher than in saliva (123).

SERUM IgD IN VARIOUS DISEASES AND CONDITIONS

The meaning of an abnormal (increased or decreased) concentration of serum IgD is not known. An increase in serum IgD does not imply the generation of antibodies of the IgD class in each individual (62).

IgD was measured in the sera of subjects with various conditions, and although the values obtained probably depended somewhat on the techniques used for measurement, the results from patients with various diseases were compared to findings obtained by the same techniques from healthy individuals, so the conclusions were valid. As just mentioned, the most important factor for the accuracy of IgD measurement is the standard used in the assays. The sensitivity of the techniques is less important when testing various patients for increased or decreased serum IgD values (in comparison to healthy subjects). A technique with low sensitivity might not detect very low levels of IgD in some patients, but this has no clinical importance. There have not been, to my knowledge (nor were any expected), reports of increased sensitivity of IgD to proteolytic enzymes in patients with certain diseases. Although the storage of specimens for IgD quantitation is of some importance when RID is used to measure IgD, this is not likely to introduce bias in the values of IgD found in patients with various diseases or conditions compared to healthy individuals if the storage was similar for all specimens. Many individuals with high levels of one or more immunoglobulin isotypes have low or normal levels of IgD, and occasionally normal or high values for serum IgD were seen in hypogammaglobulinemic patients (21, 136, 161). In a study of 58 patients with IgG paraproteinemia, of whom 34 had multiple myeloma, a negative correlation for IgD was found (151), and in 133 patients with monoclonal gammopathies, IgD concentration decreased in parallel with polyclonal immunoglobulin levels (46). Hiemstra et al. (62) studied 17 patients with high serum IgD levels (250 to 5,311 U/ml), both children and adults, and concluded that there was no apparent relationship between several clinical syndromes and the increased serum IgD. In many studies of patients with various diseases, only serum IgD levels were reported whereas in some patients with certain diseases or conditions (e.g., atopy) the amounts of other immunoglobulins were reported as well. Because this minireview is focused on IgD, the serum levels of other immunoglobulins measured in conjunction with IgD are not given.

Infections. IgD antibody seemed to behave like IgM antibody at the early stage of infection (149). There was a significant positive correlation between the levels of IgD and the titers of complement-fixing antibody to *Mycobacterium pneumoniae* (149). Specific IgD antibodies were also found in patients with rubella (139), and IgD antibodies to measles virus were found in patients with subacute sclerosing panencephalitis (96). IgD antibodies to diphtheria toxin, *Escherichia coli*, and streptolysin O were also reported (60, 67, 143, 147). A 22-year-old female with presumed coxsackievirus myocarditis had an increased serum IgD level (4).

Chronic infections were also considered to raise the concentrations of serum IgD (136); indeed, serum IgD was increased in patients with leprosy (144), tuberculosis (20, 74), salmonellosis, infectious hepatitis (133), and malaria (29). In a 7-year-old child with a history of recurrent infections, a high level of IgD was noted in serum (125). Many, but not all, patients with elevated IgD (measured by RID) had recurrent staphylococcal infections (21), and increased values of serum IgD were found in some patients with viral infections (132, 139). The clinical relevance of all of these specific IgD antibodies, if any, is not known.

