# STUDIES ON RHEUMATIC CARDITIS

## WITH SPECIAL REFERENCE TO SUB-CLINICAL RHEUMATISM.

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in which is included an experimental attempt to produce rheumatic lesions in rabbits.

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A Thesis for the Degree of Doctor of Medicine
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"She has a fibrosed mitral valve, her ventricles are not enlarged, there is no fever or other toxic symptom, neither is there any past or present manifestation of active rheumatic infection of the joints, brain, etc., yet I should be wrong if I were to assure myself that there is no active infection."

Coombs, Rheumatic Heart Disease,
Bristol, 1924, p. 295.

# C O N T E N T S.

## Volume I.

Volume II.

Illustrations, Graphs and Tables.

# INTRODUCTION.

The development of surgical treatment for mitral stenosis has provided the histologist with an opportunity of examining the left auricular appendages from patients with rheumatic heart disease while the patient is still alive. Since 1951 numerous reports have appeared from various centres on the incidence of active rheumatic lesions in these biopsy specimens. The histological criteria used in the diagnosis of active rheumatism have varied from author to author and the reported incidence ranges from 2 per cent (Tedeschi et al, 1955) to 74 per cent (Sabiston and Follis, 1952). The finding of active lesions was surprising since the patients selected for valvotomy had been carefully investigated and were believed, on clinical grounds, to be quiescent. In addition, the reported incidence of lesions in patients subjected to valvotomy was often much higher than in autopsy series of patients with rheumatic heart disease who showed no clinical evidence of activity in their final illness. To add to the difficulties of interpreting the results of the valvotomy series there has not been until recently any information on the incidence of rheumatic lesions in the left auricular appendage in post-mortem series of rheumatic heart disease. Information was available on the incidence of active lesions in the left

atrial wall (Von Glahn 1926; Gross 1935; Lendrum 1941; Koletsky 1945) but no detailed study of the left auricular appendage had been published except a specially selected series by Graef et al (1937) in which the relationship of thrombosis and active rheumatism was studied. More recently other series have been described by Kuschner and Levieff (1953), Thomas et al (1953) and McKeown (1953).

Mitral valvotomy is now a very common operation in the United Birmingham Hospitals and to date 340 cases have been available for study. The material obtained is fresh and it provides an opportunity of studying the rheumatic process before autolytic changes have occurred.

The first object of this thesis is to describe the left auricular appendages in patients subjected to valvotomy and to compare them with a post-mortem series of cases of rheumatic disease of the heart and with a control series of non-rheumatic hearts. Special attention has been directed to the changes in the collagen and to the changes in the spaces between the fibres described as "mucoid oedema" in the older literature. From these studies it has been possible to show that the exudative degenerative phase or the "pre-Aschoff nodule" stage in the development of rheumatic lesions in the heart is readily recognised in a number of the biopsy specimens and this is put forward as evidence that sub-clinical rheumatic fever is an entity.

In recent years an extensive literature has

accumulated about the intermediate substances in connective tissues and the disturbances in these elements in a group of diseases now known as the "collagen diseases". A histo--chemical investigation has been made of these changes in rheumatic disease and chemical estimations of the ratio of mucopolysaccharide to collagen have been carried out in auricular appendages.

From these studies it has been possible to derive certain criteria for the diagnosis of rheumatic lesions and to describe a possible cycle of development and retrogression of these lesions which has not been stressed in the literature.

The second object has been to prepare a clinico-pathological correlation of the valvotomy series and compare it with a post-mortem series of rheumatic heart disease comparable in age and valvular lesions. This has been done in an attempt to answer the following questions:-

a): What factors explain the difference between the high incidence reported in valvotomy cases and the low incidence in most post-mortem series?

b): Are there any clinical or laboratory tests in common use by which a positive diagnosis of active rheumatic disease could be made in patients subjected to valvotomy?

c): Is the selection of patients in the valvotomy series too narrow to permit the application of any results obtained in this series to rheumatic fever in general?

