

IgA Deficiency in Children

A Clinical Study with Special Reference to Intestinal Findings

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Savilahti, E., Pelkonen, P., and Visakorpi, J. K. (1971). *Archives of Disease in Childhood*, 46, 665. **IgA deficiency in children: a clinical study with special reference to intestinal findings.** Clinical, immunological, and intestinal studies on 26 children with IgA deficiency in the age range 2 to 16 years are reported. 9 of these children were suffering from autoimmune disease, namely thyroiditis (5), thyrotoxicosis (1), rheumatoid arthritis (2), and probable Sjögren's syndrome (1). The last-mentioned patient had defective cellular immunity. Altogether 11 patients were subject to recurrent respiratory tract infections. The symptomatology of the remaining patients was variable. In a boy with growth retardation, a chromosome anomaly was found, and endocrinological studies indicated total absence of growth hormone.

In 21 patients IgA was undetectable, while 5 had trace amounts of IgA in their sera. IgG was raised in 11 patients, and one patient had low serum IgG. IgM levels were mostly normal. Precipitating antibodies to cow's milk proteins were present in all but one serum.

Small intestinal biopsy was performed on all patients. In 3 cases total villous atrophy was detected and these probably had coeliac disease, though malabsorption symptoms were not always evident. Disaccharidase assay of biopsy specimens revealed 2 cases of isolated lactase deficiency among 8 tested.

Results show that the increased incidence of autoimmune disease reported in IgA deficiency in adults also holds true in children; i.e. that there is a raised incidence of coeliac disease with or without symptoms in IgA deficiency.

Isolated deficiency of immunoglobulin A is the commonest immunological deficiency state, with a reported incidence of from 1:700 (Bachmann, 1965) to 1:3000 (Cassidy *et al.*, 1969). IgA deficiency has been reported in association with recurrent respiratory infections (South *et al.*, 1968; Hobbs, 1968), rheumatoid arthritis (Huntley *et al.*, 1967; Hobbs, 1968; Cassidy *et al.*, 1969), systemic lupus erythematosus (Bachmann, Laurell, and Svenonius, 1965; Hobbs, 1968), and other autoimmune disease (Hobbs, 1968; Cassidy *et al.*, 1969; Claman *et al.*, 1970; Ammann and Hong, 1970), but a number of subjects who lack IgA are free of symptoms (Rockey *et al.*, 1964; Goldberg, Barnett, and Fudenberg, 1968). In addition, various gastrointestinal disorders associated with IgA deficiency have been described. Crabbé and Heremans (1966, 1967) reported three patients with steatorr-

hoea, one having coeliac disease, and other conditions include nodular lymphoid hyperplasia of the small intestine (Hermans *et al.*, 1966), ulcerative colitis (Claman *et al.*, 1970), Crohn's disease (Claman *et al.*, 1970), and lactase deficiency (Dubois *et al.*, 1970).

We report the clinical features in 26 children with IgA deficiency, who were studied with special attention to intestinal function and morphology.

Material and Methods

During 1966-1970, 26 children with isolated deficiency of IgA were found among about 5000 patients over 2 years of age whose sera were studied by immunoelectrophoresis. The main indications for immunoelectrophoretic study were recurrent respiratory infections, suspected autoimmune disease, malabsorption syndrome, urinary tract infections, and various neurological disorders. When the IgA line was invisible in immunoelectrophoresis, indicating an IgA level

