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Pathomorphologic Findings in Severe Combined Immunodeficiency and Reticular Dysgenesia*

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Summary. Pathomorphologic findings in an 11 month old boy with severe combined immunodeficiency (case 1) and in a 4 month old boy with reticular dysgenesia (case 2) are reported. Case 1: The bone marrow exhibited regular granulo-, erythro- and thrombopoiesis. The hypoplastic thymus consisted exclusively of epithelial reticulum cells. The spleen and lymph nodes showed considerable depletion of lymphocytes in both the T- and B-cell areas. There was a complete lack of all lymphatic structures in the gastrointestinal tract and aplasia of the tonsils. Death resulted from *Candida* sepsis in conjunction with giant cell pneumonia closely resembling Hecht's pneumonia in measles. Case 2: The bone marrow showed a total lack of granulopoiesis. The strongly dysplastic thymus weighed only 1 g. The spleen, the lymph nodes and the gastrointestinal tract exhibited a very strange histologic structure resulting from a complete absence of lymphocytes and plasma cells. The tonsils were aplastic, the parathyroid glands as well as the other endocrine glands were normally developed. The cause of death was *Klebsiella* sepsis and *Pneumocystis* pneumonia, the latter without the characteristic interstitial plasma cell infiltration. The importance of the immune system for activation of the nonspecific mechanisms of defense is discussed with respect to the two types of immunodeficiency states described here.

Congenital immunodeficiencies belong to those disease states that can be described as "experiments of nature". In these instances, the total or partial defect of a vital organ system permits deductions regarding the function and morphologic composition of that system. Up to now, approximately 20 different immunodeficiency syndromes have been described (Good, 1971; Good et al., 1971; Haferkamp, 1974). Their differentiation is primarily based on clinical or functional parameters since morphologic studies have only been performed in relatively few cases. This holds particularly true for the severe combined immunodeficiencies in which patients generally die shortly after birth (Good et al., 1970; Humphrey and White, 1971). At this age, the morphologic examination of the immune system is additionally complicated by the physiologic immaturity of the lymphoreticular organs during the neonatal period (Gitlin et al., 1964; Schädeli and Hess, 1972). Since we recently observed two infants with a primary immune defect who, by treatment under gnotobiotic conditions survived for 4 and 11 months respectively, the morphologic findings will be presented here. One infant was found to suffer from a severe combined immunodeficiency (Good et al., 1971) and the other from a reticular dysgenesia, a disease hitherto reported in the literature in only three cases (De Vaal and Seynhaeve, 1959; Gitlin et al., 1964).

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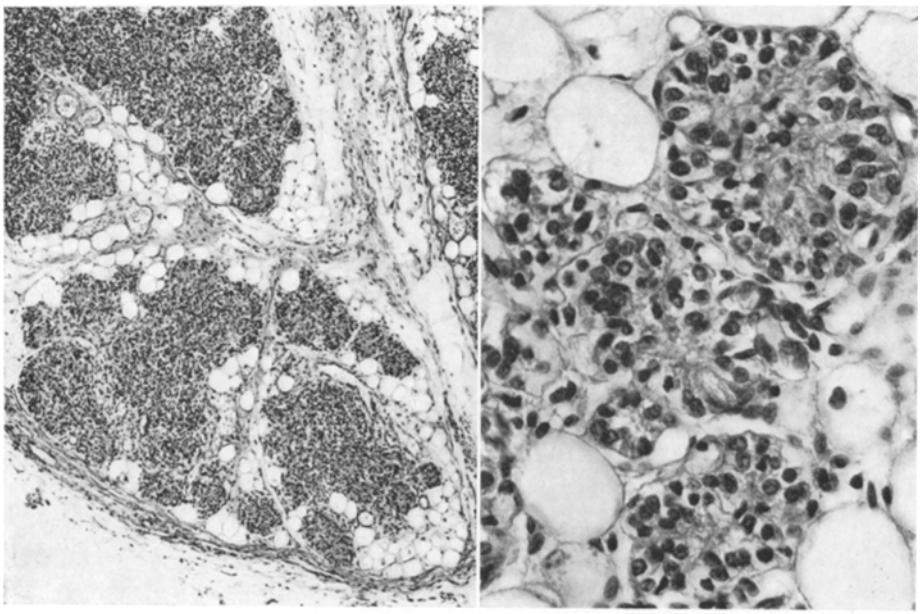
Table 1. Clinical findings

	Case 1 (Patient R.G.)	Case 2 (Patient V.V.)
Blood Cell Count		
Total Leucocytes	4,000–6,000/mm³	200–500/mm³
Granulocytes	2,000–4,000/mm³	0– 70/mm³
Lymphocytes	300–1,000/mm³	300–400/mm³
Monocytes	500–1,500/mm³	~50/mm³
Erythrocytes	4–5 × 10^6/mm³	2–4.5 × 10^6/mm³
Thrombocytes	~300,000/mm³	~300,000/mm³
Cellular Immunity		
T-Cell-Rosettes	strongly↓(4%)	strongly↓(8%)
PHA-Stimulation	negative	negative
MLC	negative	slightly↓
DNCB-Test	negative	negative
Candida-Ag-Skin-Test	negative	negative
Humoral Immunity		
Immunoglobulins	strongly↓	slightly↓
Isohemagglutinins (Anti-B)	negative	negative
Plasma Cells (Bone Marrow)	negative	negative

