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Primary Immunodeficiencies in Switzerland: First Report of the National Registry in Adults and Children

O. RYSER,[1] A. MORELL,[1] and W. H. HITZIG[2]

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This first report of a Swiss registry includes 313 patients with primary immunodeficiency syndromes (PIDS) who were observed between January 1975 and January 1985. Diagnosis of specific PIDS was made according to WHO criteria. The most frequent disorders were IgA deficiency (33%) and common variable immunodeficiency (22%), followed by selective deficiency of other immunoglobulin isotypes (9%), severe combined immunodeficiency (9%), infantile sex-linked agammaglobulinemia (7%), and Wiskott–Aldrich syndrome (6%). Frequencies of other types of PIDS varied between 0.3 and 4%. Half of the patients were in the pediatric age group. Male patients predominated (63%). In addition to respiratory and urogenital tract infections, autoimmune disorders were observed in 14 patients with IgA deficiency or common variable immunodeficiency. IgA deficiency was, furthermore, associated with atopic and neurological disorders. A comparison with other national registries revealed some differences: the frequency of severe combined immunodeficiency was high (incidence, 24.3 cases per 10^6 live births), and that of ataxia teleangiectasia was particularly low (1.4 per 10^6 live births) in Switzerland. Frequencies of the three major PIDS groups of (i) predominantly antibody defects, (ii) predominantly cell-mediated defects, and (iii) PIDS associated with other major defects agreed with those reported in the other European studies.

KEY WORDS: Primary immunodeficiency in Switzerland.

INTRODUCTION

As classical "experiments of nature," primary immunodeficiency syndromes (PIDS) have provided insight into the clinical relevance of cellular and humoral defense mechanisms against infection and possibly, cancer. Not long ago, many of these syndromes were associated with a poor prognosis and lifelong proneness to infections. Significant improvements in bone marrow transplantation and immunoglobulin replacement therapy have recently rendered PIDS more and more manageable (1). In addition, progress in molecular biology now allows characterization of these disorders at a genetic level (2). Some years ago, national registries of PIDS established in Japan, Sweden, and Italy have started to gather epidemiological information on PIDS (3–7). These studies have prompted us to organize a Swiss register in which all hospitals and laboratories involved in the clinical care and diagnosis of PIDS participated. The present paper reports data on primary specific immunodeficiencies that accumulated in a 10-year observation period, from 1975 to 1985.

METHODS

Participants

The following Swiss institutions caring for PIDS patients were contacted and agreed to participate (names of physicians in charge of PIDS patients are given in parentheses):

- Institute for Clinical and Experimental Cancer Research, University of Berne (S. Barandun, A. Morell);
- Department of Pediatrics, University of Berne (E. Rossi, A. Morell);
- Institute for Clinical Immunology, University of Berne (A. de Weck, W. Pichler);
- Department of Pediatrics, University of Zurich (W. H. Hitzig, R. Seger);

[1]Institute for Clinical and Experimental Cancer Research, University of Berne, Berne, Switzerland.
[2]Department of Pediatrics, University of Zurich, Zurich, Switzerland.

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- Laboratory of Clinical Immunology, Department of Internal Medicine, University of Zurich (P. Grob, H. Joller);
- Department of Pediatrics, Cantonal Hospital Aarau (E. Gugler);
- Department of Pediatrics, Cantonal Hospital Lucerne (O. Tönz);
- Children's Hospital Wildermeth, Bienne (R. Zurbrügg);
- Department of Pediatrics, University of Lausanne (B. Pelet);
- Department of Pediatrics and Genetics, University of Geneva (P. E. Ferrier, S. Suter);
- Division of Immunology and Allergology, University of Geneva (A. Cruchaud); and
- Department of Pediatrics and Neonatology, Regional Hospital of Sion-Hérens-Conthey (A. Spahr).

The patient's charts were made available to one of us (OR). In order to meet legal requirements of data protection, all data were coded before collection.