TABLE I
Clinical Data

Case No.	Sex	Age When Deficiency Detected (yr)	Age at Investigation (yr)	Clinical Diagnosis
1	F	13·9	15·5	Thyroiditis
2	F	9·2	9·8	Thyroiditis, malabsorption syndrome
3	F	16·2	16·2	Thyroiditis
4	F	2·9	3·2	Thyroiditis, bronchial asthma, recurrent URTI
5	F	10·5	14·3	Thyroiditis, diabetes mellitus
6	F	12·4	13·8	Thyrototoxicosis
7	M	6·1	7·4	Rheumatoid arthritis
8	F	7·5	8·0	Rheumatoid arthritis
9	F	12·5	14·1	Recurrent parotitis
10	F	4·4	7·3	Malabsorption syndrome
11	F	15·0	15·0	Malabsorption syndrome, recurrent URTI
12	M	6·9	6·9	Bronchial asthma, recurrent URTI
13	F	7·5	7·5	Bronchial asthma, recurrent URTI
14	F	4·5	9·4	Recurrent URTI
15	M	6·7	8·8	" "
16	M	3·9	5·5	" "
17	F	2·0	2·0	" "
18	F	3·3	3·4	" "
19	F	2·3	2·3	" "
20	F	6·5	6·9	" "
21	M	3·5	3·8	Pneumonia, sinusitis
22	M	7·2	10·3	Nanism, chromosome anomaly, lack of growth hormone
23	F	12·0	13·7	Recurrent urinary infections, dysplastic kidneys, mental retardation, cleft palate, convulsions
24	F	11·4	13·1	Erythema nodosum
25	M	7·9	8·3	Convulsions, transient haematuria of unknown aetiology
26	F	10·4	10·4	Obesity, herpes simplex detected from genital condylomata acuminata

* URTI, upper respiratory tract infections.

below 20–30 mg/100 ml, IgA was estimated quantitatively. Those patients whose serum IgA was below 2 mg/100 ml were included in the study. The clinical diagnoses were established and the treatment of the underlying disease began simultaneously with the detection of the IgA deficiency. Later on, after a variable period of time (Table I), these patients were readmitted for confirmation of their immunological abnormality, as well as for intestinal investigations.

Quantitative determinations of immunoglobulins were performed according to a modification (Immonen, 1967) of the method of Mancini, Carbonara, and Heremans (1965). The normal values for children determined in the same laboratory have been published by one of us (P.P.) (Immonen, 1967). The lower limit of sensitivity of the method for IgA is 2 mg/100 ml. The double diffusion micro-method (Crowle, 1958) was used to detect smaller amounts of IgA, and by this method IgA levels exceeding 0·5 mg/100 ml could be detected.

Our standard was referred to a serum sample, the immunoglobulin concentrations of which were determined in the laboratory of Dr. D. Gitlin, Philadelphia. The relation between WHO immunoglobulin reference preparation 67/97 (Rowe, Anderson, and Grab, 1970) and our standard serum is as follows. IgG: 96·2 IU/ml = 8·83 mg/ml; IgA: 95·3 IU/ml = 0·835 mg/ml; IgM: 96·2 IU/ml = 0·575 mg/ml and the immunoglobulin concentration of our standard serum is 150

IU/ml of IgG, 137 IU/ml of IgA, and 194 IU/ml of IgM. Polyvalent horse antiserum to human serum proteins was obtained from Behringwerke Laboratories, Marburg Lahn, Germany, and employed for immunoelectrophoretic analyses. Monospecific goat antisera to human IgA, IgG, and IgM were purchased from Mann Research Laboratories, N.Y., U.S.A.; these, as well as rabbit antisera to IgA, IgG, and IgM prepared in our own laboratory (Savilahti, in preparation), were used for quantification of immunoglobulins. In double diffusion experiments the rabbit antiserum was used.

Precipitating antibodies to cow's milk proteins and gluten were determined as described by Heiner *et al.* (1962). An indirect immunofluorescent technique was used to detect antinuclear antibodies. Antithyroglobulin and antimicrobial antibodies were determined as described by Roitt and Doniach (1958).

Small intestinal biopsy specimens were obtained from the upper part of the jejunum with a Crosby-Kugler biopsy capsule, paediatric size; they were studied both freshly under the dissecting microscope, and by ordinary histology. Disaccharidase activities of biopsy specimens were measured as described by Launiala *et al.* (1964).

