

Serum IgD and IgE Concentrations in Immunodeficiency Diseases

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ABSTRACT Concentrations of IgD and IgE were measured in sera from 165 patients with well-defined immunodeficiency in an effort to find information possibly relevant to the roles of antibodies of these classes in host defense. Values for both immunoglobulins were generally quite low in patients who had marked deficiencies of all three major immunoglobulins, although occasional normal or high normal values for IgD were seen in hypogammaglobulinemic patients. Group mean IgD concentrations were also depressed in patients with Wiskott-Aldrich syndrome and in those with selective IgA deficiency; IgE concentrations were depressed in patients with X-linked immunodeficiency with hyper-IgM and in those with ataxia telangiectasia. IgD and IgE were both significantly elevated in patients with extreme hyperimmunoglobulinemia E and undue susceptibility to infection and in a patient with the Nezelof syndrome; none of these patients had histories suggestive of atopy. In addition, the mean IgE concentration was significantly elevated in patients with selective IgA deficiency, many of whom were atopic, and in those with the Wiskott-Aldrich syndrome. The highest IgD concentration (163 mg/100 ml) was found in serum from a boy with variable immunodeficiency who had a lifelong history of severe recurrent pharyngeal infections, primarily streptococcal in etiology. Recurrent staphylococcal infection was a feature common to many but not all patients with elevated IgD and IgE. Depressed cell-mediated immunity was present in many patients with elevated serum IgE concentrations. These data may prove useful in the future delineation of biologic roles for antibodies in these two immunoglobulin classes.

INTRODUCTION

Numerous reports have documented a wide variety of abnormalities in concentrations of the three major im-

munoglobulins, IgG, IgA, and IgM, in patients with immunodeficiency (1). Less is known, however, about concentrations of IgE in such patients (2-10), and information on IgD concentrations in immunodeficiency can be found primarily only in limited studies (2, 11, 12) or case reports (13). Considerable knowledge has been derived from the study of patients with immunodeficiency diseases about the host defense roles played by various components of the immune system. Since it is unknown whether antibodies of the IgD and IgE classes function in host defense, knowledge of deficiencies or elevations of these proteins in particular groups of infection prone immunodeficient patients may provide some clues as to their biologic function. In the case of IgD antibodies no clearly identifiable biologic activity has yet been found, and indeed, there are only a few reports of antibody activity in molecules having the antigenic properties of IgD (14-17). It is known, however, that IgD molecules do not cross the placenta, are not present in body secretions or urine (12), and do not fix complement or sensitize guinea pig skin for passive cutaneous anaphylaxis (18, 19). IgE antibodies do not cross the placenta or fix complement but are known to be present in external secretions and to bind to basophils and mast cells (20). IgE antibodies so bound effect the release of histamine and the slow reacting substance of anaphylaxis upon combination with antigen, causing both anaphylactic and atopic types of immediate hypersensitivity.

In the present study we examined serum IgD and IgE concentrations in 165 patients who represent a spectrum of well-defined immunodeficiency diseases. While these proteins were found generally to be present in low concentrations when there were marked deficiencies in the other three immunoglobulin classes, some immunodeficient patients were found to have elevated concentrations of IgD, IgE, or both. Knowledge of clinical features of several of the latter patients may prove useful in the future delineation of biologic roles for antibodies in these two immunoglobulin classes.

Received for publication 4 June 1974 and in revised form 3 September 1974.

METHODS

Study population. Venous blood samples were obtained from 165 patients with well-defined immunodeficiency; the sera were separated by centrifugation and stored at -20°C until studied. Most of the patients were seen and/or followed at the Duke University Medical Center from 1967 to 1974, but a few were seen by physicians elsewhere who mailed the patients' sera to us. The deficiency group was composed of 10 cases of infantile X-linked agammaglobulinemia (X Ag),¹ 15 patients with non-X-linked agammaglobulinemia (Non-X Ag), 8 infants with transient hypogammaglobulinemia (Trans Ag), 3 patients with X-linked immunodeficiency with hyper-IgM (Hyp M), 9 infants with severe combined immunodeficiency (SCID), 79 patients with selective IgA deficiency (A Def), 7 cases of ataxia telangiectasia syndrome (A-T), 3 patients with cellular immunodeficiency with normal or hyperimmunoglobulinemia (Nezelof syndrome or Nez), 4 examples of immunodeficiency with thrombocytopenia and eczema (Wiskott-Aldrich syndrome or W-A) (1), 11 patients with the syndrome of extreme hyperimmunoglobulinemia E and undue susceptibility to infection (Hyp E) (4), 6 patients with other forms of variable immunodeficiency (Var ID), and 10 cases of chronic granulomatous disease of childhood (CGD).

