Virchows Arch. A Path. Anat. and Histol. 374, 87–103 (1977)

Virchows Archiv A

Review

Pathomorphology of Humoral, Cellular and Combined Primary Immunodeficiencies* **

B. Heymer, D. Niethammer, R. Spanel, J. Galle, E. Kleihauer, and O. Haferkamp

Department of Pathology (Prof. Dr. O. Haferkamp) and
Department of Pediatrics (Prof. Dr. E. Kleihauer), University of Ulm

Summary. Histologic, immunohistologic and electron microscopic findings in three children with primary immunodeficiencies are reported. Classical X-linked infantile agammaglobulinemia Bruton was present in case 1 (♂, aged 16 years), selective cellular immunodeficiency with thrombopenia in case 2 (♂, aged $2^1/_2$ years) and non-lymphopenic severe combined immunodeficiency in case 3 (♂, aged $1^3/_4$ years). At autopsy, all three cases exhibited unusual types of pneumonia. In case 2 a generalized cytomegalovirus infection was present. Case 3 disclosed panmyelopathia and chronic liver lesions due to severe GvH-reaction subsequent to bone marrow transplantation. A detailed morphologic study of the immune system revealed distinct alterations in the thymus, spleen, and lymph nodes and the lymphatic tissues of the gastrointestinal tract characteristic of an immunodeficiency state, either humoral (case 1), cellular (case 2) or combined (case 3).

Key words: Immunodeficiency – Immunologic disorders – Immune system – Thymus – Lymphatic Tissue – Congenital disorders.

Introduction

In spite of the vast literature on primary immunodeficiencies of man (Good et al., 1968; Cooper et al., 1968a; Cottier et al., 1968; Hess, 1970; Fudenberg et al., 1971; Schädeli and Hess, 1972; Graepel et al., 1972; Good, 1973) a comprehensive illustrated documentation of the pathomorphology of these disease states is not available in any single publication. Recently, we reported findings in lymphopenic severe combined immunodeficiency and reticular dysgen-

* Dedicated to Prof. Dr. Chr. Hedinger for his 60th birthday

** This paper was presented in part at the 7th Fall Meeting of the German Society for Pathology in Mainz, Oct. 29–31, 1976

For offprints contact: Prof. Dr. B. Heymer, Abteilung für Pathologie, Universität Ulm, Oberer Eselsberg, D-7900 Ulm/Donau, Federal Republic of Germany

esia (Heymer et al., 1976). In this paper three other primary immune defects—classical X-linked infantile agammaglobulinemia, cellular immunodeficiency with thrombopenia and non-lymphopenic severe combined immunodeficiency—are described. Thus, the data presented do provide a concise picture of the characteristic morphology of the major immunodeficiency types.

Clinical Findings

Patient M.Sch. (Case 1)

The parents of this child were healthy and not consanguineous. There were no siblings. The boy (blood group 0, Rh+) developed normally up to the age of 2 years when a pyogenic meningitis occurred. After appropriate treatment the child recovered, but retained a tendency to convulsions. No detailed immunologic studies were performed at that time. In the following years numerous other infections were observed such as otitis media, mastoiditis, pneumonia and peritonitis, primarily caused by *Staphylococcus aureus, Staphylococcus epidermidis* and *Haemophilus influenzae.* At the age of 4 years, for the first time, a severe permanent reduction of all serum immunoglobulins was recognized. The corresponding laboratory findings given in Table 1 are representative of data obtained repeatedly throughout life. Immunization of the boy with various vaccines induced no measurable antibody formation. In contrast to the severe deficiency of the humoral immune system, cellular immune functions and the hematopoietic system appeared undisturbed (Table 1). Based

Table 1. Clinical findings

	Case 1	Case 2	Case 3		
			Before T.	After T.	Before D.
Blood cell count					
Total leucocytes/mm^3	10,000–14,000	3,900–7,000	7,100	9,200	50
Granulocytes/mm^3	6,000–9,000	3,400–5,900	2,272	5,522	0
Lymphocytes/mm^3	2,800–3,900	195–1,260	4,260	2,024	50
Monocytes/mm^3	1,000–1,600	78–160	497	1,012	0
Erythrocytes/mm^3	$5.0–5.9 \times 10^6$	$2.3–2.5 \times 10^6$	5.1×10^6	4.4×10^6	2.8×10^6
Thrombocytes/mm^3	300,000	250–6,000	260,000	300,000	30,000
Cellular immunity					
T-cell-rosettes %	nd	65–69	5	56	nd
PHA-stimulation	positive	reduced	negative	positive	nd
MLC	positive	negative	negative	positive	nd
DNCB-test	positive	negative	negative	positive	nd
Candida-Ag-skin-test	negative	negative	negative	negative	nd
Humoral immunity					
B-cell-rosettes %	nd	27–32	80	20	nd
Plasma cells (bone marrow)	negative	positive	negative	positive	positive
IgG mg%	85–180	1,162–1,924	250	985	nd
IgA mg%	0–28	31–103	7.6	8.3	nd
IgM mg%	0–39	141–288	15	163	nd
Isohemagglutinins	negative	negative	negative	positive	positive

Before T. = before bone marrow transplant. After T. = after bone marrow transplant. Before D. = shortly before death. nd = not done

on these findings a diagnosis of Bruton's X-linked infantile agammaglobulinemia was made and the boy received constant immunoglobulin therapy for the following 12 years. In spite of this treatment he frequently developed pneumonia and showed signs of increasing pulmonary insufficiency. He finally died, aged 16 years, from failure of the right ventricle.

Patient M.W. (Case 2)

The parents of this child were unrelated and healthy. There were two brothers without evidence of increased susceptibility to infection. The boy (blood group B, Rh+) was born at term and exhibited all signs of maturity. The first recorded symptoms of disease developed at the age of 21 months when a severe enteritis occurred. Upon hospitalization, high temperatures, skin hematomata and a mucocutaneous candidiasis were observed. Detailed study of various immunologic and hematologic parameters (Table 1) revealed permanent lymphopenia, thrombopenia, decreased numbers of megakaryocytes (frequently smaller in size than usual) in the bone marrow and severely impaired cellular immune functions. In contrast, humoral immunity appeared undisturbed (Table 1). Serologic reactions for cytomegalovirus infection, within the first months of the disease, were negative. There was no evidence for the presence of anti-thrombocyte autoantibodies. The boy was treated with antibiotics, fungistatics, steroids and blood and thrombocyte transfusions. The child finally died, aged $2^1/_2$ years, from massive intracerebral bleeding.