The tests employed in the study of absorptive function and their evaluation have been described earlier (Visakorpi, Kuitunen, and Pelkonen, 1970). The criteria used in establishing the diagnosis of thyroid diseases are presented elsewhere (Mäenpää, 1971).

Result

Clinical features. In the symptomatology of the patients three separate disease entities stood out clearly, i.e. patients with autoimmune disease, those with malabsorption syndrome, and those with recurrent respiratory infections (Table I). Altogether 9 patients had autoimmune diseases, the largest group being that of 5 patients with thyroiditis. One child was suffering from thyrotoxicosis. In the 2 patients with rheumatoid arthritis the disease was relatively benign and affected several large joints. The presenting symptom in Case 9 was recurrent swelling of the parotid glands from the age of 7 years: sialectasis was shown to be present in both parotid glands; ocular and articular symptoms were absent; clinically the picture was thought to have features of Sjögren's syndrome, and her serum gave a wide range of autoimmune reactions.

Altogether 10 patients were studied because of recurrent upper respiratory tract infections: 2 of whom had bronchial asthma which had required several periods in hospital. In the remaining 8 patients the infections were fairly mild and had not required hospital treatment.

Of the remaining 5 patients, 1 (Case 22) is of special interest. He was studied because of nanism and slight mental retardation. Chromosome analysis of peripheral leucocytes showed that he had only 45 chromosomes; one D chromosome and one chromosome 18 were lacking, and an extra medium-sized submetacentric chromosome was present, which we interpreted as translocation of the type [45, XY, ?D—, t(Dq, 18p)]. Endocrinological studies indicated that the boy totally lacked growth hormone (Leisti *et al.*, in preparation).

Intestinal findings. In the majority of the patients the absorptive function was normal as studied by faecal fat and D-xylose excretion tests (Table II). Steatorrhoea was found in 2 patients,

TABLE II
Intestinal Findings

Finding	No. of Cases
Faecal fat, >5 g/day	2/18
D-xylose excretion, <20%	1/20
Total villous atrophy	3/26
Isolated lactase deficiency	2/8

and one of these also had low urinary D-xylose excretion. In both patients with steatorrhoea and in one other patient biopsy of the small intestine showed total villous atrophy. Of the 3 patients

Case 10 has coeliac disease with full response to a gluten-free diet (Visakorpi *et al.*, 1970). In Case 2 malabsorption was suspected because of severe iron deficiency anaemia which was unresponsive to oral iron: on a gluten-free diet absorptive function became normal in 7 months, but with no improvement in villous structure. The third patient in whom total villous atrophy was observed (Case 11) was investigated because of recurrent respiratory tract infections: absorptive function was normal, apart from one slightly suggestive sign—a raised serum iron-binding capacity (484 μ /100 ml). She has been placed on a gluten-free diet with a tentative diagnosis of coeliac disease.

Disaccharidase activities were measured from 8 biopsy specimens with normal villous structure, and selective lactase deficiency showed in 2 of these, but neither developed symptoms after ingestion of lactose.

Immunological findings. The criterion for selection of the patients was a serum IgA level below 2 mg/100 ml. In 21 cases no IgA was detectable by the methods used, whereas in 5 (Cases 4, 14, 17, 19, and 25) IgA was present in trace amounts. The IgG levels were mostly in the upper normal range or somewhat high (Fig. 1),

