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SERUM IMMUNOGLOBULINS IN HEALTHY CHILDREN AND ADULTS

LEVELS OF THE FIVE CLASSES, EXPRESSED IN INTERNATIONAL UNITS PER MILLILITRE

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Summary

Serum levels of IgM, IgG, IgA, IgD, and IgE were determined in serum samples of 270 healthy Dutch children (aged 4—13 years) and of 30 healthy Dutch adults, the amounts being expressed in International Units per millilitre. Special attention is given to the IgD and IgE results, since the IgM, IgG, and IgA levels in mg per 100 ml of these sera and their implications have already been reported. In the children's sera the occurrence of relatively high IgD and IgE levels was frequently observed, whereas the adult group did not show excessive variation in this respect. The mean IgD levels found for adult males and females are 21 I.U./ml and 24 I.U./ml, respectively; the mean IgE levels for the same groups are 68 I.U./ml and 88 I.U./ml, respectively. The mean IgD and IgE levels in the children of each year group were usually higher than those of the adult group, but the difference between the mean level of each of the juvenile groups and the mean level of the adult group was not statistically significant. A statistically significant influence of sex and season on the IgD and IgE levels could not be demonstrated in this material either. Three of the 270 children's sera showed an exceptionally low IgA content. In two of these cases the serum was sampled and studied a second time after an interval of four years, when the IgA deficiency proved to be still present. The IgE levels in the sera of these healthy IgA-deficient children were normal, whereas the presence of IgD could not be demonstrated.

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Introduction

The quantitative analysis of immunoglobulins (Ig) in patients' sera is performed widely at present in clinical medicine. For a proper evaluation of such data, reference values determined from healthy controls are needed. In a previous paper, data were given on the estimation of IgM, IgG, and IgA levels in healthy children (aged 4—13 years) as compared with a group of healthy adults [1]. These results were obtained with the use of a local serum standard and were expressed in mg of Ig per 100 ml serum, according to what was then current practice [2—5].

However, the data obtained by different laboratories are of limited use and are not comparable, because different standards were used by the various authors [6]. The World Health Organization (W.H.O.) therefore established international reference preparations for the human serum immunoglobulins IgM, IgG, and IgA [7], IgD [8], and IgE [9]. Furthermore, it was recommended that immunoglobulins be preferentially expressed in International Units (I.U.) per ml [10]. For clinical use, Ig values may be calculated in terms of weight unless the best available weights corresponding to one I.U., as provided by W.H.O., are used [11].

The purpose of this paper is to give the IgM, IgG, and IgA levels of 270 Dutch children aged 4—13 years and of an adult group, in I.U./ml. In addition, the IgD and IgE contents of these sera were investigated as part of our studies on the maturation of Ig levels during childhood.

Materials and methods

Data concerning the selection and composition of the material have been published elsewhere [1] and are indicated in this paper only where relevant. The sera derived from 270 healthy children aged 4 to 13 years and 30 healthy adults (over 20 years old). With respect to the children, nine year-groups were distinguished. Each group (4—5, 5—6, etc.) comprised 30 children (15 males and 15 females). When the groups were composed, children were chosen with birthdays distributed over the year as evenly as possible. The adult group too had 15 males and 15 females. Seasonal influences were studied by spreading the venipunctures throughout the year: the first samples of each year group were collected in November of 1967, the second in February, 1968, and the third in May of 1968. All subjects were in good health, free of infection, and had neither recurrent infections nor an allergic constitution; they were all caucasians and were fasting at the time of the venipuncture. Possible contaminations with innocuous pluricellular parasites or moulds were not taken into account. The serum was divided into a number of 0.5 ml aliquots and frozen at −80°C within four hours. The samples were thawed a few hours before the immunoglobulin determinations were performed.

