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Thymic Alymphoplasia

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In 1950 Glanzmann and Riniker described two infants who died at 5 and 6 months of age following severe infection. These infants during life exhibited profound lymphopenia, and at necropsy were found to have generalized hypoplasia of lymphoid tissues including the thymus. The authors named the condition 'essential lymphocytophthisis'. During the next decade additional cases were described from Europe and it was soon recognized that hypo-γ-globulinaemia was an essential feature of the condition (Kosenow and Schümmelfeder, 1953; Tobler and Cottier, 1958; Hitzig, Biró, Bosch, and Huser, 1958; Hitzig and Willi, 1961; Jeune, Larbre, Germain, and Freycon, 1959). The disorder has also been called 'thymic alymphoplasia' or the 'Swiss type' of congenital hypo-γ-globulinaemia. It has attracted much interest recently because it may represent an 'experiment of nature' which is analogous to the immunological defects observed in some animal species which have been thymectomized in the neonatal period. The relation of the experimental data to human immunological deficiency disease has recently been extensively reviewed by Peterson, Cooper, and Good (1965).

Twelve cases of thymic alymphoplasia have been recognized in Winnipeg during the past 15 years. Another case was seen at the University Hospital, Saskatoon, and we are indebted to Professor J. W. Gerrard for details of this patient.

Case Reports

The clinical, laboratory, and pathological findings in the 13 cases are summarized in Tables I and II.

The more recent cases were diagnosed during life from the clinical and laboratory features, with ultimate verification at necropsy. The earlier cases were recovered from the necropsy records by reviewing those necropsies which had exhibited marked thymic 'involution', lymphoid hypoplasia, and unusual pneumonitis.

Below follows in greater detail a description of the 'F' family (Cases 3 and 4) and also Case 11, which was our most recent case and the most fully investigated.

The 'F' family. Both parents are Mennonite and, as far as is known, unrelated. The father is one of 10 children, all but one of whom are alive and well (Fig. 1). A sister died of burns at 2 years of age. Two male children of the father's paternal uncle are reported to have died in infancy but no details are known. The mother also comes of a large family, having 11 sibs. Her father's brother had a daughter who died from unknown causes when less than 1 year of age. In September 1959, the first child, a boy, was born and died at 15 weeks (Case 3). Two years later another boy was born and is alive and well. In 1963 the third son was born and he died at 6½ months (Case 4). A fourth child, another boy, was born in 1965 and when seen at 2 weeks of age was healthy. Serum protein electrophoresis was recently performed on both parents and on the 2 surviving children, and was normal. Assay of the immunoglobulins by an immunodiffusion technique (Haworth, Norris, and Dilling, 1965) gave the results shown in Table III.

These values are within the normal range for the age of the subjects. The peripheral blood smear of the 2-week-old infant appeared normal, though at that age it was not possible to assess full immunological competence.

Case 3. This infant appeared normal at birth (weight 3·91 kg.) but was reported as being unusually irritable. At 2 months he was admitted to a local hospital because of a sore mouth and difficulty in swallowing. There he did not improve, failed to gain weight, and developed diarrhoea, vomiting, and a cough, whereupon he was transferred to St. Boniface Hospital in Winnipeg at 3 months.

Examination revealed pallor, generalized wasting, oral thrush, and scattered râles in the chest. He weighed 4·9 kg. (3rd centile) and his length was 62 cm. (50th centile). Radiographs of the chest showed increased hilar markings but were otherwise normal. *Candida albicans* was cultured from the mouth and *Proteus vulgaris* from the throat, stool, and urine. White blood cell counts over the 6-week period before death were 5900, 8100, and 5900/mm.^{3} with total lymphocyte counts of 2890, 2430, and 770/mm.^{3}, respectively. The results of serum protein electrophoresis are shown in Table IV. Therapy included nystatin, amphotericin, and γ-

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TABLE I

Clinical Details of 13 Cases of Thymic Alymphoplasia

Case No.	Sex	Age at Onset of Symptoms	Age at Death (mth.)	Lymphopenia* (1 or more counts < 2000/mm.^{3})	Hypo-γ-globulinaemia*		Racial Origin and Family History
1	F	4 mth.	6½	0	Not done	Sibs	Half-breed N. American Indian and Swiss: 2 normal sibs
2	F	2½ mth.	5	0	+		
3	M	2 mth.	4¾	+	+	Sibs	Mennonite: 2 normal sibs
4	M	Birth	6½	+	+		
5	F	Birth	3	+	+	Sibs	Mennonite
6	M	Birth	5	+	Not done		
7	M	Birth	6	Not done	Not done		Mennonite: 3 sibs died in infancy; 2 normal sibs
8	M	4 dy.	2	+	Not done		3 normal sibs
9	F	10 dy.	2	+	+		Mennonite: 1 normal sib
10	M	Birth	2	+	Not done		Mennonite: 2 normal sibs
11	M	1½ mth.	5	+	+		3 normal sibs
12	F	5 wk.	2	+	Not done		1 sib died at 3 years
13	F	3 mth.	6	+	0		2 sibs died in infancy; 2 normal sibs

* + indicates patient exhibited this feature; 0 indicates patient did not exhibit this feature.

TABLE II

Necropsy Findings of 13 Cases of Thymic Alymphoplasia

Case No.	Thymus			Nodes and Spleen Showing Lymphoid Hypoplasia*	Lung	Other Findings
	Weight (g.)	Absent Hassall's Bodies*	Lymphoid Hypoplasia*			
1	'Quite small'	+	+	+	*Pneumocystis carinii;* adenovirus pneumonia; alveolar proteinosis	Moniliasis vocal cord; fatty metamorphosis liver, patent ductus
2	1	+	+	+	Cytomegalic inclusion disease; pyogenic pneumonia	Cytomegalic inclusion disease of kidneys, gut, adrenals, ovary; colonic haemorrhage
3	5	+	+	+	Giant cell pneumonia; alveolar proteinosis	
4	< 1	+	+	+	Alveolar proteinosis; lung abscesses	Enlarged spleen
5	5	No histology		+	Pyogenic pneumonia; alveolar proteinosis	
6		Not examined		+	Pyogenic pneumonia; alveolar proteinosis	
7	—	+	+	+	Alveolar proteinosis	
8	3	+	+	+	Giant cell pneumonia	Mitral atresia, single ventricle, anomalous pulmonary drainage
9	< 2	+	+	+	Tracheobronchitis	Pyelonephritis, staphylococcal meningitis
10	1	No histology		+	Pseudomonas pneumonia	
11	< 1	+	+	+	*Pneumocystis carinii*	Moniliasis
12	'Barely identifiable'	No histology		+	Pseudomonas pneumonia	
13	2	+	+	+	*Pneumocystis carinii*	

* + indicates patient exhibited this feature.

TABLE III

Results of Assay of Immunoglobulins in Surviving Members of 'F' Family (mg./100 ml.)

	γA	γM	γG
Father	404	163	990
Mother	261	324	1056
Brother (5 years old) ..	375	216	1452
Brother (2 weeks old) ..	< 1·5	11	957

TABLE IV

Serum Protein Concentrations (g./100 ml.) in 8 Cases of Thymic Alymphoplasia

Case No.	Paper Electrophoresis						Immunoassay		
	Total Protein	Albumin	α_1 Globulin	α_2 Globulin	β Globulin	γ Globulin	γA	γM	γG
2	4·9	3·19	0·18	0·69	0·63	0·13			
3	5·5	3·94	0·22	0·54	0·61	0·19			
4	4·5	3·14	0·20	0·69	0·34	0·14	ND*	0·06	ND
		γ-globulin 5 ml. I.M.							
	4·8	3·00	0·23	0·96	0·51	0·12			
		γ-globulin 6 ml. I.M.							
5	5·0	3·32	0·30	0·49	0·47	0·15	ND	ND	0·15
		γ-globulin 4 ml. I.M.							
	5·3	3·60	0·43	0·61	0·39	0·30			
	3·7	2·35	0·37	0·49	0·30	0·18			
		γ-globulin 4 ml. I.M.							
9	4·5	3·2	0·30	0·50	0·40	0·10			
10	4·9	4·0		0·90					
11	5·4	3·85	0·25	0·70	0·50	0·11	ND	0·02	0·05
		γ-globulin 6 ml. I.M.							
	6·2	3·88	0·42	0·86	0·64	0·39			
	5·7	3·85	0·23	0·90	0·50	0·21			
		γ-globulin 6 ml. I.M.							
	6·6	4·61	0·28	0·90	0·64	0·25			
							ND	0·01	0·21
13	5·5	3·45	0·26	0·69	0·67	0·42			
		γ-globulin 18 ml. I.M.							
	5·8	3·31	0·35	0·82	0·77	0·58			

* ND = not detectable.