Immunodeficiencies. Patients with immunodeficiencies very often have various infections; hence, it is unclear whether IgD concentrations in these patients reflect immunodeficiency itself or infections. There is no uniform pattern of IgD production in defined primary immunodeficiencies; some individuals had increased levels, and some had decreased levels (94). Within the whole group of immunodeficiencies, a positive correlation of IgD with IgA and IgE was noted. A positive correlation of serum IgA and IgD levels was also found in human immunodeficiency virus-infected patients (108). With an RID assay, IgD was detected in serum in only 49% of IgA-deficient patients (21) and numerous IgD-producing plasma cells were found in the lacrimal and parotid glands, suggesting that secretory IgD plays a compensatory role in IgA deficiency (17). Some patients with hyper-IgE syndrome, who often have recurrent infections with staphylococcus, had high serum IgD levels, but the cause for this is not known (69). Low levels of IgD in the hyper-IgE syndrome were also reported (42). Group mean concentrations of IgD in plasma were depressed in patients with Wiscott-Aldrich syndrome (21). In three children with agammaglobulinemia (no B cells in the blood), the serum IgD level was higher than in healthy children (21). IgD was increased in plasma of patients with Nezelof syndrome (21) and in children with ataxia telangiectasia (105). A high serum IgD value was found in a girl with immunodeficiency and increased serum IgM (9). Serum IgD was increased in patients with impaired cell-mediated immunity, e.g., those with allergic bronchopulmonary aspergillosis (97) and sarcoidosis (20), as well as in patients with AIDS (25, 107, 108, 120). Recently, it was shown in 131 children with many types of immunodeficiencies (including CD40 ligand [CD 145] deficiency) that the serum IgD level was not of particular value in the investigation of immunodeficient children; the serum IgD level was not associated with the general picture of immune activation (94).

Autoimmune and allergic diseases. Serum IgD was increased in patients with autoimmune diseases who also had increased IgG, IgA, and IgM (83, 87, 116, 133, 141). High values of serum IgD were found in some, but not all, adults with rheumatoid arthritis (136) and in children with juvenile rheumatoid arthritis (51). Antinuclear antibodies of the IgD class were found in patients with systemic lupus erythematosus (53, 98, 128, 164), and a slight increase of serum IgD was found in patients with Sjögren's syndrome and in a patient with autoimmune thyroiditis (71). Autoantibodies of the IgD class were found in some patients with scleroderma (98) and atopic diseases (74, 77, 97, 169), e.g., atopic dermatitis (18, 69). IgD was reported to be increased or decreased in sera of patients with allergic asthma (74, 77, 97), but a considerable overlap existed between healthy and allergic subjects. In the atopic group, the mean serum IgD level did not differ significantly on the basis of age, sex, or asthmatic status (121). In patients with asthma, basophil degranulation by a high anti-IgD concentration was reported (121).

IgD against birch and timothy pollen allergens was increased in sera of atopics with IgE antibodies to birch pollen allergens, compared to sera of atopics without IgE against these allergens. The allergen specificity of IgD antibodies was confirmed with an allergen inhibition test. However, no significant correlation was found between total serum IgD and IgE (169). IgD antibodies specific for a benzylpenicilloyl epitope were found in some patients with penicillin allergy (53), and IgD was also found on red cells from patients with hemolytic anemia caused by penicillin (88), but the clinical value of these antibodies is doubtful.

Other conditions. The geometric mean of the IgD concentrations in sera of cigarette smokers was twice as high as in nonsmokers. In the smoking group, it was the highest in those who did not actively inhale smoke (fourfold higher than in nonsmokers) and the lowest in heavy smokers who inhaled (8). The IgD level was more strongly related to the number of cigarettes smoked per day than to the years of smoking. Cessation of smoking was followed by normalization of the IgD level (8). The influence of maternal smoking was more evident in newborns of nonallergic parents; even paternal smoking increased the level of cord serum IgD in these newborns (100). The reason for the increased IgD in smokers is not known; it could be because of infections. B cells may be stimulated by mild to moderate degrees of smoking but suppressed by heavy smoking (8), and it is likely that the influence of substances in tobacco smoke is not directly on B cells but on regulatory T cells.

A definite increase in serum IgD was found in patients with Hodgkin's disease several months after splenectomy (31). A correlation with the histologic type was observed; e.g., patients in the lymphocyte-depleted group had extremely high levels of IgD (log mean, 284 mg/liter). Also, patients who received treatment had significantly lower values than untreated patients (30, 31) and there was a definite tendency toward lower levels in older patients (31). A fall in serum IgD was seen after radiotherapy but not after chemotherapy in patients with lymphoma (2). When RID was used to measure IgD, the values fell in stages III and IV; IgD was not detectable in 30% of patients with lymphoma (but also in 39% of healthy controls) (2).