Patients with PIDS

The registry contains data from patients observed from January 1975 to January 1985. It is limited so far to primary specific immunodeficiency diseases (1, 8). Complement deficiency and defects of phagocytic function were excluded since diagnostic facilities were not generally available until recently. The small number of such patients collected so far was not regarded as representative for the country. For the same reason, IgG subclass deficiencies were not included in this publication. Specific PIDS were diagnosed according to WHO criteria (8). Only patients with well-established deficiencies are registered. By far the most had clinical signs and symptoms necessitating repeated physical and immunological examinations and treatment. The data were evaluated according to the following criteria:

- numbers of patients with the various PIDS,
- sex and age distribution (pediatric patients: born 1969 or later),
- numbers of patients born or deceased during the observation time, and
- numbers of Swiss patients and of citizens of other countries either residing in Switzerland or coming in for diagnosis and therapy.

Demographic figures were obtained from the Swiss Federal Office for Statistics (9).

Table I. Frequencies of Primary Immunodeficiencies

Diagnosis	Total	%	Male	Female
Infantile X-linked agammaglobulinemia	22	7.0	22	—
Ig deficiency with increased IgM	1	0.3	—	1
IgA deficiency	102	32.6	61	41
Selective deficiency of other Ig isotypes[a]	28	9.0	14	14
Immunodeficiency and thymoma	2	0.6	—	2
Transient hypogammaglobulinemia of infancy	12	3.8	9	3
Common variable immunodeficiency				
Predominant B-cell defect	57	18.2	28	29
Predominant immunoregulatory T-cell disorder	11	3.5	9	2
Combined immunodeficiency with predominant T-cell defect	9	2.9	7	2
Severe combined immunodeficiency	23	7.4	14	9
Adenosine deaminase deficiency	5	1.6	2	3
Immunodeficiency with abnormal reaction to Epstein–Barr virus	2	0.6	1	1
Transcobalamin 2 deficiency	1	0.3	1	—
Wiskott–Aldrich syndrome	20	6.4	19	1
Ataxia teleangiectasia	10	3.2	6	4
DiGeorge's syndrome	8	2.6	4	4
Total number of registered patients	313	100.0	196	117

[a]Including some patients with IgG subclass deficiency.

RESULTS

A total number of 313 patients accumulated during the observation period. Frequencies of the various PIDS are given in Table I. IgA deficiency and common variable immunodeficiency (CVID) predominated, as expected (1, 5–7). There was no obvious clinical difference between CVID with predominant B-cell defect and CVID with predominant immunoregulatory T-cell disorder. Thus, the 68 patients are considered as one major form of PIDS. Patients with selective deficiency of other immunoglobulin (Ig) isotypes, severe combined immunodeficiency (SCID), infantile X-linked agammaglobulinemia (X-LA), and Wiskott–Aldrich syndrome are well represented, with numbers ranging between 20 and 28 (i.e., 6.4–9.0% of all patients). The frequency of all other types of PIDS is considerably lower, varying between 0.3 and 3.8% of all cases. Approximately half of the patients belong to the pediatric age group (Table II). The male predominance is more pronounced here than in the whole group including adults.

Births and deaths during the observation period are listed in Table III. Of the 98 patients born between 1975 and 1985, 80 were either Swiss citizens or residents. Using recently published demographic statistics (9), the incidence of PIDS per 10^6 live births in Switzerland could be calculated (Table III). A total of 40 patients died. Mortality was

Table II. Primary Immunodeficiencies in Pediatric Patients

Diagnosis	Total	%	Boys	Girls
Infantile X-linked agammaglobulinemia	10	6.5	10	—
IgA deficiency	54	34.8	36	18
Selective deficiency of other Ig isotypes	3	1.9	2	1
Transient hypogammaglobulinemia of infancy	11[a]	7.1	8	3
Common variable immunodeficiency				
Predominant B-cell defect	14	9.0	7	7
Predominant immunoregulatory T-cell disorder	5	3.2	4	1
Combined immunodeficiency with predominant T-cell defect	8	5.2	6	2
Severe combined immunodeficiency	22[b]	14.2	13	9
Adenosine deaminase deficiency	5	3.2	2	3
Transcobalamin 2 deficiency	1	0.6	1	—
Wiskott–Aldrich syndrome	10	6.5	9	1
Ataxia teleangiectasia	4	2.6	3	1
DiGeorge's syndrome	8	5.2	4	4
Total number of registered patients	155	100.0	105	50