The immunodiffusion method used (Haworth *et al.*, 1965) was capable of detecting γA-globulin in excess of 1·5 mg./100 ml., γM-globulin in excess of 2·5 mg./100 ml., and γG-globulin in excess of 5·0 mg./100 ml.

globulin, intramuscularly. His general condition remained poor, and the signs in the chest increased in severity. A further chest radiograph shortly before death showed diffuse infiltration in both hilar areas and in the left lower lobe. Death occurred at the age of 15 weeks.

The necropsy findings are presented in Table II.

Case 4. The third child was born after a normal pregnancy and delivery (birthweight 3·63 kg.). At 1 week of age he developed an infected napkin rash for which he was given local medication and penicillin. He was first admitted to hospital at 4½ months, because the rash had spread to involve the whole body. He was an emaciated, irritable, and pale infant, weighing 5 kg., who had a generalized rash, considered to be seborrhoea, with secondary bacterial infection. The chest was clinically and radiologically clear. There was no lymphadenopathy. Local treatment of the skin resulted in improvement, but a few days after admission he developed a purulent rhinorrhoea and an abscess of the scalp from both of which sites *Staphylococcus aureus* was cultured. Following treatment, his condition improved and he was discharged home.

At 5½ months he developed diarrhoea, vomiting, and anorexia, and was readmitted to hospital. Examination showed a toxic, malnourished, and dehydrated infant. His weight was 4·8 kg. and his length 62 cm. (both less than the 3rd centile). He had seborrhoeic dermatitis of the scalp and trunk and an otorrhoea. There was cervical, axillary, and inguinal lymphadenopathy, but the liver and spleen were not enlarged. The chest was clinically clear with the exception of a few râles at the base of the right lung.

Laboratory findings. Hb on the first admission was 12·6 g./100 ml. and the white blood count 14,600/mm.^{3}, with lymphocytes 5840/mm.^{3}. Hb on the second admission was 8·7 g./100 ml. and white blood cell counts ranged from 3000-6400/mm.^{3}, with lymphocyte counts of 720-2180/mm.^{3}. Throat culture yielded pneumococci and a staphylococcus was recovered from the blood. The bone-marrow showed a granulopoietic hyperplasia. Radiographs of the chest showed infiltration in both lower and both upper lobes. The results of serum protein electrophoresis and assay of the immunoglobulins are shown in Table IV. The blood group was 0 and no anti-A or anti-B isohaemoagglutinins could be detected in the serum. A drop of 5% 2,4-dinitrofluorobenzene (DNFB) was placed on his skin, and challenge 14 days later with 0·1M DNFB produced an area of erythema (3 × 5 mm.) on two occasions. The Schick test was positive and he did not form antibodies following diphtheria toxoid immunization.

The baby was treated with oxacillin, intravenous fluids, and blood. Following the diagnosis of hypo-γ-globulinaemia, a total of 11 ml. γ-globulin was given intramuscularly. He seemed to improve at first but

soon there was a return of anorexia, abdominal distension, diarrhoea, and vomiting, necessitating further intravenous fluid therapy. The chest deteriorated clinically and radiologically. The feet became red and puffy, and there was an erythematous mottled rash on the face and trunk. Death occurred at 6½ months. The necropsy findings are summarized in Table II.

Case 11. This baby boy was the fourth child of healthy parents who have three other healthy children, aged 3 to 8 years. He was born after a normal pregnancy and delivery (weight 3·71 kg.), and was well until 8 weeks when he developed diarrhoea. He continued to gain weight in spite of this, but at 13½ weeks he became more ill and was admitted to the Children's Hospital, Winnipeg.

Examination revealed a pale, wasted, and dehydrated baby, weighing 4·85 kg. (less than the 3rd centile). The chest was clear. The tip of the spleen could just be felt. There were no palpable lymph nodes.

Pertinent laboratory findings. Hb was 12·6 g./100 ml. White blood counts ranged from 7200-16,800/mm.^{3}, with lymphocyte counts of 1680-3820/mm.^{3} Radiographs of the chest showed infiltration in the upper lobe of the right lung. Pneumococci and haemolytic streptococci were isolated from the throat and *Pseudomonas aeruginosa* was grown from the nasopharynx. Serum protein estimations are shown in Table IV. A fat balance showed that 78% of ingested fat was excreted in the stool. Sensitization with 5% DNFB and challenge with 0·1M DNFB 14 days later resulted in an area of induration 3 × 6 mm. The Schick test was positive and he did not form antitoxin following diphtheria toxoid immunization. Two attempts to culture the peripheral lymphocytes were unsuccessful.

Initially the baby was treated for gastro-enteritis. However, diarrhoea, anorexia, and weight loss continued. He also developed signs of respiratory infection and oral moniliasis.

Because of the hypoproteinaemia and hypo-γ-globulinaemia, he was given 3 g. albumin intravenously and 6 ml. γ-globulin intramuscularly. The immunological defect, the deteriorating general condition, and the increasing respiratory difficulty suggested the possibility of *Pneumocystis carinii* infection, and efforts were made to obtain a supply of pentamidine. Since this was not at first possible, stilbamidine was given in a daily dose of 20 mg. intramuscularly. Attempts were also made to obtain foetal thymus tissue to implant into the patient, but he died before this could be done. At the time of death he was 25½ weeks old. The necropsy findings are summarized in Table II.

Discussion

It was possible to find detailed reports of 27 cases of thymic alymphoplasia or the Swiss type of hypo-γ-globulinaemia (Kosenow and Schümmelfeder, 1953; Tobler and Cottier, 1958; Hitzig *et al.*, 1958; Jeune *et al.*, 1959; Hitzig and Willi, 1961; Rosen, Gitlin, and Janeway, 1962; Gitlin and Craig, 1963; Sacrez, Willard, Beauvais, and Korn, 1963; Gitlin, Rosen, and Janeway, 1964; Bonnevier, Killander, Olding, and Vahlquist, 1964; Nezelof, Jammet, Lortholary, Labrune, and Lamy, 1964; Beltaos and McCreadie, 1965; Hitzig, Kay, and Cottier, 1965; Kadowaki, Thompson, Zuelzer, Woolley, Brough, and Gruber, 1965; Rosen, Gotoff, Craig, Ritchie, and Janeway, 1966; Fireman, Johnson, and Gitlin, 1966). In addition to these cases there were 9 reported cases of vaccinia gangrenosa or progressive vaccinia (Keidan, McCarthy, and Haworth, 1953; Kozinn, Sigel, and Gorrie, 1955; Somers, 1957; Jarkowski, Mohagheghi, and Nolting, 1963; White, 1963; Flewett and Ker, 1963; Allibone, Goldie, and Marmion, 1964; Hathaway, Githens, Blackburn, Fulginiti, and Kempe, 1965) and 3 cases dying of generalized BCG infection (Bonnevier *et al.*, 1964; Falkmer, Lind, and Ploman, 1955; Ariztia, Moreno, Garces, and Montero, 1960; Bouton, Mainwaring, and Smithells, 1963) which almost certainly had the same disorder. A number of other cases were mentioned, notably by Hitzig and Willi (1961), Barandun, Stampfli, Spengler, and Riva (1959), and Peterson *et al.* (1965), but insufficient detail was available to make an adequate review of these cases. The case of 'alymphocytosis' described by Donohue (1953) has been included in most previous reviews of thymic alymphoplasia, but in our opinion does not fall into this group. The symptoms appeared much later than is usual in this disorder and the patient survived until 29 months of age: at necropsy Hassall's corpuscles were present in the thymus, and the liver and spleen were much enlarged for which there was no adequate histological explanation.