Clinical Findings

Patient R. G. (Case 1). The German parents of this child were healthy and unrelated to each other. A brother died from pneumonia at the age of 8 months after having been hospitalized previously several times because of severe infectious diseases. The male newborn (blood group A, Rh+) weighed 4.05 kg, was 55 cm long and exhibited all signs of maturity. At first the postnatal development was undisturbed. However, at two months of age a severe enteritis occurred and a mucocutaneous candidiasis was found on subsequent hospitalization. Shortly thereafter asymptomatic pulmonary infiltrations, totally resistent to therapy, were observed by X-ray studies. Detailed clinical examination of the child revealed a severe combined immunodeficiency as the underlying condition. Some of the findings that established this diagnosis are summarized in Table 1. The data collected repeatedly over a period of several months, conclusively indicated a severe functional disorder of the cellular as well as of the humoral immune system. There was considerable lymphopenia while granulo-, erythro- and thrombopoiesis were not disturbed. Since the child deteriorated under conservative therapy, he was decontaminated with antibiotics and fungistatics, transferred at the age of 10 months into a gnotobiotic environment and further treated under gnotobiotic conditions. However, this resulted in only a short improvement and the child finally died, aged 11 months, from pneumonia, enteritis and *Candida* sepsis. A sister of this patient, subsequently born and now 9 months of age, does not display any signs of an immunodeficiency state.

Patient V. V. (Case 2). The Italian parents of this child were related to each other (second cousins). There were no brothers or sisters. The boy (blood group A, Rh−) was born at term, weighed 2.5 kg, was 46 cm long and exhibited definite signs of immaturity. The first symptoms of disease were already apparent 5 days after birth when a severe enteritis occurred. The most prominent finding during subsequent hospitalization was a constant leucopenia of 200–500 white cells/mm³ with granulocyte counts ranging from 0 to 70/mm³. Erythro- and thrombopoiesis were not significantly diminished. Further detailed examination of the child established a diagnosis of congenital agranulocytosis with severe combined immunodeficiency. Some of the relevant clinical data, collected repeatedly, are given in Table 1. The child was decontaminated with antibiotics and fungistatics, transferred at the age of 19 days into a gnotobiotic environment and further treated under gnotobiotic conditions.



A B

Fig. 1 A and B. Thymus. Rudimentary lobules made up of epithelial reticulum cells, no lymphocytes, no Hassal's corpuscles (Case 1). HE. Magnif. (A) ×64, (B) ×400

However, in spite of the fact that all bacteria had been eliminated from the child except for *Klebsiella*, the boy died at the age of 4 months from pneumonia, enteritis and *Klebsiella* sepsis.

Morphologic Findings

Case 1

An autopsy, performed 36 h after death, revealed the following findings: the bone marrow of the 11 month old child (R. G.) exhibited a normal cellularity; granulo-, erythro- and thrombopoiesis were not reduced; however, there were only single lymphocytes and no plasma cells. The thymus was severely hypoplastic, weighing only 2 grams (corresponding average normal weight for this age is 25 grams). In addition, as evident on histologic examination, 60–70% of the thymus weight was due to fat tissue. Microscopically, the rudimentary thymus lobules were almost exclusively composed of epithelial reticulum cells (Fig. 1). Lymphocytes or thymocytes were only rarely visible. There was no differentiation into cortex and medulla, Hassal's corpuscles being totally absent (Fig. 1). The spleen, weighing 30 grams (normal weight for this age), exhibited only single scattered lymphocyte accumulations in the neighborhood of the central arterioles (Fig. 2). Intact Malpighian corpuscles, lymph follicles, germinal centers and plasma cells were not present. Because of the lack of lymphocytes in the Billroth's cords, the reticular matrix and the sinuses became more prominent (Fig. 2). The enlarged sinus endothelia and reticulum cells frequently showed phagocytosis of bacteria. Macroscopically, lymph nodes were detectable in the