[a]One patient listed in Table I was born before 1969 and reached adult age during the observation time.
[b]The clinical course and outcome of one patient diagnosed before 1969 and listed in Table I are not known.

highest among patients with impaired cellular immunity including SCID. Fungal, protozoal, viral, and bacterial infections caused or contributed to death in the majority of these cases.

Location of Infections

Close to 50% of the patients with humoral immunodeficiencies suffered from upper respiratory tract infections. In 9 (41%) of the patients with X-LA and in 26 (39%) of those with CVID, recurring pneumonia was observed. Gastrointestinal infections and chronic diarrhea was frequent in IgA deficiency (16/16%) and in CVID (20/29%).

Autoimmune Disorders

Autoimmune disorders were reported in IgA-deficient and in CVID patients: in five IgA deficient patients, the diagnosis was consistent with systemic lupus erythematosus. One had relapsing idiopathic thrombocytopenic purpura, and one autoimmune hemolytic anemia. In the CVID patients, idiopathic thrombocytopenic purpura was diagnosed in two and autoimmune hemolytic anemia in three, whereas in two others autoantibodies of various specificities were detected without overt disease.

Allergic Manifestations

IgA deficiency was furthermore associated with allergies such as allergic asthma and atopic dermatitis (21/21%).

Neurologic Disorders

Neurologic disorders causing epileptic seizures, as previously noticed (10, 11), were seen in seven (7%) of the IgA-deficient patients.

Malignancies

Malignancies were uncommon: One patient with CVID died of a poorly differentiated lung carcinoma. Other neoplastic disorders were not yet manifest.

Table III. Births and Deaths During the Observation Period

Diagnosis	Patients born			Patients deceased, total
	Total	Swiss citizens and residents	Incidence per 10^6 live births	
Infantile X-linked agammaglobulinemia	5	4	5.4	1
IgA deficiency	34	29	39.2	—
Selective deficiency of other Ig isotypes				4
Immunodeficiency and thymoma				1
Transient hypogammaglobulinemia of infancy	7	7	9.5	—
Common variable immunodeficiency, all cases	7	7	9.5	7
Combined immunodeficiency with predominant T-cell defect	5	5	6.8	4
Severe combined immunodeficiency, all cases	23	18	24.3	15
Wiskott–Aldrich syndrome	7	3	4.1	2
Ataxia teleangiectasia	2	1	1.4	—
DiGeorge's syndrome	8	6	8.1	6
All PIDS	98	80	108.3	40

Ethnic Distribution

Of the 313 patients, 218 were Swiss and 95 were citizens from other countries, mostly from Italy (43 patients) and from the Federal Republic of Germany (19 patients). A total of 240 patients lived in Switzerland. The uneven geographic distribution of their homes showed some regional differences (Fig. 1). This could be attributed at least partially to familial clusters of patients with SCID, Wiskott–Aldrich syndrome, and CVID. Domiciles of most patients, however, were associated with urban agglomerations and with other densely populated areas (Fig. 1). At the end of the observation period, assuming a Swiss population of 6,423,100 inhabitants (9), the overall prevalence of PIDS was 3.74 patients per 100,000 (weighted mean value).