Hypoplasia of the thymus has been found in association with other disease syndromes: (1) 'reticular dysgenesis' or 'aleucocytosis' in which, as well as hypoplasia of all lymphoid tissues, there is complete myeloid aplasia with absent or very few circulating leucocytes (De Vaal and Seynhaeve, 1959; Gitlin, Vawter, and Craig, 1964); the 3 children with this disorder, who were described, died within a few days of birth of overwhelming infection; (2) ataxia-telangiectasia (Peterson *et al.*, 1965); (3) the leprechaun syndrome (Salmon and Webb, 1963).

The case described by Robbins, Miller, Arean, and Pearson (1965) may represent another variant and possibly an incomplete form of the disorder. This was a girl who had suffered from respiratory infection all her life. At 8 years of age she was small and underweight and had signs of pulmonary infection. She had lymphopenia and hypo-γ-globulinaemia, and a lung biopsy showed *Pneumocystis carinii* pneumonia. She was treated with

TABLE V

Principal Presenting Symptoms in 22 Previously Reported Cases of Thymic Alymphoplasia (cases of progressive vaccinia and generalized BCG infection not included) and in 13 Cases in Present Series

Presenting Symptoms	Reported Cases (22)		Present Series (13)	
	No. of Cases	% Cases	No. of Cases	% Cases
Cough	11	50	6	46
Diarrhoea	7	33	5	38
Anorexia and feeding difficulty	2	9	6	46
Rash (seborrhoea, impetigo, pustules)	6	27	2	15
Vomiting	3	14	2	15
Loss of weight and 'failure to thrive'	3	14	1	8
Fever	4	18	0	0
Mouth 'sores'	3	14	1	8

pentamidine and recovered. Another patient, a boy, is also difficult to classify (Breton, Walbaum, Boniface, Goudemand, and Dupont, 1963): he had recurrent infections from the age of 3 months, and showed lymphopenia, low levels of γG and γA-globulins, but raised levels of γM-globulin in the serum. He also had a haemolytic anaemia and the direct Coombs' test was positive. He was treated with corticosteroids and thymic extracts and was alive and apparently improving at 20 months.

It was thought that it might be of value to compare the clinical and pathological features of our patients with the published reports of those with the Swiss type of hypo-γ-globulinaemia.

Sex. Of our patients, 7 were boys and 6 were girls. This approximately equal sex distribution is similar to that reported by European writers and could be explained by the defect being inherited as an autosomal recessive. The 6 reported by Gitlin and Craig (1963) in the United States were male as were 13 close relatives who died in infancy and who it seems probably had the same defect. These authors suggested that the condition was probably inherited as a sex-linked recessive trait. It appears possible that the disorder in the patient reported by White (1963) from Britain, a case of progressive vaccinia, was also inherited in the same manner, since 3 other boys on the mother's side of the family had died in infancy. Of the remaining 32 fully reported cases of thymic alymphoplasia, 21 were male and 11 were female. Thus, thymic alymphoplasia may possibly be inherited in two different ways: as a sex-linked recessive and as an autosomal recessive.

Birth history and age of onset of symptoms. All 13 of our patients were born at term and birthweights ranged from 2·78 to 3·91 kg. The birthweight was recorded in 20 of the published reports and ranged from 2·82 to 4·45 kg.

In 6 of the 13 patients in the present series the symptoms began during the first week of life; in 1 other between 1 week and 1 month of age; in 3 between 1 and 2 months of age; and in the 3 remaining patients at 2½, 3, and 4 months of age. In 2 of 27 reported cases of thymic alymphoplasia the symptoms dated from the first week of life; in 7 between 1 week and 1 month; in 5 between 1 and 2 months; in 6 between 2 and 3 months; and in 6 between 3 and 6 months. In one case the symptoms dated from 21 months of age (Gitlin and Craig, 1963). Thus, the onset of symptoms began before 3 months of age in 77% of all cases.

Of the 9 patients with vaccinia, 8 were apparently well until vaccinated between 1½ and 4 months of age; the other, who was vaccinated at 6 months of age, had had oral moniliasis at 4 months (White, 1963). The 3 patients who died of generalized BCG infection were vaccinated between 2 and 4 days of age, and symptoms of generalized infection began at 2½ months in 1 and at 6 months in the other 2.

Clinical symptoms and signs. Table V shows the principal presenting symptoms in the previously reported cases and in the present series. Cough, often of a spasmodic nature, was one of the earliest symptoms in all cases. Anorexia, feeding difficulty, and gastro-intestinal symptoms were also common in our cases.

On physical examination, respiratory system signs predominated in our series. Evidence of malnutrition was also a common feature. In 11 infants the weight on admission to hospital was at or below the 3rd centile, and the other 2 were at the 50th centile. The length of 4 of the children approximated to the 3rd centile.

Table VI summarizes the clinical features of the 39 reported cases as well as of our own series. Signs of lung infection, diarrhoea, vomiting, oral moniliasis, and wasting predominated. The patients with progressive vaccinia and generalized BCG

TABLE VI

Principal Signs and Symptoms Exhibited During Course of Illness in Previously Reported Cases of Thymic Alymphoplasia and in Present Series

Signs and Symptoms	Reported Cases* (39)		Present Series (13)	
	No. Cases	% Cases	No. Cases	% Cases
Signs of respiratory infection	33	85	13	100
Diarrhoea	28	72	10	77
Thrush	21	54	5	38
Morbilliform rash	19	49	1	8
Wasting	18	46	10	77
Vomiting	10	26	5	38
Hepatomegaly	10	26	3	23
Oedema	5	13	1	8
Convulsions	7	18	0	0
Skin sepsis	5*	13	4	31
Lymphadenopathy	6	15	2	15
Splenomegaly	2	5	0	0

* The specific manifestations of progressive vaccinia and of BCG infection are not included in this analysis.

infection originally presented with the characteristics of these conditions, but most of the cases later showed signs and symptoms similar to those of the other cases.

A morbilliform rash was seen in only one of our patients. This rash was reported to be one of the characteristic features of the condition by Hitzig and Willi (1961). It commonly occurs following injection of γ-globulin, and it has been postulated that it may be due to histamine release provoked by the reaction of antibody in the γ-globulin with some antigen in the patient. Case 6 in the series of Hitzig and Willi also developed urticaria following γ-globulin administration.

In 5 of our cases the possibility of fibrocystic disease was considered in the differential diagnosis, because of the chronic respiratory infection and diarrhoea. One case described by Hitzig and Willi (1961) exhibited the clinical manifestations of the coeliac syndrome.

Laboratory investigations. *White blood cell counts:* 44 total white blood cell counts and 45 differential counts from 12 of our patients were available for analysis. In one (Case 7) no white cell count was performed, and another (Case 12) had only a differential count.

The highest and lowest total white cell and absolute lymphocyte counts of our patients and those published are analysed in Tables VII and VIII. Total white cell counts were very variable. Leucocytosis (counts of more than 15,000/mm.^{3}) was fairly common. Terminal leucopenia and neutropenia were also frequently observed, including Case 8 in the present series.

