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THE LYMPHOID ORGANS IN CHILDREN WITH CONGENITAL CARDIOVASCULAR MALFORMATIONS

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During the daily practice of the necropsy room we were impressed by the high incidence of the heavy infectious complications, mainly pulmonary, in children with congenital cardiovascular malformations, as well as by the fact that in many cases these complications were coincident with an obvious atrophy of the thymus, as compared with its structure in healthy children of the same age. In this sense, we put to a more attentive macroscopic and microscopic examination the thymus and other lymphoid organs in such cases. Previously, one of us (*Simu* et al., 1976) proved the atrophy experimentally, sometimes irreversible of the thymus during different immune responses and discussed the possible implications of this phenomenon on the immune competence of the body.

Material and methods

The lymphoid organs (thymus, lymph nodes, spleen, digestive lymphoid structures) were studied in 50 children between O and 15 years bearing congenital cardiovascular malformations (30 males and 20 females). The thymus weight was noted and compared with Hammar's table (1926). Subsequently, pieces of this organ, as well as of the other lymphoid ones were fixed in neutral formaline or Herovici mixture and embedded in paraffin. The slides were stained with haematoxylin-eosin, van Gieson and Székely methods, Gömöri silver impregnation for reticulin fibres, Hotchikiss-Mac Manus PAS for neutral mucopolysaccharides, Brachet-Hurnick methyl | green-pyronine for nucleic acids toluidine blue and Spicer-Csaba alcian blue-safranine for mast cell granules.

Results

The following three tables show the structural state of the thymuses as well as of the other lymphoid tissues in 50 children with congenital cardiovascular malformations:

Tabel I

Thymus and lymph nodes in 50 deceased children with congenital cardiovascular malformations

	Thymus		
	Normal	Atrophied	Hypertrophied
	15	23	12
Lymphadenopathy	2	7	7
multiple	—	4	5
mesenteric	2	3	2
none	13	16	5

Tabele II

Thymus state in correlation with the age of the deceased children and the presence of the inflammatory lesions

	Thymus		
	Normal	Atrophied	Hypertrophied
Under 1 year	9	17	4
Above 1 year	6	6	8
Inflammatory lesions present	5	20	6
Inflammatory lesions absent	10	3	6

Table III

Thymus state in correlation with the nature of the cardiovascular malformation

Cardiovascular malformation	Thymus		
	Normal	Atrophied	Hypertrophied
Atrial septal defect	3	3	1
Atrial septal defect + patent ductus arteriosus	2	1	—
Ventricular septal defect	1	3	3
Ventricular septal defect + patent ductus arteriosus	1	1	—
Atrial septal defect + ventricular septal defect	—	1	1
Bilocular heart	—	2	—
Atrial septal defect + ventricular septal defect + patent ductus arteriosus	2	—	—
Patent ductus arteriosus	—	2	—
Tetralogy of Fallot	1	2	3
Transposition of great arteries	2	3	1
Common arterial trunk	—	2	—
Coarctation of the aorta	3	2	3
Pulmonary stenosis	—	1	—

Microscopic observations. The atrophic thymuses appear microscopically contracted, with enlarged interlobular spaces. The structural differentiation between the lymphicyte-rich cortex and the less cellular medulla is still maintained in moderately atrophied thymuses, but the lymphicytic density of the first structure is diminished and a starry sky pattern is several times obvious: many clear-cytoplasm histiocytes are apparent between the diminished population of lymphocytes (Fig. I). In more atrophied organs, the differentiation between cortex and medulla tends to vanish on large areas due to a partial or total disappearance of the lymphocytes. This lymphoid depletion is associated with an increased number of Hassall's corpsucles, which are larger and sometimes cystic, containing a PAS-positive material (Fig. 2). In the pericapsular tissue and in the subcapsular cortex as well, there may be seen many mast cells containing alcian blue positive but also saframine-positive granules. The latter ones are met especially in more atrophied thymuses. (Fig. 3).

When, in a few of these cases, the lymph nodes are hypertrophied, this change is due motsly to a histiocytic hyperplasia, to a sinus histiocytosis, while the lymphoid follicles are less apparent and reactive (Fig. 4). At the same time, the lymphoid follicles in the spleen or in other lymphoid structures are small and less reactive.