Patient M.Wa. (Case 3)

The parents of this child were healthy and not consanguineous. A brother suffering from severe combined immunodeficiency died from pneumonia at 7 months of age. Therefore, the second child (patient M.Wa.) was delivered by cesarean section one week before term. The boy (blood group 0, Rh−) showed all signs of maturity. Immediately after birth, he was transferred into a gnotobiotic environment. The child developed normally; no infections were observed. Extensive immunologic studies revealed a severe cellular as well as humoral immunodeficiency (Table 1). When vaccination was attempted for diphtheria, tetanus and polio no measurable antibody formation occurred. An allogenic skin transplant was not rejected. However, in spite of complete lack of immunocompetence, the child exhibited near normal lymphocyte counts (predominantly B-cells) in the peripheral blood. At the age of 9 months, HLA-compatible but Rh-incompatible allogenic bone marrow cells (6.5×10^8 cells) from the mother were transplanted. About 12–15 days thereafter a severe graft-versus-host (GvH) reaction occurred with hemorrhagic enterocolitis, jaundice and characteristic GvH dermatitis. This disappeared within 2 months. By about 5 months after transplantation, there was a complete immunologic reconstitution with significant antibody formation upon subsequent diphtheria-, tetatus- and polio-vaccinations, profound increase in serum immunoglobulin concentrations and positive in vitro correlates of cellular immunity (Table 1). However, at the same time, hemolytic anemia due to split chimerism (lymphocytes of the Rh positive donor type, erythrocytes of the host's own Rh negative type) appeared. Two further allogenic bone marrow transplants from the mother were performed but without success. Details of the therapeutic measures have been reported elsewhere (Niethammer et al., 1976). During the last 3 months of life, panmyelopathia and pulmonary insufficiency developed and the child finally died at 20 months of age from sepsis.

Morphologic Methods

Samples of all internal organs obtained at autopsy—performed 40 (case 1), 12 (case 2) or 3.5 (case 3) h after death—were fixed in 4% formalin and embedded in paraffin. The sections were stained with H & E, Giemsa, van Gieson, Gram, and for iron (Romeis, 1968). Specimens of bone marrow, lymph nodes, spleen and small intestine were deep frozen in liquid nitrogen. Then 5 μ sections were cut on a cryotome (WKF, Brandau) and reacted with FITC-labeled heavy-chain-specific antisera to human IgG, IgM and IgA (Meloy Laboratories, Springfield, Virginia, USA). Details of the immunohistologic methods employed have been described previously (Sellin et al.,

1970). In addition, small samples of thymus, lymph nodes and spleen of case 3 were fixed in 3.5% glutaraldehyde in 0.1 M Na-cacodylate buffer for 3 h, post-fixed in 1% osmium tetroxide and embedded in Araldid (Serva, Heidelberg). Ultrathin sections, cut on an ultramicrotome (LKB, Stockholm, Sweden), were studied with a Philips EM 200 electron microscope.

Morphologic Findings

General Pathomorphology

In case 1, autopsy revealed chronic bronchitis with bronchiectasis, severe cholesterol pneumonia (Fig. 1a) involving all areas of the lung, and considerable pulmonary fibrosis. There was substantial hypertrophy and dilatation of the right ventricle (cor pulmonale), and chronic congestion of all internal organs. The bone marrow – except for a lack of plasma cells – showed no pathologic changes. Pulmonary insufficiency and failure of the right ventricle were considered the primary cause of death.

Post-mortem examination of case 2 disclosed an extensive cytomegalic infection with bronchitis, peribronchial pneumonia (Fig. 1b), and minor cytomegalic lesions in the pancreas, parotid glands, and kidneys. As a consequence of the severe thrombopenia evident up until the time of death, generalized bleeding was present in the skin and almost all internal organs. The bone marrow showed reduced thrombopoiesis but normal granulo- and erythropoiesis; plasma cells could be easily identified. In addition, bone marrow, liver, spleen and lymph nodes revealed marked hemosiderosis. The endocrine glands were intact. Death resulted from massive intracerebral bleeding with perforation into the ventricular system.

At autopsy, the lungs of case 3 showed chronic bronchitis with bronchiectasis, widespread carnifying pneumonia, considerable pulmonary fibrosis, and numerous multinucleated giant cells (Fig. 1c). These giant cells, unlike those seen in a previous case of severe combined immunodeficiency (Heymer et al., 1976), did not contain inclusion bodies indicative of a virus (e.g. measles) infection but did contain lipid droplets. The right ventricle showed marked hypertrophy and dilatation (cor pulmonale). As a late consequency of the severe GvH-reaction in this child, the bone marrow disclosed a complete absence of all hematopoietic elements (Fig. 2a), and the liver considerable bile duct proliferation with chronic periportal inflammation and fibrosis (Fig. 2b). The endocrine glands did not reveal any obvious changes. In the brain, numerous areactive septic foci were detected. These were caused by anaerobic spore producing bacteria, as determined bacteriologically. Death was attributed to sepsis in conjunction with chronic pneumonia and failure of the right ventricle.

Pathomorphology of the Immune System

Thymus. The thymus of case 1, weighing 10 g (normal for the patient's age) showed dense lymphocyte populations, numerous Hassal's corpuscles, indistinct corticomedullary boundaries and large blood vessels (Fig. 3a). These are the

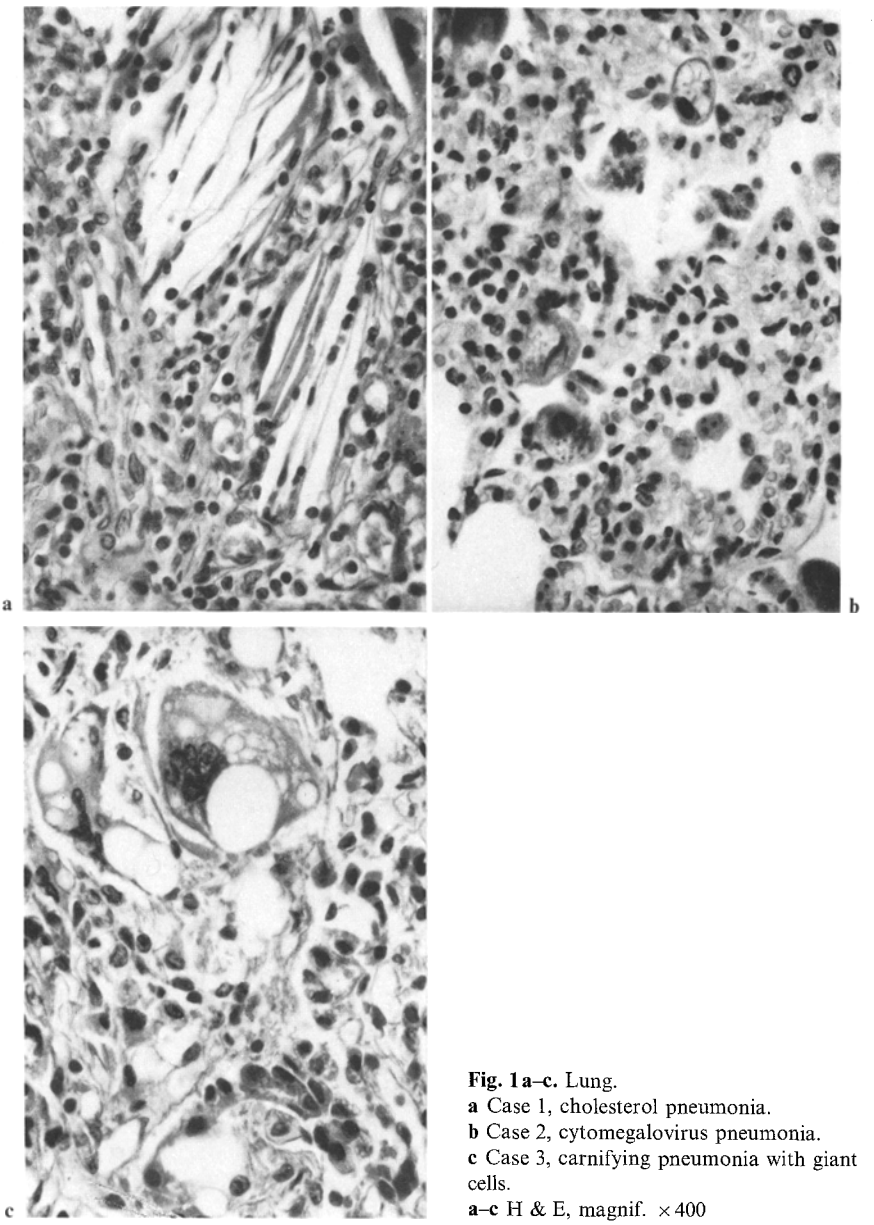


Fig. 1a–c. Lung.
a Case 1, cholesterol pneumonia.
b Case 2, cytomegalovirus pneumonia.
c Case 3, carnifying pneumonia with giant cells.
a–c H & E, magnif. ×400