Increased concentrations of serum IgD were found in other diseases and conditions, e.g., in children with kwashiorkor (136), (transiently) after allogeneic bone marrow transplantation (107); very rarely in patients with Behçet syndrome; and in those with idiopathic retinal vasculitis (79). In this latter condition, a linear correlation was found between serum IgD levels and the percentage of IgD-positive B cells in the blood (79). The geometric mean of IgD concentrations in the sera of nine children with Henöch-Schoenlein purpura was significantly higher than that in sera of control children (16.7 versus 9.1 mg/liter); increased IgD levels were found only in children who did not have nephritis (140). The geometric mean of serum IgD values was significantly higher in patients with chronic obstructive pulmonary disease than in healthy individuals (106). However, the distribution of IgD in each group showed marked positive skewedness (114). High values of serum IgD were also found in children following chemotherapy for malignancies (5) and in some patients with hyperparathyroidism (120). In some patients with central nervous system tumors, increased serum IgD levels, as well as oligoclonal bands of IgD in spinal fluid (103), suggested that systemic IgD production in these patients occurred independently of IgG (104). High IgD values (compared to those of healthy individuals) were reported in the sera of four patients with aortitis (116) and in a few patients with liver cirrhosis (116).

Monoclonal IgD. The measurement of serum IgD is most important for the monitoring (and the diagnosis) of IgD gammopathies (IgD myeloma and δ heavy-chain disease). IgD myeloma represented 1.8% (154) and 1.2% (65) of multiple myelomas in two series. It has an aggressive course, often with extramedullary involvement, amyloidosis, lymphadenopathy, splenomegaly, severe anemia, azotemia, very often (≥90%) Bence Jones proteinuria (14, 47), and short survival (82). M components (with γ-, β-, or α_2-globulin mobility), representing monoclonal IgD, were seen in only 60% of the serum protein electrophoreses of patients with IgD myeloma (14); the remaining patients had normal electrophoresis or hypogammaglobulinemia (14, 47). The range of monoclonal IgD concentrations in serum was 800 to 66,000 mg/liter (65). From 60% (14) to 90% (65) of IgD myelomas are of the λ type. The rarity of IgD κ secretion was explained by a block in the assembly, glycosylation, and secretion of this immunoglobulin or rapid intracellular catabolism of IgD κ destined for secretion (70). There is antigenic heterogeneity among monoclonal IgDs (probably allotypic variants, not subclasses, of IgD) (115, 129). A patient with IgD myeloma had separate heavy- and light-chain M components in the serum, probably because of an intracellular assembly defect (158). A monoclonal IgD had antibody activity against triglycerides, and the patient had hyperlipidemia (127). Another monoclonal IgD λ had pyroglobulin activity (precipitated irreversibly at 56°C) (153). Finally, an increased serum viscosity of 6.8 U (reference, <1.8 U) was reported for a monoclonal IgD (117). Only three patients with monoclonal IgD of undetermined significance were reported (13, 75, 113). The only patient with δ heavy-chain disease reported so far was a 70-year-old male who presented with symptoms of multiple myeloma and died with kidney complications (157).