IgM, IgG, IgA, and IgD were determined by the radial immunodiffusion method of Mancini et al. [12] with a slight modification [13]. The antisera used to determine IgM, IgG, and IgA, as well as the local standard, have been described elsewhere [1,14]. The local standard used at that time was by good fortune included in an international trial sponsored by W.H.O. in 1968. As a

result, the IgM, IgG, and IgA levels of this particular serum were established and expressed in I.U./ml, which enabled us to convert our original data into I.U./ml. The conversion factors for this particular standard are 1.54 for IgM, 0.11 for IgG, and 0.54 for IgA. In cases where IgA could not be demonstrated with the radial immunodiffusion method, a mixed radio-immunosorbent assay [15,16] was used. This made it possible to determine very low IgA levels as well as to demonstrate anti-IgA antibodies if present.

The IgD levels in these sera were determined in 1970, in serum samples which had not been previously thawed. The anti-IgD serum was prepared by immunizing rabbits with a mixture of purified monoclonal IgD proteins. The antiserum was absorbed with IgG and in addition with a small quantity of serum from a patient with a Bruton-type agammaglobulinemia. The specificity was tested in double immunodiffusion assays and by immunoelectrophoresis. The international research standard (67/36) for IgD [8] was used to test our own IgD serum standard, which consisted of pooled serum of about 30 healthy blood-donors; the samples were stored in 0.5-ml aliquots and refrigerated at −30°C until use. The standard proved to contain 49.5 I.U. IgD/ml. According to Rowe et al. [8], this level corresponds with about 7 mg IgD per 100 ml. About 4 I.U./ml (ring diameter smaller than 4 mm) was the lower limit of the IgD concentration to be estimated with our method. The upper limit was about 50 I.U./ml (ring diameter about 7.5 mm). The amount of protein precipitated in IgD estimations is of course very small. Accordingly, the rings obtained are very faint and very hard to read. We therefore treated the diffusion plates with a solution of 1% tannic acid for 5 minutes [17] just before reading. This treatment bleaches the precipitates and consequently facilitates reading. Lipoproteins in the test sera sometimes interacted with agar, giving rise to precipitin-like rings, which could hamper reading. A highly purified agarose was therefore used to prepare the gels.

IgE was determined in 1972 in freshly thawed serum samples by a non-competitive sandwich-type radio-immuno assay in which labelled antibodies were used [18,19]. Anti-IgE bound to cellulose was incubated overnight with the test sample, after which the material was washed and incubated overnight with ^{125}I-labelled anti-IgE antibodies. After a second washing step the amount of radio-activity bound to the cellulose was determined. The procedures have been described in detail elsewhere [20]. Anti-IgE serum was prepared by immunizing rabbits with an enriched IgE preparation from the serum of a patient suffering from Mansoni's schistosomiasis [21]. The anti-IgE antibodies were isolated from this antiserum as described by Aalberse et al. [22], and labelled with ^{125}I by the chloramine-T method [23]. IgE levels were quantitated against the W.H.O. research standard (68/341) containing 10 000 I.U. per ampoule or 9346 I.U./ml [9]. The lower limit of the IgE measurements is about 10 I.U./ml.

Statistical analysis of the IgD and IgE values was done essentially as described earlier [1] for IgM, IgG, and IgA.

Results

The mean levels and the range for IgM, IgG, IgA, IgD, and IgE of the various age groups are given in I.U./ml in Table I. The data are shown for

