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THE THYMUS IN RHEUMATIC HEART DISEASE

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SUMMARY

Thymic biopsy specimens obtained during thoracic surgery from 113 patients suffering from rheumatic heart disease, congenital heart disease and certain other miscellaneous diseases were studied at the light microscope level.

Thymuses from patients with rheumatic heart disease showed certain changes consistent with the effects of a chronic inflammatory process, and which included in 37% of the cases, formation lymph follicles with germinal centres. The thymuses of adults with congenital heart disease showed a much lower incidence (10%) of such follicles as compared with those of children in this group, 25% of which showed this change. However, there was a relative absence of other thymic abnormalities in both children and adults with congenital heart disease. Patients suffering from a variety of other diseases, several of which are accepted as being of an autoimmune nature and in which thymic pathology is already well documented, also showed a high incidence (47%) of germinal centre formation within the thymus, and in certain instances other thymic changes.

Lymph follicles with germinal centres presumably reflect a response to antigen, and it is suggested that these structures may occasionally arise in the thymus of normal individuals, particularly children and adolescents. However, in rheumatic heart disease, the formation of increased numbers of these structures within the thymus occurring in association with the other changes described, are interpreted as reflecting a chronic inflammatory process or 'thymitis'. The possibility is discussed that this might represent an autoimmune reaction against a thymic component, and that this reaction could be triggered off by a common antigenic determinant shared with a streptococcus.

INTRODUCTION

In recent years there has been much re-awakened interest in the thymus with regard to its

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role in the development and maintenance of normal immune competence, and its relationship to disease processes associated with disordered immunological function. It has been known for some time that thymic lesions exist in patients with myasthenia gravis, thyrotoxicosis and Addison's disease (Weigert, 1901; Sloan, 1943; Castleman & Norris, 1949), and in the last decade thymic abnormalities have been described in a number of diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (Hutchins & Harvey, 1964; Mackay & de Gail, 1963), many of the immunological deficiency syndromes (Hitzig & Willi, 1961; Gitlin, Vawter & Craig, 1964; Peterson, Cooper & Good, 1965), and in haemopoietic insufficiency states (Havard & Bodley-Scott, 1960). However, the decision as to whether any thymic abnormality present is relevant to the disease under investigation is difficult, for not only does the thymus undergo normal 'age' or 'physiological' involution following puberty, but it also exhibits extensive and often extremely rapid involution in conditions of stress such as serious illness, following X-ray therapy and the administration of metabolically active steroids and radiomimetric drugs, and in pregnancy and lactation. This type of involution is called 'stress' or 'accidental' involution, is mediated through the adrenal-pituitary axis (Selye, 1936), and is due to massive depletion of the lymphoid population. In thyrotoxicosis, the thymus may show hyperplasia of its lymphoid elements without any other change, and is further evidence that endocrine control mechanisms may affect thymic structure. Failure to appreciate hormonal influences and the effects of stress, together with the fact that there is a wide variation in thymic weights at different ages (Hammar, 1926), may lead to an erroneous diagnosis of a hyperplastic, aplastic or persistent thymus. Because of this difficulty in evaluation of thymic changes in patients dying in hospital, in whom age, sex and nature, duration and treatment of the disease must be considered, and in whom there is the added disadvantage of the time lapse between death and autopsy, it was decided to investigate thymic biopsy material from patients undergoing cardiopulmonary by-pass procedures for either rheumatic or congenital heart disease. These patients formed an ideal study group for the following reasons; first, rheumatic heart disease is a condition in which autoimmune processes are thought to play some part (Glynn & Holborow, 1965) and thus of interest with regard to changes present in the thymus; second, most patients were at the time of operation relatively fit, free of infection, and not receiving treatment other than for their cardiac condition, and third, the thymic biopsies obtained from the congenital heart disease patients would serve as controls.

In addition, by also studying biopsy material obtained from patients undergoing thoracic surgery for other conditions, it was hoped to determine whether there were changes present in the thymus in chronic rheumatic heart disease which differed from those occurring in other conditions.

MATERIALS AND METHODS

A total of 120 thymic biopsies were obtained, of which 113 were satisfactory. The number obtained from patients with rheumatic heart disease (RHD), congenital heart disease CHD), and with a variety of miscellaneous diseases, is shown in Table 1. The biopsies obtained from the latter two groups were subdivided into those obtained from adults and children, since there were no children in the RHD group.

One woman with RHD and six patients with CHD also suffered from other diseases, and

therefore the biopsies obtained from these patients were placed in the miscellaneous disease group, since it was felt that the additional diseases from which they suffered were of themselves capable of inducing thymic changes. With three exceptions the thymic biopsies were performed as soon as the chest was opened, the exceptions being patients with myasthenia gravis in whom material was taken from the thymectomy specimen.

Two blocks were taken from each biopsy specimen and fixed in 10% neutral formalin and formol mercury. An average of six sections per block were cut, and stains included haematoxylin and eosin, and methods to demonstrate the presence and type of mucin secreted by the thymic epithelial cells (Henry, 1966).

