Immunopathology of Juvenile-onset Diabetes Mellitus

I. IgA Deficiency and Juvenile Diabetes

William I. Smith, Jr., M.D., Bruce S. Rabin, M.D., Ph.D., Alan Huellmantel, M.D., David H. Van Thiel, M.D., and Allan Drash, M.D., Pittsburgh

SUMMARY

There is an increased prevalence ($P < 0.001$) of IgA deficiency in children with juvenile-onset insulin-dependent diabetes mellitus (9/366) but not in adults with insulin-dependent diabetes (0/421). The juvenile diabetics with IgA deficiency have other immune-associated diseases, such as thyroiditis and chronic active hepatitis, and have a history of infections. Four of the nine IgA-deficient diabetics we studied have autoantibodies to endocrine organs. Seven of eight have the HLA-B8, a proportion significantly ($P < 0.05$) greater than control populations. Based on the clinical findings of IgA deficiency and multiple autoantibodies in patients with ataxia-telangiectasia and chronic mucocutaneous candidiasis, diseases associated with thymus deficiency, we suspect that thymus deficiency and autoimmunity may play a role in the pathogenesis of some types of juvenile-onset diabetes mellitus. In addition, an excess morbidity of the IgA-deficient juvenile diabetic population may explain the lack of IgA deficiency in older insulin-dependent diabetic individuals. DIABETES 27:1092-97, November, 1978.

The etiology of juvenile-onset insulin-dependent diabetes mellitus remains obscure. Evidence suggesting a role for abnormal immune responses, including autoimmune reactions, in the pathogenesis of juvenile diabetes mellitus includes (a) the presence of autoantibodies to pancreatic islet cells, especially in newly diagnosed diabetics;[1-3] (b) the presence of lymphocytic infiltrates in the pancreas of patients dying soon after the onset of diabetes mellitus;[4] (c) macrophage inhibitory factor (MIF) production by lymphocytes from patients with diabetes mellitus in response to pancreatic extract;[4,5] (d) a high prevalence of autoantibodies to nonpancreatic tissues such as the stomach, thyroid, and adrenal in juvenile insulin-dependent diabetics;[6,7] (e) the association of diabetes with other autoimmune diseases, such as idiopathic Addison's disease, hypoparathyroidism, gonadal failure, and Graves' disease;[8-10] and (f) the association of juvenile-onset insulin-dependent diabetes mellitus with HLA antigens B8, BW15, and DW3.[11-15]

Autoimmune disease is found frequently in association with immunoglobulin deficiency disease.[16] In particular, selective IgA deficiency has been associated with autoimmune diseases, including Graves' disease, idiopathic Addison's disease, and pernicious anemia.[17] In contrast, with the exception of isolated case reports,[18-25] juvenile-onset insulin-dependent diabetes mellitus has not been considered to be associated commonly with selective IgA deficiency. Because the demonstration of an association between diabetes mellitus and selective IgA deficiency would provide further evidence for altered immune function in some individuals with juvenile-onset diabetes mellitus, and, in an effort to determine the prevalence of IgA deficiency in the insulin-dependent diabetic population, we screened children and adults with insulin-dependent diabetes for IgA deficiency.

From the Departments of Pathology, Medicine, and Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261.

Accepted for publication June 8, 1978.

MATERIALS AND METHODS

Patient Populations

Adults with insulin-dependent diabetes mellitus were obtained from three sources: (a) the Diabetes Clinic of the Oakland VA Hospital, Pittsburgh, Pennsylvania (152 patients); (b) Falk Clinic, University of Pittsburgh Health Center Hospitals (91 patients); and (c) private outpatients seen by Drs. Ralph Schmeltz and Jerome Aarons, Pittsburgh (178 patients). The adult control population consisted of 3,600 consecutive adult admissions to the University of Pittsburgh Health Center Hospitals. Children with diabetes were obtained from two sources: (a) the Diabetes Clinic of Children's Hospital, Pittsburgh (193 patients); and (b) the Joslin Clinic, Boston, Massachusetts (173 patients). Controls for the children's population consisted of age-, sex-, and environmentally matched outpatient children. The mean age of the children with diabetes and children controls was 11 years, with a range of 3 to 16 years.