characteristic features of an involuted non-dysplastic thymus (Good et al., 1968; Cooper et al., 1968). In contrast, the thymus of case 2, positioned normally but weighing only 1.5 g (age-corresponding normal weight is 15–22 g), displayed primitively organized lobules, tiny fibrous septa, and slight amounts of fat tissue (Fig. 3b). The lobules were composed of epithelial reticulum cells, arranged in rosettes and whorls; they contained no lymphocytes and no Hassal's

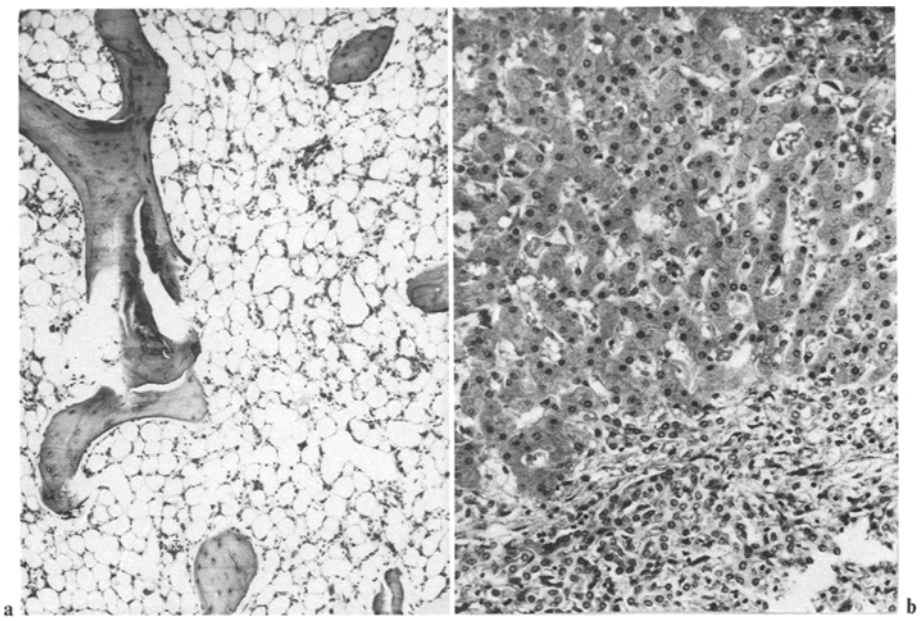
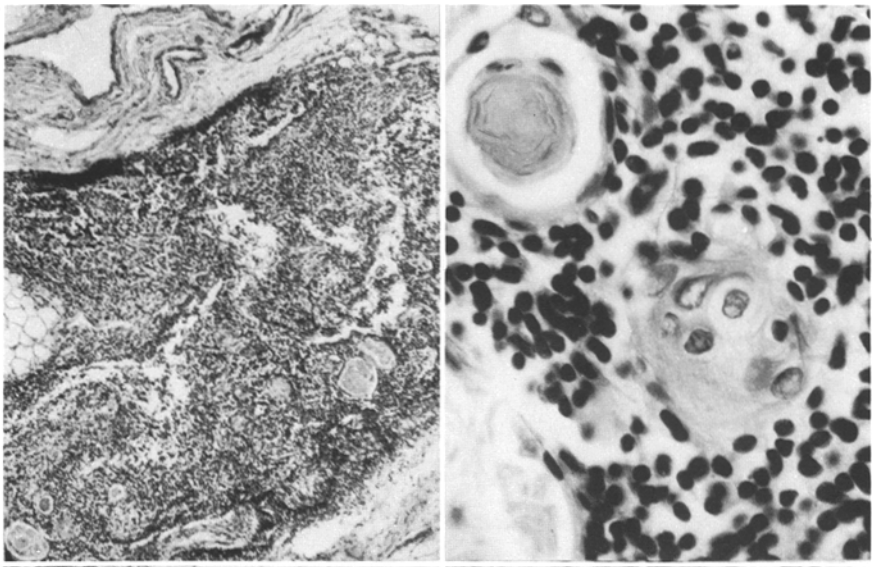


Fig. 2a and b. Late consequences of GvH-reaction. **a** Case 3, panmyelopathia. **b** Case 3, chronic periportal inflammation and bile duct proliferation in liver. **a** and **b**: H & E, magnif. **a** ×64, **b** ×160

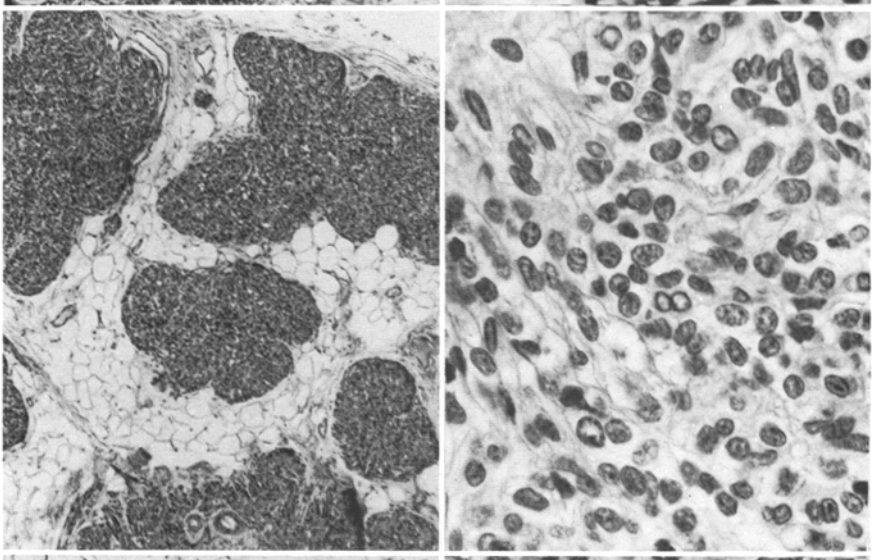
corpuscles. In case 3, the thymus had descended incompletely and weighed only 1 g (age-corresponding normal weight is 15–22 g). The vestigial gland consisted of single lobules embedded in abundant fat tissue and totally lacked any differentiation (Fig. 3c). The lobules were almost exclusively made up of epithelial reticulum cells and contained only single lymphoid cells; Hassal's corpuscles were absent. The thymic blood vessels, as in case 2, appeared extremely small.