TABLE I

SERUM IMMUNOGLOBULIN LEVELS IN I.U./ml IN 270 HEALTHY CHILDREN AND 30 HEALTHY ADULTS*

Age group	IgM				IgG				IgA	
	Male		Female		Male		Female		Male	
	Mean value, range	S.D.	Mean value, range	S.D.	Mean value, range	S.D.	Mean value, range	S.D.	Mean value, range	S.D.
4	98 49—146	31	144 62—256	60	96 63—123	16	99 63—139	25	66 16—133	32
5	83 37—136	28	140 57—259	60	97 57—138	20	104 66—154	24	44 5— 88	21
6	114 86—197	41	125 68—279	57	105 76—146	19	101 65—154	26	59 21—105	24
7	94 48—197	40	134 55—253	54	91 57—163	25	107 76—137	17	56 21—131	27
8	91 40—154	37	129 75—185	32	99 79—123	12	118 87—148	20	59 17—130	27
9	92 20—157	35	130 71—214	38	102 62—155	26	111 78—168	23	68 9—157	35
10	102 52—177	35	134 69—228	48	107 63—181	32	114 73—168	23	69 1—139	37
11	116 48—209	51	134 68—226	47	109 74—161	21	115 82—163	25	70 42—125	24
12	85 40—145	30	141 86—367	69	101 59—146	25	109 73—146	19	59 9— 99	28
Adults	144 85—217	47	168 57—300	62	107 73—154	22	117 64—179	32	109 56—218	45

* According to W.H.O. recommendations [16] 1 I.U. IgM corresponds to 8.47 μg, 1 I.U. IgG to 80.4 μg, 1 I.U. IgA to 14.2 μg.

males and females separately, with the standard deviations. Figs 1 and 2 show the results of individual IgD and IgE determinations in relation to age; the corresponding data for IgM, IgG, and IgA can be found in our first article [1].

As for IgM, IgG, and IgA, the range of levels in each year group was very wide for IgD and IgE. It is apparent from Figs 1 and 2, however, that the IgD and IgE levels of the adult group are less scattered than the values of the child group, where high levels occur in each group. This is divergent with respect to IgM, IgG, and IgA, since the latter levels are scattered for both children and adults.

TABLE II

DISTRIBUTION IN PERCENTAGES OF LOW AND HIGH IgD AND IgE LEVELS IN CHILD AND ADULT SERA

	Low IgD (≤4)	High IgD (≥70)	Low IgE (≤10)	High IgE (≥500)
270 children	18.8%	11.1%	8.8%	13%
30 adults	6.6%	3.3%	20.0%	0%

IgA		IgD				IgE			
Female		Male		Female		Male		Female	
Mean value, range	S.D.	Mean value, range	S.D.	Mean value, range	S.D.	Mean value, range	S.D.	Mean value, range	S.D.
56	28	39	53	36	46	134	169	309	941
24—117		4—208		4—187		10— 670		10—3700	
57	25	21	130	29	29	390	530	382	676
9—105		4— 68		4—100		10—1790		10—2210	
52	24	40	38	27	24	309	685	188	176
11— 96		4—131		4— 82		15—2600		10— 610	
44	19	29	20	34	31	418	737	143	155
1— 88		4— 63		4—126		10—2600		10— 515	
62	34	22	16	27	27	119	149	248	392
17—155		4— 55		4— 87		10— 625		10—1530	
63	24	28	31	19	16	167	242	185	248
29— 97		4—101		4— 50		10— 950		15— 865	
57	17	35	41	40	34	275	589	712	970
27— 90		4—148		4—130		10—2280		10—3200	
77	36	43	30	50	43	272	625	331	595
42—181		6— 90		4—144		15—2500		15—2300	
60	17	41	25	30	23	128	199	197	275
35— 96		4— 99		4— 84		10— 715		10— 990	
94	40	21	14	24	20	68	72	88	96
29—185		4— 47		4— 70		10— 235		10— 290	