Immunologic Testing

Screening for IgA deficiency was performed using an Ouchterlony double diffusion method in gel. Goat anti-human IgA serum (Meloy Laboratories, Fairfax, Virginia) was placed in the central well, and undiluted patient samples were placed in the peripheral wells. Those patient sera with low IgA levels, as determined by the lack of a precipitin line, were quantitated by radial immunodiffusion using specially prepared plates for the detection of immunoglobulin levels to 0.5 mg. per deciliter (Meloy Labs). IgA deficiency was defined as a serum level of less than 10 mg. per deciliter and, where possible, was confirmed by Ouchterlony analysis of secretions for secretory IgA.

Antibodies to endocrine organs were evaluated by an indirect immunofluorescence technique, except for the thyroid antibodies, which were measured by hemagglutination methods. For the fluorescence tests, fluorescein-conjugated antiserum to human immunoglobulins (Meloy Laboratories, Springfield, Virginia) were used. Sera were evaluated at a dilution of 10, a titer previously determined to be negative in 450 adult, hospitalized patients with no known endocrine disease. Substrates included normal human adrenal, normal human testis, human parathyroid adenoma, normal human pancreas, mouse stomach (for parietal cell), and mouse liver (for reticulin antibody and ANA). In adults, hemagglutinating thyroglobulin antibodies (Burroughs Wellcome, Beckenham, England) were screened at a dilution of 1:50 and thyroid microsomal antibody (Ames Co., Elkhart, Indiana) at a dilution of 1:100. In children, thyroid antibodies were screened at a dilution of 1:2, a titer necessary for detecting patients with disease.[26] HLA tissue typing was performed using the modified cytotoxicity method of Amos.[27]

Statistical Analysis

The chi-square analysis using the Yates' correction for continuity was used for statistical analysis. Results were considered significant at a P-value < 0.05.

RESULTS

The prevalence of IgA deficiency among the various populations studied is shown in table 1. As noted, there is a highly significant ($P < 0.001$) prevalence of IgA deficiency among juveniles with insulin-dependent diabetes mellitus when compared with adults with insulin-dependent diabetes.

The hospitalized adult population, from which the IgA-deficient controls were obtained, had a bimodal age distribution. Twenty-one per cent of the population were less than 32 years of age, with a mode of 25 years; a second mode was present at 60 years of age. Even though 62 per cent of the hospitalized population were older than 45 years, the oldest IgA deficient patient was 27 years of age (table 2). Thus patients with IgA deficiency are characteristically young ($P < 0.01$). This increased prevalence of IgA deficiency in young adults as compared with older individuals has

TABLE 1

Incidence of IgA deficiency

	Incidence
(1) Children—control population	0/120
(2) Children with diabetes mellitus	9/366*
(3) Adults—control population	8/3600
(4) Adults with diabetes mellitus	0/421*

*Group 2 significantly different from group 4, $P < 0.001$.

TABLE 2

IgA-deficient, hospitalized controls—clinical findings and IgA levels

Age (yr.)	Serum IgA mg./dl.	Diagnosis
22	0	Pelvic pain, etiology unknown
18	6.2	Cystitis, abdominal pain
27	0	Normal pregnancy
21	0	Insulin-dependent diabetes mellitus
25	0	Normal pregnancy
21	4	Rapidly progressive glomerulonephritis
22	0	Normal pregnancy
N.A.	0.9	N.A.

N.A., not available.