The third object has been to examine tissues other than the left auricular appendages from patients undergoing valvotomy to determine if any alteration can be detected in the collagen or the tissue spaces in situations other than the heart. This has been carried out in view of the fact that in acute rheumatic fever lesions are found in other situations e.g. joints, blood-vessels and sub-cutaneous tissues. In addition to these focal lesions Bywaters et al (1951) and Ansell et al (1953) have shown an alteration in the behaviour of the spreading factor in the skin of patients suffering from acute rheumatic fever and have postulated a diffuse alteration in the connective tissues. The cardiac surgeons have collaborated by providing skin and muscle from the chest wall of a group of sixty patients undergoing valvotomy.

The fourth object has been an attempt to produce rheumatic fever experimentally in rabbits. In view of the changes found in the mucopolysaccharides of the connective tissues, an experiment was designed in the light of two groups of observations which have been described by other workers.

Glynn and Holborrow (1952a) reported that antibodies could be produced to various plant polysaccharides, e.g. agar and sodium alginate by incubating Group A beta haemolytic streptococci with these substances and injecting them into animals. They later reported that antibodies

could be produced by a similar method to chondroitin sulphate, an animal mucopolysaccharide (1952b).

Prior to this, Murphy and Swift (1949) described the production of rheumatic like lesions in the hearts of rabbits by repeated intra-dermal injections of living Group A beta haemolytic streptococci, injections of different types of these organisms being carried out monthly over a prolonged period. This work has been confirmed by Kirschner and Howie (1952).

The design of the experiment was to combine the work of these investigations. The full experiment is described in Chapter 13, but a brief resumé is given at this stage.

A group of rabbits received intra-dermal injections of Group A beta haemolytic streptococci which had been incubated in chondroitin sulphate. Half of the animals were injected with living organisms and the other half with heat-killed organisms. Injections were made in increasing doses at intervals of 3 or 4 weeks. Control groups received injections of similar types of streptococci which had not been incubated with chondroitin sulphate.

At the beginning of the experiment the supply of chondroitin sulphate was very limited. Later a further supply of the same material was obtained and the experiment of Glynn and Holborrow (1952b) was repeated.

The results of these experiments were negative. Antibodies to chondroitin sulphate were not demonstrated.

Myocarditis was observed in a proportion of rabbits receiving intra-dermal injections but the majority of the lesions did not resemble rheumatic lesions.

## DEFINITIONS.

Some of the disagreements in the interpretation of lesions in valvotomy specimens are due to the terminology employed and for the purpose of description a few definitions are required. The validity of defining the terms in the following manner will be discussed more fully at a later stage.

For the purpose of this thesis the basic assumption is made that mitral stenosis in the adult is the result of rheumatic heart disease. It is generally accepted that rheumatic fever is a specific disease although it has been suggested that the disease is one in which different aetio--logical factors give rise to a similar histological pattern. All the lesions in the cases examined conform to the types described for rheumatic fever in the past and no evidence has been found to suggest a different disease.

The disease known as rheumatic fever shows a great variation in symptomatology and also in its histological appearances, depending partly on the stage at which the disease is seen and partly on other factors which have not yet been elucidated. Rarely the disease is of sufficient intensity to kill in its first attack. Sometimes chorea is the first manifestation and cardiac damage appears some time later. In some patients there is no history of an

acute attack of rheumatic fever or chorea but valvular disease of the heart is detected on clinical examination.

Acute and sub-acute rheumatic fever (or rheumatism) are here used in the clinical sense to indicate the disease or the stage of the disease which may arise abruptly, accompanied by fever, "toxicity" and carditis, sometimes associated with an acute flitting arthritis, chorea, subcutaneous nodules or certain skin eruptions. The division between acute and sub-acute is arbitrary depending on the severity of the disease or on the time the attack lasts. In this group, there is a definite constitutional upset in addition to the local effects on the heart. The term is applied to first or recurrent attacks of rheumatic fever.

Sub-clinical rheumatic fever is here used to indicate a variety of the disease which arises insidiously without any overt acute or sub-acute attack, or as a continuation of the rheumatic process in a patient who has had previous acute or sub-acute rheumatic fever, evidence of constitutional upset being absent in both groups, i.e. a carditis is present which is not causing general symptoms.