Spleen. The spleen of case 1, weighing 185 g (age-corresponding normal weight is 85–125 g), exhibited a complete lack of lymph follicles, germinal centers and plasma cells (Fig. 4a). In addition, there was appreciable lymphocyte depletion, least pronounced in the periarteriolar sheaths. In contrast, the spleen of case 2, weighing 45 g (age-corresponding normal weight is 40–45 g), did possess lymph follicles with germinal centers and did contain plasma cells (Fig. 4b). However, considerable depletion of lymphocytes was present in all areas of the organ. The spleen of case 3, weighing 85 g (age-corresponding normal weight

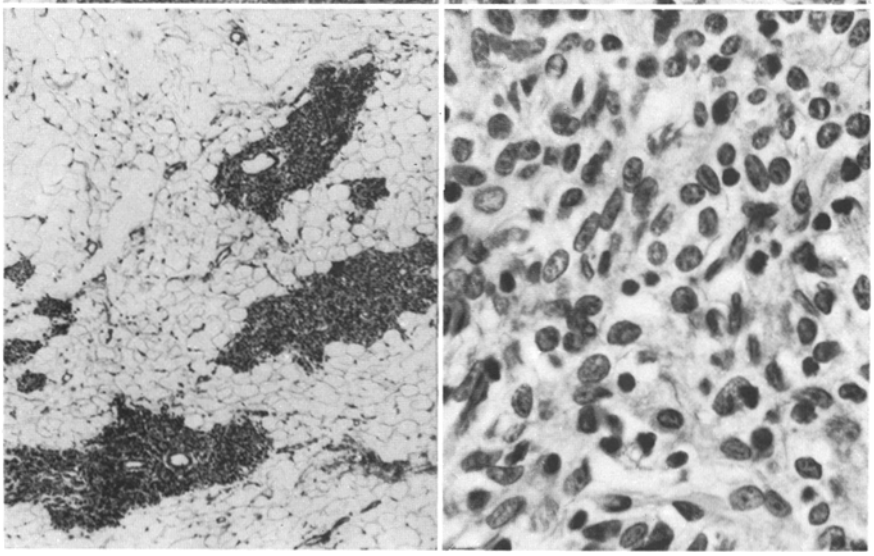
Fig. 3a–c. Thymus. **a** Case 1, atrophic thymus with numerous Hassal's corpuscles and dense lymphocyte populations. **b** Case 2, dysplastic thymus with primitive lobules composed of epithelial reticulum cells. **c** Case 3, dysplastic thymus consisting of single undifferentiated lobules within fat tissue. **a–c**: H & E, magnif. left ×64, right ×640



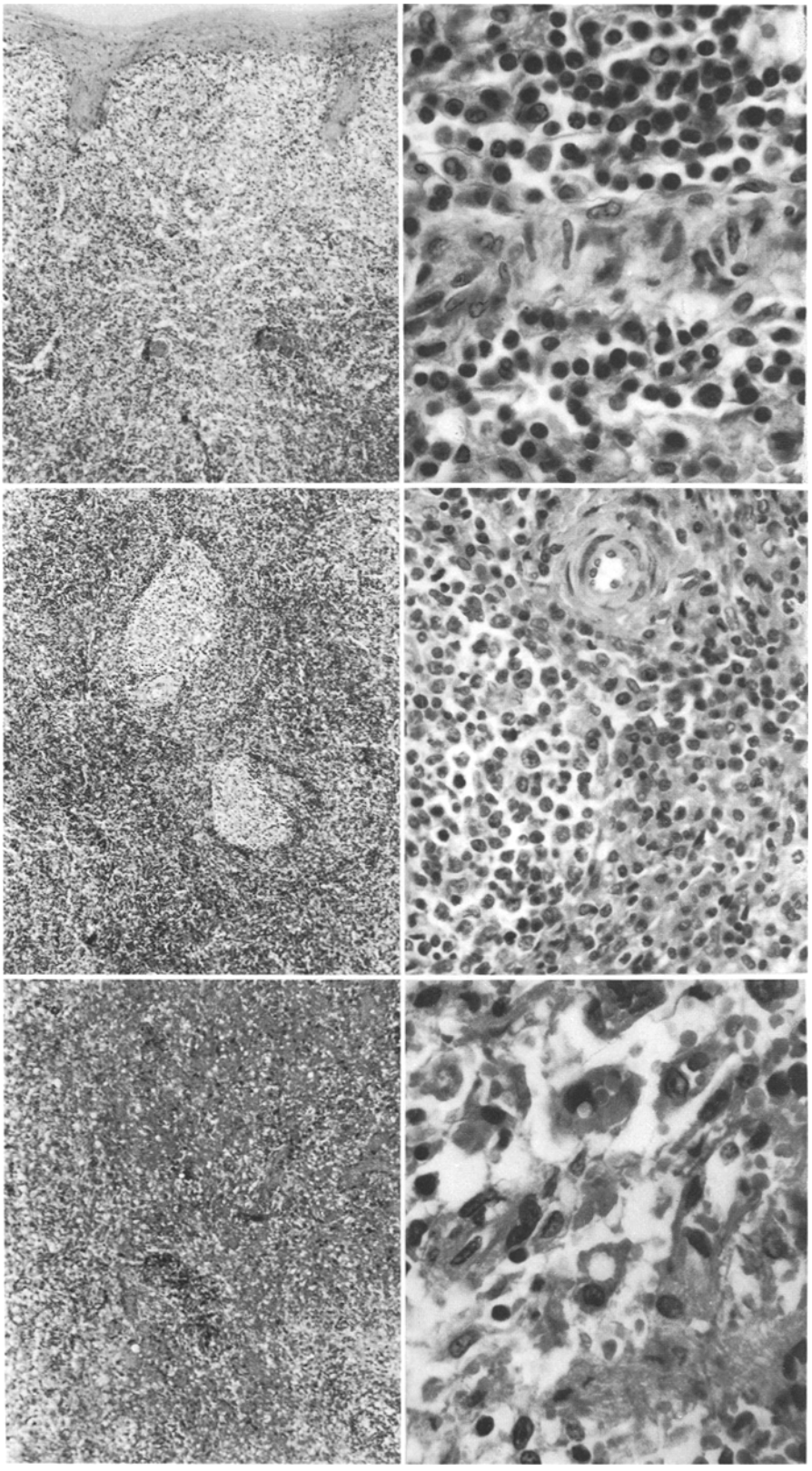
a



b



3c



a

b

4c

is 30–40 g), disclosed the most severe changes. The white pulp was practically absent (Fig. 4c). Nevertheless, at high magnification single lymphocytes and plasma cells were visible. The sinuses contained large foam cells and macrophages showing erythrophagocytosis (Fig. 4c).