TABLE 1. Distribution of thymic biopsy material

Diagnosis	No. of patients	Age (years)
Rheumatic heart disease	32	17–62
Congenital heart disease	62	
	43	1–12
	19	15–59
Miscellaneous diseases	19	
	2	7 and 11
	17	16–71

The sections were examined for the presence or absence of lymph follicles with germinal centres, changes in the epithelial cell component, the numbers of plasma cells, eosinophils and PAS cells present, and degrees of hyperplasia or involution inappropriate to the age of the patient. Mucin secretion by the epithelial cells and Hassall's corpuscles was graded quantitatively using a system of from one to four pluses, three plus and over being regarded as excessive. In all cases clinical history, treatment—in particular steroid therapy—and relevant laboratory tests were recorded.

OBSERVATIONS

Rheumatic heart disease

Typical lymph follicles with germinal centres were present in the medullae of twelve out of the thirty-two thymuses from this group of patients (Figs. 1, 2 and 3). There were usually one or two of these structures in each section, their presence was not related to the degree of 'age' involution, and in only one case (Fig. 1b) were they seen in large numbers. In four instances, these structures were the only significant finding but in the other eight they occurred in conjunction with epithelial cell abnormalities. Not infrequently they were seen with islands of epithelial cells and Hassall's corpuscles ranged around them (Fig. 3a). Changes in the epithelial cell component, present either alone or in association with lymph follicles with germinal centres were found in twenty-six out of the thirty-two RHD biopsies. The changes ranged from increased numbers of epithelial islands and slight generalized epithelial cell hyperplasia, to striking and often widespread areas of epithelium usually with formation of cysts and clefts (Figs. 3 and 4). This latter process is referred to as epithelialization. In biopsies showing lesser degrees of epithelial cell change, Hassall's corpuscles were

numerous and often cystic, but in the more advanced epithelialized glands containing cysts and clefts, Hassall's corpuscles were few in number and often absent completely as recognizable structures. Indeed, the process of cyst and cleft formation appeared to arise from

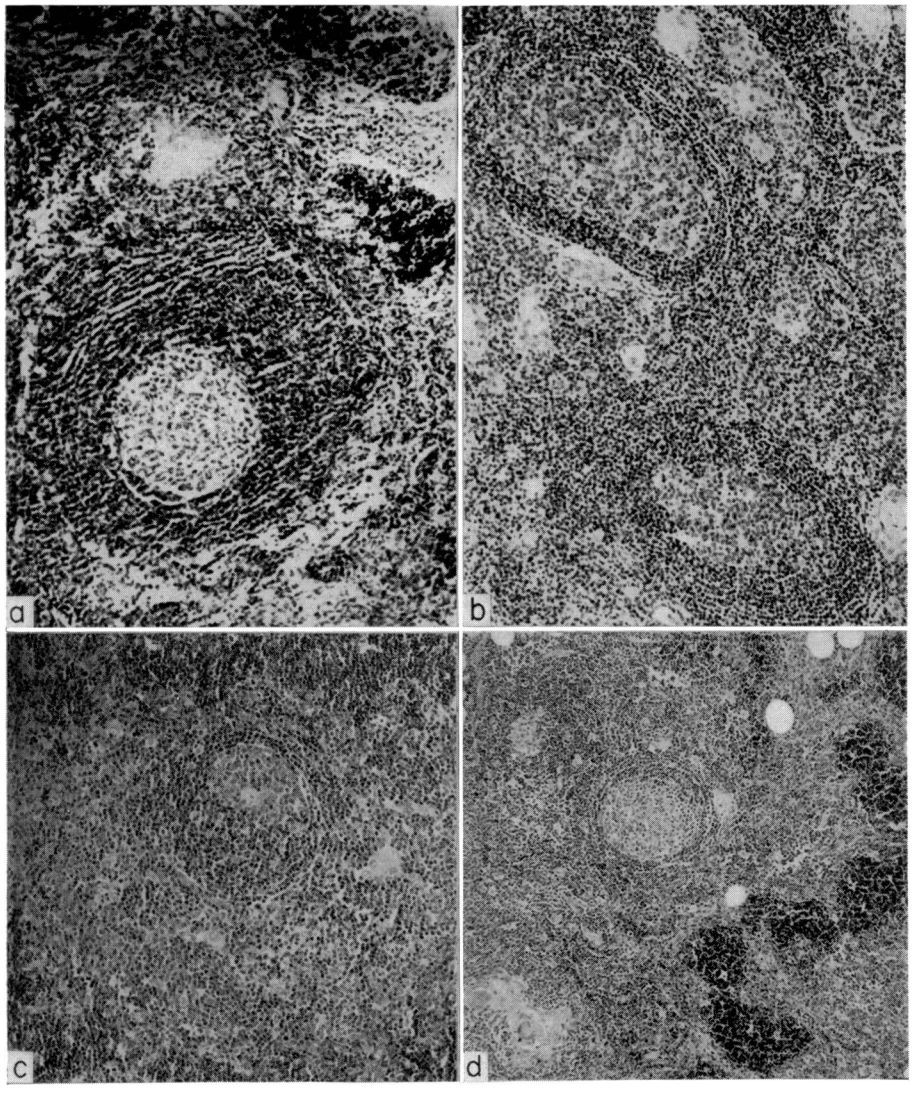

FIG. 1. Thymus from patients with chronic rheumatic heart disease, showing typical lymph follicles with well defined germinal centres in the thymic medulla. All sections stained with haematoxylin and eosin. (a) Male 39 years. × 120. (b) Male 30 years. × 110. (c) Female 27 years. × 90. (d) Male 24 years. × 58.

gradual cystic enlargement and fusion of the Hassall's corpuscles. Spindle cell change in the epithelial component was not a feature, but the epithelial areas did sometimes resemble the elongated 'archipelagos' found in thymuses of patients with SLE (Hutchins & Harvey, 1964).

