The Frequency of Aschoff Bodies in Atrial Appendages of Patients with Mitral Stenosis
Relationship to Age, Atrial Thrombosis, and Season

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SMALL PORTIONS of the atrial appendage from numerous patients with mitral stenosis have been examined histologically ever since the introduction of mitral commissurotomy.1 Although many reports on this subject have been published, there is still considerable divergence of opinion on certain questions.

Mitral valvotomy is usually performed only in the absence of clinical rheumatic activity. Nevertheless, all the authors who examined biopsies from such operations have reported a definite but variable percentage of Aschoff bodies. These are generally considered to be specific lesions indicative of rheumatic activity. This lack of correlation between histologic activity and the absence of clinical signs has not, so far, been adequately explained. The histologic criteria adopted by different observers have varied greatly. There is also uncertainty whether the atrial biopsy yields tissue representative of the rest of the heart.2 Finally the relationship of rheumatic activity to atrial thrombosis and fibrillation requires clarification.3 4

Material and Methods
The clinical and histologic findings in patients with mitral stenosis who underwent valvotomy at this hospital during 1949 to 1959 have been correlated. Three hundred and sixteen left atrial appendages were obtained during surgery. The patients had all been previously studied in order to exclude clinically active rheumatic disease. The tissue received in 4 per cent formaldehyde was trimmed into blocks. The amount of material varied considerably, so that the number of blocks obtained fluctuated from 1 to 10. Usually all the tissue was embedded. All specimens were stained with hematoxylin and eosin. Seventy-five of these were also stained by Van Gieson's method for collagen, Mallory's phosphotungstic acid-hematoxylin (PTAH), toluidine blue, and the periodic acid-Schiff (PAS) technic. In addition some specimens were stained with crystal violet, by Gomori's reticulin method, by the Masson stain, and by Verhoeff's technic for elastica.

Twenty-five hearts with mitral stenosis were collected from the autopsy files of this hospital. Eight of the patients had died within 2 weeks of mitral valvotomy at which the atrial appendages had been obtained. The appendages of the other 17 hearts were examined in a similar manner. From each heart a left ventricular block was taken as recommended by Gross, Antopol, and Sacks.5

As controls the left atrial appendages from 20 necropsies were examined. These were selected so that the average age of this group was similar to that of the patients operated upon for mitral stenosis. Cases of myocarditis or pericarditis were excluded.

Results
Anatomic Observations
Aschoff bodies are very variable in appearance and therefore difficult to define. In this investigation the criteria of Gross and Ehrlich6 have been applied as far as possible. Some Aschoff cells have nuclei resembling those of the Anitschkow myocyte. Others have vesicular nuclei with prominent nucleoli. The cytoplasm is generally basophilic. An Aschoff node is formed by round or oval collections of these cells, some of which are usually multinucleated. The great majority of Aschoff bodies in this investigation were embedded in altered collagen and resembled the “mosaic” variety of Gross and Ehrlich and also the “banded” type described by MacCallum7 as characteristic of rheumatic activity in the left atrium (fig. 1). Gross and Ehrlich’s “coronal” Aschoff body was seen less fre-
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Part of large "mosaic" type Aschoff body in sub-endocardium. The endocardium is at the upper left. Hematoxylin and eosin stain.

Figure 1

Part of large "mosaic" type Aschoff body in sub-endocardium. The endocardium is at the upper left. Hematoxylin and eosin stain.

Appendages obtained at valvotomy were divided into three groups: those with Aschoff bodies, those with nonspecific granulomas, and those without either lesion. The task of separating Aschoff bodies from nonspecific granulomas was difficult. A determined effort was made to use the same criteria for this distinction throughout the investigation. Marked variation in the frequency of Aschoff bodies was observed in different blocks from the same specimen. On this account and because of the variable amount of tissue received from different patients an assessment of the frequency of Aschoff bodies in the positive specimens was not attempted. The transition from "early" to "senescent" Aschoff bodies was so gradual that subdivision into such categories seemed impracticable.