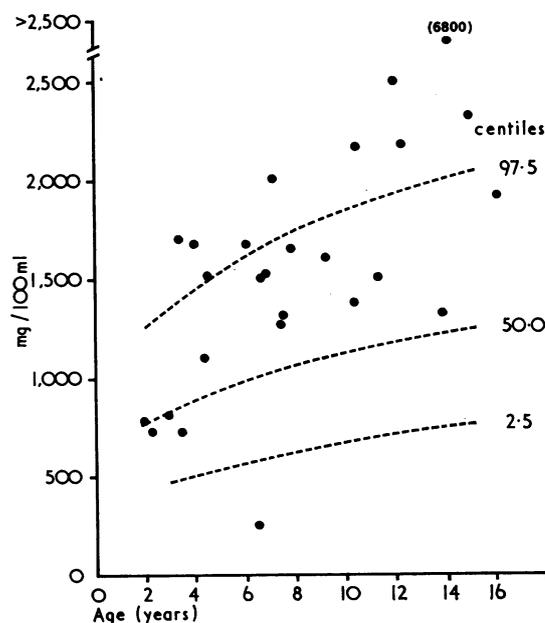


FIG. 1.—IgG levels in 26 cases at the time of initial investigation. (The mean, 2.5, and 97.5 centiles are indicated.)

but in one (Case 9), there was a marked polyclonal increase of IgG (6800 mg/100 ml) and in another (Case 20) a low level of IgG was observed. In most cases IgM was in the normal range (Fig. 2).

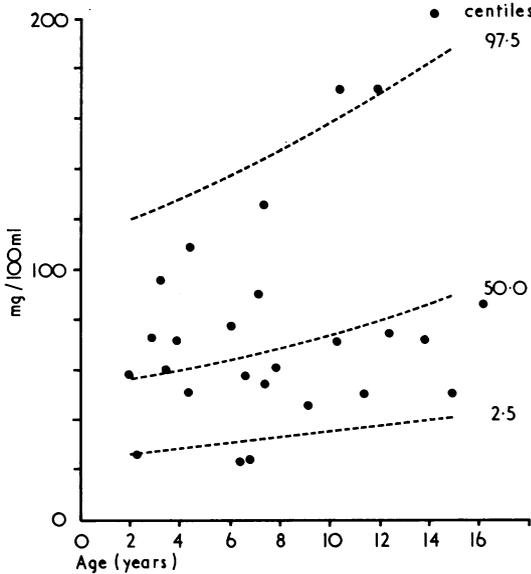


FIG. 2.—IgM levels in 26 cases at the time of initial investigation.

In Table III are presented the results of other immunological tests. All patients with thyroid disease had antithyroid antibodies at some time of their disease. In addition, antimicrobial antibodies were present in the sera of two other patients (Cases 9 and 23). One patient with rheumatoid

TABLE III
Immunological Data

Data	No. of Cases
Antithyroid antibodies	8/26
Antimicrobial antibodies	6/26
Antithyroglobulin antibodies	5/26
Antinuclear antibodies	2/26
Positive rheumatoid serology (Latex fixation and Waaler-Rose)	2/26
Precipitating antibodies to cow's milk	25/26
Precipitating antibodies to gluten	4/26

arthritis (Case 7) had positive rheumatoid serology, while in the other these tests were negative but the test for antinuclear antibodies was positive. The patient with recurrent parotitis (Case 9) gave positive reactions in rheumatoid tests (Waalser-Rose

over 800 and positive Latex fixation), and in addition had antinuclear antibodies, parietal cell antibodies, antimicrobial antibodies, and panagglutinins in her serum. She had normal peripheral lymphocyte counts, but her lymphocytes did not react to phytohaemagglutinin stimulation. Her skin test for tuberculin (PPD 10 IU) was negative in spite of BCG vaccination in early infancy, and no reaction to candida antigen (Oidiomycin 1 : 50) was visible.

In the serum of 25 patients precipitating antibodies to cow's milk were detected. 4 had precipitins to gluten but only 2 of these were patients with villous atrophy.

Discussion

As our series is a highly selected group of hospital patients, no far-reaching conclusions regarding the prevalence of various diseases in IgA-deficient children can be made. It has been shown earlier that a considerable number of persons with IgA deficiency suffer from autoimmune disease (Bachmann *et al.*, 1965; Huntley *et al.*, 1967; Goldberg *et al.*, 1968; Hobbs, 1968; Cassidy *et al.*, 1969; Ammann and Hong, 1970).