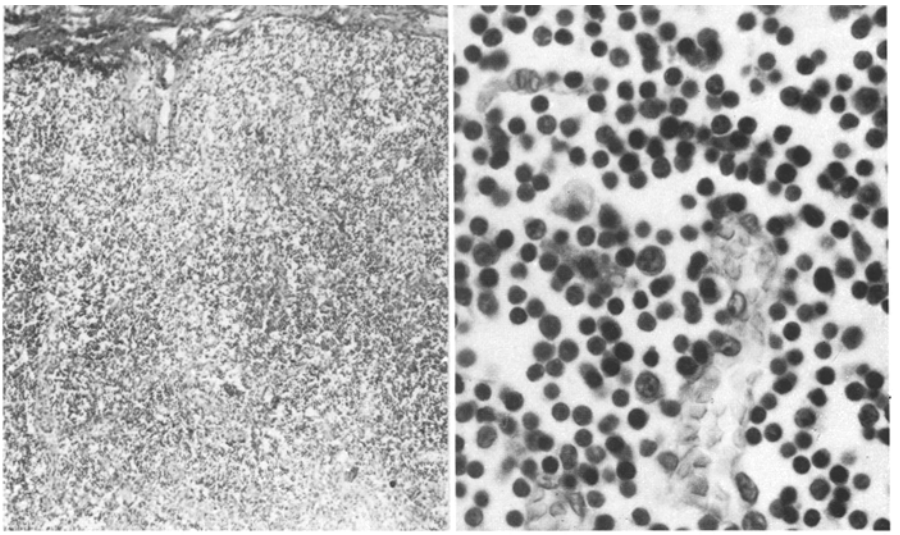
Lymph Nodes. In case 1, lymph nodes were easily detectable macroscopically. Microscopically, they showed a complete lack of follicles, germinal centers and plasma cells, whereas rather dense accumulations of lymphocytes were found scattered throughout the lymph node parenchyma (Fig. 5a). In contrast, the lymph nodes of case 2 did possess follicles with germinal centers and did contain numerous plasma cells (Fig. 5b). Lymphocytes were present, but appeared reduced in number, in the cortex and medulla. In case 3, lymph nodes were not detectable macroscopically. However, serial sections through the mesentary and the mediastinal tissues revealed single small lymph nodes which exhibited a completely irregular structure (Fig. 5c). There was no corticomedullary differentiation; follicles and germinal centers were lacking. Nevertheless, within a prominent reticular matrix single lymphocytes and plasma cells were visible. The sinuses contained many foam cells and cells phagocytizing erythrocytes (Fig. 5c). Postcapillary venules, easily detectable in cases 1 and 2, were hardly recognizable in the lymph nodes of case 3.

Gastrointestinal Tract. Case 1 exhibited severe hypoplasia of the lymphatic tissues in the gastrointestinal tract. Peyer's patches, germinal centers and plasma cells were absent. However, single lymph follicles could be detected in the mucous membrane of the small intestine and the lamina propria did contain lymphocytes. The tonsils showed only slight hypoplasia. In case 2, the lymphatic tissue of the gut disclosed a regular appearance; Peyer's patches, solitary follicles (sometimes possessing germinal centers) and lymphocytes and plasma cells were present (Fig. 6a). The tonsils did not exhibit any obvious pathologic changes. In contrast, there was aplasia of all lymphatic structures along the gastrointestinal tract and aplasia of the tonsils in case 3. The appendix, totally lacking lymph follicles, germinal centers and plasma cells, showed extensive "subepithelial fibrosis" (Fig. 6b), characteristic of the combined immunodeficiency state (Cottier et al., 1968; Hitzig, 1974).

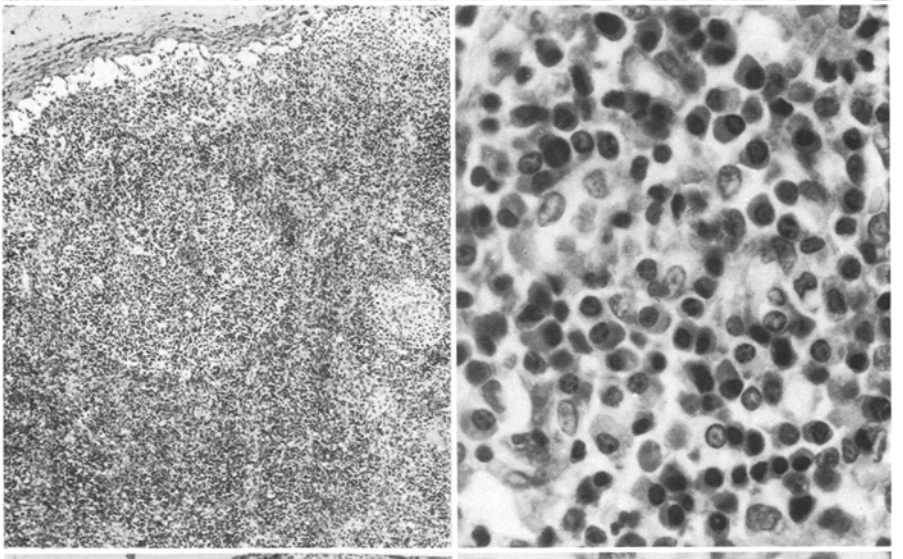
Immunohistologic Findings

Results of the immunohistologic studies are summarized in Table 2. In case 1, none of the lymphatic organs investigated contained cells positive for IgG, IgM or IgA. In contrast, in case 2 numerous immunoglobulin-producing cells were present in the lymph nodes (Fig. 7a), spleen and small intestine. Such

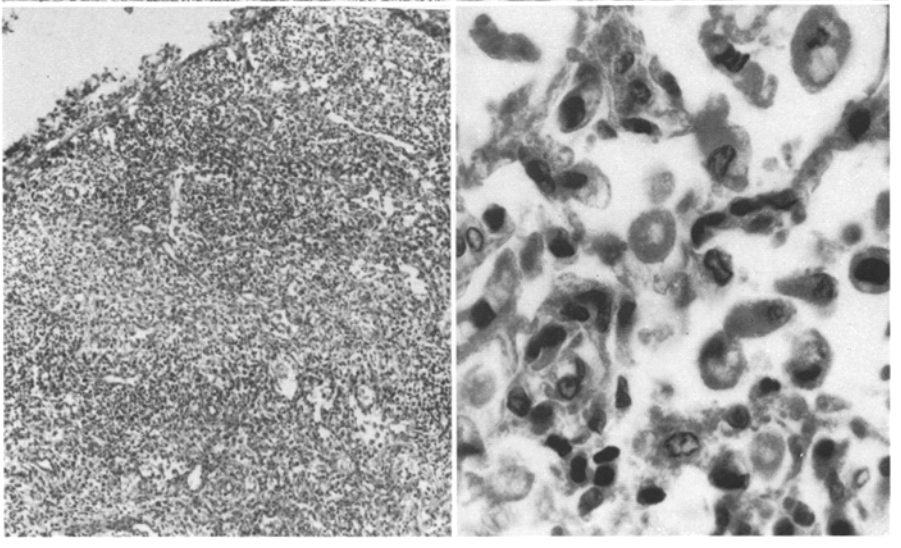
Fig. 4a–c. Spleen. **a** Case 1, absence of follicles, germinal centers and plasma cells; moderate lymphocyte depletion. **b** Case 2, follicles, germinal centers and plasma cells present, considerable lymphocyte depletion. **c** Case 3, complete absence of withe pulp; abundant erythrophagocytosis. **a–c**: H & E, magnif. left ×64, right **a** and **c** ×640, **b** ×400