Normal controls for serum IgD concentrations consisted of 23 infants, 105 children, and 57 adults; normal controls for serum IgE concentrations included 12 infants, 55 children, and 51 adults. These subjects were selected from hospital personnel and patients attending the Duke Pediatric Outpatient and Cardiac Clinics. Verbal informed consent was obtained for the venous blood collections. Inquiry was made about personal histories of recurrent infection, parasitism, atopic disorders, or autoimmune diseases, and individuals with positive histories were excluded.

Measurement of IgD and IgE. Concentrations of IgG, IgA, and IgM were determined by single radial diffusion using antisera specific for each of these human immunoglobulins and primary reference standards prepared in this laboratory (21). IgD concentrations were measured by a similar method using commercial goat anti-human IgD agarose plates (Meloy Laboratories Inc., Springfield, Va.). The secondary IgD reference standard was calibrated against a research IgD standard (67/37) obtained from the WHO Reference Center for Immunoglobulins, Springfield, Virginia. This method was capable of detecting concentrations as low as 1 mg/100 ml. All sera giving rings of precipitate on the goat antihuman IgD and/or IgE (see below) agarose plates were also tested on agarose plates containing either 10, 50, or 100 μl of normal goat serum/15 ml aga-

rose to detect antiruminant antibodies which would give false positive rings of precipitate (22); all sera reacting on these plates were absorbed with normal goat serum until they no longer gave rings of precipitate and then were retested.

IgE concentrations were measured by two methods. Sera were screened initially for high IgE values with commercially available goat antihuman IgE agarose plates (Meloy Laboratories Inc.) which permitted measurement of concentrations as low as 697 U/ml. All sera which had no detectable IgE by single radial diffusion were tested by a modification of the double antibody method of Gleich, Averbek, and Swedlund (23) which was capable of detecting IgE concentrations less than 1 U/ml. In the early part of this study, the reagents employed in the assay included: (a) sheep anti-IgE (ND) antiserum, kindly provided by Dr. David S. Rowe of the WHO International Reference Center for Immunoglobulins; (b) rabbit antigoat IgG prepared by immunizing 12 rabbits with DEAE cellulose purified goat IgG and repeatedly absorbing the pooled antisera with normal human serum; and (c) purified IgE (PS), isolated by ion exchange and gel filtration chromatography from serum obtained from Dr. O. Ross McIntyre and labeled with ^{125}I by the method of Hunter and Greenwood (24). When antiruminant antibodies present in many of the study patients' sera (especially those with either A Def or W-A) were found to give falsely high results in this modification, the method required further revision so as to eliminate ruminant antisera. Assays involving sera containing antiruminant antibodies or sera from patients entering the study during the latter part included the following reagents: (a) rabbit anti-Fc IgE, raised against PS Fc fragment isolated by agarose block electrophoresis of papain-digested, purified PS, (b) pony antirabbit IgG, prepared by immunizing a pony with DEAE cellulose purified rabbit IgG and repeatedly absorbing the antiserum with normal human serum, and (c) purified Bedore IgE myeloma protein, obtained from Dr. Roy Wood of the Immunoglobulin Reference Center, Springfield, Va. and radiolabeled as above. Serum from one of the study patients (B. S.) with extreme hyperimmunoglobulinemia E and undue susceptibility to infection (4) was calibrated against a research standard (68/341) for IgE, obtained from the WHO Reference Center for Immunoglobulins, and found to have 22,300 U/ml. B. S. serum was used as the secondary reference standard in all IgE assays. Because of lack of agreement among various investigators as to the absolute concentration of IgE in the WHO reference standard (25), all IgE data are expressed as units per milliliter, the stated value of 9,346 U/ml in the WHO standard being used as a reference.