DISCUSSION

The present paper reports the first results of the Swiss PIDS registry, excluding IgG subclass deficiencies and nonspecific disorders such as defects of the complement and of the phagocytic system. A juxtaposition of our report with the Italian, Japanese, and Swedish registries reveals both similarities and discrepancies. In order to allow an optimal comparison, only specific PIDS are listed in Table IV. Furthermore, the IgG subclass deficiencies and the antibody deficiencies with normal or hypergammaglobulinemia (1, 8) are excluded since registration of these two PIDS was limited to one study each (3–6). Under these premises, it is noteworthy that the numbers of pediatric patients with specific PIDS in Sweden and Switzerland were similar. This agrees with the equal population size of the two countries. Thus, calculations of epidemiological data such as prevalence and incidence of certain PIDS appear to be meaningful. Accordingly, the incidence of X-LA and Wiskott–Aldrich syndrome of 6.1 and 3.7 per 10^6 live births in Sweden is close to the Swiss figures of 5.4 and 4.1 (Table III). On the other hand, the incidence of SCID in Sweden (12.5 per 10^6 live births) is only about half of that in Switzerland (Table III). Considerably more PIDS patients were registered in Italy and in Japan. However, in view of the population of these two countries, which exceeds that of Switzerland and Sweden by approximately one order of magnitude, the figures of 706 and 525 patients with specific PIDS are rather modest. The most likely explanation is that access to persons and facilities engaged in clinical immunology may be easier in some countries than in others and that, therefore, many PIDS patients may still go undetected.

A comparison of the relative frequencies of specific forms of PIDS reveals striking differences: IgA deficiency, known to be the most common PIDS, accounts for 33 to 50% of all PIDS in the European studies but for only 15% in the Japanese registry. This situation is paralleled by the frequencies of asymptomatic IgA deficiency in health blood donors: in European countries, Australia, and the United States, figures between approximately 1:300 and 1:3000 were reported (4, 12), whereas in Japan, a much lower prevalence was found. According to Kanoh *et al.* (13), only 1 in 14,840 blood donors had a serum IgA concentration of less than 0.1 g per liter, and 1 in 31,800 had less than 0.01 g/liter. These epidemiological data suggest racial differences as the cause for the lower incidence of both the asymptomatic and the disease-associated forms of IgA deficiency. Other PIDS also show some variations in frequency: in Japan, the proportion of X-LA is almost twice as high and that of ataxia teleangiectasia is considerably higher than in the other countries. In Switzerland, SCID is relatively more frequent than in the other countries, as mentioned, and ataxia teleangiectasia seems to be particularly rare.

In Fig. 2, the various PIDS are displayed as three major groups of (i) predominantly antibody defects including CVID, (ii) predominantly cell-mediated immunity defects, and (iii) immunodeficiencies associated with other major defects (Wiskott–Aldrich syndrome and ataxia teleangiectasia). It is evident that in all European studies, frequencies of these major groups agree well. In contrast, the Japanese registry clearly differs from the others by a lower proportion of antibody defects, due to the relative lack of IgA deficiency, and by the higher frequencies of cell-mediated PIDS and, particularly, of immunodeficiencies associated with other major defects.

The sex distribution shows a male predominance in the three studies where it was analyzed. In the present report, 63% of all patients and 68% of those in the pediatric age group are male. This figure is somewhat higher than the 57% boys reported in the Swedish register but close to the 70% of the Japanese study including mainly pediatric patients. In our study, frequencies and types of atopic and autoimmune disorders occurring mainly in patients