a



b



5c

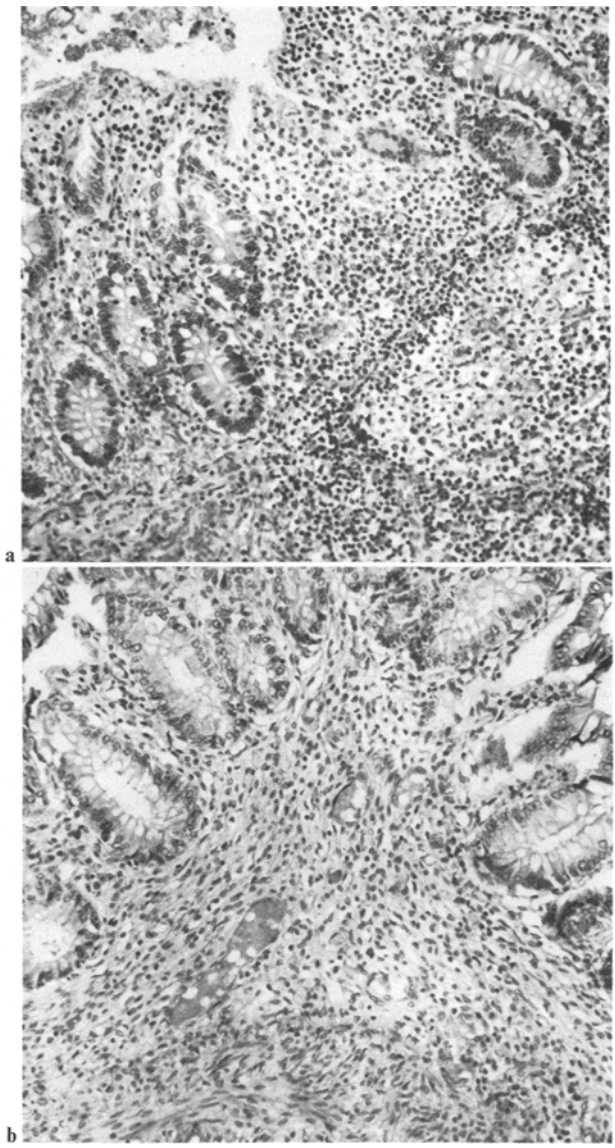


Fig. 6a and b. Appendix.
a Case 2, lymph follicle with germinal center within mucosa.
b Case 3, complete absence of lymphatic tissue; "subepithelial fibrosis".
a and **b** H & E, magnif. $\times 160$

Fig. 5a–c. Lymph node. **a** Case 1, absence of follicles, germinal centers and plasma cells; diffuse dense lymphocyte populations. **b** Case 2, follicles, germinal centers and numerous plasma cells present; considerable lymphocyte depletion. **c** Case 3, complete lack of normal lymph node structure; severe lymphocyte depletion; foam cells within sinuses. **a–c**: H & E, magnif. left $\times 64$, right $\times 640$

Table 2. Immunohistologic findings

	Case 1			Case 2			Case 3		
	IgG	IgM	IgA	IgG	IgM	IgA	IgG	IgM	IgA
Bone marrow	−	−	nd	+	+	nd	−	−	nd
Lymph node	−	−	nd	++	++	nd	+	+	nd
Spleen	−	−	nd	++	+	nd	+	+	nd
Small intestine	−	−	−	+	+	++	−	−	−

Grading system: ++ = strongly positive, + = slightly positive, − = negative, nd = not done

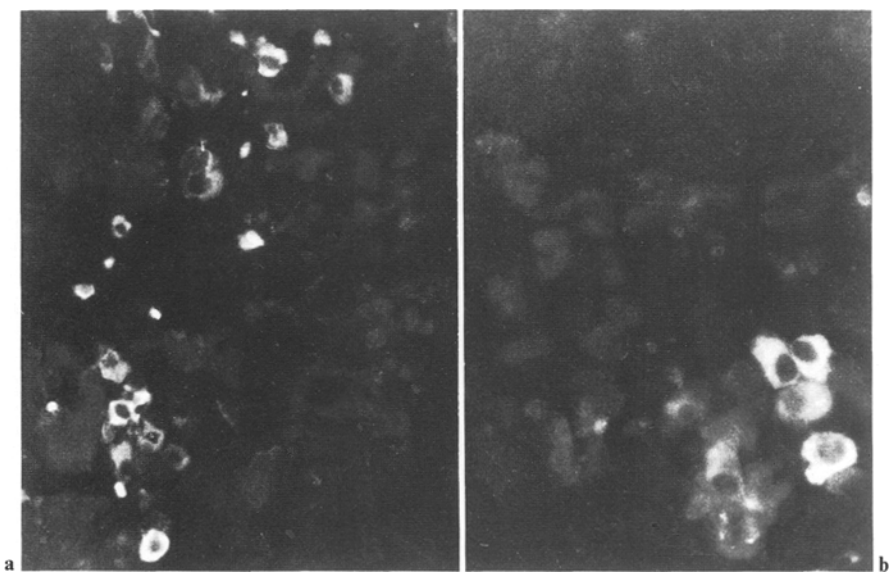


Fig. 7a and b. Immunohistologic demonstration of IgG producing cells in lymph nodes. **a** Case 2, magnif. ×400, **b** Case 3, magnif. ×640

cells were also detectable in the bone marrow, although to a lesser extent. In case 3, single cells definitely positive for IgG or IgM were found in the lymph nodes (Fig. 7b) and spleen. However, no immunoglobulin-producing cells could be detected in the bone marrow and small intestine (Table 2).

Electron Microscopic Findings

Ultrastructural observation of the thymus of case 3 revealed abundant collagen around the epithelial reticulum cells, composing the primitive lobules of the severely dysplastic gland (Fig. 8). In addition, single lymphoid cells and scattered mast cells—also observed in dysplastic thymuses by other authors (Huber, 1968)—were present (Fig. 8). The abnormal structure and the extensive secondary changes of the spleen made identification of characteristic elements practi-