TABLE III

STATISTICAL DATA ON THE SERUM IMMUNOGLOBULINS IN 270 HEALTHY CHILDREN AND IN 30 HEALTHY ADULTS

	IgD mean value		Significance *P* of difference of adult level		IgE mean value		Significance *P* of difference of adult level	
	Male	Female	Male	Female	Male	Female	Male	Female
4— 5 years	39	36	N.S.	N.S.	134	309	N.S.	N.S.
5— 6 years	21	29	N.S.	N.S.	390	382	0.028	N.S.
6— 7 years	40	27	0.077	N.S.	309	188	N.S.	0.063
7— 8 years	29	34	N.S.	N.S.	418	143	0.078	N.S.
8— 9 years	22	27	N.S.	N.S.	119	248	N.S.	N.S.
9—10 years	28	19	N.S.	N.S.	167	185	N.S.	N.S.
10—11 years	35	40	N.S.	N.S.	275	712	N.S.	0.021
11—12 years	43	50	0.017	0.046	272	331	N.S.	N.S.
12—13 years	41	30	0.013	N.S.	128	197	N.S.	N.S.
Adults	21	24			68	88		

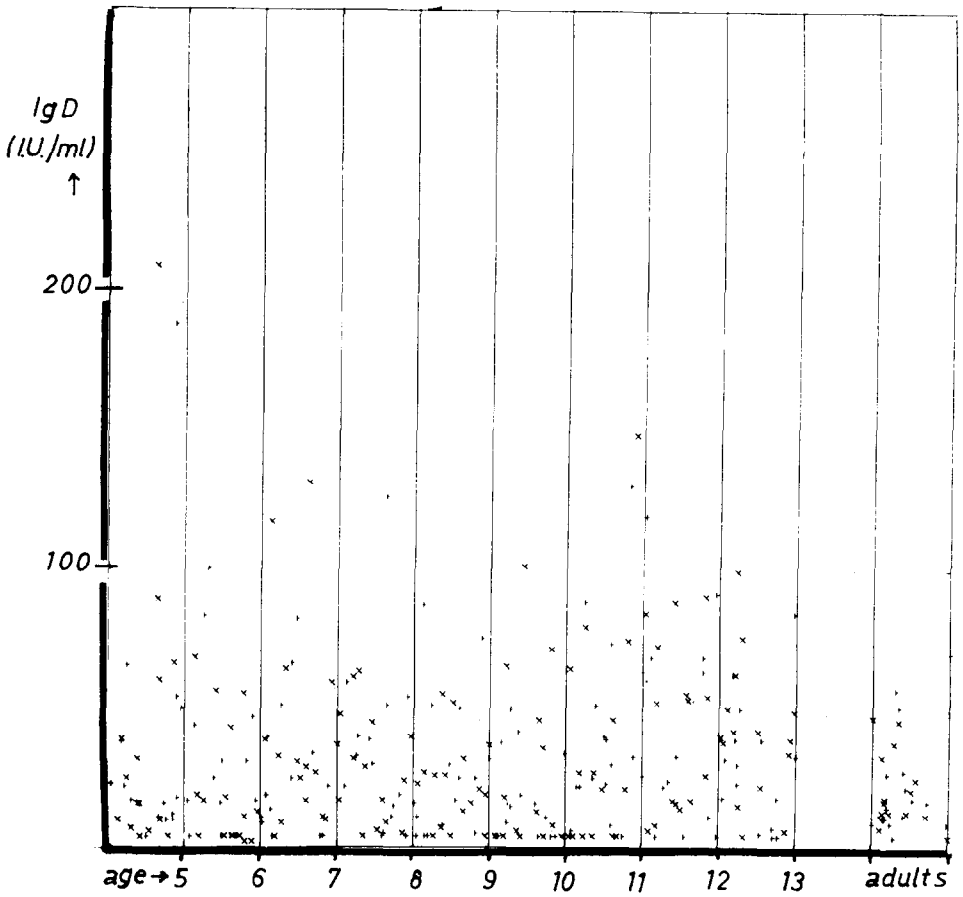

Fig. 1. Serum IgD levels of 135 healthy boys, 15 healthy men, 135 healthy girls and 15 healthy women. X, males; +, females.

The phenomenon is further illustrated by the data in Table II, showing the distribution (in percentages) of low IgD and IgE levels (⩽4 I.U. IgD/ml and ⩽10 I.U. IgE/ml) and high IgD and IgE levels (⩾70 I.U. IgD/ml and ⩾500 I.U.