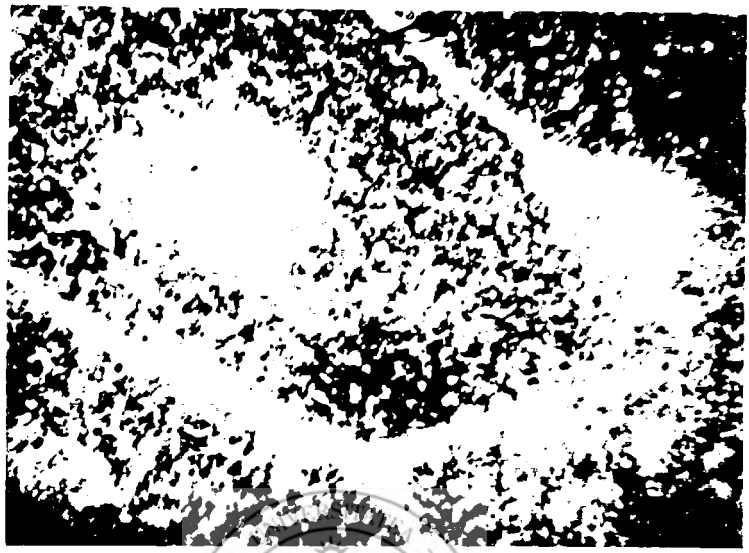

Fig. 1. Early lymphoid cortical depletion („starred sky" pattern) in the thymus of a child with congenital cardiovascular malformation deceased following lobular pneumonia. H—E, 6×10.

Fig. 2. Advanced atrophy of the thymus in a similar case. Disappearance of the cortical-medullary differentiation; cystic Hassall's corpuscles containing PAS-positive material. H—PAS, 10×10.

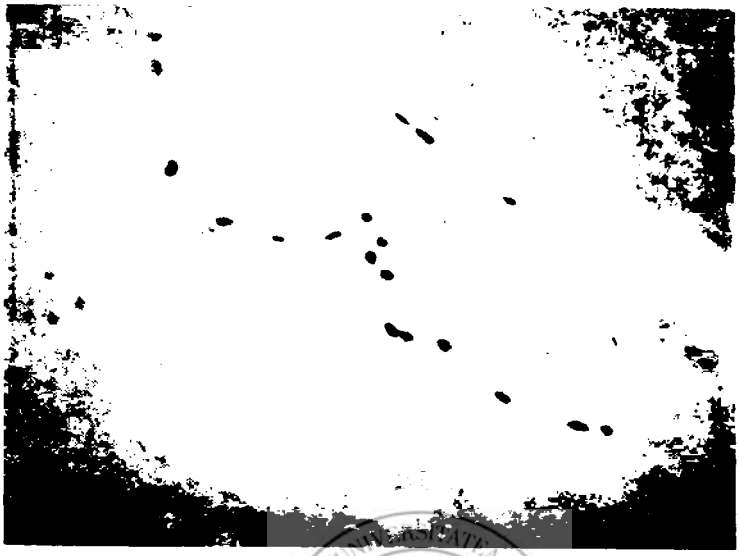

Fig. 3. Atrophied thymus cotaining numerous mast cells. Spicer Csaba alcian blue-safranine. 10×10.

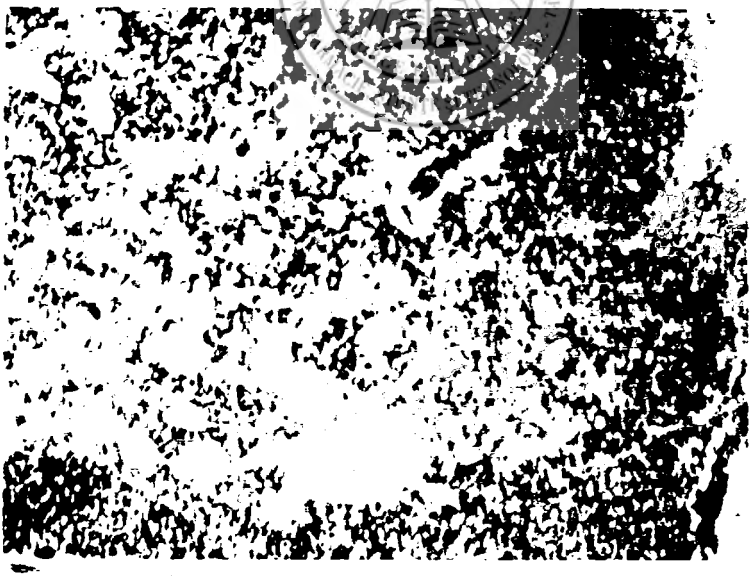

Fig. 4. Lymph node in a child with atrophied thymus: histiocytic hyperplasia with sinus histiocytosis; cortical follicles and paracortical area sligntly developed. H—E, 10×10.