In one thymus examined the entire gland was converted into a system of ramifying cystic spaces and clefts lined by squamous epithelium, the surrounding thymic parenchyma being involved in a fibrosing chronic inflammatory process (Fig. 4b). In this case too, the epithelial lining of the clefts showed infiltration with chronic inflammatory cells, and germinal centre formation was present in the few small remaining areas of recognizable thymic tissue. Occasionally the degree and character of the epithelial cell hyperplasia mimicked the appearance seen in some predominantly epithelial thymomas (Fig. 5), the abnormal epithelium showing bizarre, multi-nucleate cells but few mitotic figures. Increased mucin secretion was associated with hyperplasia of the epithelial cells and Hassall's corpuscles,

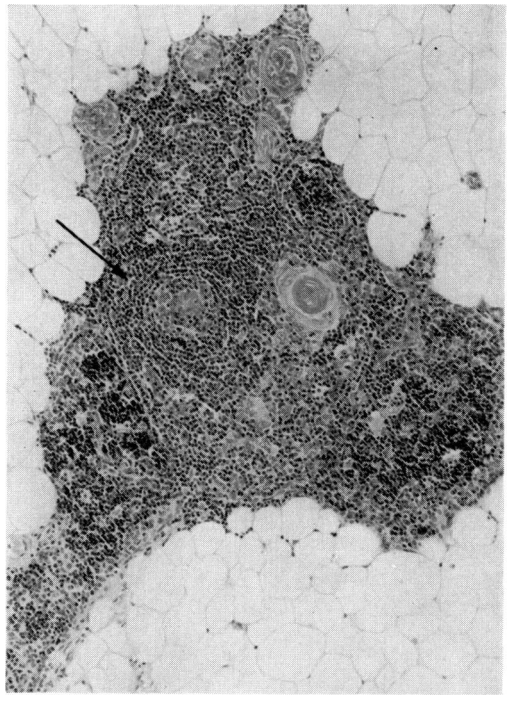

FIG. 2. Thymic biopsy from a 62-year-old female with chronic rheumatic heart disease. There is fatty infiltration due to normal 'age' or 'physiological' involution, but a lymph follicle with germinal centre (arrow) can be seen in the medullary zone of the thymic lobule. H & E, × 120.

but was diminished or absent in the grossly epithelialized glands with cysts and clefts. Increased numbers of plasma cells were invariably present in the abnormal glands in the medulla and interstitial tissues (Figs. 3 and 4). They seemed to have a particularly close association with the epithelial cell component, for they were often seen in large numbers adjacent to epithelialized areas (Fig. 4) and in the tissues surrounding cystic spaces and clefts.

Congenital heart and miscellaneous diseases

In contrast to the RHD group, only two of the nineteen adults with CHD showed the presence of lymph follicles with germinal centres in their thymic biopsies (Fig. 6). These were a woman of 27 and a man of 30 with atrial septal defect (ASD) and ventricular