The term "chronic" as applied to rheumatic heart disease is frequently used in at least two senses, (1) to indicate progressive damage to the heart due to attacks of acute or sub-acute rheumatic fever occurring in close succession or due to sub-clinical rheumatism or (2) to indicate the end result of the disease i.e. fibrosis of the

myocardium and valvular deformity along with the symptoms of cardiac failure, pulmonary hypertension etc., which are believed to be the result of previous rheumatic damage.

In this thesis the term chronic rheumatic carditis is used in the latter sense and one of the conclusions reached is that a large proportion of patients diagnosed as chronic rheumatic carditis are suffering from sub-clinical rheumatic fever.

"Active" rheumatism will here be used in a histological sense and denote a tissue process detected on microscopic examination, presumed on the basis of changes described by previous workers and my own observations to be character--istic of the disease "rheumatic fever". The term is used in a dynamic sense to indicate all stages in the develop--ment of the process until the obvious scarring stage. In the classification of previous workers it includes the stages before the development of the "Aschoff nodule" and the Aschoff nodule itself at least until the fibrillary stage. This term "active" rheumatism therefore includes the changes found in acute, sub-acute and sub-clinical rheumatic fever but excludes these found in chronic rheumatic carditis.

"Ground Substance" has been used in the past to denote two components of connective tissues which may or may not be the same. The term is sometimes used to denote (a) the material within the collagen fibre which binds the fibrils together i.e. the cement substance as Maximow and Bloom

(1952) describe it or (b) the substance in which all the cells and fibres of the connective tissues are embedded. Klemperer (1953) believes the latter is synonymous with the term "tissue spaces".

Even if the material within the collagen fibre proves to be the same as the material between the fibres and cells, from the viewpoint of descriptive histology it is necessary to draw a distinction.

In this thesis if the term "ground substance" is employed it will be used to denote the material between the fibres and cells. The material within the fibre will be called the cement substance.

## CHAPTER 1.

## HISTOLOGY OF THE LEFT AURICULAR APPENDAGE IN NON-RHEUMATIC AND RHEUMATIC HEARTS.

175 left auricular appendages removed during mitral valvotomy were used in this study.

Only one fresh surgical specimen of left auricular appendage from a non-rheumatic heart was available as a control. This specimen was removed during pneumonectomy for bronchial carcinoma and was infiltrated with carcinoma. The endocardium was, however, not invaded and in histology it did not differ from the post-mortem series of controls to be described. In view of the virtual absence of surgical control specimens a series of 90 left auricular appendages and 90 right auricular appendages was examined from hearts showing no macroscopic evidence of rheumatic heart disease at autopsy.

The bulk of the specimens removed during valvotomy were from patients aged 25 - 50 years. (Fig. 115).

Of the 90 controls 33 cases were in the age group 25 - 50 years, ten were below age 25 and the remainder above age 50. No significant difference in histology was found in the different age groups.

The specimens were fixed in 10 per cent formal-saline for 24 - 48 hours. Formal-saline has many disadvantages as a fixative (Lendrum 1941) but it preserves the inter-

-mediate substances of the connective tissues and as it is used in this department for routine histological procedures, it was selected as the fixative for these studies.

The surgical specimens were placed in the fixative immediately after removal. The auricular appendage varied considerably in size but in the first 100 specimens all the tissue was embedded, blocks being cut transversely across the lumen from the tip. Some tissue was removed for other examinations in the remaining 75 cases.

In the post-mortem specimens the time interval between death and fixation ranged from 2 hours to 72 hours. Three blocks of tissue were trimmed from the tip of the left auricular appendage transversely across the lumen. The right auricular appendages from the same hearts were also taken and treated in the same way for comparison with the left auricular appendages.

All tissues were embedded in paraffin and sections cut at 7$\mu$.

Sections of all cases were stained with well ripened Ehrlich's haematoxylin and eosin and Weigert's haematoxylin and Van Gieson. Samples were stained for elastic tissue, for reticulin, with phosphotungstic acid haematoxylin and Lendrum's picro-Mallory and eosin-phloxine tartrazine.