TABLE 3

Clinical and immunologic data of IgA-deficient diabetics

Patient	Age (yr.)	Sex	Complications and/ or other diseases	IgG (mg./dl.)	IgA (mg./dl.)	IgM (mg./dl.)	HLA	Autoantibodies present* (titers)
P.T.	8	F	Chronic active hepatitis, thyroiditis	4300	0	180	A1, B8/ A1, B8	Thyroid microsomal (8) Thyroglobulin (2) Reticulin
S.S.	15	M	Graves' disease Septic arthritis Asthma	730	4	162	A1, B8/ A11, BW40	Adrenal
M.V.	10	M	None	1707	5	89	A1, B8/ A3, B5	None
S.M.	15	F	Thyroiditis Diabetic retinopathy	2275	0	162	A2, B8/ A3, BW18	None
J.M.	14	M	None	930	0	205	A2, B12/ A3, BW35	None
K.M.	16	M	None	N.D.	0	53	A1, B8/ AW24, BW16	None
D.B.	16	F	None	N.D.	0	120	ND+	Thyroglobulin (8)
S.O.	14	M	Mental and physical retardation; bronchitis	N.D.	0	135	A3, B8/ A3, B8	Adrenal
T.F.	N.A.	M	N.A.	N.D.	0	145	A1, B8/ AW24, B5	None

N.D., not done; N.A., not available.
*Autoantibodies screened at a titer of 10, except for thyroglobulin and thyroid microsomal, which were screened at titer of 2.

been recognized previously.[28] The clinical characteristics of the patients with juvenile-onset diabetes mellitus and IgA deficiency are listed in table 3. The IgA-deficient diabetics had an unusually high incidence of the histocompatibility antigen HLA-B8 (seven of eight). In addition, four of nine had autoantibodies to endocrine organs (table 3). Because of limited amounts of available serum, IgG levels could not be quantitated in four of the patients with IgA deficiency (K.M., D.B., S.O., and T.F.). None of the patients has received exogenous gamma globulin therapy.

Sputum and duodenal juice were obtained from the first five patients listed in table 3. These secretions were deficient in IgA, thus confirming the presence of IgA deficiency.

When immunoglobulin concentrations were measured in the parents and siblings of five of the patients with IgA deficiency and insulin-dependent diabetes, none of the parents was IgA deficient, but one sibling (of J.M.) was found to be IgA deficient.

DISCUSSION

Although the etiology of diabetes mellitus remains unknown, it has been suggested that autoimmune mechanisms may participate in its pathogenesis by contributing to pancreatic tissue destruction as either a primary or a secondary event. A major criterion for the presence of any autoimmune disease, according to Witebsky and Milgrom,[24] is the presence of circulating antibody of cell-mediated immunity directed against antigens of the target organ. In regard to diabetes mellitus, some diabetics demonstrate autoantibodies to pancreatic extracts.[4,5,20] In addition, some diabetics have autoantibodies to other endocrine organs, especially to the adrenal, the thyroid, and the parietal cells of the stomach.[6,7] Moreover, diabetes mellitus is associated with other well-recognized autoimmune diseases such as Graves' disease.[8-10]

An additional finding suggesting abnormal immune function in juvenile insulin-dependent diabetic patients is the increased prevalence of IgA deficiency in these individuals. The prevalence of IgA deficiency in our general adult population is 1 in 450, in healthy children it is 0 in 120, and in adults with insulin-dependent diabetes it is 0 in 421 (table 1). In contrast, the prevalence of IgA deficiency in children with insulin-dependent diabetes is 1 in 41, a prevalence 10 times that of the adult diabetic population ($P < 0.001$). In four patients, a concomitant deficiency in IgG could not be ruled out. These patients could have deficiencies of both IgG and IgA, but they lacked the clinical syndromes usually associated with severe hypogammaglobulinemia.

Although IgA deficiency has been reported in association with many other presumed autoimmune diseases such as rheumatoid arthritis, systemic lupus

erythematosus, thyroiditis, Addison's disease, and pernicious anemia,[17] there have been relatively few cases associating IgA deficiency with diabetes mellitus.[18-25] Our finding that IgA deficiency is restricted to the juvenile population explains the previous failure to recognize the association of IgA deficiency and diabetes, as most previous studies of IgA deficiency were completed by screening of adult populations. There are several possible explanations for the assocation of IgA deficiency with juvenile-onset diabetes mellitus in children and not in adults.