The lymphocyte count in normal infants between 2 and 6 months of age is 5000 to 6000/mm.^{3} (Tobler and Cottier, 1958; Smith and Vaughan, 1964). Two of the published cases had isolated total lymphocyte counts greater than 5000/mm.^{3}, one following a thymic transplant and the intravenous injection of foetal liver (Hitzig *et al.*, 1958; Hitzig *et al.*, 1965). In another case an isolated count of 4200/mm.^{3} was recorded (Gitlin and Craig, 1963). A male Negro infant with thymic alymphoplasia described by Kadowaki *et al.* (1965) had XX/XY chimerism in the peripheral lymphocytes. The authors postulated an early intrauterine graft of

TABLE VII

Highest and Lowest Total WBC Counts in Previously Reported Cases of Thymic Alymphoplasia and in Present Series

Count/mm.^{3}	Reported Cases (39)		Present Series (11)	
	Lowest	Highest	Lowest	Highest
< 1000	3 (8)	—	1 (9)	—
1000-2999	9 (23)	4 (10)	1 (9)	—
3000-4999	13 (33)	4 (10)	2 (18)	—
5000-6999	5 (13)	5 (13)	2 (18)	2 (18)
7000-9999	4 (10)	7 (18)	2 (18)	2 (18)
10,000-15,000	3 (8)	10 (26)	1 (9)	1 (9)
> 15,000	2 (5)	9 (23)	2 (18)	6 (55)

The figures show the number of cases with total WBC counts in the group indicated and figures in parentheses are percentages of the total cases.

TABLE VIII

Highest and Lowest Absolute Lymphocyte Counts in Previously Published Cases of Thymic Alymphoplasia and in Present Series

Counts/mm.^{3}	Reported Cases (39)		Present Series (12)	
	Lowest	Highest	Lowest	Highest
0-99	8 (21)	—	2 (17)	2 (17)
100-499	12 (31)	5 (13)	3 (25)	—
500-999	12 (31)	11 (28)	2 (17)	1 (8)
1000-1999	6 (15)	14 (36)	3 (25)	3 (25)
2000-2999	—	2 (5)	2 (17)	1 (8)
> 3000	1 (3)	7 (18)	—	5 (42)

The figures show the number of cases with lymphocyte counts in the range indicated and figures in parentheses are percentages of the total cases.

maternal cells. This patient showed total lymphocyte counts of 3000-5000/mm.^{3}, but when a calculation was made of the circulating lymphocytes formed by the patient's own system, lymphopenic values prevailed.

Five of our patients showed lymphocyte counts greater than 3000/mm.^{3} on one or more occasions (Cases 1, 2, 4, 8, and 11). Case 2 had a peripheral lymphocyte count of 8000/mm.^{3} on 2 occasions, and Cases 4, 8, and 11 each had a single lymphocyte count of approximately 6000/mm.^{3} The latter 3, however, had other lymphocyte counts of less than 2000/mm.^{3} on one or more occasions.

It has been suggested that in these patients the lymphocyte counts decrease towards the end of their lives. This was so in a number of the reported cases, but in our experience it was not an invariable finding. Of the 8 patients in whom two or more lymphocyte counts were recorded, 4 had lower counts terminally than on initial examination, and in the other 4 patients the final counts were higher.

Thus, the lymphocyte count is obviously variable in this condition. Lymphopenia may be present at birth or may develop later in the course of the disease.

Other haematological findings. Of the infants in the present series, 3 developed anaemia severe enough to require blood transfusion; in one (Case 2) the anaemia was preceded by gastro-intestinal haemorrhage and was associated with thromboctyopenia. The other 2 had microcytic hypochromic anaemias and no source of blood loss was detected. 8 other infants in whom Hb values were recorded showed no anaemia.

A terminal pancytopenia was recorded in 3 of the previously published cases (Hitzig *et al.*, 1958; Hathaway *et al.*, 1965) and 2 others had thrombocytopenia (Gitlin and Craig, 1963). Four in our series had bone-marrow examinations during life. In all of them plasma cells were absent. Three of them showed granulopoietic hyperplasia, and in the fourth (Case 8) with neutropenia, there was granulopoietic hypoplasia.

Serum protein concentrations. Serum protein estimations were performed by paper electrophoresis in 7 patients in the present series, and in another, the albumin and globulin fractions were measured. In 3 of the patients the immunoglobulins were estimated by immunoassay. The results are shown in Table IV. Hypo-γ-globulinaemia was found in 6 patients; in the seventh (Case 13) the γ-globulin levels were within the normal range for an infant of 4 to 6 months of age. Immunoassay showed no detectable γA-globulin and very low or undetectable amounts of γM-globulin. In Case 4, γG-globulin could not be detected by immunoassay despite a γ-globulin concentration of 140 mg./100 ml., as estimated by paper electrophoresis.

Absence or gross deficiency of the immunoglobulins was found in most of the cases of thymic alymphoplasia reported. However, in one the concentration of the immunoglobulins in the serum was normal (Nezelof *et al.*, 1964), in another γG-globulin was decreased, but γA- and γM-globulins were normal (Kadowaki *et al.*, 1965), and in a third γG and γA were deficient but the concentration of γM-globulin was increased (Fireman *et al.*, 1966). In each of these three cases plasma cells were seen in various lymphoid tissues. It thus appears that in man, plasma cells, the immunoglobulin-producing cells, may develop independently of the thymus and the small lymphocyte. In the chick the bursa of Fabricius is necessary for the development of the immunoglobulin-producing system, and Petersen *et al.* (1965) suggested that in man the palatine tonsil, and perhaps other lymphoid tissue in the gastro-intestinal tract, may be the homologue of the chick bursa. However, in the case described by Fireman *et al.* (1966) there was hypoplasia of the lymphoid tissue in the gastro-

intestinal tract, including the tonsil, with absence of germinal centres and plasma cells, and so evidently the site of origin of plasma cells in man remains uncertain.

Immunological findings. As stated above, Cases 4 and 11 did not form antibodies following immunization with diphtheria toxoid, and the Schick test remained positive. Case 4 also had no isohaemagglutinins in the serum. Both cases, however, showed delayed hypersensitivity when challenged with DNFB and this was a most unexpected finding. These were 2 of the cases which showed the greatest number of circulating lymphocytes, and it must be presumed that the lymphocytes in these infants were capable of producing a degree of cellular immunity. Gitlin *et al.* (1964) could demonstrate no delayed hypersensitivity in one patient following challenge with DNFB, dinitrochlorobenzene (DNCB), and *Candida albicans* antigen (though the latter became positive following a thymic transplant, the donor being hypersensitive to the antigen). In addition, rejection of skin and thymic tissue grafts did not occur in this patient. Hitzig *et al.* (1965) reported absence of the delayed hypersensitivity reaction following challenge with DNCB on a number of occasions, and that a skin homograft was not rejected. Fireman *et al.* (1966) also found that the skin did not result in any demonstrable sensitivity to challenge with DNFB.

In the 3 cases of generalized BCG infection, tuberculin skin tests were negative. No neutralizing antibodies to vaccinia virus or antibodies in low titre were found in 5 of the cases of progressive vaccinia.

Radiographic findings. One or more chest radiographs were obtained in all cases with one exception (Case 9). Case 13 was found to have pneumothorax on admission to hospital, and in the others diffuse densities were reported in one or more lobes of the lungs. The radiographs of 7 patients have recently been reviewed by Dr. A. E. Childe: in all of them the thymus looked small, giving rise to a narrow superior mediastinal shadow in the antero-posterior view and a translucent area behind the sternum in the lateral view. We are doubtful whether the failure to demonstrate thymus radiographically can be used as a diagnostic aid in thymic alymphoplasia, because in many chronic debilitating illnesses in patients of this age the thymus is very small.

Radiographs of the pharynx in 4 patients revealed no adenoid tissue: this abnormality may be an important aid in diagnosis, as it is in the Bruton type of hypo-γ-globulinaemia (Margulis, Feinberg, Lester, and Good, 1957).