Statistical methods. All data were transformed logarithmically for statistical analysis, since concentrations of immunoglobulins G, A, and M have been shown to have a logarithmic gaussian distribution (26). For the logarithmic transformation, undetectable IgD values were called 0.1 mg/100 ml and IgE values 1 U/ml. Since both the IgD and IgE concentrations in the control groups were found to have multimodal distributions, however, the differences between group IgD and IgE concentrations were tested by the Mann-Whitney U test for differences of medians (27). Student's *t* test was also used to test differences between group mean log IgD and IgE concentrations. 95% confidence intervals were obtained by taking the antilogs of the mean logarithms ± 2 pooled SD of the logs of the data, as previously described (21).

¹ *Abbreviations used in this paper:* A Def, selective IgA deficiency; A-T, ataxia telangiectasia; CGD, chronic granulomatous disease of childhood; Hyp E, extreme hyperimmunoglobulinemia E and undue susceptibility to infection; Hyp M, X-linked immunodeficiency with hyper-IgM; Nez, Nezelof syndrome or cellular immunodeficiency with normal or hyperimmunoglobulinemia; Non-X Ag, non-X-linked agammaglobulinemia; PS, purified IgE; SCID, severe combined immunodeficiency; T, thymus-derived; Trans Ag, transient hypogammaglobulinemia; Var ID, variable immunodeficiency; W-A, Wiskott-Aldrich syndrome or immunodeficiency with thrombocytopenia and eczema; X Ag, infantile X-linked agammaglobulinemia.

TABLE I
Serum IgD Concentrations in Immunodeficiency Patients

Group	Number	Ages	Range	Geom. mean	P value (t test)	Median	P value (Mann-Whitney)
			<i>mg/100 ml</i>				
Transient hypogammaglobulinemia	8	(3-20 mo)	<1	<0.1	NS	0.1	NS
Severe combined immunodeficiency	9	(3-17 mo)	(<1-2)	0.1	NS	0.1	NS
X-linked agammaglobulinemia	10	(3-16 yr)	(<1-20.6)	0.4	0.02	0.1	NS
Non-X-linked agammaglobulinemia	15	(6-35 yr)	(<1-14.4)	0.2	<0.0001	0.1	0.0007
X-linked immunodeficiency with Hyper-IgM	3	(7 mo-21 yr)	(<1-5.1)	0.4	NS	0.1	NS
Selective IgA deficiency	79	(5 mo-50 yr)	(<1-39.3)	0.7	<0.0001	0.1	0.0005
Ataxia telangiectasia syndrome	7	(5-14 yr)	(<1-19.2)	2.6	NS	5.6	NS
Nezelof syndrome	3	(8 mo-3 yr)	(2-22)	7.0	NS	7.8	NS
Wiskott-Aldrich syndrome	4	(8 mo-12 yr)	(<1-7.8)	0.7	NS	1.4	NS
Extreme hyperimmunoglobulinemia E	11	(3-31 yr)	(2.7-159)	14.4	<0.0001	16.1	0.0004
Other variable immunodeficiency	6	(1-14 yr)	(<1-163.4)	3.6	NS	7.4	NS
Chronic granulomatous disease	10	(6 mo-17 yr)	(<1-53.1)	4.8	NS	4.6	NS
Normal infants	23	(6 wk-19 mo)	(<1-1.6)	0.1 (0-0.6)*	—	0.1	—
Normal children	105	(3-14 yr)	(<1-36)	1.6 (0-70)*	—	3.0	—
Normal adults	57	(21-55 yr)	(<1-11.2)	2.4 (0-61)*	—	4.6	—

*95% confidence interval.

RESULTS

Serum IgD concentrations. Group median serum IgD concentrations were found to be significantly depressed in patients with Non-X Ag and A Def when compared with the appropriate normal group data (Table I and Fig. 1). Group medians were also quite low in Trans Ag, SCID, X Ag, Hyp M, and W-A, although these differences did not prove to be statistically significant in the Mann-Whitney U test. The group median IgD concentration was significantly elevated in patients with Hyp E; medians for A-T, Nez, and CGD patients were also elevated but differences were not significant in the Mann-Whitney U test. IgD was not detectable in the sera of a majority of individuals in groups with very low mean IgD values, but three patients with X Ag, three with Non-X Ag, one with Hyp M, two with W-A (Fig. 1), and 39 with A Def had measurable quantities ranging from 1.4 to 39 mg/100 ml.