This is also true in our series. The proportion of patients with thyroid disease is higher in our material, however, than in other reports. This may partly be due to the fact that a study of thyroid disease was undertaken simultaneously (Kuitunen *et al.*, 1971). In that study IgA deficiency was observed in 5 out of 25 children with thyroiditis.

Frequent upper respiratory tract infections have been reported as a common feature in persons with IgA deficiency (South *et al.*, 1968; Hobbs, 1968). However, a clearly increased frequency of respiratory tract infections was recorded in less than half of our patients.

Association of IgA deficiency and chromosome-18 aberrations has been reported lately in several patients (Finley *et al.*, 1969; Stewart *et al.*, 1970), while other patients with similar chromosome anomalies have had normal levels of IgA. Of the 3 patients whose karyotypes were studied, 1 (Case 22) had a chromosome anomaly of a type not previously reported in connexion with IgA deficiency, and further had a deficiency of growth hormone. Whether the three different disorders in this patient are coincidental, or whether the deficiency of growth hormone and IgA are related to the loss of chromatid material (possibly from the D chromosome) and to the chromosome translocation, cannot be settled.

Several reports of patients with IgA deficiency and coeliac disease have been presented (Crabbé

and Heremans, 1967; Hobbs, 1968; Claman *et al.*, 1970; Gelzayd *et al.*, 1971) but the true incidence of this combination is unknown. Since coeliac disease may give rise to very few symptoms in children of over 2 (Visakorpi *et al.*, 1970), we wanted to study the incidence of this disease in IgA-deficient children. Of the 3 patients with villous atrophy, 1 has confirmed coeliac disease, in the second the history is highly suggestive of this, and the third patient has no signs of any other disease that could have resulted in total villous atrophy, and probably also has coeliac disease. Thus we found 3 cases with coeliac disease among 26 children with IgA deficiency. As the incidence of coeliac disease has been estimated to be 1 : 1850 (McCrae, 1969), this frequency is highly significant ($P < 0.001$ as tested by Poisson distribution). We have diagnosed 113 cases with coeliac disease up to the end of 1970 and 3 of these have IgA deficiency. If the incidence of IgA deficiency is of the order of 1 : 700 (Bachmann, 1965), it occurs in significantly increased frequency ($P < 0.01$) in coeliac disease.

How gluten induces the small intestinal damage in coeliac disease, is still obscure, but the finding of a high incidence of coeliac disease in IgA-deficient children suggests that immunological mechanisms may be involved.

It has lately been claimed that disaccharidase deficiency is a common feature in immunological deficits (Dubois *et al.*, 1970). In this series we found 2 cases of isolated lactase deficiency among 8 tested. As the prevalence of lactase deficiency in the same age group is 6% (Sahi *et al.*, in preparation), this finding is not significant.

The selection of these patients was based on the finding of a serum IgA level below the detecting capacity of the single radial diffusion technique, i.e. below 2 mg/100 ml. The more sensitive method revealed trace amounts of IgA in the sera of 5 of these patients. As there is no general agreement about the definition of IgA deficiency, these patients were also included in this study. Moreover, they had immunological features in common with the patients with no detectable IgA (Savilahti, in preparation). The increase in IgG in 10 cases was probably related to the active disease process, for in many cases normal levels of IgG were seen later on.

Data on cellular immunity in IgA deficiency are sparse (Goldberg *et al.*, 1968; Hobbs, 1968; Ammann and Hong, 1970), but this is usually assumed to be normal. One child with well-documented impairment of cellular immunity has recently been described (Schlegel *et al.*, 1970). This aspect was not studied systematically in our

series, but we found one patient (Case 9) who had clearly defective cellular immunity, as judged by lymphocyte stimulation and skin tests.