Age at death. In our series the average age at death was 4 months and all were dead by the age of 7 months. The average age of death in the previously reported cases of thymic alymphoplasia was rather greater than in ours (mean 8·4 months, range 3-24 months) and girls died younger than boys (mean ages 6·6 and 9·4 months, respectively). Some of the cases which survived longest were in the series of Gitlin and Craig (1963), in which the disorder was possibly inherited as a sex-linked recessive trait.

The immediate cause of death in all our cases appeared to be pneumonia, with a coexisting congenital heart lesion in one. Case 5 inhaled a milk feeding just before death. Two of the reported cases had terminal cor pulmonale (Gitlin and Craig, 1963), and another, who had oedema and ascites, also probably died in cardiac failure (Tobler and Cottier, 1958). Three infants had terminal convulsions, one associated with a haemorrhagic uraemic syndrome (Hitzig *et al.*, 1958; Gitlin and Craig, 1963).

Racial origin and family history. Seven of the patients reported here were from 5 Mennonite families. This ethnic group immigrated to central Canada from Russia and Eastern Europe during the latter decades of the last century and have generally married within their own order. It has not been possible to link the families together, though cousin marriages are common in the Mennonite group, and it seems likely that the families may be distantly related. As far as can be determined, these Mennonite families did not originate in Switzerland, and we can trace no connexion between them and the cases of thymic alymphoplasia reported from that country (W. H. Hitzig, 1966, personal communication).

Cases 5 and 6 were brother and sister and came of a large family. There is consanguinity on the father's side, the grandparents being second cousins. As far as is known there have been no infant deaths on this side of the family but several of the maternal great grandmother's children by her first marriage are reported to have died in infancy.

Case 7 was also a Mennonite. He died in 1950 and it has not been possible to trace the family recently. He was the sixth child of whom only 2, both girls age 7 and 3 years, were living. Three other children, 2 boys and a girl, had died at 1, 2, and 3 months of age, respectively, the first two from pneumonia and the third following an illness which had included skin pustules, diarrhoea, and pneumonia.

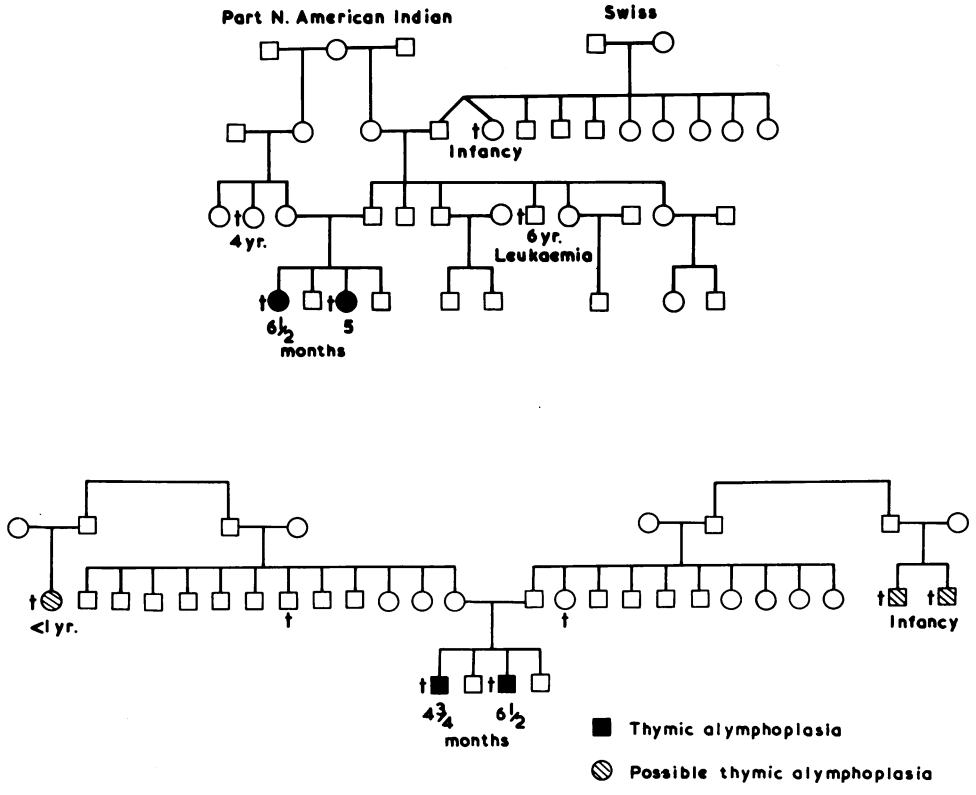

FIG. 1.—*Pedigrees of Family 'E' (above) and Family 'F' (below).*

Case 9, another Mennonite who lived in Northern Saskatchewan, had one brother aged 1 year who is alive and well. There is no consanguinity.

The family of Case 10 is also Mennonite. Our patient had 2 healthy sibs and the mother is now pregnant again. Serum was obtained from the mother for immunoglobulin assay and this was normal. Unfortunately the father and other children could not be prevailed upon to submit to venepuncture. The only finding of possible significance in this family is that 2 sisters of the father died in infancy, one at a few months of age from 'stomach-ache' and the other at 2 weeks of age from pneumonia.

The fifth Mennonite family ('F', Cases 3 and 4) has already been described in greater detail (Fig. 1).

The other patients were not Mennonites. The parents of Cases 1 and 2 were first cousins, their mothers being half sisters (Family 'E', Fig. 1). The patients' paternal grandfather was Swiss and the paternal grandmother part North American Indian. Case 11 was almost certainly Anglo-Saxon. The racial origins of the other patients are unknown.

The remaining patient with a significant family history is Case 13. This infant was the fifth child of unrelated parents and the only girl. The 2 first-born children were alive and well, being 10 and 6 years old at the time of admission of our patient. The next boy was well until 6 weeks of age when he developed a cough, sores in the mouth, and was admitted to hospital in another province. Total white blood counts ranged from 1050 to 3500/mm.^{3}, with lymphocytes 120 to 520/mm.^{3} Sputum culture revealed *Candida albicans*. He died at 4 months of age and at necropsy was found to have suppurative bronchopneumonia and a low-grade meningitis. The next child developed thrush, salmonella dysentery, and pneumonia at 7 weeks of age. One white blood cell count showed 5500/mm.^{3}, with only 160 lymphocytes/mm.^{3} He also died at 4 months of age. No necropsy was performed. There seems little doubt that these 2 children also had thymic alymphoplasia.

Previously reported cases, including those with progressive vaccinia and disseminated BCG infection, were seen in Switzerland, France, Britain, and

the United States. Family 'Fi' reported by Hitzig (Hitzig and Willi, 1961; Hitzig *et al.*, 1965) were Jewish and the cases of Gitlin and Craig (1963) were probably of British descent (D. Gitlin, 1965, personal communication). Two cases have been reported in American Negro infants (Kadowaki *et al.*, 1965; Rosen *et al.*, 1966). The racial origins of the other cases were not specifically stated. The 39 reported cases belonged to 31 different families. In one family (family 'Fi' previously referred to), 4 of 7 children were affected. In the other 29 families there were 15 sibs who died in early infancy and it seems they likely also had thymic alymphoplasia. In these families there were also 38 unaffected children.

The parents of only two of our cases were known to have been related before marriage (Cases 1 and 2). Consanguinity was present in parents of 10 of the 39 published cases.

Treatment. At the present time no treatment has been shown to prolong life in this disorder. Most of the reported cases, as well as those in the present series, were treated with antibiotics and γ-globulin. Four of our patients (Cases 1, 2, 10, and 11) received corticosteroids for varying periods during their last illnesses. The steroids had no obvious effect upon the patients' lymphocyte counts; indeed Cases 1 and 2 were the 2 children who never exhibited lymphopenia.