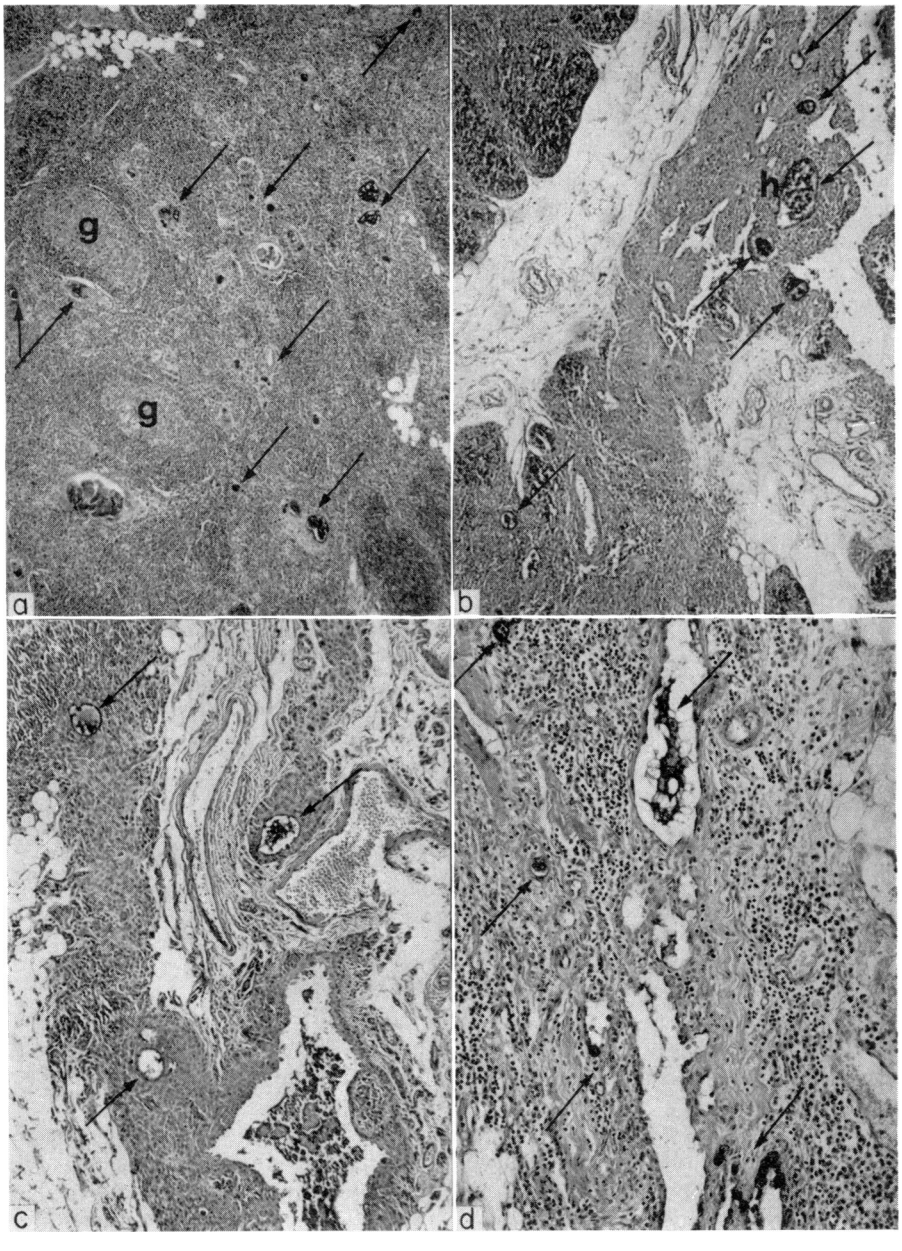

FIG. 3. Varying degrees and types of change seen in the epithelial cell component of thymuses from patients with rheumatic heart disease. The main sites of mucin secretion are indicated by arrows. (a) Thymic medulla showing increased numbers of epithelial cells and Hassall's corpuscles ranged around two lymph follicles with germinal centres (g). Mucin secretion is prominent. Male 30 years. Alcian-blue/PAS, ×45. (b) Somewhat involuted gland showing a fairly extensive epithelial area. The Hassall's corpuscles are tending to undergo cystic change (h). Female 19 years. PAS, ×63. (c) Moderately advanced epithelialization, with formation of clefts. The epithelium is becoming squamous in character, although mucin secretion is still

septal defect (VSD), respectively. However of the forty-three children with CHD as many as eleven showed this change (Fig. 6), and of these eleven five had a history of recurrent upper respiratory tract infection and tonsillitis. The follicles and germinal centres in these cases tended to be fewer in number than in the RHD groups, although there was no marked difference in the size of these structures. Thymuses from patients with miscellaneous disease showed a high incidence of germinal centre formation, this feature being present in nine out of nineteen biopsy specimens, notably three out of three biopsies from myasthenics, two out of three from patients with chronic bronchitis and asthma, two out of three from those with bronchiectasis, one out of four from cases of carcinoma of bronchus, and the one biopsy from the patient with a suspected toxic goitre (Table 2). Only in the

TABLE 2. Incidence of lymph follicles with germinal centres in the miscellaneous disease group

Diagnosis	Incidence
Myasthenia gravis	3/3
Rheumatoid arthritis	0/1
Bronchiectasis	2/3
Chronic bronchitis and asthma	2/3
Addison's disease + bronchitis and asthma	0/1
Carcinoma of bronchus	1/4
Suspected toxic goitre	1/1
Degenerative cardiac conditions	0/3

myasthenic thymuses were these structures numerous, their numbers in the miscellaneous diseases being about the same or rather less than in the RHD group. The actual number and percentage of germinal centre formation in all three disease groups is given in Table 3.

TABLE 3. Incidence and percentage of lymph follicles with germinal centres in all disease groups

	Rheumatic heart disease	Congenital heart disease		Miscellaneous diseases	
Age (years)	17–62	0–12	15–59	0–11	16–71
No. of patients	32	43	19	2	17
No. and percentage with follicles	12	11	2	1	8
	(37%)	(25%)	(10%)	(47%)	

present. Male 39 years. Alcian-blue/PAS, × 90. (d) Grossly abnormal thymus showing derangement of normal architecture. There is formation of cysts and clefts, and extensive infiltration with chronic inflammatory cells, including plasma cells. Intracellular mucin can be seen within the epithelial cells including those lining the cystic spaces. Male 30 years. Alcian-blue/PAS, × 110.