One patient each with Hyp E and Nez and three with

Var ID had IgD values well above the appropriate normal group bounds (Table II). 11 of the 20 patients in these three groups had IgD concentrations greater than 10 mg/100 ml, and only two had no detectable IgD. As can be seen, elevated IgD was not always associated with increased concentrations of the other types of immunoglobulins; in patients J. T., J. C., and D. C. it was associated with abnormally low concentrations of one or more of the other classes.

Serum IgE concentrations. Group median IgE concentrations were significantly depressed in patients with Trans Ag, SCID, X Ag, Non-X Ag, Hyp M, and A-T when compared with the appropriate normal group data (Table III and Fig. 2). Group median IgE concentrations were significantly elevated in patients with A Def, W-A, and Hyp E; Var ID and CGD median values were also elevated but the differences were not significant in the Mann-Whitney U test. In groups with low IgE, the mean values were all under 10 U/ml and

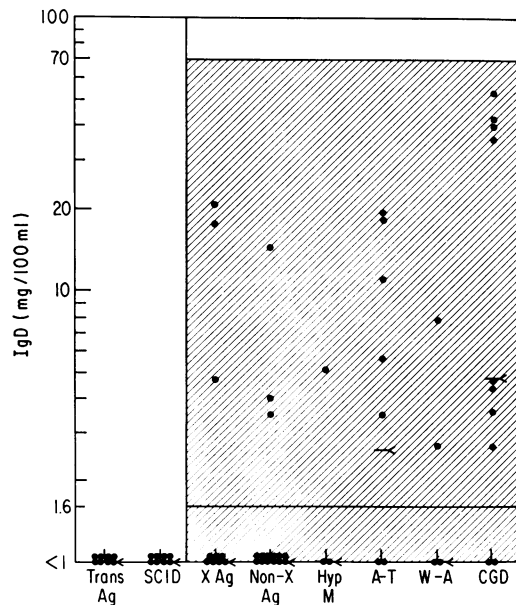


FIGURE 1 Serum IgD concentrations in Trans Ag, SCID, X Ag, Non-X Ag, Hyp M, A-T, W-A, and CGD. The cross-hatched area represents the 95% confidence interval for 105 normal children studied in this laboratory; the normal geometric mean of 1.6 mg/100 ml is indicated by the horizontal line. Trans Ag and SCID patient values were compared with those of 23 normal infants whose geometric mean and 95% confidence interval were 0.1 (0-0.6) mg/100 ml. Individual immunodeficient patient IgD values are depicted by the dots and the geometric means of the patient groups by the horizontal arrows.

the individual values, with one exception, were all lower than the group mean for normal children and adults (Fig. 2). The exception was a 9-mo-old infant with SCID who had been given a large quantity of gamma globulin a few days before the serum sample was obtained; however, since the amount of IgE in commercial gamma globulin is negligible and the half-life of IgE in serum is 2-3 days, it is likely that the IgE was produced by the infant.

It is apparent that the presence of atopy had a major influence on the serum IgE concentrations in A Def's (Fig. 3) since, when those patients were grouped according to the presence or absence of atopy, the IgE concentration of the nonatopic A Def's did not differ significantly from normal (Table IV). On the other hand, the atopic A Def median of 270 U/ml was highly significantly different. Since the W-A patients by definition all had a pruritic dermatitis resembling allergic eczema, it is likely that atopy is also related to their elevated serum IgE concentrations (Fig. 2).

In contrast to the above groups, the patients with Hyp E, Nez, and Var ID, who in many cases had extremely elevated concentrations of IgE, did not have

histories suggestive of atopy. One patient in the CGD group had an IgE value above the 95% confidence interval of the normal group (Fig. 2). The latter patient was not atopic but had multiple staphylococcal liver abscesses at the time the blood sample was obtained.

Relationship between IgD and IgE concentrations. Since patients with Hyp E had the highest mean IgD concentration of any of the groups, this raised the question of a possible positive correlation between the concentrations of these two immunoglobulins. This association was also seen in CGD patients and in Nez patient DR and Var ID patient DC. Nevertheless, the correlation was not borne out in the other groups, since patients with A-T had elevated IgD and decreased IgE, and patients with W-A and A Def had decreased IgD and increased IgE.