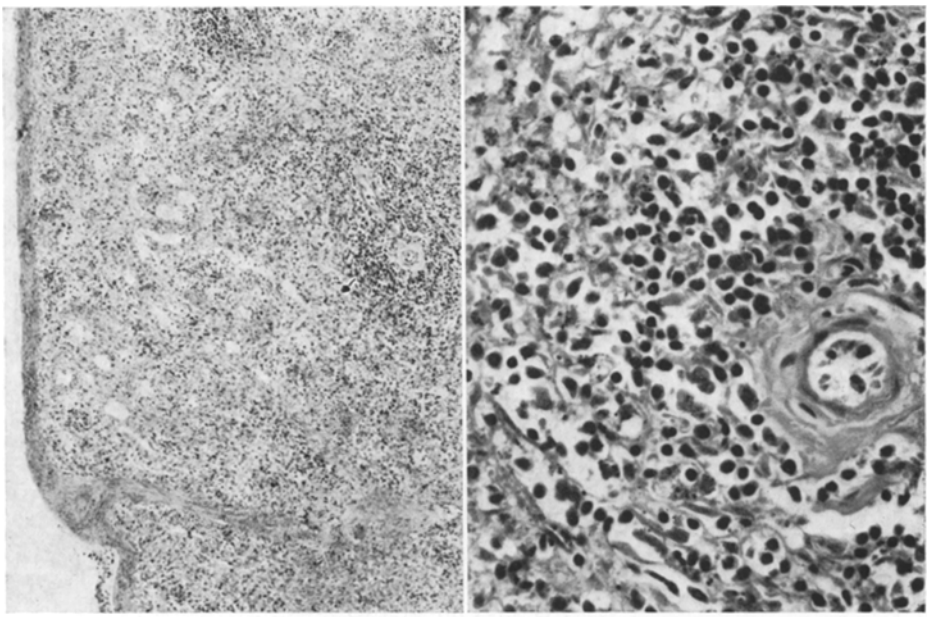


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Fig. 2A and B. Spleen. Sparse lymphocyte accumulations around central arterioles, no intact follicles, no germinal centers, no plasma cells (Case 1). HE. Magnif. (A) ×64, (B) ×400

mesenterium and close to the tracheal bifurcation. Histologically, differentiation of the nodes into cortex and medulla was lacking. Sparse cell accumulations resembling lymph follicles were occasionally found (Fig. 3). At high magnification, lymphocytes became visible diffusely scattered over the whole organ and localized within a prominent reticular matrix, germinal centers and plasma cells being totally absent. The gastrointestinal tract, including the appendix, exhibited a complete lack of all lymphatic structures (solitary follicles, Peyer's patches, etc.). Only single lymphocytes, but no plasma cells, were seen within the atrophic mucous membrane of the small intestine. In spite of the severe enteritis, resistent to any therapy and persistent until death, no inflammatory cellular infiltrations were found in the intestinal mucosa. There was aplasia of the palatinal and pharyngeal tonsils. The parathyroid glands, the thyroid gland, and the other endocrine glands showed a normal age-corresponding structure; the cortex of the suprarenals, however, was atrophied. In the liver as well as in the spleen, lymph nodes, and bone marrow, a strong activation of the reticuloendothelial elements was apparent. In addition, the liver exhibited a moderate degree of fatty change. The brain showed severe edema. There was no pathologic finding in either the kidneys or the pancreas. The heart, in particular the right chamber, was strongly dilatated.

According to our autopsy findings, the primary cause of death was a severe intraalveolar giant-cell pneumonia, involving all areas of the lungs and morphologically closely resembling Hecht's pneumonia in measles (Fig. 4). There were

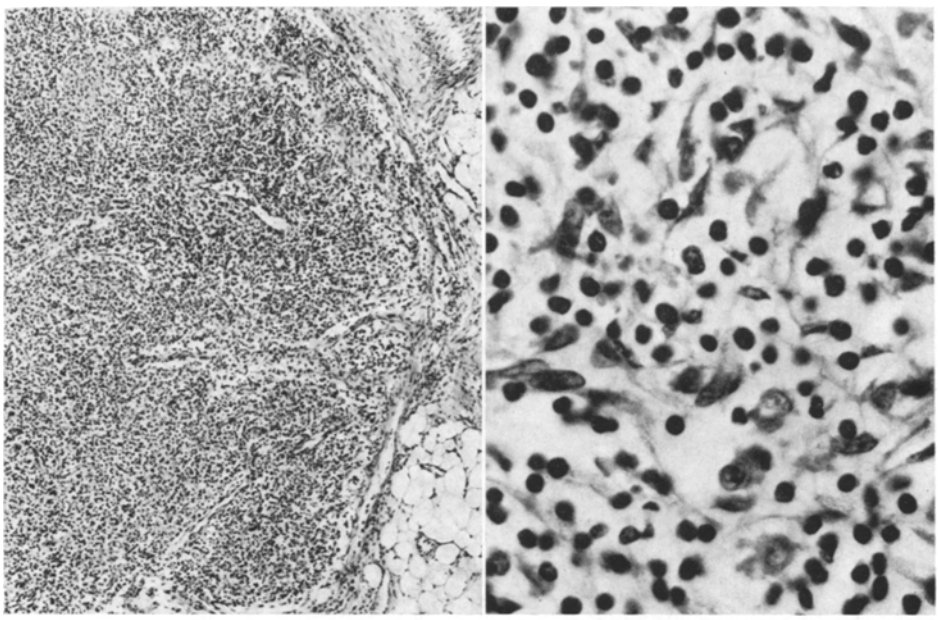

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Fig. 3A and B. Mesenteric lymph node. Lack of differentiation into cortex and medulla. Scattered lymphocytes within a prominent reticular matrix, no follicles, no germinal centers, no plasma cells (Case 1). Giemsa. Magnif. (A) ×64, (B) ×640