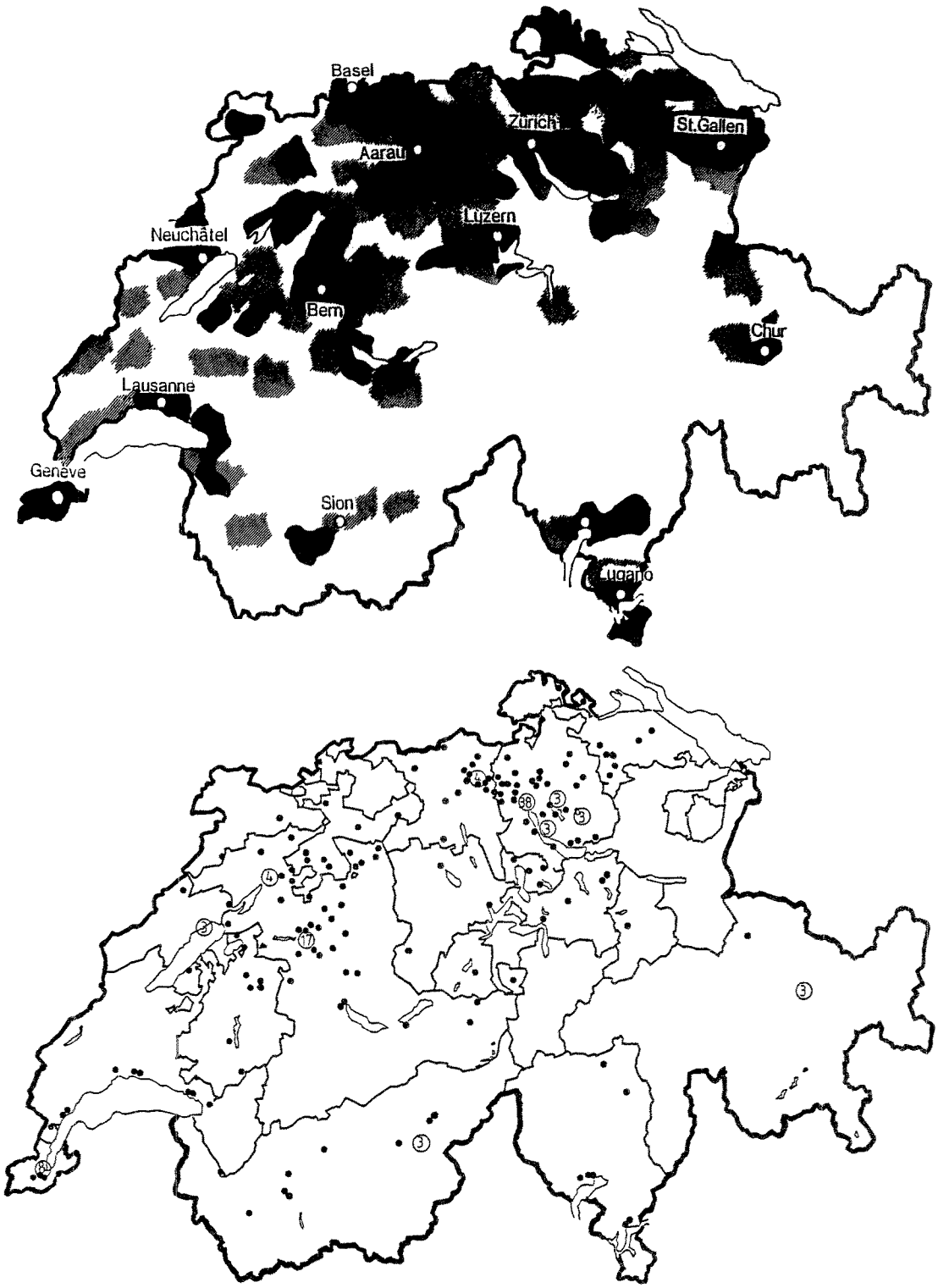

Fig. 1. (Top) Domiciles of 240 patients with PIDS in Switzerland. Individual patients are represented by black points. Accumulations of patients in one place are indicated by open circles with the number of patients inside. (Bottom) Population density in Switzerland. Black areas, more than 200 population per km^2; hatched areas, 100–200 population per km^2; white areas, less than 100 population per km^2. Locations of some cities and towns are indicated.

Table IV. Comparison of Frequencies of Primary Specific Immunodeficiency Diseases[a]