TABLE IV

Ig-LEVELS IN I.U./ml OF THREE IgA DEFICIENT HEALTHY CHILDREN

	Age	IgM	IgG	IgA	IgD	IgE	anti IgA
D.H.	5— 6	77	119	<2*	<4	780	n.d.***
	11—12	60	115	0.23**	<4	19	negative**
X	7— 8	103	100	<2*	<4	45	n.d.***
E.K.	10—11	82	182	<2*	<4	130	n.d.***
	15—16	69	164	0.55**	<4	70	negative**

* Determined by radial immunodiffusion [23].
** Determined by mixed immunosorbent radioimmunoassay [3].
*** n.d., not done.

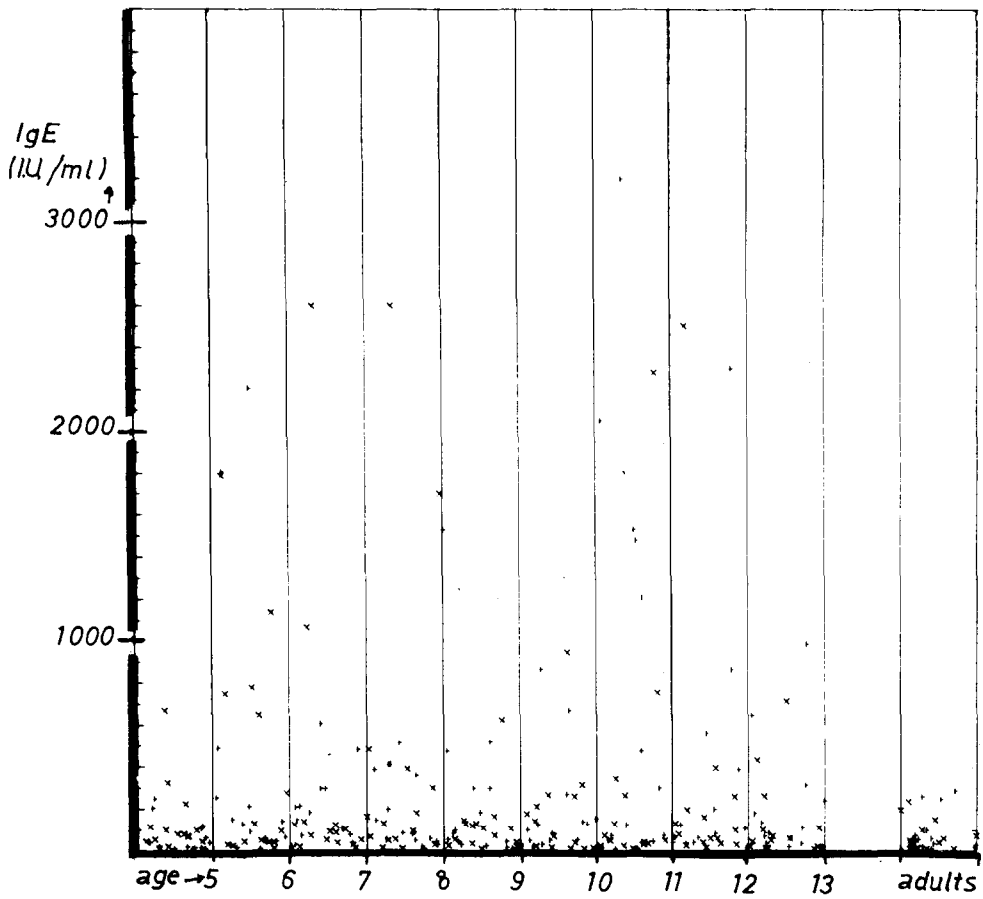

Fig. 2. Serum IgE levels of 135 healthy boys, 15 healthy men, 135 healthy girls and 15 healthy women. X, males; +, females.