In a later section certain histochemical investigations will be described (see Chaps. 4 and 5).

Although there are descriptions of the normal structure of the left atrial wall in the literature (Von Glahn 1926; Gross 1935) descriptions of the normal left auricular appendage are scanty and incomplete. To facilitate description of the changes found in the rheumatic group a short account of the structure of the normal left and right auricular appendages is given first. This description is based on that of Von Glahn for the left atrial wall. He in turn had adapted it from Koniger (1903) and Nagaya (1903).

Structure of the left auricular appendage in non-rheumatic hearts.

The left auricular appendage consists of the endo--cardium, the subendocardium, the myocardium and the epicardium.

The endocardium consists of the following layers:-

(1) Endothelial lining, a thin flattened layer similar to the blood vessel endothelium.

(2) Subendothelial layer, a narrow zone containing fine collagen fibres, occasional elastic and reticulin fibres and a few fibrocytes. In addition there is occasionally haematoxyphil material in the spaces between the fibres. This is not however a very prominent or consistent feature.

(3) Elastic layer which varies considerably in thickness from area to area of the same specimen and in different specimens. In addition to the elastic tissue there are collagen and reticulin fibres and occasional fibrocytes.

On the inner surface of the elastic layer between the elastica and the subendocardial layer there is an inter--rupted layer of smooth muscle fibres. This is sometimes only one cell thick but is occasionally more prominent. In a few specimens this layer is absent.

The subendocardium lies between the elastic layer and the myocardium. It consists of a loose areolar tissue with fairly fine but prominent collagen bundles, a few elastic fibres and reticulin fibres. No haematoxyphil material was present between the fibres except in four specimens. Two of these specimens were from (a) a man aged 71 years who died of a ruptured dissecting aneurysm of aorta due to mucoid and fatty degeneration of the media and (b) a man aged 23 years who died from muscular dystrophy. In two other cases small focal areas were present in the subendo--cardium. Isolated cells mainly fibroblasts but also a few histiocytes are present in the subendocardial layer but there are no focal cellular collections. (Figs. 1 - 3).

The myocardium varies considerably in thickness and the bundles of muscle fibres are separated by fine collagen bundles mostly condensed around blood vessels. This fibrous stroma is continuous with the subendocardium and the epicardium. No haematoxyphil material was detected between the collagen fibres or muscle fibres of the myocardium.

The epicardium consists of a network of collagen and elastic fibres and reticulin fibres in which adipose

tissue is present in varying amounts. It is covered by a single layer of endothelium. A few cells including lymphocytes, histiocytes and fibroblasts are present in this layer.

The endocardium of the right auricular appendage is much thinner than the left; its elastic layer is practically absent and the smooth muscle layer can barely be recognised.

Histological changes in left auricular appendages removed during mitral valvotomy.

The histology of the left auricular appendage removed at valvotomy has been described in numerous publications (Pinniger 1951; Kuschner et al 1952; Catto, Taylor and Smith 1952; Waaler 1952; Biörck et al 1952; Sabiston and Follis 1952; Decker et al 1953; Thomas et al 1953; Enticknap 1953; McKeown 1953; Manchester et al 1955; Tedeschi et al 1955; Chiari 1955; Clark and Anderson 1955) but it is noticeable that only Chiari and Clark and Anderson describe the haematoxyphil material associated with rheumatic lesions which was described in the older literature as mucoid oedema, (Talalajew 1929). Oedema is frequently mentioned, the inference being that the spaces are empty or have lost their contents during fixation. For the sake of completeness the changes in the auricular appendage are described in some detail, special reference being made to this haematoxyphil material and to changes in the collagen.

Endocardium and subendocardium.

For descriptive purposes the changes are divided into

two groups (a) thickening and fibrosis which have probably resulted from previous rheumatic damage or organising thrombus and (b) changes which suggest a continuing inflammatory process interpreted as active rheumatism.

In six cases in this series, the structure of the auricular appendage is within normal limits.

(a): Fibrosis.