Diagnosis	Italy		Japan		Switzerland[b]				Sweden	
	Total	%	Total	%	Total	%	Pediatric patients	%	Pediatric patients	%
Infantile X-linked agammaglobulinemia	33	4.7	72	13.7	15	6.3	7	5.7	12	8.0
Ig deficiency with increased IgM	6	0.7	—		1	0.4	—		3	2.0
IgA deficiency	354	50.1	80	15.2	79	32.9	44	35.7	75	50.0
Selective deficiency of other Ig isotypes	22	3.1	15	2.9	27	11.2	2	1.6	—	
Immunodeficiency and thymoma	—		9	1.7	1	0.4	—		—	
Transient hypogammaglobulinemia of infancy	—		38	7.2	12	5.0	11	8.9	3	2.0
Common variable immunodeficiency, all cases	117	16.6	111	21.1	49	20.4	15	12.2	19	12.7
Combined immunodeficiency with predominant T-cell defect	58	8.2	—		9	3.8	8	6.5	—	
Severe combined immunodeficiency, all cases	45	6.4	60	11.4	22	9.2	21	17.1	17	11.4
Transcobalamin 2 deficiency	—		—		1	0.4	1	0.8	—	
Wiskott–Aldrich syndrome	14	2.0	46	8.8	14	5.8	6	5.0	8	5.3
Ataxia telangiectasia	50	7.1	58	11.0	4	1.7	2	1.6	8	5.3
DiGeorge's syndrome	8	1.1	36	6.9	6	2.5	6	4.9	5	3.3
All specific PIDS	706		525		240		123		150	

[a]Numbers of cases taken from the national registers include only primary specific immunodeficiencies. Nost listed are the PIDS "antibody deficiency with normal or hypergammaglobulinemia" and "IgG subclass deficiencies."
[b]Patients with a domicile in Switzerland.

with IgA deficiency and CVID were comparable with those reported in the other registries. On the other hand, cancer, although carefully searched for, clearly was less often observed in our study than reported in the literature (4, 6, 14–16).

Scope of National Registries

Apart from its epidemiological value, a national registry of PIDS may have some practical aspects as well. According to Table I, approximately 90 patients, including 29 children, suffer from PIDS due to antibody defects and they need regular intravenous immunoglobulin replacement therapy. For this purpose, IgG doses of 0.4 g per kg body weight per month are considered to be adequate in most instances (17). Under these assumptions, the total amount of intravenous IgG needed in Switzerland for this indication would be of the order of 15 to 20 kg per year.

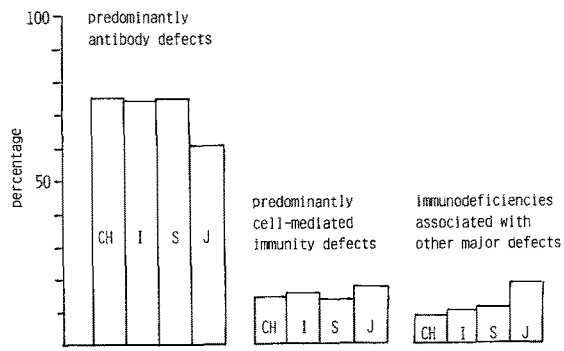

Fig. 2. Percentage distribution of patients with PIDS in national registries. PIDS are subdivided into the three major groups, as described in the text. Columns represent percentages of patients. CH, Switzerland; I, Italy; S, Sweden; J, Japan.

Today, severe PIDS, particularly SCID and Wiskott–Aldrich syndrome, can be cured by bone marrow transplants from histocompatible family members (18, 19) and, with appropriate preparation of the marrow suspension, also from haploidentical donors (20). As a consequence of this technical innovation, in the future each patient will have at least two potential donors, i.e., both his parents (21). Until recently Switzerland had no bone marrow transplantation facility for infants and small children with PIDS. This study demonstrates that 48 patients were observed in a 10-year period who would have been candidates for this treatment. This is a reasonable figure for a small transplantation unit. The fact that out health authorities now granted the establishment and operation of a PIDS bone marrow transplantation team was partly also influenced by the first results of this national registry.