DISCUSSION

Although IgD was discovered over 9 yr ago (28) and much information has been obtained pertaining to its physicochemical structure (28), metabolism (29), biologic activity (18, 19), and distribution in body fluids and tissues (12), there are few clues as to its role in the immune response and in host defense. Of considerable interest is the recent observation that a high proportion of human peripheral blood lymphocytes bear surface

TABLE II
Serum Immunoglobulin Concentrations*
in Hyp E, Nez, and Var ID

Patient	Age(yr)/ Race/Sex	IgG	IgA	IgM	IgD	IgE
Hyperimmunoglobulinemia E						
B. S.	14/W/M	580	100	81	5.6	22,300‡
R. B.	14/W/M	1,080	175	42	60	6,600‡
E. N.	31/N/F	1,500	35‡	113	3.3	15,600‡
V. D.	11/W/F	4,100‡	360	220‡	29.2	38,400‡
A. Y.	16/N/M	2,700‡	510	153	2.7	40,000‡
P. D.	7/N/F	2,440‡	240	256‡	30.0	25,600‡
G. D.	13/N/F	1,880	488	280‡	2.7	2,150‡
F. D.	3/N/M	1,960‡	175	210‡	16.1	2,788‡
C. C.	13/W/M	1,520‡	448	200‡	19	6,400‡
T. F.	11/W/M	1,800‡	158	133‡	159‡	9,000‡
F. K.	22/W/M	2,280‡	570	81	15.9	12,362‡
Nezelof syndrome						
D. R.	8/12/W/M	1,850‡	1,000‡	360‡	22‡	7,000‡
R. S.	2/W/M	980	55	72	2	5
A. C.	3/W/F	1,225‡	490‡	260‡	7.8	5
Variable immunodeficiency						
J. T.	7/W/M	450‡	800‡	32	163‡	98
S. O.	7/W/F	410‡	25‡	14‡	<1	11
B. F.	14/W/M	400‡	30‡	44	<1	45
J. C.	1/N/M	155‡	0‡	41	33‡	32
D. C.	2/N/M	230‡	0‡	42	11‡	2,880‡
A. P.	8/W/F	44‡	0‡	84	4	1,850‡

* Expressed as mg/100 ml except in the case of IgE where values are in U/ml.

‡ Indicates abnormally high value for age for this laboratory.

§ Indicates abnormally low value for age for this laboratory.

TABLE III
Serum IgE Concentrations in Immunodeficiency Patients

Group	Number	Ages	Range	Geom. mean	P value (t Test)	Median	P value (Mann-Whitney)
			<i>U/ml</i>				
Transient hypogammaglobulinemia	8	(3-20 mo)	(2-31)	6	0.05	5	0.0269
Severe combined immunodeficiency	9	(3-17 mo)	(<1-82)	2	<0.0001	2	0.0018
X-linked agammaglobulinemia	10	(3-16 yr)	(<1-5)	2	<0.0001	1	<0.0001
Non-X-linked agammaglobulinemia	15	(6-35 yr)	(1-10)	3	<0.0001	3	<0.0001
X-linked immunodeficiency with hyper-IgM	3	(7 mo-21 yr)	(<1-2)	1	<0.0001	1	0.0016
Selective IgA deficiency	74	(5 mo-50 yr)	(3-3,800)	124	<0.0001	174	0.0001
Axataxia telangiectasia syndrome	7	(5-14 yr)	(<1-54)	7	<0.0001	10	0.0005
Nezelof syndrome	3	(8 mo-3 yr)	(5-7,000)	55	NS	5	NS
Wiskott-Aldrich syndrome	4	(8 mo-12 yr)	(135-720)	381	<0.0001	487	0.0020
Extreme hyperimmunoglobulinemia E	11	(3-31 yr)	(2,150-40,000)	11,305	<0.0001	12,362	<0.0001
Other variable immunodeficiency	6	(1-14 yr)	(11-2,880)	142	NS	70	NS
Chronic granulomatous disease	10	(6 mo-17 yr)	(<1-3,160)	88	NS	100	NS
Normal infants	12	(2-19 mo)	(3-81)	18 (1-222)*	—	25	—
Normal children and adults	106	(2-55 yr)	(2-549)	55 (5-621)*	—	55	—

* 95% confidence interval.