The thickening and fibrosis of the endocardium and subendocardium may be focal or diffuse, in some cases extending uniformly around the whole circumference. In the endocardium proper, the thickened areas show hyperplasia of elastic tissue often associated with an increase in collagen (figs. 4 and 5). Where the thickening is focal it may project into the lumen. Organising thrombus is frequently present and easily recognised as such but transitions can be seen between the thickened areas of endocardium and organising thrombus which strongly suggest that the thickened endocardium is due at least, in part to incorporation and organisation of thrombus (fig.6 ). In view of the work of Harrison (1948) the appearances of the increased elastica would support this view. Thrombus in all stages of organisation is observed and the thrombus itself often contains interstitial haematoxyphil material. In 50 specimens recognisable organising thrombus was observed.

The smooth muscle layer is more prominent than in the

non-rheumatic group and is frequently hypertrophied. This is probably part of the general hypertrophy of muscle in the left atrium due to mitral stenosis. Similar appearances have been noted in the wall of the left atrium by Koletsky (1945). The subendocardium is also thickened in the majority of specimens and again the thickening may be focal or diffuse. In some specimens the main feature of the thickening is the presence of collagen fibres which are thicker than those usually found in this layer. It is observed that in the subendocardial layer beneath an organising thrombus capillary channels are not very frequently present and the cellular reaction of organisation does not often extend to the subendocardium. For this reason and for other reasons to be described later it is considered that the thickening in the subendocardial layer is due almost entirely to rheumatic damage. It is note--worthy that apart from the thickened collagen bundles it is difficult to pick out the sites of previous focal lesions in the subendocardium. 57 specimens showed either thickening and fibrosis of the endocardium or subendocardium without any evidence of an active inflammatory process.

(b): Changes suggesting an active disease process.

Various changes are present, the commonest and most striking feature being the presence of focal cellular lesions mainly in the subendocardium but also in the endocardium. These lesions show a variety of patterns

but basically they consist of various types of cells grouped around or between swollen, eosinophilic, fused and sometimes apparently fragmented collagen. In the spaces between the cells and the fibres and in the surrounding tissues there is a substance which stains blue with Ehrlich's haematoxylin. This substance is vacuolated and is condensed on the surface of fibres and cells or fills the spaces between them. Since this material lies in the tissue spaces, for descriptive purposes it has been called "interstitial haematoxyphil substance" and because of frequent reference to it in the text the initials I.H.S. will be used as an abbreviation.

There is a considerable variation in the types and numbers of cells present, in the amount and appearance of the altered collagen and in the amount of I.H.S. The shape and size of the lesions are very variable. They may be small, round, or oval foci or they may be diffuse and elongated.

The descriptive terms applied to the cells found in rheumatic lesions have varied from author to author. The nomenclature of Gross and Ehrlich (1934 a and b) is adopted in these descriptions, except for the term "mesenchymal cells" which they used to describe cells which resembled lymphocytes.

The characteristic cell of the rheumatic lesion is the "Aschoff" cell. The description of this cell has shown

considerable variation in recent publications. Gross and Ehrlich described three types of nuclei in the Aschoff cell - the fibrocytoid nucleus, the owl eye nucleus and the pyknotic nucleus. It is perhaps worth while quoting the description given by Gross and Ehrlich (p. 478) "The nuclei may occur in three forms commonly found in all varieties of Aschoff bodies. The type of nucleus found most frequently in the small cell coronal Aschoff body is round or oval with a delicate sometimes folded nuclear membrane and a fine dust-like chromatin structure which may at times show irregular concentrations or bar-like arrange--ments with fine projections radiating from the bar. Because of its resemblance to the fibrocyte (fibroblast) this nucleus will be referred to as the fibrocytoid nucleus. The next most frequently occurring variety is the owl eye nucleus. This has been termed the "target" nucleus by Whitman and Eastlake. It is somewhat irregularly circular, possesses a heavy nuclear membrane with a distinctly dark and at times somewhat stellate nucleolus. The space between the nucleolus and the nuclear membrane tends to be poor in chromatin material----------. In a considerably smaller percentage of cells the nucleus is somewhat poly--morphous in shape and generally quite large. It stains solidly and is therefore designated pyknotic nucleus".