Buckley and Dees (1969) and Huntley *et al.* (1971) reported a high frequency of precipitating antibodies to cow's milk proteins and to ruminant serum proteins in IgA-deficient subjects. In our series all but one had precipitating antibodies to cow's milk. It is known that these antibodies are often associated with coeliac disease (Heiner *et al.*, 1962), but this was excluded in 23 of our patients, who had a normal small intestinal mucosa despite precipitins to cow's milk. It may therefore be presumed that these antibodies reflect lack of protective function in local IgA.

REFERENCES

- Ammann, A. J., and Hong, R. (1970). Selective IgA deficiency and autoimmunity. *Clinical and Experimental Immunology*, **7**, 833.
- Bachmann, R. (1965). Studies on the serum γ A-globulin. III. Frequency of A- γ A-globulinemia. *Scandinavian Journal of Clinical and Laboratory Investigation*, **17**, 316.
- Bachmann, R., Laurell, C.-B., and Svenonius, E. (1965). Studies on the serum γ^1 A-globulin level. II. γ^1 A-deficiency in a case of systemic lupus erythematosus. *Scandinavian Journal of Clinical and Laboratory Investigation*, **17**, 46.
- Buckley, R. H., and Dees, S. C. (1969). Correlation of milk precipitins with IgA deficiency. *New England Journal of Medicine*, **281**, 465.
- Cassidy, J. T., Burt, A., Petty, R., and Sullivan, D. (1969). Selective IgA deficiency in connective tissue diseases. *New England Journal of Medicine*, **280**, 275.
- Claman, H. N., Merrill, D. A., Peakman, D., and Robinson, A. (1970). Isolated severe gamma A deficiency: Immunoglobulin levels, clinical disorders, and chromosome studies. *Journal of Laboratory and Clinical Medicine*, **75**, 307.
- Crabbé, P. A., and Heremans, J. F. (1966). Lack of gamma A-immunoglobulin in serum of patients with steatorrhea. *Gut*, **7**, 119.
- Crabbé, P. A., and Heremans, J. F. (1967). Selective IgA deficiency with steatorrhea. *American Journal of Medicine*, **42**, 319.
- Crowle, A. J. (1958). A simplified micro double-diffusion agar precipitin technique. *Journal of Laboratory and Clinical Medicine*, **52**, 784.
- Dubois, R. S., Roy, C. C., Fulginiti, V. A., Merrill, D. A., and Murray, R. L. (1970). Disaccharidase deficiency in children with immunologic deficits. *Journal of Pediatrics*, **76**, 377.
- Finley, S. C., Cooper, M. D., Finley, W. H., Uchida, I. A., Noto, T. A., and Roddam, R. F. (1969). Immunological profile in a chromosome 18 deletion syndrome with IgA deficiency. *Journal of Medical Genetics*, **6**, 388.
- Gelzayd, E. A., McCleery, J. L., Melnyk, C. S., and Kraft, S. C. (1971). Intestinal malabsorption and immunoglobulin deficiency. *Archives of Internal Medicine*, **127**, 141.
- Goldberg, L. S., Barnett, E. V., and Fudenberg, H. H. (1968). Selective absence of IgA: a family study. *Journal of Laboratory and Clinical Medicine*, **72**, 204.
- Heiner, D. C., Lahey, M. E., Wilson, J. F., Gerrard, J. W., Schwachman, H., and Khaw, K. T. (1962). Precipitins to antigens of wheat and cow's milk in celiac disease. *Journal of Pediatrics*, **61**, 813.
- Hermans, P. E., Huijzenga, K. A., Hoffman, H. N., II, Brown, A. L., Jr., and Markowitz, H. (1966). Dysgammaglobulinemia associated with nodular lymphoid hyperplasia of the small intestine. *American Journal of Medicine*, **40**, 78.
- Hobbs, J. R. (1968). Immune imbalance in dysgammaglobulinemia type IV. *Lancet*, **1**, 110.
- Huntley, C. C., Robbins, J. B., Lyerly, A. D., and Buckley, R. H. (1971). Characterization of precipitating antibodies to ruminant serum and milk proteins in humans with selective IgA deficiency. *New England Journal of Medicine*, **284**, 7.