(1) The patients start to synthesize IgA as they mature. Previous studies have shown IgA-deficient children can, at some later date, become IgA sufficient.[31] Such patients presumably have delayed maturation of the immune system. Five of our patients have been followed for two years and remain persistently IgA deficient. Since secretory IgA immunity matures many years before serum IgA reaches adult levels,[32] the absence of IgA in secretions obtained from the children we studied confirms their IgA deficiency.

(2) Phenytoin (Dilantin) and penicillamine are drugs that can induce IgA deficiency in some individuals.[33,34] Therefore, such treatment has been ruled out in our diabetic patients.

(3) The IgA-deficient juvenile diabetic patients die and are thus not represented in the older diabetic population. The combination of IgA deficiency and diabetes mellitus may be particularly lethal. We believe that this possibility is the most likely explanation for our findings. Infectious diseases are more frequent in IgA-deficient individuals.[16,17] Moreover, infections are a particularly important cause of diabetic morbidity and mortality. Consistent with this postulate are the observations that the patient we described previously[24] has died and that two of the nine IgA-deficient diabetic children we are now reporting on have poor prognoses—chronic active hepatitis (P.T.) and severe retinopathy at an early age (S.M.). Two of the others have had unusual infections—nontraumatic septic arthritis (S.S.) and chronic bronchitis (S.O.). As described for other patients with IgA deficiency,[16,17] the population of juvenile diabetics with selective IgA deficiency that is included in this report may be more susceptible to frequent and serious infections.

When the general population is examined for IgA deficiency, an excess of young people with IgA deficiency is found ($P < 0.01$). Although the general population we screened for IgA deficiency had a bimodal age distribution, all the IgA-deficient patients were 27 years of age or less. This excess of young individuals with IgA deficiency is not unique to our population but has been noted previously.[28] There is no good explanation for this fact at present. As we proposed for IgA-deficient juvenile diabetics, there also may be an increased mortality for the IgA-deficient population at large. At least one of our IgA-deficient control patients (J.I.) has a poor prognosis; he had rapidly progressive glomerular nephritis in 1972 and was treated by bilateral nephrectomy and kidney transplantation.

Patients with IgA deficiency and diabetes mellitus have an unusual distribution of HLA antigens (table 3), with seven of the eight having the HLA-B8 antigen. In Pittsburgh, HLA-B8 is present in 17 per cent (35 of 208) of the population, as determined by tissue typing of healthy relatives of hospitalized patients.[35] Thus, the IgA-deficient diabetic population in Pittsburgh has a statistically higher prevalence of HLA-B8 ($P < 10^{-5}$; when corrected for 18 antigens, $P < 0.005$) than does the control population. Since the HLA-B8 antigen occurs with increased frequency in insulin-dependent diabetics,[11,12] the proper control population for the IgA-deficient diabetics would be non-IgA-deficient diabetics. Since we have not typed a sufficiently large number of diabetics to make this comparison, we used published data. Using the data of Cudworth,[12] 148 of 288 (51 per cent) insulin-dependent diabetics had HLA-B8. Seignalet[11] had a frequency of 23 out of 100. The present IgA-deficient population is significantly different from the French[11] population ($P < 0.01$) but not different from the English[12] population ($\chi^2 = 2.75$, $P = 0.10$). When the published data are combined, the IgA-deficient diabetics again have a higher prevalence of HLA-B8 ($P < 0.05$). Ambrus et al. reported six patients who had autoimmune disease (two had diabetes) and IgA deficiency with the haplotype HLA-A1/B8.[23] Our prevalence of HLA-B8 in IgA-deficient diabetics is significantly different from that in our control population ($P < 0.005$). More importantly, the prevalence of the HLA-B8 antigen in IgA-deficient diabetics is also greater than the prevalence of the HLA-B8 antigen in the published insulin-dependent diabetics ($P < 0.05$). At least four other autoimmune diseases associated with HLA-B8 (ref. 36) also have a high frequency of selective IgA deficiency—gluten enteropathy,[17,20] myasthenia gravis,[37] Graves' disease,[17] and Addison's disease.[17]