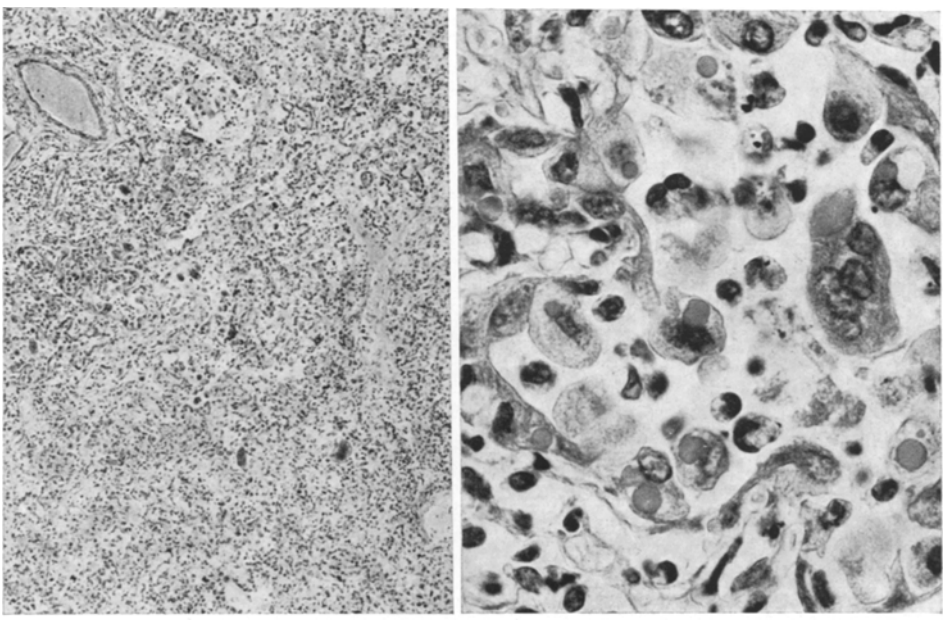

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Fig. 4A and B. Lung. Giant-cell pneumonia with intracytoplasmic inclusion bodies (Case 1). HE. Magnif. (A) ×64, (B) ×640

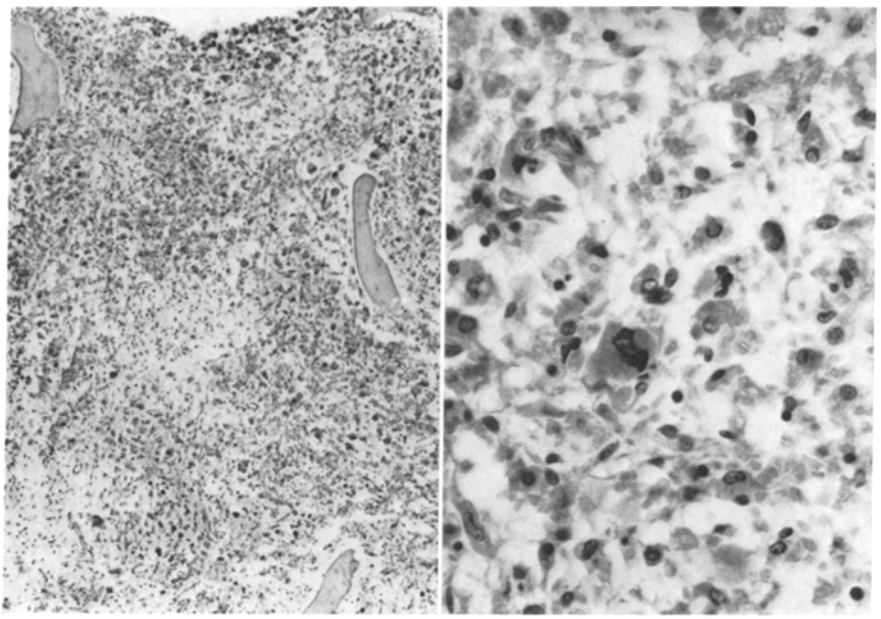

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Fig. 5A and B. Bone marrow. Complete lack of granulopoiesis. Prominent megakaryocytes and reticulum cells (Case 2). HE. Magnif. (A) ×64, (B) ×400

numerous round inclusion bodies in the cytoplasm of the mono- or multinucleated giant cells (Fig. 4). As in all other internal organs of the child, no inflammatory granulocytic, lymphocytic or plasma cell infiltrations were present in the lungs.

Case 2

At autopsy, performed 2 h after death, morphologic changes of the central and peripheral immune organs found in this 4 month old child (V. V.) were even more pronounced than in the patient just described. During his lifetime, 0–70 granulocytes per mm^3 were detectable in the peripheral blood. Correspondingly, the bone marrow exhibited a complete lack of granulopoiesis (Fig. 5). Erythropoiesis appeared to be slightly reduced but thrombopoiesis was undisturbed. There were no lymphocytes or plasma cells. The morphologic picture of the bone marrow was dominated by numerous prominent reticulum cells and megakaryocytes (Fig. 5). In this context it should be mentioned that no extramedullary hematopoiesis was found in the liver, spleen, or lymph nodes. The thymus was severely hypoplastic, weighing only 1 gram (age-corresponding average normal weight is 18 grams). Histologically, it consisted of small primitive lobules which were surrounded by broad bands of connective tissue (Fig. 6). The thymus parenchyma was exclusively made up of epithelial reticulum cells; lymphocytes or thymocytes and Hassal's corpuscles were completely absent (Fig. 6). There was no differentiation into cortex and medulla, the latter being recognizable only