IgE/ml) in juvenile and adult sera. The mean IgD and IgE levels in almost all of the year groups were higher than the adult levels; but this observation was grosso modo not statistically significant (Table III). At the age of twelve, the mean IgE level of both males and females is higher than the mean adult level, but there is a tendency for these values to fall to the adult level.

A statistically significant influence of sex on the concentration of IgD and IgE could not be demonstrated, and this also holds for a statistically significant influence of season. Table IV shows the levels of the five Ig classes in three juvenile sera with an exceptionally low IgA level among the 300 sera investigated. Two of these three healthy children could be investigated again in 1972, and displayed the same immunoglobulin pattern except for a remarkable decrease in the IgE level of one of them (D.H.).

Discussion

The determination of serum levels of IgM, IgG, and IgA is mainly carried out in diseases with a recognized or expected immunological component. IgD

and IgE still seem to be assessed less frequently, although the technical problems have been solved. Antibody activity of IgD has so far only been detected by indirect methods [24]. In view of the presence of IgD on lymphocyte membranes [25] and of the possible lack of effector roles of circulating IgD, it is questionable whether serum IgD determination in disease has any significance. This problem can only be solved by further functional studies in addition to the determination of serum IgD levels in thoroughly documented patients.

The biological function of IgE as carrier of reaginic activity [26] is well established, and elevated IgE levels are usually found in the serum of patients with atopic disease [21,27–29]. The elevation of serum IgE levels in parasitic diseases has been documented [30,31]; a protective role of IgE is still not proven in these cases. IgE deficiency has been observed in IgA-deficient patients suffering from ataxia telangiectasia [32]. Patients with an isolated IgA deficiency, however, usually show normal IgE levels [33]. The intimate linkage between IgA and IgE deficiency was found to be related to a particular vulnerability for sinopulmonary infections in ataxia telangiectasia patients, which suggested a protective role of IgE at mucous surfaces [34], but the observations of Polmar et al. [35] in 44 patients with ataxia telangiectasia failed to support this concept.

The introduction of the W.H.O. reference sera for human immunoglobulins makes it possible to compare Ig levels throughout the world. As a starting point for comparison, Rowe [36] was the first to publish, as the result of a collaborative investigation, the serum concentrations of IgM, IgG, and IgA in healthy young males from ten countries, expressed in I.U./ml. As mentioned above, we are now able to add to these values the IgM, IgG, and IgA levels in I.U./ml, of normal Dutch children and adults according to age and sex. Except in relation to other publications concerning Ig levels in I.U./ml, the results have already been discussed [1] and need little further comment. The mean levels of the 15 adult males reported here are in good agreement with the geometric means of 100 Dutch males aged 20 to 30 years determined in our laboratory and presented by Rowe [36]. The results concerning the children's IgM, IgG, and IgA levels are in good agreement with those obtained by Cejka et al. [38] in American children.

With regard to IgD, our results show that there is a wide variation in serum levels of children as compared to adults. Most of the juvenile levels were higher than the mean adult levels, although the difference between the two was not statistically significant in most cases. The distribution of the IgD levels in children and in adults illustrates this phenomenon. High levels of 70 up to 208 I.U./ml were found in 11.1% of the children sera, whereas the adult group had only one high-level serum. An analysis of the IgD levels of a group of British children, all of them hospital patients (61 individuals, aged 8 months to 15 years), and of a group of healthy British adults (95 individuals) disclosed no extremely high levels in either group; furthermore about 22% of the sera of both children and adults had a low IgD level. These results led to similar distribution curves for British children and adults [37]. The findings of Berg and Johansson [27] in Swedish children aged 3 to 15 years, also showed hardly any high IgD levels; these authors observed a slow and even increase of IgD during childhood. In a study on Gambian children and Gambian adults [39]