An analysis of the family members of our IgA-deficient juvenile diabetics revealed one sibling (a brother) who also had an IgA deficiency, but none of the

parents had an IgA deficiency. This finding supports a polygenic mode of inheritance[38-40] for IgA deficiency. If a single locus were coded for IgA deficiency, as either a recessive or a dominant, increased numbers of siblings and relatives of the IgA-deficient patients also would be IgA deficient.

The pathogenetic mechanisms for IgA deficiency are unknown. There are at least two plausible explanations for IgA deficiency. First, it is well known that the IgA system matures late, with serum levels not reaching adult normal levels until puberty. Thus, a delayed physiologic maturation of the IgA system could account for an increased prevalence of IgA deficiency in young patients.[32] However, in normal children with low serum IgA, the secretory immune system matures by one or two years of age. In five of the patients we have tested thus far, the secretory immune system also has been deficient for IgA. Therefore, these patients have a truly pathologic IgA deficiency and not simply physiologic immaturity of the circulating immune system. The second mechanism proposed for IgA deficiency is partial thymic deficiency. Mice deficient in T-cell function have poor IgA production.[41] Further, obese chickens, a strain known to develop spontaneous thyroiditis and possibly to have a defect in suppressor T-lymphocytes, have been found also to have a high incidence of selective IgA deficiency.[42] The alleles to the major histocompatibility locus of the chicken are linked to the trait of IgA deficiency.[43] Clinically, ataxia-telangiectasia and chronic mucocutaneous candidiasis, two disease states known to be associated with T-cell defects, are also known to have a high incidence of IgA deficiency.[44,45] Therefore, the finding of IgA deficiency in a population of juvenile diabetics suggests the possibility that T-cell defects may also be present in these patients.

ACKNOWLEDGMENTS

We thank John Craighead, M.D., Professor and Chairman, Department of Pathology, University of Vermont, School of Medicine, for the serum samples from the Joslin Clinic.

This work was supported in part by a grant from the American Diabetes Association.

REFERENCES

[1]Bottazzo, G. F., Florin-Christensen, A., and Doniach, D.: Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet *2*:1279-82, 1974.

[2]MacCuish, A. C., Irvine, W. J., Barnes, E. W., and Duncan, L. J. P.: Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. Lancet *2*:1529-31, 1974.

[3]Lendrum, R., Walker, G., and Gamble, D. R.: Islet-cell antibodies in juvenile diabetes mellitus of recent onset. Lancet *1*:880-83, 1975.

[4]Egeberg, J., Junker, K., Kromann, H., and Nerup, J.: Autoimmune insulinitis: pathological findings in experimental animal models and juvenile diabetes mellitus. Acta Endocrinol. *83* (Suppl. 205):129-44, 1976.

[5]Irvine, W. J., MacCuish, A. C., Campbell, C. J., and Duncan, L. J. P.: Organ-specific cell-mediated autoimmunity in diabetes mellitus. Acta Endocrinol. *83*:65-75, 1974.

[6]Irvine, W. J., Scarth, L., Clarke, B. F., Cullen, D. R., and Duncan, L., Jr.: Thyroid and gastric autoimmunity in patients with diabetes mellitus. Lancet *1*:163-68, 1970.

[7]Ungar, B., Stocks, A. E., Martin, F. I. R., Whittingham, S., and Mackay, I. R.: Intrinsic factor antibody, parietal cell antibody, and latent pernicious anemia in diabetes mellitus. Lancet *2*:415-17, 1968.

[8]Perlman, L. V.: Familial incidence of diabetes in hyperthyroidism. Ann. Intern. Med. *55*:796-99, 1961.