The patients with progressive vaccinia received hyperimmune vaccinial γ-globulin, and 5 of them were treated with N-methylisatin-β-thiosemicarbazone.

In six reported cases, attempts have been made to populate the patients' lymphoid tissues with small lymphocytes and replace deficient immunological activity by the transplantation or intravenous infusion of thymus, liver, spleen, bone-marrow, or combinations of these tissues (Rosen *et al.*, 1962; Gitlin *et al.*, 1964; Hitzig *et al.*, 1965; White, 1963; Allibone *et al.*, 1964; Rosen *et al.*, 1966). All these patients died of their disorder, but in one Hitzig *et al.* (1965) restored the peripheral lymphocyte count to normal and produced temporary clinical improvement by transplants of foetal thymus tissue with simultaneous and subsequent infusions of foetal liver cells. In another case (Rosen *et al.*, 1966) thymic transplants did not restore immunological competence, but the subsequent infusion of maternal bone-marrow cells resulted in a rise in the lymphocyte count and the transfer of delayed hypersensitivity.

It has been suggested that the failure to date to replace the deficient immunological activity in thymic alymphoplasia by these means may be partly because of the development of graft versus host reactions (Hitzig *et al.*, 1965).

Hathaway *et al.* (1965) speculated whether the transfusion of leucocytes into 2 patients with progressive vaccinia and thymic alymphoplasia might have produced a graft versus host reaction, because of the development of an erythematous rash, diarrhoea, and pancytopenia, but these symptoms are commonly seen in patients with this disorder who have not been transfused.

Necropsy findings. The pathological findings in thymic alymphoplasia have recently been fully reviewed by Gitlin and Craig (1963). The findings in our patients conform to those previously described (Table II). All infants exhibited the anatomical features of lymphoid hypoplasia with complete absence of plasma cells.

Twelve of the 13 children possessed abnormally small thymuses, a not unusual feature in any child who has died of a chronic illness associated with

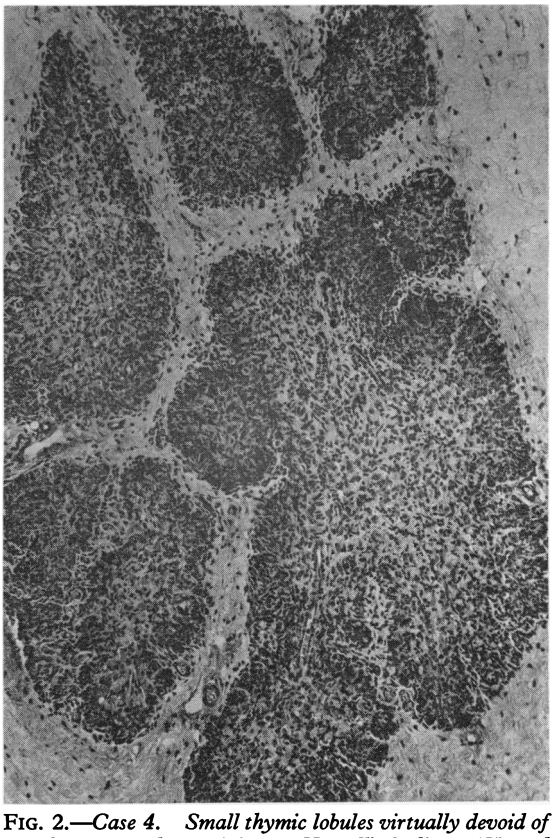

FIG. 2.—*Case 4. Small thymic lobules virtually devoid of lymphocytes, and containing no Hassall's bodies. (H. and E. × 80.)*

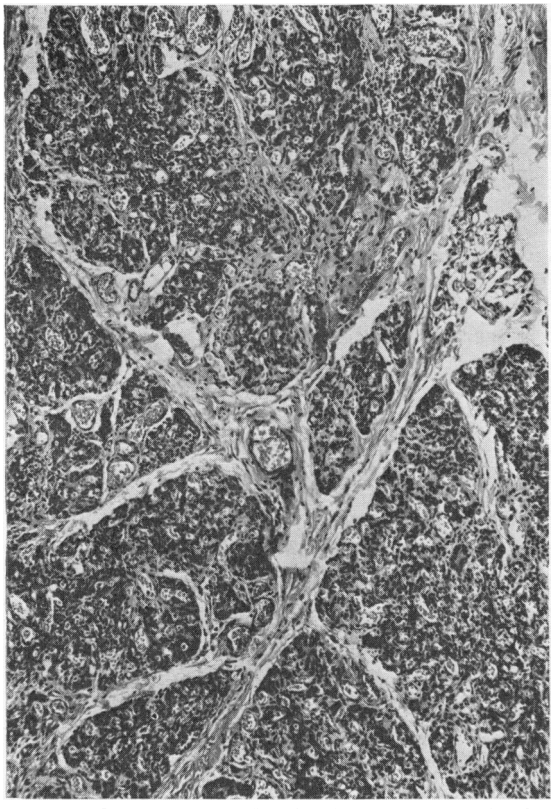

FIG. 3.—*Case 11. Vascular thymic stroma containing few lymphocytes and no Hassall's bodies. (H. and E. × 80.)*

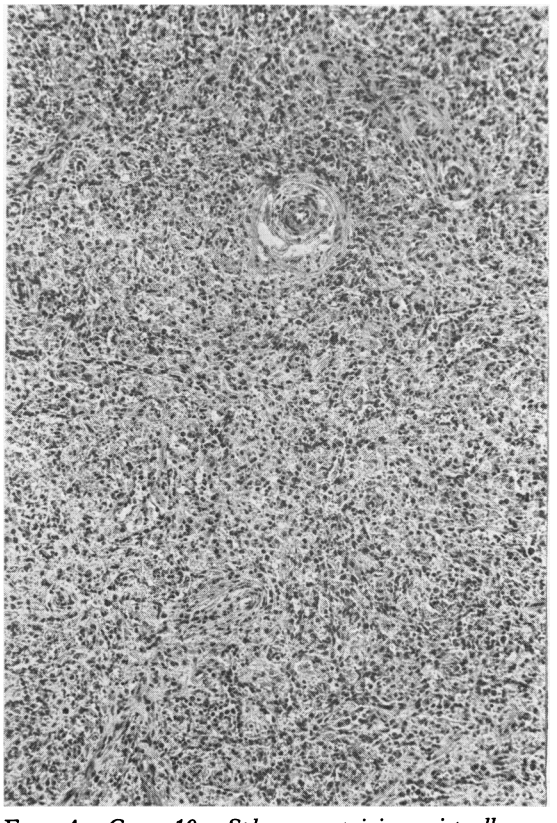

FIG. 4.—*Case 10. Spleen containing virtually no lymphocytes and no periarteriolar lymphoid aggregates. (H. and E. × 80.)*

infection. In the 9 infants in whom thymic tissue was available for histological study, however, the features were not merely those of 'accidental involution', for not only was there a marked depletion of lymphocytes from the stroma, but there was a complete absence of Hassall's bodies (Fig. 2). In 5, there was complete absence of lymphocytes, but in 2 there were very minimal collections of cells resembling lymphocytes. The remaining reticular stroma of the thymus often appeared unusually vascular (Fig. 3).

In 3 of the 4 infants where thymic tissue was not available for histological study, the thymus was described as minute or weighing less than 1 g., except in Case 5 where it weighed 5 g. These 4 children showed marked lymphoid hypoplasia in sites other than the thymus, with absence of Malpighian bodies in the spleen (Fig. 4) and absence of lymphocytes from lymph nodes (as in Fig. 5), and intestinal tract.