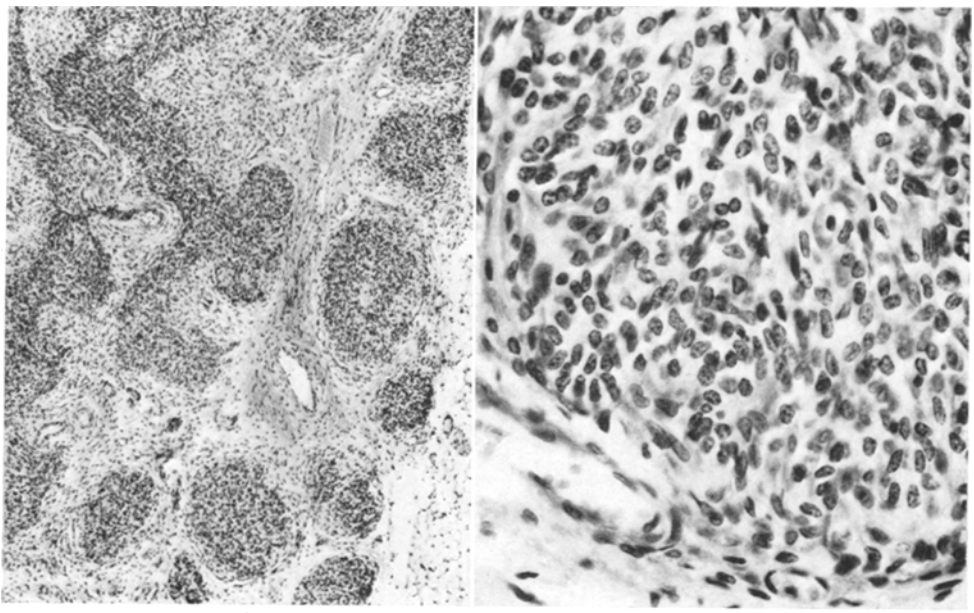

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Fig. 6A and B. Thymus. Primitive lobules consisting of epithelial reticulum cells, no lymphocytes, no Hassal's corpuscles (Case 2). HE Magnif. (A) ×64, (B) ×400

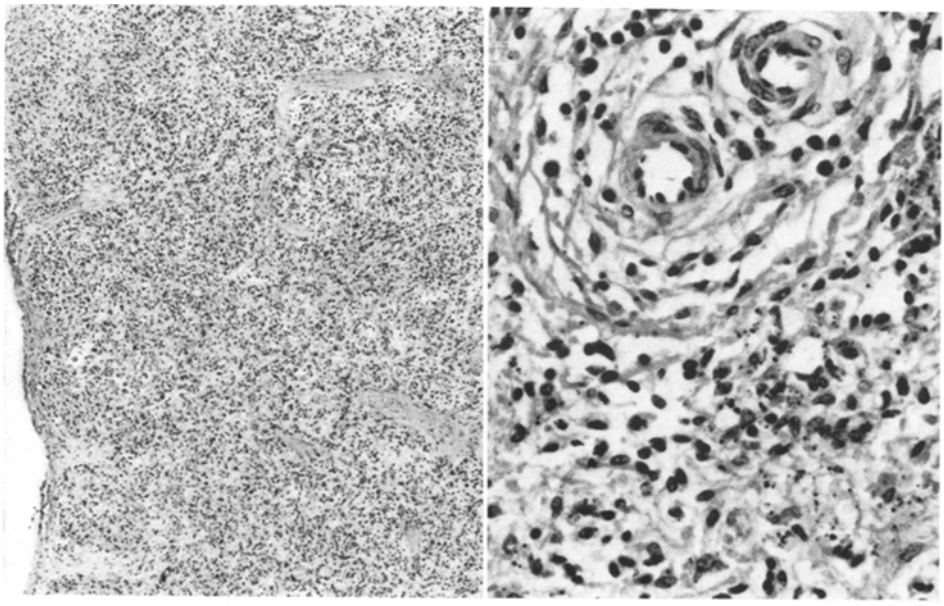

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Fig. 7A and B. Spleen. Complete absence of white pulp. Central arterioles surrounded by concentric connective tissue lamellae. Prominent reticular matrix and sinusoids (Case 2). HE. Magnif. (A) ×64, (B) ×400