IgD (30, 31) and that most of these lymphocytes (75-86%) also bear IgM (32). There is evidence that both of these immunoglobulins are produced by the cells carrying them, as opposed to being nonspecifically absorbed to their surfaces (32). The simultaneous presence of immunoglobulin molecules of two different heavy chain types on the surface of a single lymphocyte is unique since, in general, lymphocytes bearing IgG or IgA have only one class on their membranes (33). The finding of a high percentage of IgD-bearing lymphocytes in the peripheral blood was also quite surprising since normally concentrations of this protein in serum are quite low (34) and very few plasma cells containing IgD can be found in lymphoid tissues (12). These observations have led to speculation that IgD antibody molecules may function primarily as membrane receptors which may send a signal to the lymphocyte that results in a differentiation pattern distinct from that triggered by the IgM receptor (32). Since abnormalities in lymphocyte differentiation have been implicated as the basis for deficiencies in production of other classes of immunoglobulins (34), it is possible that some of the abnormalities in serum IgD concentrations found in the present study could be due to differentiation defects.

While several studies have been made of serum IgD concentrations in normal individuals (25-37), very little is known about IgD levels in disease states or in im-

munodeficient humans. The finding in the present study of detectable IgD in only 39 of 79 (49%) A Def's as compared with its detection in 75 of 105 (71%) normal children, and 46 of 57 (81%) normal adults is similar to the findings of Johansson, Hogmån, and Killander (11). This suggests that IgD deficiency may be common among A Def patients. While IgD was found to be undetectable in 85% of 78 patients with idiopathic hypogammaglobulinemia studied by Rowe, Crabbé, and Turner (12), concentrations up to 33 mg/100 ml were found in the remainder. This is in keeping with the finding in the present study of normal to high normal concentrations of IgD in a few patients with X Ag and Non-X Ag.

Patients in this study who had the highest concentrations of IgD did not bear any obvious clinical resemblance to each other, except that recurrent staphylococcal infections predominated among the CGD and Hyp E patients, and Var ID patients J. C. and D. C. In contrast, Var ID patient J. T., who had the highest serum IgD concentration (163 mg/100 ml) had as his sole clinical problem recurrent and severe pharyngeal infections; the latter were proven to be of streptococcal etiology on a number of occasions. Despite this, the patient had very low titers of anti-DNase B, anti-NADase, and antigroup A carbohydrate streptococcal antibodies. The restriction of this boy's infections to the naso-

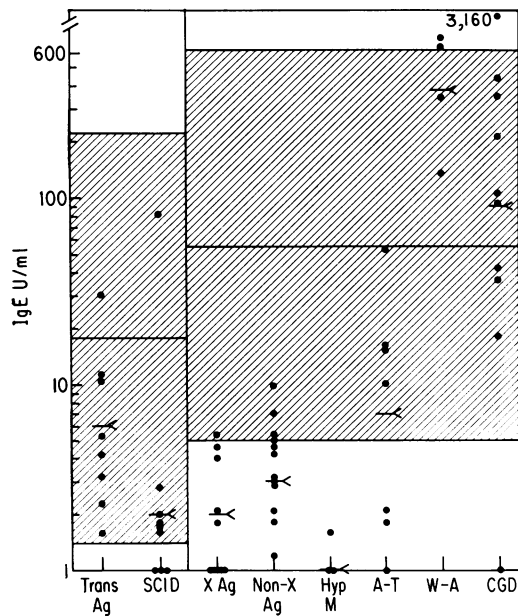


FIGURE 2 Serum IgE concentrations in X Ag, Non-X Ag, Trans Ag, Hyp M, SCID, A-T, W-A, and CGD. The cross-hatched area on the left represents the 95% confidence interval for 12 normal infants; the normal geometric mean of 18 U/ml is indicated by the middle horizontal line. The cross-hatched area on the right represents the 95% confidence interval for 106 normal children and adults; the normal geometric mean of 55 U/ml is indicated by the middle horizontal line. Individual immunodeficient patient IgE values are depicted by the dots and the geometric means of the patient groups by the horizontal arrows.