IgD was invariably demonstrated in 133 children aged 4 to 40 months, whereas it was undetectable in 10 to 12% of the adult sera. A wide variation persisted throughout childhood and adolescence, but after the age of 20 years, high levels were observed less frequently and the distribution came to resemble that found in British adults. It was concluded from the Gambian study that the absence of IgD in Gambian adults would not indicate an inherited inability to synthesize the protein [39]. Since a certain percentage of both children and adults in The Netherlands show very low or no IgD, an inherited incapacity for synthesis cannot be excluded. As in the Gambians, very high levels of IgD are observed less frequently in Dutch adults than in children. This seems to indicate that a decrease in the IgD concentration takes place in adolescence. Recently, this phenomenon was described by Geny et al. [40]. What, then, is the reason, if any, for high IgD levels in childhood? Are they a reflection of antigenic stimulation, and thus a selective response in terms of antibody class, or do they represent a so-far-unrecognized signal? Increased IgD concentrations have been reported in a few cases of chronic infections [37]. The children in the present study were, however, selected as normal.

Since no extensive series of normal IgD levels expressed in I.U./ml have been published so far, comparison of our values with those in the literature can only be done by accepting the statement of Rowe et al. that 1 I.U. is roughly the equivalent of 1.41 μg IgD [8]. On this basis, our results for adults lie in the range of the American [41], British [38], and Gambian [39] sera. The mean IgD levels of the Dutch children tend to be a little higher than those of the Swedish children [27] but are in fairly good agreement with recently published values for French children [40]. Concerning the influence of sex on the IgD levels, our results are consistent with the findings of Berg and Johansson [27].

With regard to IgE, our data indicate that there is a much greater variation in the levels in children than in adults. Very high levels, ranging from 500 I.U. up to 3700 I.U./ml, occur in 13% of the child sera. From the data of the adult group it must be concluded that the occurrence of high levels in children is by no means a permanent situation. It is recognized that high IgE levels can result from some parasitic infections [30,31]. Since this criterion was not taken into account in the selection of the sera, an acceptable explanation for the occurrence of high IgE levels could be a contamination of certain children with *Enterobius vermicularis*. Due to the high IgE levels in our children, logarithmic transformation did not produce a Gaussian distribution curve. In addition, the mean juvenile IgE levels in this study invariably lie higher than the mean adult levels. This is contradictory to the findings made in Swedish [27,28] and American children [42] where IgE levels in childhood were found to rise slowly but steadily to the adult level; moreover, there were no children with extremely high levels in those studies. However, Rowe and Wood [43] found higher IgE levels in children from Bristol than in adults from Lausanne. It therefore remains uncertain whether the reason for the differences must be sought in the selection of the subjects or in genetic and environmental factors. The mean IgE levels for the Dutch adult group are consistent with the mean value of 77 I.U./ml obtained in 51 healthy Swiss male donors [44] and are inconsistent with higher values found in adults in the U.S.A. [42] and Sweden [27]. Here too, genetic and environmental factors could have influenced the results.

High IgE levels in sera of children generally did not coincide with a high IgD level, which suggests a different cause for each of these phenomena. Six of our children's sera (about 2%) had both a low IgD and a low IgE, which is consistent with the predicted number (1.7%). As mentioned previously [1], three of the 270 juvenile sera showed an exceptionally low IgA. Bachman [45] reported a frequency of 1 : 700 for adults, which is much lower than the frequency of IgA deficiency in our child sera. Two of our three IgA-deficient juvenile sera could be investigated again in 1972. Since they showed the same Ig pattern then (Table IV), a delayed maturation of the capacity to synthesize IgA can be excluded. In addition, these healthy IgA-deficient children had normal or even high IgE levels (Table IV), which is consistent with observations made by Collins-Williams et al. [46]. It is striking that in all three IgA-deficient sera the IgD level was low or undetectable (Table IV). If it were purely a matter of chance, this phenomenon would occur in only 0.2% of the sera. Additional data from other series are needed to evaluate this finding.

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