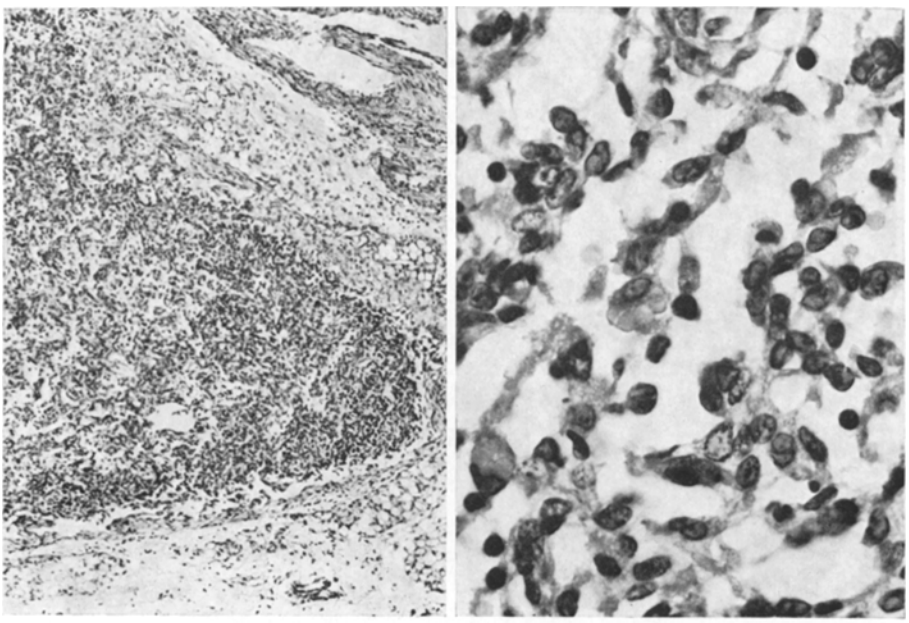

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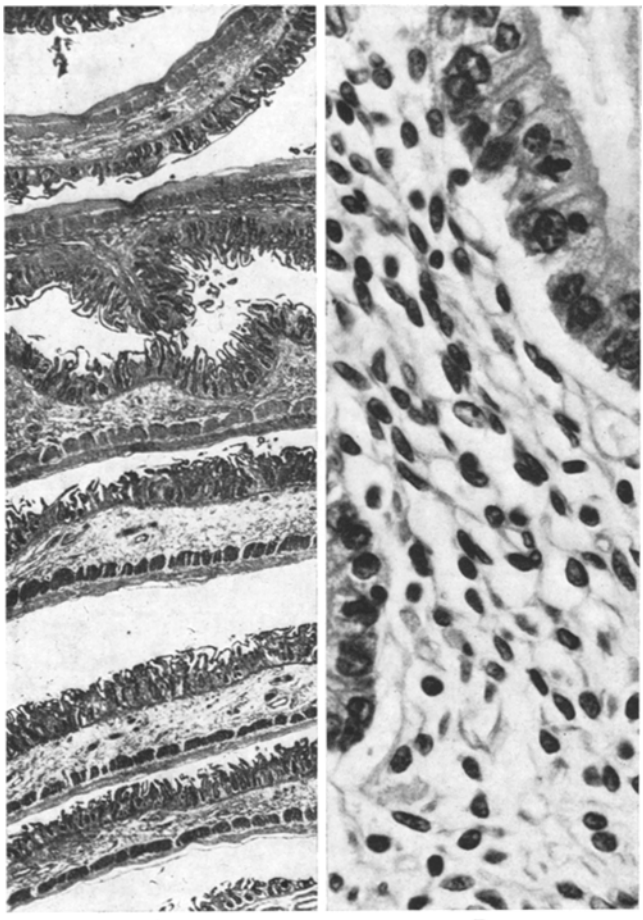
Fig. 8A and B. Mesenteric lymph node. Complete absence of lymph follicles, lymphocytes and plasma cells. Erythrophagocytosis within sinuses (Case 2). Giemsa. Magnif. (A) ×64, (B) ×640

because of the more numerous blood vessels in this region. The spleen, weighing 14 grams (normal for this age), microscopically exhibited a very strange structure (Fig. 7); the white pulp was completely absent and the central arterioles could only be identified by the onion-shell-like arrangement of their perivascular connective tissue lamellae (Fig. 7). Without lymphocytes, plasma cells, and granulocytes, the reticular matrix, the sinuses and the sinus endothelia became prominent (Fig. 7). Macroscopically, lymph nodes were not detectable. In serial sections through the mesenteric, mediastinal and cervical tissues, single small lymph nodes were found (Fig. 8). These lymph nodes did not show any differentiation into cortex and medulla and totally lacked lymph follicles, germinal centers, lymphocytes, and plasma cells. Their parenchyma exclusively consisted of the reticular matrix, the vascular connective tissue, and the sinuses. Within the sinuses extensive erythrophagocytosis was frequently present (Fig. 8). The gastrointestinal tract exhibited complete aplasia of all lymphatic structures (Fig. 9). There was considerable atrophy of the mucosa in the small intestine and strong edema of the submucosa. Neither lymphocytes nor plasma cells could be detected. In spite of the severe enteritis evident until death, no inflammatory cellular infiltrations were present in the mucous membrane of the gastrointestinal tract (Fig. 9). The pharyngeal and palatinal tonsils were aplastic. The parathyroid glands and the thyroid gland as well as the other endocrine glands did not exhibit any obvious pathologic changes. In the liver, strong activation of the reticuloendothelial system with extensive erythrophagocytosis was evident. The blood



A B

Fig. 9A and B. Small intestine. Aplasia of lymphatic structures, complete absence of lymphocytes and plasma cells. No inflammatory cellular infiltration (Case 2). HE. Magnif. (A) ×16, (B) ×640

present in the dilatated sinusoids, as in all other internal organs, did not contain any granulocytes. There were numerous septic-metastatic foci in the myocardium, consisting of a torpid necrosis surrounded by granulation tissue totally lacking any inflammatory cells. In the center of these foci a great number of bacilli was regularly present. Bacteriologically, massive growth of *Klebsiella* was found in tissue samples from the lungs, heart, liver, kidneys, spleen, and lymph nodes, collected two hours after death. The primary cause of death was a severe *Pneumocystis* pneumonia in conjunction with *Klebsiella* sepsis (Fig. 10). The morphology of this pneumonia was atypical since interstitial plasma cell infiltration, characteristic of *Pneumocystis* infection of the lungs, was not present (Fig. 10). Similar observations have previously been made on patients with immunodeficiencies (Humphrey and White, 1971; Good et al., 1971).