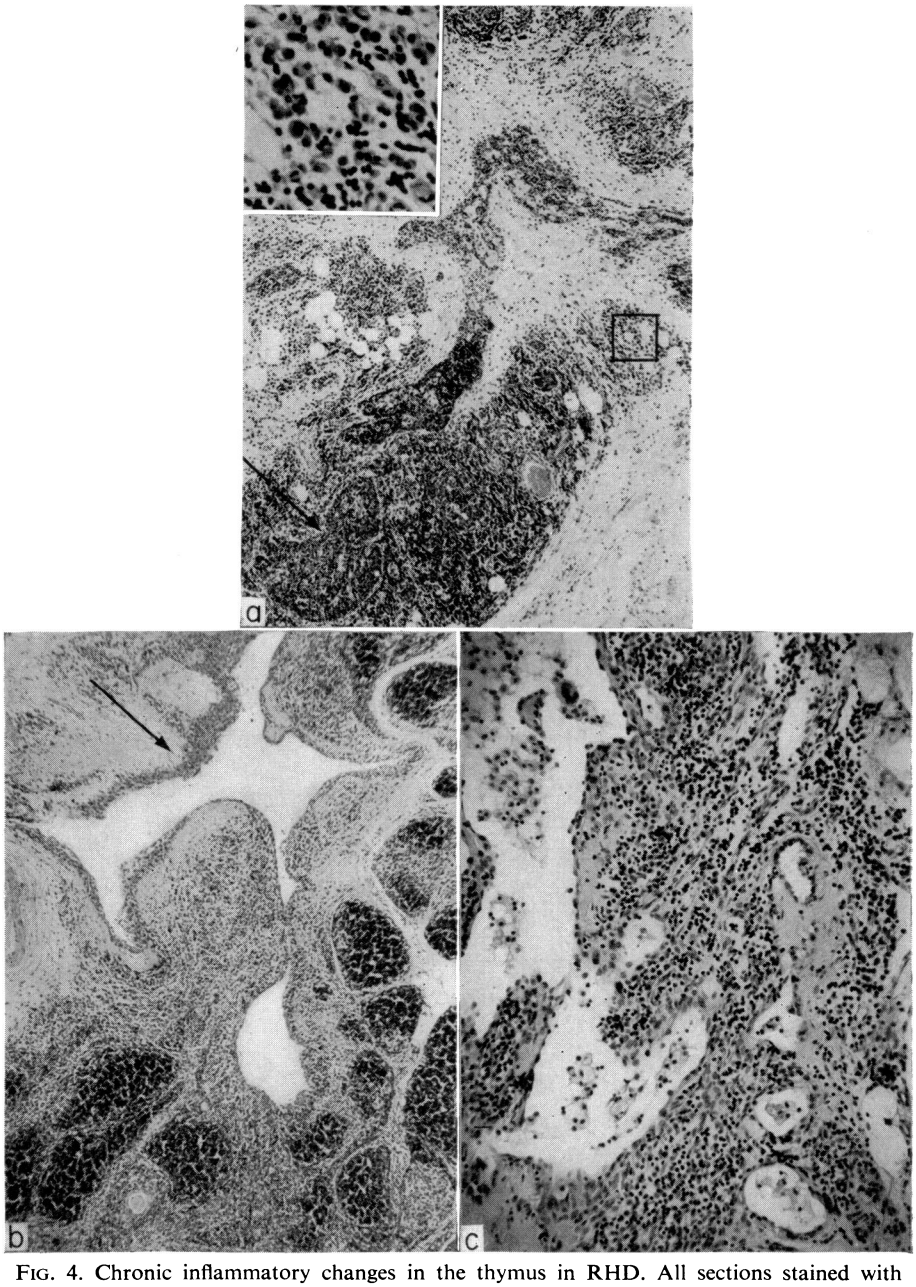

FIG. 4. Chronic inflammatory changes in the thymus in RHD. All sections stained with haematoxylin and eosin. (a) In addition to infiltration of the thymic parenchyma with lymphocytes and plasma cells, there are also aggregates of these cells (see inset) in the surrounding tissue. The well demarcated epithelial island (arrow) is somewhat reminiscent of the 'archipelagos' of epithelium characteristic of SLE. Male 42 years. × 50. (b) Same case as (a). The major part of the thymus is converted into a system of communicating cystic spaces lined by epithelium of squamous character. This abnormal epithelium (arrow) and the surrounding parenchyma show infiltration with chronic inflammatory cells and fibrosis. Aggregates of

The marked epithelial cell changes found in the RHD group (Table 4) occurred in none of the children with CHD, and in only one adult with CHD, a woman of thirty-two with