In 12 children with enlarged thymus, microscopically, the thymic cortex is thick, dense, rich in lymphoid cells, Hassall's corpuscles are fewer and smaller and the mast cells are very scarce. When the lymph nodes ar hypertrophied they contain distinctly visible lymphoid follicles, with reactive germinal centres besides sinusal histiocytosis and obvious paracortical area. Well distinguished follicles may be seen also in other lymphoid structures (tonsils, Peyer's patches, appendix).

Discussion

The results show that in many cases of (23 of 50) children with congenital cardiovascular malformations, deceased usually by pulmonary infectious complications (20 of 23) an important atrophy of the thymus is manifest, associated with a hypoplasia of other lymphoid organs. When, rarely, the lymph nodes are hypertrophied, their enlargement results mainly from a histiocytic hyperplasia and in a lesser degree from a lymphoid hyperplasia. The microscopic pattern of the lymphoid tissues suggests in these cases a diminished immune response which besides the pulmonary blood stasis predisposes to pulmonary infectious complications. A certain predilection for pulmonary complications and thymus atrophy is observed in children with severe pulmonary stasis (ventricular septal defect, double septal defect including bilocular heart, common arterial trunk) (Table III).

Transient thiymus involutions in conditions related to stress, inclusively in infectious diseases are well-known for a long time *(Selye*, 1936; *Landy* et al., 1965; *Simu* et al., 1976), the organ recovering its normal structure in a few weeks. These recoveries are not always complete, the imprints of the previous involution may persist under the form of cystic lesions and fibrosis leading to a diminution of the lymphoid tissue *(Toma* and *Simu*, 1973). The last observation generates the supposition that in these little cardiac patients repeated pulmonary complications inducing successive thymic involutions could lead in the course of time to incomplete regenerations and even to irreversible thymic involutions.

The thymic atrophy is more often met during the first year of life (17 of 23 cases) permitting also the supposition that the cardiovascular malformation may be accompanied by other defects, for instance a lymphoid, in the first place a thymic hypoplasia as happens in other polymalformative conditions as well. In patients with normal or hypertrophied thymus the infectious complications are met less frequently (5 cases of 15 and 6 of 12, respectively), these patients deceasing usually by cardiac failure, in more anadvanced age. An adrenal insufficiency, predisposing to cardiovascular acute accidents has to be taken in consideration in children with hypertrophied thymuses.

The importance of the thymic atrophy is emphasized by the essential role of this organs at birth as well as during the childhood in ensuring a normal immune response. This role was supposed as far back as in 1956 by *Good* and *Zak*, in relation with the thymic hypoplasia observed in children sensible to infections and was experimentally proved by Miller (1961) by neonatal thymectomy in mice followed by heavy immune deficiency. In

the light of these observations the thymus appears as the site of T lymphocyte proliferation and maturation. Coming from the bone marrow the T lymphocyte progenitors are instructed in the thymus to recognize and to react with certain antigens, afterwards they colonize the peripheral lymphoid organs, during the perinatal period. This flux of T lymphocytes continues in a lesser degree after brith, decreasing in puberty and especially after 40 years of life *(Miller and Mitchell*, 1969).

The intimate correlation in the thymic tissue between the indigenous epithelial cells and the lymphoid intruders suggested the conclusion about the secretion by the former of certain factors responsible for the instruction of the latter. In fact, several active principles were isolated and purified from the thymus *(Milcu* et al., 1975; *Goldstein* et al., 1974; *Goldstein*, 1975; *Falchetti* et al., 1977; Bedő, 1965). They stimulate a T lymphocyte proliferation and differentiation, increase their number in lymphoid tissues and in blood, as well as their ability to produce cytotoxic and delayed hypersensitivity responses. The thymic epithelial cells secreting such principles could be identified by immunofluorescent or immunoenzymatic methods *(Aita* et al., 1984). A certain role in these events seem to have also the interdigitating cells present in the thymus as well as in the thymus dependent areas of the lymph nodes, forming, by their interdigitating prolongations, networks containing T lymphocytes *(Kaiserling* and *Lennert*, 1974).

Summing up, the thymus involution met in many cihldren with congenital cardiovascular malformations exhibiting infectious complications appears as a reason of the immunodepressive state observed in these patients. As in other pathological conditions, a vicious chain is set down, the pulmonary stasis predisposing to repeated pulmonary infections which lead to a thymus involution which increases the susceptibility to infections.

From a practical point of view, our observations argue for the necessity of an early surgical reparation of the cardiovascular defect, before this vicious chain is set down. Otherwise, an immunostimulatory treatment, aiming at the increease of the T lymphocyte functional capacity, seems to be very advisable especially preoperatively.

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