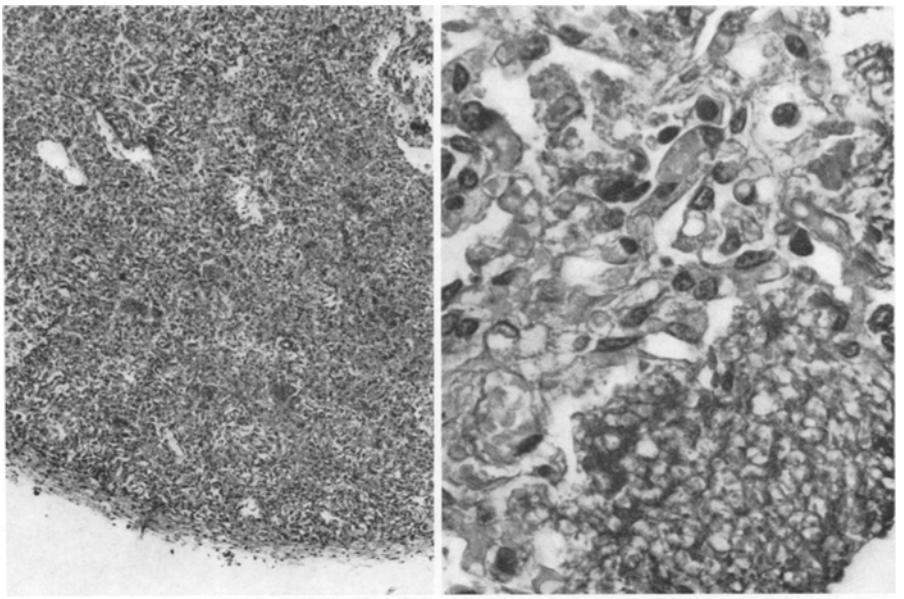


Fig. 10A and B. Lung. Pneumocystis pneumonia without interstitial plasma cell infiltration (Case 2). PAS. Magnif. (A) ×64, (B) ×640

Discussion

In both cases described here the clinical diagnosis of severe combined immunodeficiency (case 1) or reticular dysgenesia (case 2) was confirmed at autopsy by corresponding morphologic findings in the central and peripheral immune organs. Both diseases are characterized by thymus dysplasia and a defect of the humoral as well as the cellular immune systems (Humphrey and White, 1971; Schädeli and Hess, 1972). However, in reticular dysgenesia, the immunodeficiency (thymic alymphoplasia) is further complicated by congenital agranulocytosis. Consequently, not only are those mechanisms of defense mediated by lymphocytes defective but also those represented by peripheral blood granulocytes. Hence, all three children with reticular dysgenesia reported thus far died within the first few days of life from fulminating sepsis (De Vaal and Seynhaeve, 1959; Gitlin et al., 1964). Also, individuals with severe combined immunodeficiency have been observed to survive usually for only a few months (Good et al., 1971). About 3–4 months after birth, at a time when the maternal antibodies, diaplacentally transferred are eliminated, various kinds of infections occur which are frequently lethal (Humphrey and White, 1971). In the two cases described here, treatment under gnotobiotic conditions resulted in survival times of 4 and 11 months, respectively. This permitted a detailed clinical follow-up with a number of selective immunologic function tests (see Table 1) and allowed distinction between merely immature lymphoreticular tissue in the neonatal period and defective development of the immune system (Graepel et al., 1972; Schädeli and Hess, 1972).

Thymus dysplasia, an almost complete absence of white pulp in spleen, lymphocyte depletion in lymph nodes, lack of lymphatic tissue in gastrointestinal tract, and aplasia of tonsils, as observed in case 1, are the morphologic characteristics of the combined immunodeficiency state (Good et al., 1971). In lymph nodes, defective B-cell (cortical follicles) as well as T-cell areas (paracortical zone) are evident. The bone marrow does not exhibit any fundamental pathologic changes, except for the lack of plasma cells. Mucocutaneous candidiasis and virally induced (measles virus?) giant-cell pneumonia represent complications characteristic of an immunodeficiency state with thymus dysplasia; the latter primarily affects the function of T-cells which are responsible for resistance to fungal and viral infections (Good et al., 1971; Haferkamp, 1974).