Of 316 biopsies, 130 (41 per cent) were positive for Aschoff bodies and 72 (23 per cent) showed nonspecific granulomas. The average age of patients with Aschoff bodies...
was 4 years less than that of those with nonspecific granulomas and more than 7 years less than that of patients without any inflammatory foci in the endocardium (table 1). The differences between these means were statistically significant, since they amounted to considerably more than twice their standard errors.

Organized endocardial thrombi consisting of vascularized fibrous tissue with occasional hemosiderin deposits (fig. 4) were seen in more than a quarter of all specimens (76). Collections of inflammatory cells, mostly lymphocytes and plasma cells with occasional foreign-body giant cells (fig. 5), were often seen near these areas of organization. Table 2 shows that Aschoff bodies were rare (9 of 63 or 13 per cent) in patients with atrial thrombosis. Most of these (53 of 63 or 84 per cent) also had atrial fibrillation. Patients with fibrillation were subdivided into two groups. Of those with fibrillation but without thrombosis 47 per cent (23 of 49) had Aschoff bodies in their biopsy compared with only 6 per cent (3 of 53) of those with both thrombosis and fibrillation. The difference between these groups is statistically highly significant ($\chi^2 = 22.6; p<0.001$). Therefore thrombosis and not fibrillation is the principal factor associated with a lowered incidence of Aschoff bodies. Among patients with regular rhythm only 10 had organized thrombi, too few for statistical evaluation.

Enlargement of cardiac muscle fibers and interstitial myocardial fibrosis were frequent but variable. Binucleate cardiac muscle fibers were common and occasional fibers with more nuclei could be found (fig. 6). Myocardial hypertrophy was particularly striking in specimens with organized thrombi. Mitotic figures were not seen in any muscle fibers and the shape of some of these hypertrophied nuclei was so irregular that it suggested the possibility of amitotic division. No Aschoff bodies were observed that could be interpreted as indubitably myocardial in location. The atrial appendage has such a convoluted structure that lesions that are apparently embedded in the atrial wall may actually be quite close to a pocket of endocardium.

The pericardial and subpericardial tissues contained no Aschoff bodies. Foci of lymphocytes and fibrosis were, however, seen in most specimens. Table 3 shows that in 108 of the 316 appendages the pericardial lining had undergone metaplasia and resembled cuboidal or even columnar epithelium (fig. 7). Forty-seven per cent of the specimens with this pericardial "cubing" also showed endocardial or subendocardial Aschoff bodies compared with 37 per cent of the appendages without pericardial cubing. This difference is
"Nonspecific" subendocardial granuloma. Hema
toxylin and eosin stain.

statistically not significant ($\chi^2 = 2.5 \ p>0.1$). Rather surprisingly, cubing was also seen in 40 per cent (8 of 20) of control necropsies on patients without any evidence of rheumatic disease. Cubing therefore appears to be an entirely nonspecific change, as was found previously by Enticknap.

Autopsy material was available from eight patients who died within 2 weeks of mitral valvotomy and from 16 patients who had not been operated upon. Since the average age of both groups was similar, they were considered together. In 22 of 24 cases the ventricular myocardium and the atrial appendage presented similar findings. In this autopsy series 33 per cent of patients (8 of 24) showed rheumatic activity in the left atrial appendage. This is slightly lower than the 41 per cent recorded in the biopsy series. The average age of both series was almost identical, and it seems probable that there was no significant difference in the severity of the rheumatic process in the autopsy and biopsy series. Presumably other factors such as valvular and myocardial scarring were principally responsible for the fatal outcome in patients coming to autopsy.

Erythrocyte Sedimentation Rates and Aschoff Bodies

A sedimentation rate above 10 mm. per hour was recorded as often in patients with Aschoff bodies as in those with negative biopsies. Values of 30 mm. or more were seen more frequently in patients with Aschoff bodies but numbers were too small for statistical evaluation. It is therefore concluded that in patients with mitral stenosis a moderate elevation of the sedimentation rate did not necessarily indicate rheumatic activity. Preoperative values above 30 mm., however, may suggest a greater likelihood of finding Aschoff bodies.