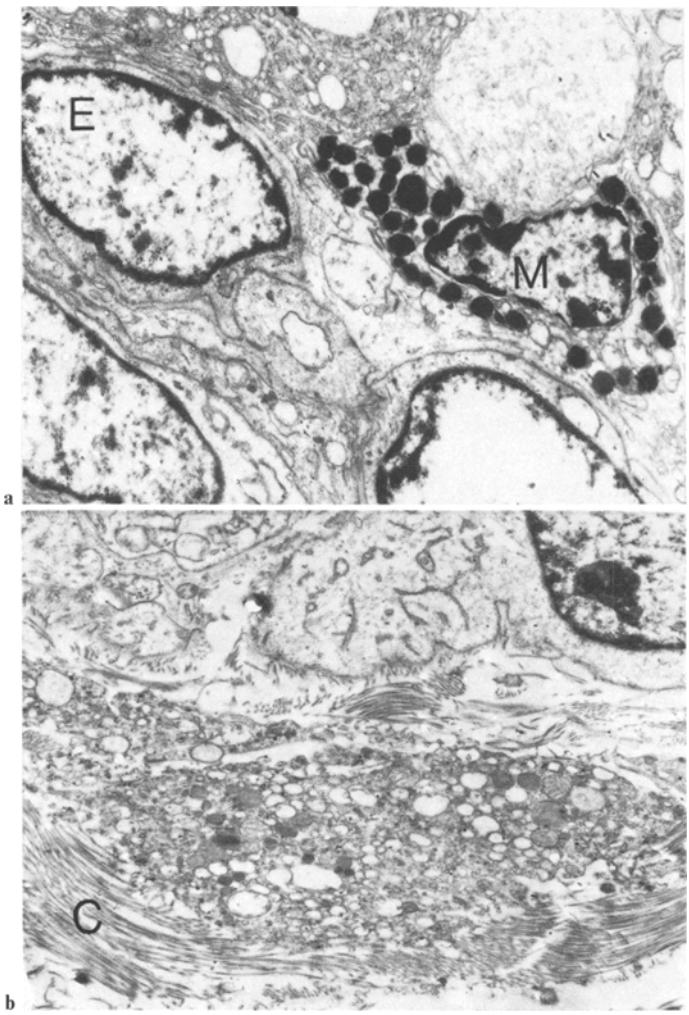


Fig. 8a and b. Electron micrographs of thymus of case 3. *E* epithelial reticulum cell, *M* mast cell, *C* collagen. Some loss of fine structure may be due to autolytic changes. Magnif. **a** ×6800, **b**×7400

cally impossible. In the lymph nodes, post-capillary venules, barely recognizable in routine histologic sections, were easily detectable by electron microscopy. These blood vessels are known to be of fundamental significance for the recirculation of T-cells (Hess, 1970).

Discussion

The data presented clearly indicate that the cases described in this paper represent three different primary immune disorders that, in principle, can be classified

as humoral (case 1), cellular (case 2) or combined immunodeficiency (case 3). This assumption is not only based on clinical observations and results of immunologic function tests, but also on characteristic morphologic findings.

Although classical X-linked infantile agammaglobulinemia (Bruton, 1952) is probably the best known congenital immune defect of man, it is a rare disease, much less frequent than the severe combined immunodeficiency state (Hitzig, 1974). From early infancy, patients with Bruton's agammaglobulinemia exhibit recurrent infections by extracellular pyogenic bacteria (*Pneumococcus, Staphylococcus, Meningococcus*), invariably low serum levels of all three major immunoglobulins (IgG, IgM, IgA), and lack of antibody production upon vaccination; in contrast, the cellular immune response is undisturbed (Good et al., 1968; Stiehm, 1973; Haferkamp, 1974; Hitzig, 1974). Morphologic findings are also very characteristic. The thymus shows a normal structure or changes that can be readily identified as secondary (Cooper et al., 1968; Good et al., 1968). As in case 1, lymph nodes and spleen disclose a complete absence of follicles, germinal centers and plasma cells, while the number of lymphocytes is only slightly reduced (Good et al., 1968; Good, 1973). The bone marrow, except for the absence of plasma cells is unaltered. Surprisingly, only about 50% of cases exhibit hypoplasia of the lymphatic tissues in the gastrointestinal tract (Hitzig, 1974). Nevertheless the pathomorphology of lymph nodes and spleen can be considered pathognomonic for a selective humoral immunodeficiency.

Basically, clinical as well as morphological findings in the second patient indicate a specific defect of the cellular immune system: the history of chronic mucocutaneous candidiasis, the complete absence of cellular immunocompetence as revealed by immunologic function tests, constant lymphopenia, dysplasia of the thymus, and lymphocyte depletion in lymph nodes and spleen. The presence of normal serum immunoglobulin and antibody levels and the existence of lymph follicles, germinal centers and plasma cells within the lymphatic tissues also support this conclusion indirectly. However, thrombopenia, a major clinical symptom from the very onset of the disease and cause of the lethal intracerebral bleeding, does not quite fit into this concept. Thrombopenia represents a characteristic feature of the Wiskott-Aldrich syndrome (Wiskott, 1937; Aldrich et al., 1954), an immunological disorder thought to be based on disturbances of the macrophage function (Cooper et al., 1968; Spitler et al., 1972). In particular, during the later stages of this disease, an increasing cellular immunodeficiency is frequently observed (Cooper et al., 1968; Blaese et al., 1968; Levin et al., 1970). The Wiskott-Aldrich syndrome however, in addition to recurrent infections, thrombopenia and an impaired cellular immune response, is characterized by eczema, inability to produce antibodies to certain polysaccharide antigens and low serum IgM levels (Amman and Hong, 1973; Hitzig, 1974). Since these latter symptoms were lacking in case 2, this diagnosis appears highly unlikely. A selective cellular immunodeficiency is present in the DiGeorge's syndrome, in which aplasia of the thymus is combined with aplasia of the parathyroid glands (DiGeorge, 1968). Thus, hypoparathyroidism complicates the immunologic disorder (Stiehm, 1973; Hitzig, 1973). Since our patient had a dysplastic thymus and possessed normal parathyroid glands, the DiGeorge's syndrome must also be excluded. The closest similarity, clinically as well as morphologically, seems to exist with a case reported by Nezelof (1968). In both instances,

severe lymphopenia, thymus dysplasia, lymphocyte depletion of lymph nodes and spleen, low platelet counts, but normal numbers of plasma cells and near-normal serum immunoglobulin concentrations were present. However, Nezelof (1968) did not find lymph follicles, germinal centers and Peyer's patches; immunologic function tests were not performed. Therefore, some authors do not accept this case as an example of a selective cellular immunodeficiency (pure alymphocytosis), but consider it an abortive form of the combined immunodeficiency state (Cottier et al., 1968). In contrast, findings in the second patient described here do suggest a defect restricted to the cellular immune system. Nevertheless, a major symptom, thrombopenia, cannot be explained.

Most patients with severe combined immunodeficiency exhibit profound lymphopenia (Hoyer et al., 1968; Good et al., 1968). However, more recently, it has been observed that this symptom is not mandatory (Hitzig, 1974). Similarly, case 3, although showing the clinical and morphological characteristics of the combined immunodeficiency state, had normal lymphocyte counts before allogenic bone marrow transplantation induced GvH-reaction with progressive panmyelopathia. In principle, morphologic findings in our patient are broadly comparable to those previously described by other authors (Good et al., 1968; Cottier et al., 1968; Hess, 1970; Hoyer et al., 1968; Hitzig, 1974). The presence of normal immunoglobulin levels in case 2 before any treatment (e.g. blood transfusion) indicates the a priori existence of the patient's own functionally active plasma cells. However, in case 3, such cells in the lymph nodes and spleen at autopsy may have been derived from the transplanted bone marrow. This assumption is substantiated by the observation that immunologic reconstitution with formation of near-normal serum immunoglobulin concentrations occurred after transplantation. Likewise, panmyelopathia and chronic periportal inflammation of the liver cannot be ascribed to the underlaying disease. Both kinds of lesions are known as late consequences of a GvH-reaction after bone marrow transplantation (Slavin and Santos, 1973; DeVries et al., 1968; Miller, 1968; Buckley, 1973). In contrast, all other morphologic findings in case 3 can be considered as characteristic features of the severe combined immunodeficiency state.

Acknowledgements. The clinical immunologic studies were performed by Drs H.-D. Flad and S.F. Goldmann, Department of Clinical Physiology, University of Ulm. We also thank Drs. R.J. Haas and U. Bienzle for their helpful discussion.