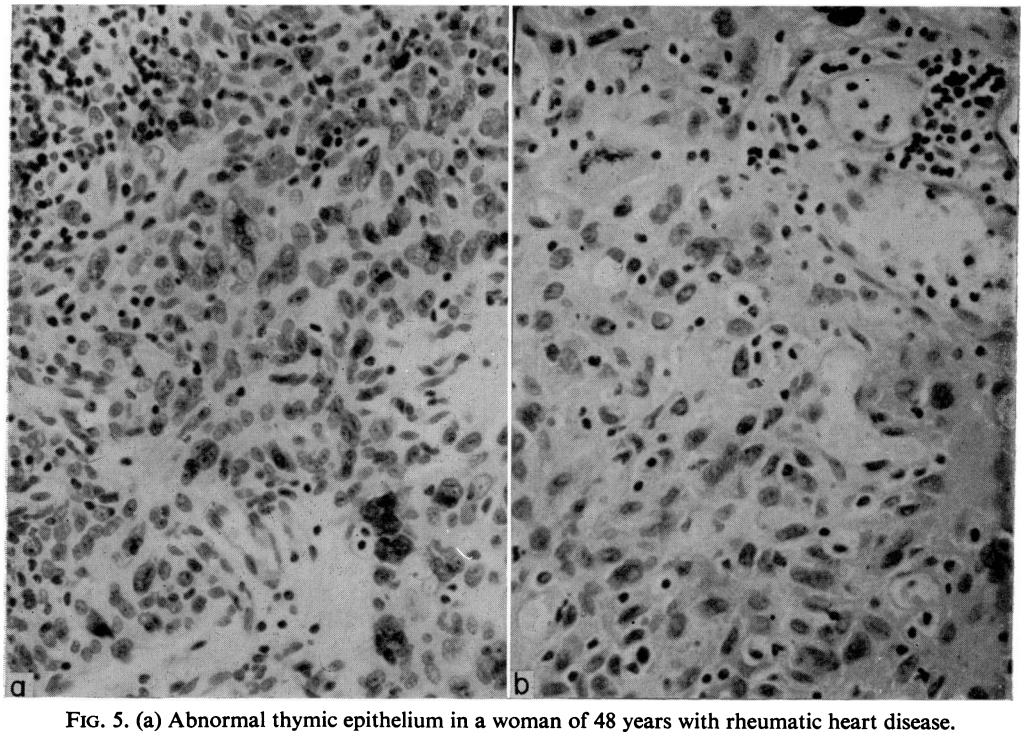

FIG. 5. (a) Abnormal thymic epithelium in a woman of 48 years with rheumatic heart disease. The epithelial cells are hyperplastic, with many bizarre multinucleate forms, but mitotic figures are few. Mucin secretion and Hassall's corpuscles are absent. H & E, × 305. (b) Section from a mixed epithelial lymphocytic type of thymoma for comparison. H & E, × 305.

sub-valvular aortic stenosis, and this patient gave a history of rheumatic fever and arthritis in childhood. In the miscellaneous disease group two biopsy specimens showed fairly extensive epithelialization but without cyst or cleft formation, and were obtained from a woman of fifty-three with a pulmonary hamartoma and rheumatoid arthritis, and a man of seventy-one with a retrosternal goitre, chronic bronchitis and asthma who was receiving steroid therapy. A slight increase in the epithelial cell component either alone or in conjunction with lymph follicles, was seen in five adults and three children with CHD, and in six of the miscellaneous disease groups (Fig. 7). Chronic inflammatory changes as evidenced by increased numbers of plasma cells and medullary lymphocytes were not observed in the non-rheumatic biopsies, with the exception of those from the 32-year-old woman with sub-valvular stenosis already referred to, a woman with ASD and suspected toxic goitre, a 16-year-old boy with saccular bronchiectasis and two of the three cases of myasthenia gravis.

lymphoid tissue are randomly distributed, there are no recognizable Hassall's corpuscles and no evidence of mucin secretion. × 50. (c) The normal cortico-medullary relations are completely destroyed. There is extensive infiltration with chronic inflammatory cells, and many cystic Hassall's corpuscles and clefted areas. Female 31 years. × 120.

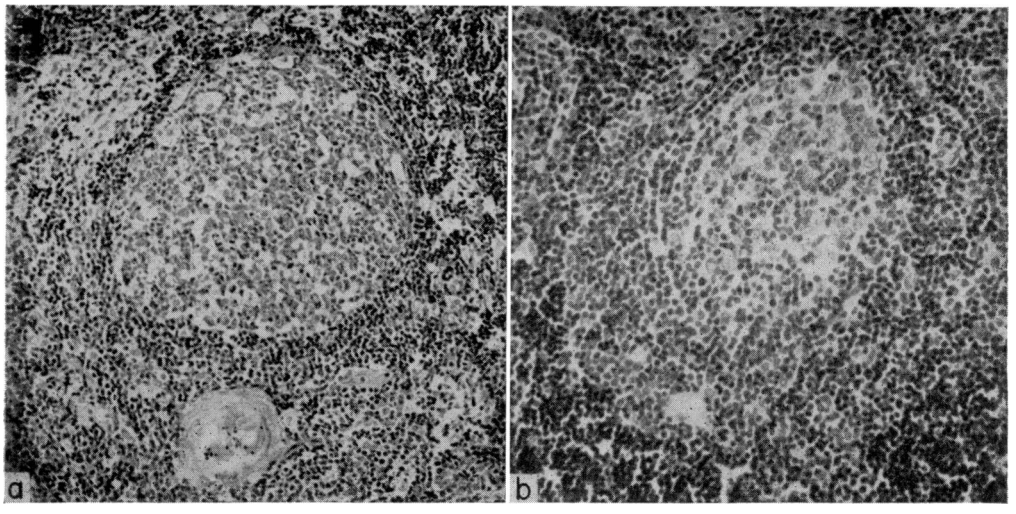

FIG. 6. Germinal centre formation in otherwise normal thymuses from two patients with congenital heart disease. (a) Child 9 years. H & E, ×140. (b) Adult 22 years. H & E, ×160.