Aschoff Bodies in the Two Sexes

Age and sex were known in 295 patients of the total of 316. Table 4 shows that the number of female patients in this group was more than twice the number of males. Nevertheless, the percentage of biopsies with Aschoff bodies was almost identical in the two sexes. The incidence of nonspecific granulomas was also not significantly different in the two sexes ($\chi^2 = 0.6; \ p>0.3$).

Relationship of Aschoff Bodies to Age

The percentage of Aschoff bodies was highest in the youngest patients. It fell from 66 per cent in those aged 15 to 20 years to 14 per cent in patients over 55 years (fig. 8). Of 178 patients aged 40 years or less, 52 per cent had appendages with Aschoff bodies. Only 27 per cent of 117 patients aged more than 40 years had positive biopsies. This difference was statistically highly significant ($\chi^2 = 18.7; \ p<0.01$). It diminished, but did not disappear, if patients with organized thrombi were excluded.
Annual Incidence of Aschoff Bodies

The 316 atrial appendages on which this study is based were obtained during the years 1949 to 1959. During this period, the percentage of positive reports tended to diminish (fig. 9). The greatest drop occurred between 1951 (52 per cent) and 1952 (34 per cent). This fall, however, was statistically not significant ($\chi^2 = 0.9; p > 0.3$).

Seasonal Changes in Aschoff Bodies

Seasonal changes in the incidence of Aschoff bodies were also investigated (table 5). The proportion of positive biopsies was lowest in June (25 per cent) and maximal in September (65 per cent). The differences between the four quarters were statistically highly significant ($\chi^2 = 13.9; p < 0.01$). Fibrinoid change of the cardiac connective tissue showed a similar seasonal fluctuation but this did not reach statistical significance.

Discussion

The percentage of Aschoff bodies found by previous authors in atrial appendages obtained at mitral valvotomy has varied from 74 to 19 per cent. The mean percentage of biopsies with Aschoff bodies in 3,347 specimens examined by 39 previous authors was 39.2 per cent. This figure is very similar to 41 per cent, the frequency of positive biopsies in this investigation, which dealt with 316 patients.

The extreme variation in the results reported by different authors requires explanation. Chiari suggested that geographic variation of the disease might be responsible. This seems unlikely because the two groups of investigators reporting the highest and the lowest percentage of Aschoff bodies both work in the same part of the United States of America. Krymski attributed the high frequency of Aschoff bodies in his series to the examination of many sections from each specimen. This may be a factor, but Sabiston and Follis, whose percentage was even higher, examined only one section per block. It therefore does not seem likely that examination of different numbers of sections per block will account for the variation.

The disagreements among previous authors are almost certainly due to differences in morphologic criteria for the Aschoff body. Some considered fibrinoid degeneration to be the earliest precursor of an Aschoff body rather than a nonspecific lesion. Their percentage of positive biopsies was therefore high. Others employed much stricter criteria. Tedeschi, Wagner, and Pani divided atrial Aschoff bodies into "active" and "quiescent" lesions. They insisted on myofibril damage, connective-tissue alterations, and a surrounding inflammatory reaction before considering an Aschoff body to be "active." In the present investigation, connective-tissue
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Figure 7
Pericardial metaplasia ("cubing"). Hematoxylin and eosin stain.

Changes and an inflammatory reaction were found almost invariably in the presence of Aschoff bodies. Myocardial damage depended on the proximity of the Aschoff body to the atrial myocardium and not on the freshness of the lesion. The histologic criteria of Tedeschi, Wagner, and Pani for "activity" were therefore found to be inapplicable. Moreover there was little evidence that their patients with "active" lesions differed clinically from those with "quiescent" Aschoff bodies. It must be admitted that the definition of an Aschoff body remains subjective. The similarity of the percentage of Aschoff bodies in this investigation (41 per cent) to the mean of all the previously reported series (39 per cent) does, however, suggest that the criteria adopted here resemble those of most previous investigators.