References

Aldrich, R.A., Steinberg, A.G., Campbell, D.C.: Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics **13**, 133–139 (1954)

Ammann, A.J., Hong, R.: Cellular immunodeficiency disorders. In: E.R. Stiehm, V.A. Fulginiti (edits.), Immunologic disorders in infants and children, pp. 236–272. Philadelphia-London-Toronto: W.B. Saunders Co. 1973

Blaese, R.M., Brown, R.S., Strober, W., Waldmann, Th.A.: The Wiskott-Aldrich syndrome. A disorder with a possible defect in antigen processing or recognition. Lancet **1968**, 1056–1060

Bruton, O.C.: Agammaglobulinemia. Pediatrics **9**, 722–727 (1952)
Buckley, R.H.: Transplantation. In: E.R. Stiehm, V.A. Fulginiti (edits.), Immunologic disorders in infants and children, pp. 591–623. Philadelphia-London-Toronto: W.B. Saunders Co. 1973
Cooper, M.D., Chase, H.P., Lowman, J.T., Krivit, W., Good, R.A.: Immunologic defects in patients with Wiskott-Aldrich syndrome. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 378–385. Baltimore: The National Foundation 1968
Cooper, M.D., Perey, D.Y., Peterson, R.D.A., Gabrielsen, A.E., Good, R.A.: The two-component concept of the lymphoid system. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 7–12. Baltimore: The National Foundation 1968
Cottier, H., Bürki, K., Hess, M.W., Hässig, A.: Pathological considerations of immunologic deficiency diseases in man. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 152–164. Baltimore: The National Foundation 1968
Fudenberg, H., Good, R.A., Goodman, H.C., Hitzig, W., Kunkel, H.G., Roitt, I.M., Rosen, F.S., Rowe, D.S., Seligmann, M., Soothill, J.R.: Primary immunodeficiencies. Report of a World Health Organization Committee. Pediatrics **47**, 927–946 (1971)
DiGeorge, A.M.: Congenital absence of the thymus and its immunologic consequences: Concurrence with congenital hypoparathyroidism. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 116–121. Baltimore: The National Foundation 1968
Good, R.A.: Crucial experiments of nature that have guided analysis of the immunologic apparatus. In: E.R. Stiehm, V.A. Fulginiti (edits.), Immunologic disorders in infants and children, pp. 3–15. Philadelphia-London-Toronto: W.B. Saunders Co. 1973
Good, R.A., Peterson, R.D.A., Perey, D.Y., Finstad, J., Cooper, M.D.: The immunological deficiency diseases of man: Consideration of some questions asked by these patients with an attempt at classification. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 17–34. Baltimore: The National Foundation 1968
Gotoff, S.P.: Neonatal immunity. J. Pediat. **85**, 149–154 (1974)
Graepel, P., Sordat, B., Cottier, H.: Das immunbiologisch aktive Gewebe. Pädiat. Fortbild. Prax. **35**, 1–12 (1972)
Haferkamp, O.: Der schutzlose Organismus. Dtsch. med. Wschr. **99**, 203–210 (1974)
Heymer, B., Niethammer, D., Haas, R., Meister, H., Haferkamp, O.: Pathomorphologic findings in severe combined immunodeficiency and reticular dysgenesia. Virchows Arch. Abt. A Path. Anat. and Histol. **370**, 151–162 (1976)
Hess, M.W.: Lymphatischer Apparat, insbesondere Thymus, in der Pathogenese der Defektimmunopathien. In: H.W. Altmann et al. (Herausg.), Handbuch der allgemeinen Pathologie, Bd. 7, Teil 3, S. 182–236. Berlin-Heidelberg-New York: Springer 1970
Hitzig, W.H.: Immunmangel-Krankheiten, Pathophysiologie und Klinik. In: H. Schwiegk (Herausg.), Handbuch der inneren Medizin, Bd. 7, Teil 1, S. 681–760. Berlin-Heidelberg-New York: Springer 1974
Hitzig, W.H.: Congenital thymic and lymphocytic deficiency disorders. In: E.R. Stiehm, V.A. Fulginiti (edits), Immunologic disorders in infants and children, pp. 215–235. Philadelphia-London-Toronto: W.B. Saunders Co. 1973
Hoyer, J.R., Cooper, M.D., Gabrielsen, A.E., Good, R.A.: Lymphopenic forms of congenital immunologic deficiency: Clinical and pathologic patterns. In: D. Bergsma, R.A., Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 91–103. Baltimore: The National Foundation 1968
Huber, J.: Experience with various immunologic deficiencies in Holland. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 53–66. Baltimore: The National Foundation 1968
Levin, A.S., Spitler, L.E., Stites, D.P., Fudenberg, H.H.: Wiskott-Aldrich syndrome, a genetically determined cellular immunologic deficiency: Clinical and laboratory responses to therapy with transfer factor. Proc. nat. Acad. Sci. (Wash.) **67**, 821–828 (1970)
Miller, M.E., Graft-vs-host reactions in man with special reference to thymic dysplasia. In:

D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 257–263. Baltimore: The National Foundation 1968

Nezelof, Chr.: Thymic dysplasia with normal immunoglobulins and immunologic deficiency: Pure alymphocytosis. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 104–112. Baltimore: The National Foundation 1968

Niethammer, D., Goldmann, S.F., Haas, R.J., Dietrich, M., Flad, H.-D., Fliedner, T.M., Kleihauer, E.: Bone marrow transplantation for severe combined immunodeficiency with the HLA-incompatible but MLC-identical mother as donor. Transpl. Proc. (in press)

Romeis, B.: Mikroskopische Technik. München-Wien: Oldenbourg 1968

Schädeli, J., Hess, M.W.: Neuere Erkenntnisse zur Frage der Pathogenese menschlicher Defektimmunopathien. Pädiat. Fortbild. Prax. **35**, 61–68 (1972)

Sellin, D., Heymer, B., Smith, Th.B., Bültmann, B., Haferkamp, O.: Streptococcal A-carbohydrate antigen in granulomata of mouse liver after intravenous injection of heat-killed group A-streptococci. Arch. Path. **90**, 17–21 (1970)

Slavin, R.E., Santos, G.W.: The graft versus host reaction in man after bone marrow transplantation: Pathology, pathogenesis, clinical features and implications. Clin. Immunol. Immunopath. **1**, 472–498 (1973)

Spitler, L.E., Levin, A.S., Stites, D.P., Fudenberg, H.H., Pirofsky, B., August, Ch.S., Stiehm, E.R., Hitzig, W.H., Gatti, R.A.: The Wiskott-Aldrich syndrome. Results of transfer factor therapy. J. clin. Invest. **51**, 3216–3224 (1972)

Stiehm, E.R.: Immunodeficiency disorders: General considerations. In: E.R. Stiehm, V.A. Fulginiti (edits.), Immunologic disorders in infants and children, pp. 145–167. Philadelphia-London-Toronto: W.B. Saunders Co. 1973

Vries, M.J. de, Dooren, L.J., Cleton, F.J.: Graft-Versus-Host or autoimmune lesions in the Swiss type of agammaglobulinemia: Their relation of a deficient development of the thymic epithelium. In: D. Bergsma, R.A. Good (edits.), Immunologic deficiency diseases in man. Birth defects original article series, Vol. IV, No. 1, pp. 173–187. Baltimore: The National Foundation 1968

Received January 22, 1977