Those children who exhibited a histologically abnormal thymus, with absence of Hassall's bodies and absence of lymphocytes, exhibited variable degrees of lymphoid hypoplasia in other sites. In some, for example, there was complete absence of Malpighian bodies from the spleen, while in others the Malpighian bodies were present but small. In 2, the Malpighian bodies were quite prominent and numerous, with the presence of small secondary centres in one case (Fig. 6). The degree of lymphoid hypoplasia was similarly variable in lymph nodes and intestinal tract (Fig. 8), despite the fact that the thymus was histologically abnormal with complete lack of Hassall's bodies. One infant (Case 4) with thymic alymphoplasia and absence of Hassall's bodies exhibited palpable lymphadenopathy during life. These lymph nodes, although moderately enlarged, were nevertheless histologically abnormal (Fig. 7) possessing only ill-defined follicles.

Case 8 exhibited marked granulopoietic hypoplasia in addition to thymic alymphoplasia, absent Hassall's bodies, and lymphopoietic hypoplasia.

Pulmonary complications were the cause of death in all children, and in all cases the pulmonary

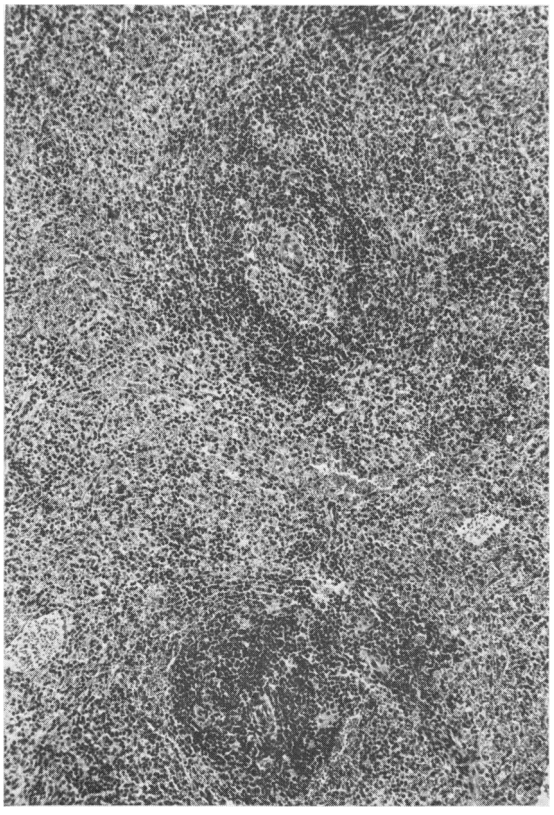

FIG. 5.—*Case 4. Spleen, with fairly prominent Malpighian bodies, one containing a small secondary centre. (H. and E. × 80.)*

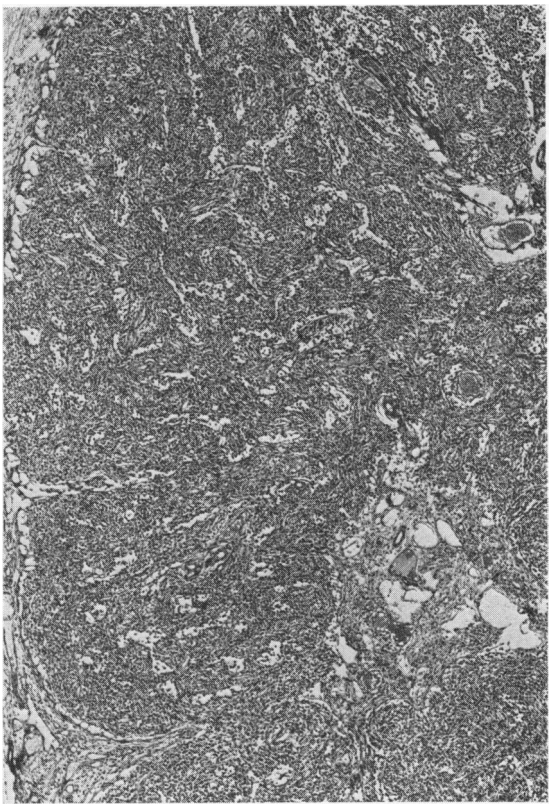

FIG. 6.—*Case 13. Mesenteric lymph node devoid of lymphocytes, and constising only of stromal cells. (H. and E. × 32.)*

histology was unusual. The following pulmonary histological lesions being noted: *Pseudomonas aeruginosa* pneumonia, giant cell pneumonia, adenovirus pneumonia, cytomegalic inclusion disease, *Pneumocystis carinii* pneumonia (Fig. 9), and a lesion closely resembling if not identical to alveolar proteinosis (Fig. 10). The pulmonary lesion in any one child often consisted of a combination of some of the above lesions. For example, the lungs of one child (Case 1) exhibited the histological features of adenovirus pneumonia, *Pneumocystis carinii* pneumonia, and alveolar proteinosis. *Pneumocystis carinii* pneumonia was evident in 3 children, giant cell pneumonia in 2 children, and generalized cytomegalic inclusion disease was present in one child. A lesion closely resembling if not identical to alveolar proteinosis was present in 6 children (Fig. 10). Further studies of this latter lesion and its possible relationship to hypo-γ-globulinaemia are in progress.

In summary, in our experience, thymic alymphoplasia with complete absence of Hassall's bodies may be associated with a variable degree of lymphoid hypoplasia in other sites. Plasma cells were consistently absent. Enlarged lymph nodes may be evident during life, or may be found at necropsy in children with thymic alymphoplasia and absent Hassall's bodies. In no case was the spleen smaller than normal, while in one case the spleen was twice normal weight (Case 4).

While younger infants tended to exhibit a greater degree of lymphoid hypoplasia than older infants with this disorder, this was not consistent. There was no established evidence in this series that greater degrees of lymphoid hypoplasia were associated with greater immunological defects.

Necropsies were performed on 35 of the recorded cases: the thymus is specifically mentioned in 25 of these. In 2, no thymic tissue could be found in spite of being specifically looked for (White, 1963; Allibone *et al.*, 1964). Other descriptions vary, e.g. 'practically non-existent', 'a few strands identified', 'hypoplastic'. In some cases the thymus had not descended to its normal position and remnants were

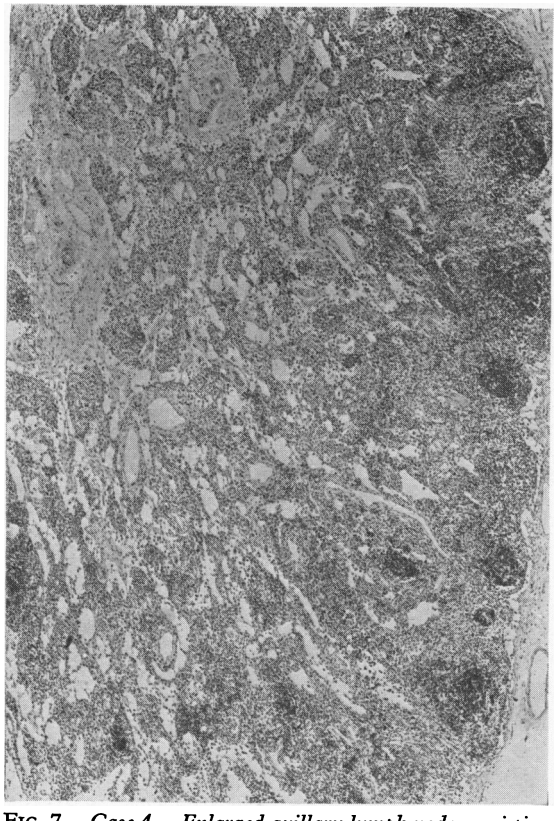

FIG. 7.—*Case 4. Enlarged axillary lymph node consisting predominantly of stromal cells, but containing small primary follicles.* (*H. and E.* × *32.*)

found in the neck. In 12 cases weights of the thymuses were recorded and ranged from 0·7 to 15 g. Hassall's bodies were absent in most of them but in one case a few atrophic Hassall's bodies were seen (Bonnevier *et al.*, 1964).