[9]Solomon, N., Carpenter, C. J. C., Bennette, I. L., and Harvey, A. M.: Schmidt's syndrome (thyroid and adrenal insufficiency) and coexistent diabetes mellitus. Diabetes *14*:300-04, 1965.

[10]Frey, H. M. M., Vogt, J. H., and Nerup, J.: Familial polyendocrinopathy. Acta Endocrinol. (Copenhagen) *72*:401-16, 1973.

[11]Seignalet, J., Mirouze, J., Jaffiol, C., Selam, J. L., and Lapinski, H.: HLA in Graves' disease and in diabetes mellitus insulin-dependent. Tissue Antigens *6*:272-74, 1975.

[12]Cudworth, A. G., and Woodrow, J. C.: Genetic susceptibility in diabetes mellitus. Analysis of the HLA association. Br. Med. J. *2*:846-48, 1976.

[13]Cudworth, A. G., and Woodrow, J. C.: Evidence for HLA-A linked genes in juvenile diabetes mellitus. Br. Med. J. *3*:133-35, 1975.

[14]Nelson, P. G., Pyke, D. A., Cudworth, A. G., Woodrow, J. C., and Batchelor, J. C.: Histocompatibility antigens in diabetic identical twins. Lancet *2*:193-94, 1975.

[15]Thomsen, M., Platz, P., Andersen, O. O., Christy, M., Lyngsoe, J., Nerup, J., Rasmussen, K., Ryder, L. P., Staub Nielsen, L., and Svejgaard, A.: MLC typing in juvenile diabetes mellitus and idiopathic Addison's disease. Transplant. Rev. *22*:125-47, 1975.

[16]Hermans, P. E., Diaz-Buxo, J. A., and Stobo, J. D.: Idiopathic late-onset immunoglobulin deficiency. Clinical observations in 50 patients. Am. J. Med. *61*:221-37, 1976.

[17]Ammann, A. J., and Hong, R.: Selective IgA deficiency: presentation of 30 cases and a review of the literature. Medicine (Baltimore) *50*:223-36, 1971.

[18]Hagen, G. A., Bolman, R. M., III, and Frank, J. P.: Atypical adrenal insufficiency with failure of the pituitary feedback receptor: a case with associated diabetes mellitus and selective IgA deficiency with steatorrhea. Am. J. Med. *59*:882-88, 1975.

[19]Penny, R., Thompson, R. G., Polmar, S. H., and Schultz, R. B.: Pancreatic malabsorption and IgA deficiency in a child with diabetes. Pediatrics *78*:512-16, 1971.

[20]Mann, J. G., Brown, W. R., and Kern, F.: The subtle and

variable clinical expression of gluten-induced enteropathy. An analysis of twenty-one consecutive cases. Am. J. Med. *48*:357-66, 1970.

[21]Zegers, B. J. M., Maertzdorf, W. J., Van Loghem, E., Mul, N. A. J., and Stopp, J. W.: Kappa-chain deficiency: an immunoglobulin disorder. N. Engl. J. Med. *294*:1026-30, 1976.

[22]Silver, H. K. B., Shuster, J., Gold, P., Hawkins, D., and Freedman, S. O.: Endocrinolopathy and IgA deficiency. Clin. Immunol. Immunopathol. *1*:212-19, 1973.

[23]Ambrus, M., Hernadi, E., and Bajtai, G.: Prevalence of HLA-A1 and HLA-B8 antigens in selective IgA deficiency. Clin. Immunol. Immunopathol. 7:311-14, 1977.

[24]Van Thiel, D. H., Smith, W. I., Jr., Rabin, B. S., Fisher, S. E., and Lester, R.: A syndrome of immunoglobulin A deficiency, diabetes mellitus malabsorption, and a common HLA haplotype. Ann. Intern Med. *86*:10-19, 1977.

[25]Coeffier, B., Viala, J. J., Francois, R.: Deficit en IgA associe a un diabete insulino-prive, une anemie de biermer, une anemie hemolytique auto-immune et une insuffisance pancreatique externe. Lyon Medical *237*:399-403, 1977.