In order to assess the significance of Aschoff bodies in the atrial appendage removed at mitral valvotomy it is clearly important to determine whether lesions in the atrial appendage indicate similar lesions in the rest of the heart. A few authors have expressed some doubts about this correlation. Study of material from 24 autopsies in this department and review of the literatures show that Aschoff bodies in the atrial appendage are usually accompanied by evidence of rheumatic activity in the rest of the heart. Absence of atrial lesions does not necessarily imply absence of Aschoff bodies from the ventricle.

Aschoff cells are generally considered to be of connective-tissue origin. Nevertheless Murphy recently reaffirmed his belief that Aschoff cells originate from cardiac muscle or even from smooth muscle of the endocardium. In this investigation Aschoff nodes were never found in the atrial myocardium. Hypertrophic cardiac muscle fibers, however, with two or even more nuclei were frequently seen, particularly in biopsies with organized thrombi. These specimens had a strikingly low incidence of Aschoff bodies (table 2). Moreover, Aschoff cells could easily be distinguished from other cardiac giant cells such as hypertrophic muscle fibers (fig. 6) and giant cells of foreign-body type (fig. 5). We therefore agree with the majority of previous investigators who considered the Aschoff cell to be the response of the cardiac connective tissue to rheumatism.

The significance of endocardial inflammatory lesions that do not fulfill the criteria for Aschoff bodies has been widely debated. With the exception of Saphir most of these authors considered that such lesions probably indicate some rheumatic activity. Patients with such lesions ("nonspecific granulomas")
in this series, figure 3) were intermediate in age between patients with Aschoff bodies and subjects without any inflammatory endocardial foci (table 1). There seem to be two possible explanations for this result. Either older subjects react less specifically to rheumatism or nonspecific granulomas include both rheumatic lesions no longer histologically typical and also inflammatory foci of unknown origin. After exclusion of patients with organized thrombi the age difference between subjects with nonspecific granulomas and those without inflammatory foci diminished strikingly. We are therefore in favor of the second explanation, namely that the group of nonspecific granulomas is not homogeneous and contains some rheumatic lesions and others of unknown origin.

The relationship between mural thrombosis and the degree of rheumatic activity has been discussed by many previous investigators. De la Chapelle, Graef, and Rottino found thrombosis more frequently in active carditis. Tedeschi, Wagner, and Pani could find no correlation between thrombi and Aschoff bodies in the atrial appendage. Most previous authors, however, have only rarely seen Aschoff bodies in biopsies from patients with atrial thrombosis. We are in agreement with these investigators. Rheumatic activity is well known to diminish with increasing age. The average age of our patients with organized thrombi was slightly higher than that of the series as a whole (41.5 compared to 37 years). Nevertheless, the low incidence of Aschoff bodies in the presence of thrombi remains highly significant. Most patients with atrial thrombosis also have fibrillation. Previous authors have been unable to determine whether the decreased incidence of Aschoff bodies in these patients is due to the thrombosis per se or to the fibrillation. Analysis of our results shows the Aschoff bodies are significantly less frequent in biopsies from patients with both fibrillation and organized thrombi than in those with fibrillation but without thrombi. We therefore conclude that thrombosis, rather than fibrillation, is the principal factor associated with a lowered incidence of Aschoff bodies in the atrial appendage. Presumably patients in this group form a significant proportion of those who show no rheumatic lesions in the appendage but have Aschoff bodies in the rest of the heart. The results of this study therefore agree with previous work indicating that fibrillation alone produces no histologic changes. McGoon and Henly in an autopsy study found that atrial thrombosis did not affect rheumatic activity in the ventricular myocardium. It therefore seems that thrombosis may protect the appendage by a local effect. Mechanical factors thus appear to be important in determining the site of Aschoff bodies. It seems very likely that the preferential localization of rheumatic lesions in certain parts of the heart is also largely determined by mechanical forces.
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Previous attempts to correlate the presence of Aschoff bodies with clinical activity in mitral valvotomy patients have produced contradictory results. Some\textsuperscript{10, 11, 14, 17, 32, 41} considered there was some correlation between rheumatic activity and laboratory tests. Others\textsuperscript{1, 2, 22, 26, 42} could not confirm these claims. The most popular test for rheumatic activity has been the erythrocyte sedimentation rate. The antistreptolysin titer and C-reactive protein test were also performed in some investigations. Our results agree with those who found that an elevated erythrocyte sedimentation rate is no more frequent in patients with Aschoff bodies than in those without histologic activity. From a study of the literature it seems probable that other laboratory tests presently available are not much more successful. Since absence of clinical activity is one of the criteria that must generally be fulfilled before patients are considered for operation, the failure of attempts to correlate clinical and histologic activity is perhaps not surprising.