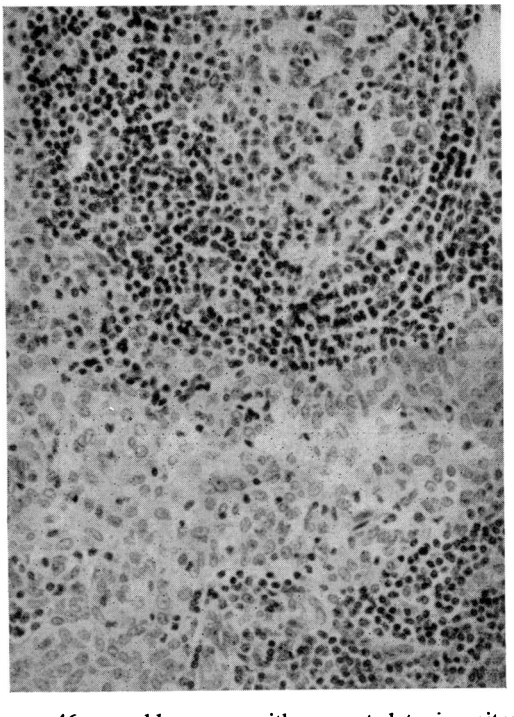

FIG. 7. Thymus from a 46-year-old woman with suspected toxic goitre showing a lymph follicle with germinal centre adjacent to an island of plump ovoid epithelial cells. H & E, ×245.

Additional findings in all disease groups

Eosinophils were present in all the biopsies except the 71-year-old man with the retrosternal goitre, chronic bronchitis and asthma who was receiving steroid therapy. The eosinophils were located mainly in the interlobular septa and medulla, but sometimes also within Hassall's corpuscles and were present in largest numbers in the thymuses from children. Both mature and immature forms were seen, and there was no correlation with germinal centre formation or epithelial cell change.

TABLE 4. Changes present in the epithelial cell component (including Hassall's corpuscles)

Diagnosis	No. of patients	Degree of epithelial change		Increased mucin secretion
		Slight	Moderate to severe	
Rheumatic heart disease	32	12	14	12
Congenital heart disease				
1–12 years	43	3	0	6
15–59 years	19	3	1	1
Miscellaneous diseases	19	4	2	4

TABLE 5. Increased mucin secretion related to germinal centre formation and epithelial cell change

Diagnosis	No. showing increased secretion	Germinal centre formation only	Epithelial cell* change only	Both epithelial cell change and germinal centre formation	No abnormality
Rheumatic heart disease	12	0/4†	7/18	5/8	0/2
Congenital heart disease					
1–12 years	6	0/10	0/2	0/1	6/30
15–59 years	3	0/2	2/6	0/0	1/11
Miscellaneous diseases	4	0/5	2/4	2/4	0/6

* All degrees.

† Number showing increased mucin secretion/number with morphological change specified.

Mucin secretion was present, though variable in amount, in all but the most severely epithelialized glands of the type seen in chronic RHD, in which the epithelium tended to be of an epidermoid character, and to be associated with evidence of chronic inflammation. From the results of a study of mucin secretion by the thymic epithelium (including Hassall's

corpuscles) the mucin was found to be an acid, probably sulphated, mucopolysaccharide (Henry, 1966), similar to other epithelial mucins. The number of thymuses in this study showing increased mucin secretion is shown in Table 4, and by reference to Table 5, it can be seen that although there is no correlation between increased secretion and germinal centre formation, there is perhaps some indication of a positive correlation with changes in the epithelial cell component. Six children with CHD however, showed increased mucin secretion in otherwise normal glands, suggesting that increased secretion *per se* may not itself be abnormal, but might represent a physiological response.

DISCUSSION

In most accounts of the histology of the human thymus, it is generally stated that lymph follicles with germinal centres do not occur. In fact Mackay (1966) states that the normal human thymus at all ages characteristically contains no germinal centres.

Germinal centre formation in this organ together with increased numbers of lymphocytes in the medulla was first described in cases of myasthenia gravis (Sloan, 1943), the incidence of these structures being about 80% in non-neoplastic glands (Castleman, 1955). Indeed, it was the microscopical appearance of the thymus in this disease and its resemblance to that of the thyroid in Hashimoto's disease that first prompted the suggestion that myasthenia gravis was of an autoimmune nature (Smithers, 1959). The subsequent observations that germinal centre formation took place in the thymuses of patients with other autoimmune diseases (Burnet & Mackay, 1962; Gunn, Michie & Irvine, 1964) including autoimmune thyroid disease led to the suggestion that this particular finding was a feature of autoimmune disease (Burnet & Mackay, 1965). Sloan (1943) however, found lymph follicles with germinal centres not only in myasthenia gravis and other conditions such as thyrotoxicosis and Addison's disease, but also in fourteen out of 150 cases of sudden death in presumed normal people. Germinal centres have also been noted in four out of twenty thymic biopsies obtained from children with congenital heart disease (Bhathal & Campbell, 1965), and recently Middleton (1967) has recorded the incidence of lymph follicles with germinal centres in seventy-one apparently healthy patients killed in road accidents as 50%, rising to 70% if only the age group 6–39 years was considered. Furthermore, he states that in 714 hospital deaths the overall incidence of these structures in the thymus was 5%, but rose to 31% in patients dying within 3 days of the onset of their illness. Middleton (1967) interprets these findings as indicating nothing more than normal immunological processes occurring in response to antigen, and in no way implying an autoimmune disease. However, it should be borne in mind that clinical details were not available in the cases of sudden or accidental death, the individuals merely being presumed to be healthy, that when these structures were present they were few in number as compared with diseases such as myasthenia gravis, and that there is no comment on the epithelial cells in these thymuses.