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REFERENCES

1. Rosen FS, Cooper MD, Wedgwood RJP: The primary immunodeficiencies. N Engl J Med 311:235–242, 300–310, 1984
2. Conley ME, Brown P, Pickard AR, Buckley RH, Miller DS, Raskind WH, Singer JW, Fialkow PJ: Expression of the gene defect in X-linked agammaglobulinemia. N Engl J Med 315:564–567, 1986
3. Hayakawa H, Jwata T, Kobayashi N: Primary Immunodeficiency syndrome in Japan. I. Overview of a national-wide survey on primary immunodeficiency. J Clin Immunol 1:31–39, 1981
4. Hayakawa H, Matsumoto S, Kabayashi N, Yata J: Genetically determined immunodeficiencies. *In* The Nature, Cellular, and Biochemical Basis and Management of Immunodeficiencies, Symposia Medica Hoechst 21, RA Good, E Lindenlaub (eds). Stuttgart, New York, Schattauer Verlag, 1987, pp 39–60
5. Fasth A: Primary immunodeficiency disorders in Sweden: Cases among children 1974–1979. J Clin Immunol 2:86–92, 1982
6. Fasth A: Immunodeficiency in children in Sweden 1974–1983. From the Swedish register of primary immunodeficiency disorders. *In* Progress in Immunodeficiency Research and Therapy, Vol I, C Griscelli, J Vossen (eds). Amsterdam, New York, Elsevier, 1984, pp 461–467
7. Luzi G, Businco L, Aiuti F: Primary immunodeficiency syndromes in Italy: A report of the National Register in children and adults. J Clin Immunol 3:316–321, 1983
8. World Health Organization: Report of a scientific group on immunodeficiency. Clin Immunol Immunopathol 28:450–475, 1983
9. Bundesamt für Statistik: Statistisches Jahrbuch der Schweiz. Basel, Birkhäuser Verlag, 1984
10. Morell A, Muehlheim E, Schaad U, Skvaril F, Rossi E: Susceptibility to infections in children with selective IgA- and IgA-IgG subclass deficiency. Eur J Pediatr 145:199–203, 1986
11. Fontana A, Grob PJ: Immunoglobulin deficiency, HLA antigens and seizures. Ann Intern Med 88:429, 1978
12. Clark, JA, Callicoat PA, Brenner NA, Bradley CA, Smith DM: Selective IgA deficiency in blood donors. Am J Clin Pathol 80:210–213, 1983
13. Kanoh T, Mizumoto T, Yasuda N, Koya M, Ohno Y, Uchino H, Yoshimura K, Ohkubo Y, Yamaguchi H: Selective IgA deficiency in Japanese blood donors: Frequency and statistical analysis. Vox Sang 50:81–86, 1986
14. Kinlen LJ, Webster ADB, Bird AG, Haile R, Soothill JF, Thompson RA: Prospective study of cancer in patients with hypogammaglobulinemia. Lancet 1:263–266, 1985
15. Filipovich AH, Spector BD, Kersey J: Immunodeficiency in humans as a risk factor in the development of malignancy. Prev Med 9:252–259, 1980
16. Spector BD, Perry GS III, Kersey JH: Genetically determined immunodeficiency disease (GDID) and malignancy: Report from the immunodeficiency-cancer registry. Clin Immunol Immunopathol 11:12–29, 1978
17. Cunningham-Rundles C, Siegal FP, Smithwick EM, Lion-Boulé A, Cunningham-Rundles S, O'Malley J, Barandun S, Good RA: Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. Ann Intern Med 101:435–439, 1984
18. O'Reilly RJ, Brochstein J, Dinsmore R, Kirkpatrick D: Morrow transplantation for congenital disorders. Semin Hematol 21:188–221, 1984
19. Fischer A, Griscelli C, Friedrich W, Kubanek B, Levinsky R, Morgan G, Vossen J, Wagemaker G, Landais P: Bone marrow transplantation for immunodeficiencies and osteopetrosis: European survey, 1968–1985. Lancet 2:1080–1084, 1986
20. Beatty PG, Clift RA, Michelson EM, Nisperos BB, Flournoy N, Martin PJ, Sanders JE, Stewart P, Buckner CD, Storb R, Thomas ED, Hansen JA: Marrow transplantation from related donors other than HLA-identical siblings. N Engl J Med 313:765–771, 1985
21. Friedrich W, Goldmann SF, Kleihauer E: Treatment of primary immunodeficiencies by bone marrow transplantation. *In* The Nature, Cellular, and Biochemical Basis and Management of Immunodeficiencies, Symposia Medica Hoechst 21, RA Good, E Lindenlaub (eds). Stuttgart, New York, Schattauer Verlag, 1987, pp 95–105