The discrepancy between clinical and histologic features has been explained by questioning the significance of these biopsy lesions.\textsuperscript{9} Since our observations and those of others \textsuperscript{4, 20, 22, 23, 40, 51, 52} agree that such Aschoff bodies generally indicate a widespread rheumatic carditis, this explanation cannot be valid. Antibiotic and steroid prophylaxis has been considered responsible for the lack of correlation between clinical and histologic findings.\textsuperscript{11} Only 43 of our patients were known to have had penicillin or sulfonamide and 42 per cent of these had positive biopsies. Penicillin and sulfonamide were thus frequently unable to suppress histologic evidence of rheumatism. Only 10 patients were receiving salicylates or adrenal steroids. Clearly the lack of correlation between clinical state and histologic features cannot be explained by prophylaxis. Lannigan\textsuperscript{4} came to similar conclusions. Some patients received chemotherapy because of suspected clinical activity. In addition the duration of administration was often inadequate. It seems possible, nevertheless, that prevention of recurrent rheumatic fever by penicillin or sulfonamide is less effective histologically than it appears to be clinically. Cortisone or salicylates may produce better results but the number of patients in this series (10) was too small for statistical evaluation.

The morbidity due to rheumatic fever in this country is impossible to determine. Ac-

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According to the Vital Statistics Reports of the U.S.A. for 1958 the mortality for both sexes is identical (0.5 per 100,000). This suggests that morbidity of acute rheumatic fever also may not greatly differ in the two sexes. The number of female patients with mitral stenosis in this series, as in other reports, was more than twice the number of males (table 4). Nevertheless, the incidence of positive biopsies was almost identical in both sexes (42.5 per cent and 41.5 per cent). In the only large series analyzed previously for sex incidence a somewhat higher percentage of positive biopsies was found in female patients. The similarity in the proportion of positive biopsies in this study suggests that histologic rheumatic activity in patients with mitral stenosis, like the incidence of rheumatic fever in the general population, is equal in the two sexes.

The frequency of positive biopsies diminished strikingly with increasing age. Previous investigators have observed this inverse relationship. Figure 8 shows the variation with age of the percentage of positive biopsies in this series and of the incidence of acute rheumatic fever in the United States. A comparison of the two curves suggests that histologic rheumatic activity, while diminishing with advancing age, often persists for 20 to 30 years after the disease has become clinically quiescent. This conclusion, based on epidemiologic data, is similar to that reached by Bürek et al. after studying the case histories of patients submitted to valvotomy.

During the period covered by this investigation, the percentage of positive biopsies fell slightly (fig. 9). During the same period, the indications for mitral valvotomy were widened. Older patients were operated upon and a history of peripheral embolism was no longer considered a contraindication. The average age of patients submitted to the operation therefore rose from 26.5 to 38.5 years. This rise in average age and the increase in atrial thrombosis are probably sufficient to account for the fall in the percentage of positive biopsies. There thus seems to have been no significant change in the percentage of positive biopsies during the past 10 years. While there has been a considerable fall in the mortality from acute rheumatic fever, the number of patients admitted to this hospital with the disease fell only slightly—from 46 in 1950 to 35 in 1958. If it is accepted that these Baltimore figures reflect the incidence of acute rheumatic fever in the U.S.A., then it becomes probable that the marked fall in mortality has not been accompanied by a corresponding decrease in the incidence of the disease.