pharynx is of interest in view of the fact that adenoids were shown by Rowe et al. (12) to have far greater numbers of IgD-containing plasma cells than human spleen, lymph nodes, or intestinal lymphoid tissue. Patient J. T. had his tonsils and adenoids removed at age 14 mo but required further removal of posterior pharyngeal lymphoid tissue at age 5 yr. Unfortunately, none of this tissue was examined by immunofluorescence for IgD-containing plasma cells. Membrane immunofluorescence studies of J. T.'s peripheral blood lymphocytes did, however, reveal an elevated percentage (19%) of IgD-bearing lymphocytes. The presence of a continued marked elevation of serum IgD in this patient several years after his adenoids were removed indicates that IgD is still being produced in very large quantity, since the half-life of IgD in serum is only 2.8 days (29). A serum IgD concentration of this magnitude was observed by Barth et al. (13) in an immunodeficient girl who also had markedly elevated serum IgM. None of the Hyp M patients in the present study, however, had elevated IgD levels.

The possibility that chronic infection alone could cause elevated concentrations of IgD has been raised

previously (12). The finding of elevated IgD in tuberculosis (38), leprosy (12), and in the CGD and Hyp E patients in the present study would suggest this. Contrary to this is the fact that many other of the study patients who were chronically infected had low or undetectable quantities of IgD, including some of the CGD patients. Moreover, Rowe, McGregor, Smith, Hall, and Williams (37) found IgD concentrations to be normal in malaria and in members of a West African (Gambian) community where chronic parasitic infestation and infections are likely to be common. IgD was found to be normal in patients with various types of autoimmune diseases (12) but elevated approximately threefold over normal in pregnant women (39).

The observed deficiency of serum IgE in X Ag, Non-X Ag, SCID, and A-T is in keeping with the findings of others (5-10) and is not surprising since all but the A-T have generally inadequate production of all or most types of immunoglobulins. Interest in the possible role

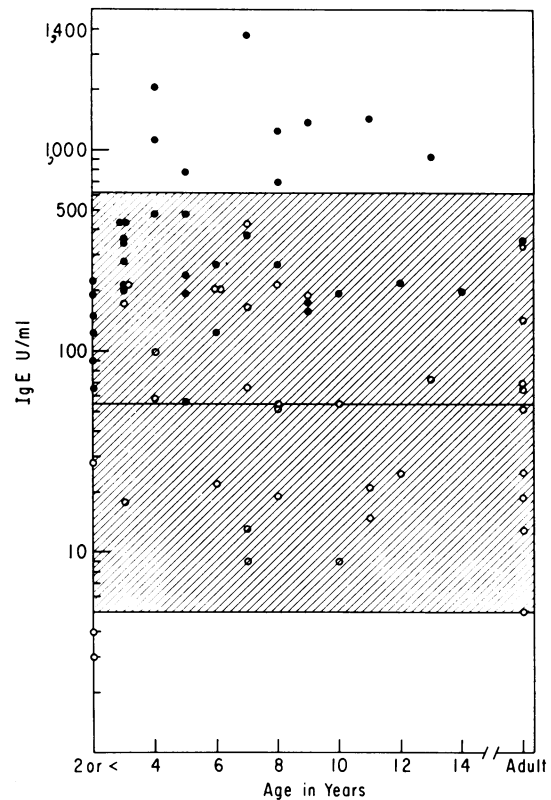


FIGURE 3 Serum IgE concentrations in 74 patients with selective IgA deficiency. The cross-hatched area represents the 95% confidence intervals for 106 normal children and adults studied in this laboratory; the normal geometric mean of 55 U/ml is indicated by the middle solid line. Individual atopic A Def patient IgE values are depicted by the closed circles and the nonatopic A Def values by the open circles.

TABLE IV
Comparison of Serum IgE Concentrations in Atopic and Nonatopic Patients with Selective IgA Deficiency

Group	Number	Range	Geom. mean	P value (t test)	Median	P value (Mann-Whitney)
		U/ml				
Atopic A Def's	38	(56-3,800)	330	<0.0001	270	<0.0001
Non-Atopic A Def's	36	(3-430)	44	NS	52	NS
Normal children and adults	106	(2-549)	55	—	55	—
			(5-561)*			

* 95% confidence interval.

of IgE in host defense was stimulated by the report of Ammann, Cain, Ishizaka, Hong, and Good (40) in 1969 that susceptibility to infection in A-T patients was correlated with a combined deficiency of IgA and IgE but not with IgA deficiency alone. This correlation was not confirmed in a larger group of A-T patients studied by Polmar, Waldman, Balestra, Jost, and Terry (5), however, nor was it found in three groups of non-A-T A Def patients (3, 5, 8). Indeed, the converse was found, e.g., there was a very high frequency of respiratory tract disease in A Def's who were not IgE deficient (5). Moreover, healthy IgE-deficient patients have been found (41) and as noted below, a number of examples have now been found where undue susceptibility to infection is associated with abnormally elevated serum IgE concentrations (4, 7, 42).