[26]Loeb, P., Drash, A., and Kenny, F.: Prevalence of low titer and negative antithyroglobulin antibodies in biopsy proven juvenile Hashimoto's thyroiditis. J. Pediatr. *82*:17-21, 1973.

[27]Amos, B.: Manual of Tissue Typing Techniques. Washington, D. C., DHEW Publication no. (NIH)77-545, 1974, pp. 23-26.

[28]Koistinen, J.: Selective IgA deficiency in blood donors. Vox Sang. *29*:192-202, 1975.

[29]Milgrom, F., and Witebsky, E.: Autoantibodies and autoimmune diseases. J.A.M.A. *181*:706-16, 1962.

[30]MacCuish, A. C., Jordan, J., Campbell, C. J., Duncan, L. J. P., and Irvine, W. J.: Cell-mediated immunity in diabetes mellitus: lymphocyte transformation by insulin and insulin fragments in insulin-treated and newly diagnosed diabetics. Diabetes *24*:36-43, 1975.

[31]Buckley, R. H.: Immunodeficiency in Man and Animals. Sunderland, Massachusetts, Sinaver Associates, 1975, pp. 134-42.

[32]Tomasi, T. B., Jr.: The Immune System of Secretions. Englewood Cliffs, N. J., Prentice-Hall, Inc., 1976, pp. 41-56.

[33]Seager, J., Wilson, J., Jamison, D. L., Hayward, A. R., and Soothill, J. F.: IgA deficiency, epilepsy, and phenytoin treatment. Lancet *2*:632-35, 1975.

[34]Hjalmarson, O.: IgA deficiency during D-penicillamine treatment. Br. Med. J. *1*:549, 1977.

[35]Birnbaum, N. S., Rodnan, G. P., Rabin, B. S., and Bassion, S.: Histocompatibility antigens in progressive systemic sclerosis. J. Rheumatol. *4*:425-28, 1977.

[36]Svejgaard, A., Platz, P., Ryder, L. P., Staub Nielsen, L., and Thomsen, M.: HLA and disease. Transplant. Rev. *22*:3-43, 1975.

[37]Behan, P. O., Simpson, J. A., and Behan, W. M. H.: Decreased serum IgA in myasthenia gravis. Lancet *1*:593-94, 1976.

[38]Grundbacher, F. J.: Genetic aspects of selective immunoglobulin A deficiency. J. Med. Genet. 9:344-47, 1972.

[39]Koistinen, J.: Familial clustering of selective IgA deficiency. Vox Sang. *30*:181-90, 1976.

[40]Douglas, S. D., Goldberg, L. S., and Fudenberg, H. H.: Familial selective deficiency of IgA. J. Pediatr. 78:873-75, 1971.

[41]Guy-Grand, D., Griscelli, C., and Vassali, P.: Peyer's patches, gut IgA plasma cells and thymic function: study in nude MKE bearing thymic grafts. J. Immunol. *115*:361-64, 1975.

[42]Luster, M. I., Leslie, G. A., and Cole, R. K.: Selective IgA deficiency in chickens with spontaneous autoimmune thyroiditis. Nature (London) *263*:331, 1976.

[43]Luster, M. I., Bawn, L. D., Rose, N. R., and Leslie, G. A.: Immunogenetic and ontogenetic studies of chickens with selective IgA deficiency and autoimmune thyroiditis. Cell. Immunol. *32*:417-23, 1977.

[44]Biggar, W. D., and Good, R. A.: Immunodeficiency in Man and Animals. Sunderland, Massachusetts, Sinaver Associates, 1975, pp. 271-75.

[45]Provost, T. T., Garrettson, L. K., Zeschke, R. H., Rose, N. R., and Tomas, T. B., Jr.: Combined immune deficiency, autoantibody formation, and mucocutaneous candidiasis. Clin. Immunol. Immunopathol. *1*:429-44, 1973.