Pathologic changes in the central and peripheral immune organs, as observed in case 2, can be considered pathognomonic for the morphology of reticular dysgenesia. All three cases described thus far (De Vaal and Seynhaeve, 1959; Gitlin et al., 1964) exhibited an agranulocytopoietic bone marrow, a rudimentary thymus with small primitive lobules, a complete absence of white pulp in the spleen, a lack of regular lymph node structure, and a total absence of all lymphatic tissues in the gastrointestinal tract. Furthermore, the prominence of the reticular matrix in lymphatic organs, the strong activation of the reticuloendothelial system with erythrophagocytosis in the spleen, liver, and lymph nodes, and the lack of extramedullary myelopoiesis was similarly evident. In reticular dysgenesia as well as in congenital agranulocytosis (Kostmann, 1956) normal or increased numbers of monocytes are observed (Hedenberg, 1959; MacGillivray et al., 1964; Gitlin et al., 1971). The differentiation of the hypothetical bone marrow stem cell into monocytes is apparently not disturbed. This is supported by the observation that Kupffer cells, which are most likely derived from blood monocytes (van Furth et al., 1972; Leder, 1967), found in the liver of patients with reticular dysgenesia appear to be intact. Thus, the primary lesion in reticular dysgenesia could be a defective differentiation of bone marrow stem cells into both lymphocytes (migrating into the thymus) and granulocytes. On the other hand, a selective defect in differentiation into lymphocytes is thought to be responsible for the combined immunodeficiency state (Good and Fisher, 1971).

Bacterial, viral or mycotic infections are a major aspect of all kinds of immunodeficiency states. The atypical morphology of inflammatory processes occurring in these states impressiveley demonstrates to what extent the immune system is involved in the induction of a "normal" inflammatory reaction. Both cases described here had persistent severe enteritis and pneumonia; in addition, sepsis developed shortly before death. Nevertheless, at autopsy none of the inflammatory lesions exhibited any of the cellular elements (e.g. granulocytes) characteristic of the "normal" inflammatory reaction. This statement holds true at least for the child with the combined immunodeficiency state (R. G.) who had sufficient peripheral blood granulocytes. However, these cells are apparently not mobilized into the affected areas because the complement system which possesses the execution function of most immune reactions (Opferkuch, 1975), can not be activated. Lack of complement activation results not only in failure of neutralization, opsonization, and lysis of microorganisms, but also prevents release of mediators of inflammation, such as leucotaxins, that induce immi-

gration of granulocytes. In the absence of the first line of defense, the granulocytes, the second line of defense, the pluripotent active mesenchyme (RHS), predominates. Thus, the strange morphology of inflammatory lesions as observed in the two patients described here results from a total inability to produce "normal" inflammatory reactions and a profound stimulation of the active mesenchyme.

References

Furth van, R., Cohn, Z. A., Hirsch, J. G., Humphrey, J. H., Spector, W. G., Langevoort, H. L.: The mononuclear phagocyte system: a new classification of macrophages, monocytes and their precursor cells. Bull. Org. mond. Santé, Bull. Wld Hlth Org. **46**, 845–852 (1972)

MacGillivray, J. B., Dacie, J. V., Henry, J. R. K., Sacker, L. S., Tizard, J. P. M.: Congenital neutropenia: A report of five cases. Acta paediat. (Stockh.) **53**, 188–203 (1964)

Gitlin, D., Vawter, G., Craig, J. M.: Thymic alymphoplasia and congenital aleukocytosis. Pediatrics **33**, 184–192 (1964)

Good, R. A.: Disorders of the immune system. In: R. A. Good and D. W. Fisher (Edit.), Immunobiology, pp. 1–16. Stamford, Conn.: Sinauer Ass. Inc. 1971

Good, R. A.: Immunologic reconstitution: The achievement and its meaning. In: R. A. Good and D. W. Fisher (Edit.), Immunobiology, pp. 231–238. Stamford, Conn.: Sinauer Ass. Inc. 1971

Good, R. A., Biggar, W. D., Park, B. H.: Immunodeficiency diseases of man. In: B. Amos (Edit.), Progress in Immunology, pp. 699–722. New York and London: Academic Press 1971

Graepel, P., Sordat, B., Cottier, H.: Das immunbiologisch aktive Gewebe. Pädiat. Fortbildk. Praxis **35**, 1–12 (1972)

Haferkamp, O.: Der schutzlose Organismus. Dtsch. med. Wschr. **99**, 203–210 (1974)

Hedenberg, F.: Infantile agranulocytosis of probably congenital origin. Acta paediat. (Stockh.) **48**, 77–84 (1959)

Humphrey, J. H., White, R. G.: Immunologie. Stuttgart: Georg Thieme 1971

Kostmann, R.: Infantile genetic agranulocytosis. Acta paediat. (Stockh.) **45**, Suppl. 105, 1–78 (1956)

Leder, L.-D.: Der Blutmonocyt. Berlin-Heidelberg-New York: Springer 1967

Miller, D. R., Freed, B. A., Lapey, J. D.: Congenital neutropenia. Amer. J. Dis. Child. **115**, 337–346 (1968)

Opferkuch, W., Schmidt, U.: Das Komplementsystem. (In print)

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

DeVaal, O. M., Seynhaeve, V.: Reticular dysgenesia. Lancet **1959 II**, 1123–1125

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