Germinal centres are regarded as the morphologic expression of antibody production, and their relative absence in the human thymus supports the results of various experimental procedures which show that the thymus is not normally concerned with antibody production, being rather the lymphoid centre controlling cellular immunity (Miller, 1964; Good *et al.*, 1966). Thus the presence of these structures alone in the thymus in the cases reported in this communication is of interest, although not necessarily pathological, or suggestive of the presence of an autoimmune disease, since it indicates that antibody is being produced

in response to available antigen. In completely healthy individuals it is a possibility that occasional germinal centre formation could be a normal event, since it has been amply demonstrated that the blood thymus barrier proposed by Marshall & White (1961) is by no means complete (Clark, 1964). In children with congenital heart disease, in whom in this series the incidence of these structures is 25%, a continued antigenic stimulation such as might occur in recurrent upper respiratory tract infections might be a factor, or the altered circulatory dynamics present in these heart cases might lead to increased permeability of the blood thymus barrier with the result that antigen is more accessible than under normal conditions.

In many of the miscellaneous diseases and in the rheumatic heart disease cases, the incidence of germinal centres could also be explained on this basis. However the increased number of these structures in the biopsies obtained from RHD patients, considered in conjunction with the high incidence of other thymic abnormalities, suggests that at least in this disease, other mechanisms are operating. For whereas lesser degrees of change in the epithelial cell component are only slightly higher in RHD than in the other two groups (Table 4) and could perhaps be explained on the basis of stress, the high incidence of prominent epithelial abnormalities associated with evidence of chronic inflammation is seen only in RHD. This latter finding cannot be attributed to the effects of continued stress, for some of the most severe and long-standing cases of heart failure were patients with CHD, who did not show this change. In some respects the abnormalities present in the thymuses of RHD patients resemble those found in the non-neoplastic thymuses of patients suffering from myasthenia gravis and SLE, abnormalities which are variously referred to by different authors. Mackay (1966) considers the structural changes present as being of a dysplastic nature, whereas Goldstein (1966) feels that the germinal centre formation and increased numbers of plasma cells seen in myasthenic thymuses represents a chronic inflammatory process, and that the term 'thymitis' is more appropriate. In RHD also it would seem preferable to apply the term 'thymitis' to describe the changes present in the gland. The process of chronic inflammation is visualized in the following way. Initially, within the medulla, there is active germinal centre formation, hyperplasia of epithelial cells and Hassall's corpuscles secreting increased amounts of mucinous material, and infiltration with increased numbers of plasma cells and lymphocytes. If the stimulus producing these effects continues, then eventually the thymus may be converted into the chronically inflamed lymphocyte depleted epithelialized gland with disruption of normal architecture in which the epithelium is often strikingly epidermoid in character and may show infiltration with chronic inflammatory cells. Cystic spaces and clefts are formed, but mucin secretion is markedly reduced, and in extreme cases the thymus shows the appearance of a fibrosing granulomatous process. The structural changes present resemble in many ways those characteristic of the thyroid in Hashimoto's disease or the salivary glands in Sjogren's syndrome, diseases in which autoimmune phenomena are implicated (Roitt & Doniach, 1965). This suggests that the chronic inflammatory process occurring in the thymus in chronic RHD may have an autoimmune component.

The question as to why the thymus should be involved in a chronic inflammatory process in chronic RHD remains to be answered. Possible explanations in line with current concepts of autoimmune processes are that normally sequestered thymic tissue antigens in some way become accessible to antibody forming cells, or undergo some alteration so that normal immunologically competent cells produce antibody against them. Another possibility

however, at present under investigation, is that the heart reactive antibody present in some cases of RHD might also react with thymic epithelial cells. In other words, the common antigenic determinant shared by cardiac and skeletal muscle and by some groups of streptococci, notably the group A β haemolytic streptococci (Kaplan & Meyerserian, 1962; Nakahla & Glynn, 1967) may also be present in thymic epithelial cells, in the same way that certain antigenic determinants are common to cardiac and skeletal muscle and to thymic epithelial cells in myasthenia gravis (Strauss *et al.*, 1965; Van der Geld & Strauss, 1966). Thus the thymus in susceptible individuals might be the site of an antigen–antibody reaction resulting from a streptococcal infection with subsequent formation of an autoantibody reactive against thymus constituents. It would not appear justifiable however to suggest that the perpetuation or initiation of chronic rheumatic heart disease is primarily induced by changes arising in the thymus gland.

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