HIDS. The new syndrome HIDS (MIM 260920) (so named in 1995) was described in 1984 by Van der Meer et al. (156) and seems to have boosted the measurement of serum IgD in various patients in the hope of detecting more patients with HIDS and also of finding increased IgD in other conditions. In 1983, Prieur and Griscelli described eight patients with juvenile onset of periodic fever and joint disease who were later shown to have increased serum IgD, as seen in HIDS (124). Originally described in patients from Holland, HIDS was found mostly in European countries (32) and later also in the United States (56). HIDS was found in patients with periodic fever that resembles familial Mediterranean fever (MIM 249100) and chronic, infantile, neurological, cutaneous, and articular syndrome. To my knowledge, 144 cases have been recorded in the international registry by the end of 1999. This syndrome is characterized by recurrent febrile attacks accompanied by abdominal pain, arthralgia, headache, and skin lesions. In the first reported cases of HIDS, IgD was measured by RID in specimens of serum to which ε-aminocaproic acid was added to inhibit proteolysis. Skin manifestations occurred in 80% of patients with HIDS but did not correlate with the serum IgD levels (57). During the febrile episodes, all patients had serum IgD values above 60 mg/liter (35) or 100 U/ml measured, if possible, on two occasions at least 1 month apart (36). Between attacks, IgD was as low as 11, 15.1, and 39 U/liter in three patients but rose to 656, 1,743, and 600 U/liter, respectively, during attacks (36). In two patients, the clinical symptoms of HIDS preceded the rise in serum IgD, indicating that elevated IgD concentration is not the cause of the clinical symptoms in this syndrome (59).

HIDS is probably inherited as an autosomal recessive trait (33). Very recently, mutations in the mevalonate kinase gene were shown to cause HIDS (41, 64). It has been proposed that patients exhibit an uncontrolled type III hypersensitivity reaction, possibly with involvement of IgD-containing complexes (16). Complement deficiencies or decreases in serum C3 and C4 were not found, albeit circulating immune complexes were detected in 20% of patients during or between attacks (36). A linear correlation was observed between serum IgD level and serum IgD complexes (62). During the febrile episodes, inflammatory cytokines, e.g., IL-6, TNF-α, and gamma interferon, were increased together with naturally occurring inhibitors such as IL-1 receptor antagonist and soluble TNF receptor (37). It was suggested that the underlying distur-

bances in HIDS may be in the T-cell regulation resulting in abnormal production of IgD primarily of the κ type, as well as of IgA, IgM, and IgG3 (59).

IgD was also increased (>100 U/ml) in many children with periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome (119), which was described in 1987 by Marshall et al. (101). This syndrome differs from HIDS and is self-limited (HIDS can persist throughout life) and responds dramatically to a single oral dose of corticosteroids (119).

CONCLUDING REMARKS

Although considerably more is known now about IgD than several decades ago soon after it was discovered, most of the recent information pertains to membrane-bound, not to serum, IgD. Recently, renewed interest in serum IgD measurement came from the chance discovery that some children with periodic fever had increased levels of serum IgD during the attacks (156). Increased serum IgD was found in many conditions but not always with consistency and has no practical value. A decreased level of serum IgD also has no clinical value. Serum IgD measurement can be important for monitoring of IgD myelomas, and it has been recently restated that monoclonal immunoglobulins are more accurately quantitated by measuring the protein concentration of the M spike in serum protein electrophoresis than by measuring the specific monoclonal immunoglobulin (73). The former procedure could be more difficult to perform for IgD because it migrates faster than IgG in serum protein electrophoresis, often together with other beta globulins, and sometimes the homogeneous IgD band is faint (154). The increased sensitivity of IgD to proteolysis could give false elevated levels when IgD is measured by RID in specimens that were not properly stored and to which protease inhibitors were not added. Expression of results in international units versus mass units (milligrams per liter) remains debatable, especially since no new IRP of IgD is available. To measure serum IgD in many patients only for the purpose of retaining competency (39) is unwarranted because measurement of IgD is not technically different from or more demanding than other routine measurements, and no clinical value of a finding of increased or decreased serum IgD has been shown. The possibility of finding a disease or another syndrome always associated with high serum IgD is very remote and likely of no clinical relevance. From experience, it seems that a specific role for serum IgD will not be found in the near future. In the present climate of cost containment in clinical laboratories, it is not justifiable to continue routinely measuring IgD every time other immunoglobulins (e.g., IgG, IgA, and IgM) are quantitated, or even separately, except in the cases of patients with monoclonal IgD in the serum or patients suspected of having HIDS.

ACKNOWLEDGMENTS

I thank R. Tomar, H. Spiegelberg, and D. Rappette for helpful information and J. Teitz for preparing the manuscript.

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