Many different forms of pulmonary lesions were observed in the previously reported cases. These included pneumonia of various types, bronchiectasis, and necrotizing bronchitis, emphysema, fibrinous pleurisy, moniliasis, etc. Five of the cases had *Pneumocystis carinii* pneumonia (Gitlin and Craig, 1963; Sacrez *et al.*, 1963; Bonnevier *et al.*, 1964; Hathaway *et al.*, 1965; Falkmer *et al.*, 1955; Bouton *et al.*, 1963).

Those cases, which in addition to thymic alymphoplasia had progressive vaccinia and generalized BCG infection, naturally showed the pathological changes due to these conditions, which will not be discussed here.

Summary

Thirteen infants (7 male and 6 female) with thymic alymphoplasia have been described. 7 of the infants were from 5 Mennonite families. The Mennonite sect is a much interbred group which immigrated to Canada from Eastern Europe around the turn of the century. The clinical, laboratory, and pathological findings in the present series have been compared with those in 39 previously reported cases of thymic alymphoplasia.

Affected infants appeared normal at birth, but

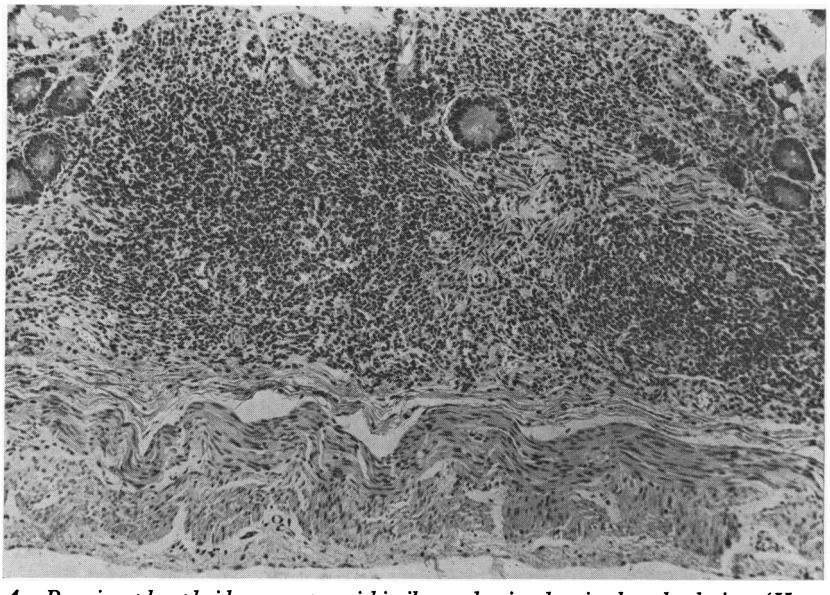

FIG. 8.—*Case 4. Prominent lymphoid aggregates within ileum, despite thymic alymphoplasia.* (*H. and E.* × *80.*)

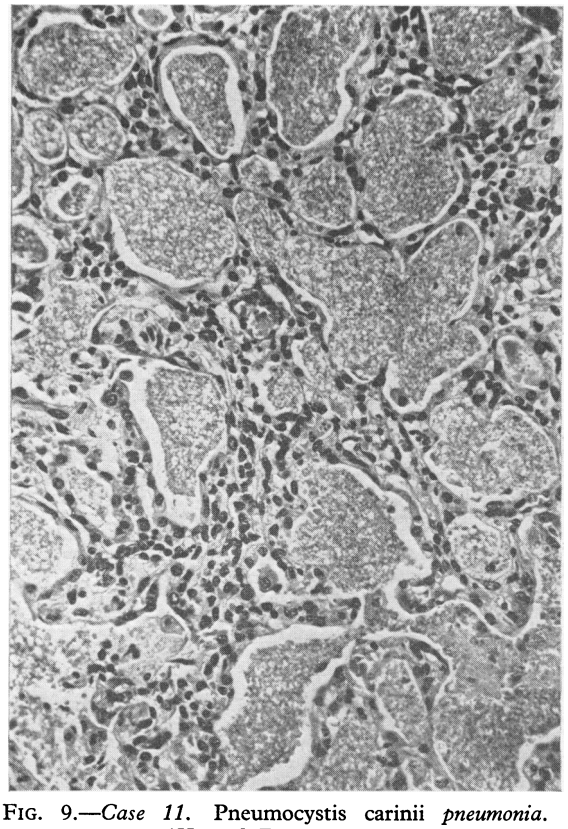

FIG. 9.—*Case 11.* Pneumocystis carinii *pneumonia.* (*H. and E.* × *200.*)

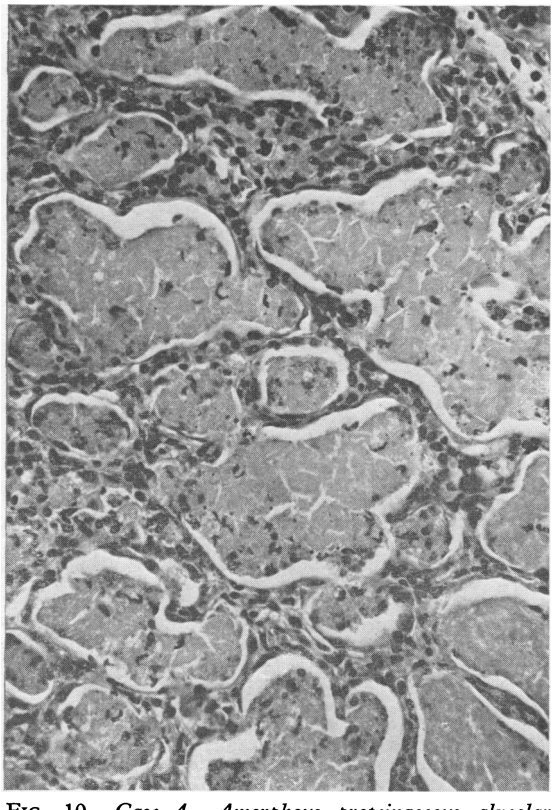

FIG. 10.—*Case 4. Amorphous proteinaceous alveolar contents in lung.* (*H. and E.* × *200.*)

within a few days or weeks they developed respiratory and gastro-intestinal symptoms and began to lose weight. In more than three-quarters of the cases symptoms appeared before the age of 3 months. The condition was characterized by a progressively downhill course, with increasing signs of respiratory infection, diarrhoea, vomiting, and loss of weight. Staphylococcal, monilial, and Gram-negative micro-organisms were often isolated from the respiratory tract, skin, stool, and urine. The condition was invariably fatal, and death occurred on an average 2 to 5 months after the onset of symptoms and all patients in the present series were dead by 7 months of age.

A peripheral lymphopenia (less than 2000 lymphocytes/mm.^{3}) was an almost invariable finding at some stage of the disease. However, normal or even high lymphocyte counts were found on occasion. Hypo-γ-globulinaemia was present in 6 of the cases in the present series and in most of the cases reported in the literature. In 3 reported cases, however, levels of one or more of the γ-globulins were normal, and in these plasma cells were seen in various lymphoid tissues. Circulating antibodies were absent and could not be stimulated by the injection of antigens. Delayed hypersensitivity in 3 previously published cases was absent. 2 in the present series showed delayed hypersensitivity to DNFB.

Necropsies were performed in all cases in the present series. In 12, the thymus was examined and was abnormally small, and in 9, where the thymic tissue was available for histological examination, there was a marked depletion of lymphocytes and absence of Hassall's corpuscles. Lymphoid hypoplasia was generally prominent in lymph nodes, spleen, and gastro-intestinal tract but was not invariable, for some had prominent Malpighian bodies in the spleen. Pulmonary infection was almost invariable, and findings included pneumonia due to *Pseudomonas aeruginosa*, *Pneumocystis carinii*, *Candida albicans*, and various viruses. In 6 cases a lesion closely resembling pulmonary alveolar proteinosis was found.

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