Investigation of seasonal changes in the percentage of positive biopsies (table 5) showed that the proportion of positive biopsies was lowest in June (29 per cent) and maximal in September (65 per cent). The mean age of patients operated upon did not change significantly from month to month. This seasonal variation in the percentage of Aschoff bodies suggests that in patients submitted to mitral valvotomy the rheumatic process is intermittently active in spite of the absence of clinical signs. Previous authors found no seasonal trend. Their series were, however, smaller, and the study of McNeeley, et al. was based on observations at two hospitals where histologic criteria may have differed. Acute rhei-

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Table 5
Changes in the Proportion of Positive Biopsies Obtained at Valvotomies Performed in Different Months (316 Patients)
matic fever is well known to have a seasonal incidence. In this investigation the admission dates of 193 patients admitted for acute rheumatic fever to several Baltimore hospitals during 1956 to 1959 were used to estimate the seasonal incidence of the disease. As in a previous report the greatest number of patients with acute rheumatic fever was admitted to the hospital during April. The month with the highest percentage of positive biopsies thus lags approximately 5 months behind the maximum incidence of the onset of the disease (fig. 10). This interval of 5 months appears to represent the average age of Aschoff bodies in the atrial appendage of our valvotomy patients. Gross and Ehrlich and McKeown estimated, by clinicopathologic correlation, the total life span of an Aschoff body to be 6 to 9 months. The conclusion that the Aschoff bodies dealt with in this investigation have a mean age of 5 months is thus consistent with previous work.

It is concluded that rheumatic activity continues in many patients with mitral stenosis long after presently available laboratory tests have become negative. In addition, we have shown that the histologic process in such patients undergoes seasonal exacerbations. We consider that these results establish the concept of a "subclinical" rheumatic process, which has been postulated by many previous investigators.

Summary

Three hundred and sixteen biopsies of atrial appendages obtained at mitral valvotomy were studied histologically. They were divided into those with Aschoff bodies (41 per cent), those with nonspecific granulomas (23 per cent), and those without either lesion. These findings were compared with those of previous investigators.

A study of 24 hearts with mitral stenosis and survey of the literature showed that Aschoff bodies in the left atrial appendage are usually accompanied by similar lesions in the rest of the heart.

The average age of patients with Aschoff bodies in their atrial biopsy was 4 years less than that of those with "nonspecific granulomas" and more than 7 years less than that of patients without inflammatory foci in the endocardium. The etiology of "nonspecific granulomas" is discussed.

Aschoff bodies were rare in patients with organized atrial thrombi, most of whom were fibrillating. Statistical analysis showed that thrombosis rather than fibrillation was the principal factor associated with a lowered incidence of Aschoff bodies. It was concluded that mechanical factors may determine the localization of rheumatic lesions in the heart.

Elevated sedimentation rates were recorded as often in patients with negative biopsies as in those with Aschoff bodies.

The percentage of positive biopsies fell from 66 per cent in patients aged 15 to 20 years to 14 per cent in patients aged over 55 years. The age incidence of Aschoff bodies has been compared with that of acute rheumatic fever, which is rare after the age of 15 years. It is concluded that in patients with mitral stenosis, histologic activity may continue for 20 years or more in the absence of clinical signs and symptoms.

The proportion of positive biopsies was lowest in June and maximal in September. This seasonal change suggests that the histologic process is only intermittently active. The seasonal variation in the percentage of Aschoff bodies is discussed in relation to the seasonal incidence of acute rheumatic fever.

Our results appear to establish the concept of a "subclinical" rheumatic process which has been postulated by many previous investigators.

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