The elevated concentrations of IgE in our A Def population are similar to those reported previously in a smaller portion of the group (3). It would appear that a high incidence of atopy in these patients is the primary reason for this. Since most of the A Def individuals in the present and previous study were drawn from patients referred to an allergy clinic, however, it is impossible to say whether the observed increased incidence of atopy reflects an increase in atopy among A Def patients in general.

The elevated IgE concentrations found in the W-A patients in this report are in keeping with those found by others (2, 6) and are possibly related to these patients' dermatitis. An alternative hypothesis, however, is that the impaired cell-mediated immunity in this condition, in the Hyp E patients, in Nez patient D. R., and in Var ID patient A. P., is causally related to the augmented IgE production. A precedent for such a relation is seen in the experimental work of Tada and coworkers (43-45) who have produced enhanced IgE antihapten antibody formation in rats by treating them with small doses of antithymocyte serum, 400 R whole body irradiation, adult thymectomy and splenectomy, or by giving various immunosuppressive drugs before or shortly after immunization. The common facilitating factor in those

treatments appeared to be depression of T (thymus-derived)-cell immunity, since other studies by these workers showed that administration of syngeneic carrier-specific T lymphocytes to such animals could abrogate the enhanced IgE antibody production (46). In support of the possibility that overproduction of IgE may be related to depressed T-cell immunity in man is that, except for the A Def patients in the present study, all immunodeficiency patients with excessive IgE production in this and other reports (4, 7, 42) have also had impaired cell-mediated immunity. It is possible that even A Def patients may have a T-cell subpopulation deficit, since they recently have been shown to have decreased percentages of T-cell rosettes (34) and impaired interferon production by phytohemagglutinin-stimulated lymphocytes (47).

A third factor possibly related to increased IgE production in certain of these immunodeficiency patients is chronic infection, particularly with staphylococcal organisms. Features of the nine additional patients with extreme hyperimmunoglobulinemia E and undue susceptibility to infection (Table II) discovered since the original report (4) will be reported in detail elsewhere.² In brief, all had lifelong histories of recurrent severe staphylococcal and, in many cases, fungal infections, and all had evidence of depressed cell-mediated immunity. Patients with CGD, and Var ID patients D. C. and A. P. also had a high frequency of staphylococcal infections. Elevated IgE was noted by Arbesman, Ito, Wypych, and Wicher (48) in a patient with chronic osteomyelitis, but no organism was mentioned. Against a major role for chronic infection per se in augmenting IgE production, however, is the fact that most of the CGD patients in the present study had values within the 95% confidence interval for the normal group and we found elevated serum IgE concentrations in only 2 of 56 patients with cystic fibrosis.³

² Manuscript in preparation.

³ Unpublished observations.

Although no clear patterns of infection susceptibility associated with deficiencies or excesses of IgD and IgE production emerge from the observations in this report, it is hoped that the trends noted will prove helpful in the future definition of biologic roles for these proteins.

ACKNOWLEDGMENTS

We are grateful to Dr. David S. Rowe for his donation of sheep anti-Fc (ND) antiserum, to Dr. O. Ross McIntyre for giving us PS serum, to Dr. Mary Ann Passero for assistance in preparing the Fc(PS), to Dr. Roy Woods for his gift of purified Bedore IgE paraprotein, to Dr. C. E. Buckley for help with statistical analysis of the data, and to Dr. Susan C. Dees and the many other physicians who referred us patients for study or sent us their sera. We also acknowledge the skilled technical assistance of Mr. Craig P. Prokos and Mrs. Carolyn Stopford and the excellent secretarial assistance of Mrs. Lora B. Whitfield.

Supported by Asthma and Allergic Diseases Center Grant (AI 12026-01), Allergic Diseases Academic Award (AI 70830-01), a grant from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health (RR-30), and in part by a grant from the North Carolina Lung Association.

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