- Huntley, C. C., Thorpe, D. P., Lyster, A. D., and Kelsey, W. M. (1967). Rheumatoid arthritis with IgA deficiency. *American Journal of Diseases of Children*, **113**, 411.
- Immonen, P. (1967). Levels of the serum immunoglobulins γ A, γ G and γ M in the malabsorption syndrome in children. *Annales Paediatricae Fenniae*, **13**, 115.
- Kuitunen, P., Mäenpää, J., Krohn, K., and Visakorpi, J. K. (1971). Gastrointestinal findings in autoimmune thyroiditis and in nongoitrous juvenile hypothyroidism in children. *Scandinavian Journal of Gastroenterology*, **6**, 335.
- Launiala, K., Perheentupa, J., Visakorpi, J., and Hallman, N. (1964). Disaccharidases of intestinal mucosa in a patient with sucrose intolerance. *Pediatrics*, **34**, 615.
- Leisti, J., Leisti, S., Pelkonen, P., Perheentupa, J., Savilahti, E., and Åkerblom, H. Chromosome anomaly 45 XY, D-, t (Dg, 18p) and deficiency of growth hormone and IgA. (In preparation.)
- McCrae, W. M. (1969). Gluten-enteropathy in childhood. In *Malabsorption*, p. 221. Ed. by R. H. Girdwood and A. N. Smith. Edinburgh University Press, Edinburgh.
- Mäenpää, J. (1971). Juvenile goitrous autoimmune thyroiditis. *Acta Paediatrica Scandinavica*. (In the press).
- Mancini, G., Carbonara, A. O., and Heremans, J. F. (1965). Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry*, **2**, 235.
- Rockey, J. H., Hanson, L. Å., Heremans, J. F., and Kunkel, H. G. (1964). Beta-2A aglobulinemia in two healthy men. *Journal of Laboratory and Clinical Medicine*, **63**, 205.
- Roitt, I. M., and Doniach, D. (1958). Human auto-immune thyroiditis: serological studies. *Lancet*, **2**, 1027.
- Rowe, D. S., Anderson, S. G., and Grab, B. (1970). A research standard for human serum immunoglobulins IgG, IgA and IgM. *Bulletin of the World Health Organization*, **42**, 535.
- Sahi, T., Isokoski, M., Jussila, J., and Launiala, K. (1971). Lactose malabsorption in Finnish children at school age. *Acta Paediatrica Scandinavica*. (In the press.)
- Savilahti, E. IgA deficiency in children: Immunoglobulin containing cells in the mucosa of the small intestine and immunoglobulins in the intestinal juice. (In preparation.)
- Schlegel, R. J., Bernier, G. M., Bellanti, J. A., Maybee, D. A., Osborne, G. B., Stewart, J. L., Pearlman, D. S., Ouelette, J., and Biehuse, F. C. (1970). Severe candidiasis associated with thymic dysplasia, IgA deficiency, and plasma antilymphocyte effects. *Pediatrics*, **45**, 926.
- South, M. A., Cooper, M. D., Wollheim, F. A., and Good, R. A. (1968). The IgA system. II. The clinical significance of IgA deficiency: studies in patients with agammaglobulinemia and ataxia-teleangiectasia. *American Journal of Medicine*, **44**, 168.
- Stewart, J. M., Go, S., Ellis, E., and Robinson, A. (1970). Absent IgA and deletions of chromosome 18. *Journal of Medical Genetics*, **7**, 11.
- Visakorpi, J. K., Kuitunen, P., and Pelkonen, P. (1970). Intestinal malabsorption: a clinical study of 22 children over 2 years of age. *Acta Paediatrica Scandinavica*, **59**, 273.

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