In the small cell coronal types there is a narrow rim of basiphilic cytoplasm. In the large cell coronal types

the cytoplasm is more abundant and has ragged edges and sometimes cytoplasmic streamers.

It should be noted that in the opinion of Gross and Ehrlich the "fibrocytoid" nucleus only at times shows "bar-like" arrangement of chromatin with radiating projections. This latter type of arrangement was called "myocyte" by Anitschow (1913) and "lattice cell" by Lendrum (1941).

It should also be noted that in the description of the reticular Aschoff body Gross and Ehrlich do not describe the cells but in the succeeding paper (1934 b) they describe the cells in this form as "small cells, round or ovoid with scant basiphilic cytoplasm. Occasionally larger cells with a scattering of owl eye, fibrocytoid, and pyknotic nuclei" are present. For the small round cells "indistinguishable from lymphocytes" which are found in the earliest forms of lesion, they use the term "mesenchymal cells".

It can be seen from this description that the "Aschoff cell" has a very variable appearance.

For descriptive purposes therefore the cells in the auricular appendages taking part in the rheumatic lesions will be known as "Aschoff cells" if they have basiphilic cytoplasm and a nucleus recognisable in any of the forms described above, lymphocytes if they have small, round, dark nuclei and barely recognisable cytoplasm, and mono--nuclear cells if they are larger than lymphocytes with

oval or round deeply staining nuclei and a narrow rim of cytoplasm.

Other types of cell are encountered and they will be described in association with the lesions in which they occur.

In all descriptions given below, various stains have been employed, but the description of the lesions in haematoxylin and eosin preparations are based on Ehrlich's haematoxylin and eosin. This stain does not give a very clear photographic representation since the background in many of these lesions stains blue and nuclear detail is not so evident as with e.g. Mayer's haemalum. It has however been used to give an indication of the changes occurring in the tissue spaces.

Numerous photomicrographs, some in colour, have been used to supplement and sometimes to replace the descriptions in the text.

For descriptive purposes the lesions have been separated into several categories but it is not contended that the divisions are clear cut.

An attempt has been made to give an idea of the incidence of the various lesions encountered, based on the first 175 cases examined. Because of the lack of clear cut dividing lines between the various types these figures are at best only an approximation.

It is also impossible to convey in descriptions the

variability in the numbers of lesions present in different specimens. A rough guide to the numbers of lesions in each specimen is given with each case history in the appendix.

Although the analysis is based on 175 cases, 340 were available for study and some of the photomicrographs are taken from cases not included in the analysis, because they illustrate some point better.

## Description of the various types of lesion in the endocardium and subendocardium.

The lesions have been divided into two categories.

Group 1 lesions are those which I believe are varieties of rheumatic lesions similar to those described in the literature in the ventricles, valves, left atrial wall, etc., by a great number of authors. They mostly conform to descriptions in the modern literature in auricular appendages in mitral valvotomy cases but some of the lesions are I believe earlier forms than any demonstrated in these recent publications.

All these lesions show some alteration in the collagen with a variable degree of cellular proliferation. They include lesions from the earliest traces of collagen damage to fibrillar lesions.

Group 2 changes are much less specific and are not in themselves diagnostic. It is part of the intention of this thesis to show that this group of changes is also part of the

rheumatic process. Some of them have been described as non-specific changes in the literature but other changes have received little attention in descriptions of valvotomy specimens.

Group 1 lesions:

A): Lesions in which Aschoff cells are present usually associated with altered collagen and interstitial haematoxy--phil substance.

(a): Focal lesions:

This type of lesion forms a number of patterns which correspond to the coronal or mosaic types of Aschoff nodule (Gross and Ehrlich 1934 a and b). In addition to coronal and mosaic patterns the collagen fibres within some of the nodular lesions form a reticular pattern. This reticular pattern does not, however, in my opinion, correspond to the reticular Aschoff body as described by Gross and Ehrlich which I believe is similar to the "Fruhinfiltrat" of Klinge. The cells associated with these lesions are usually larger types of Aschoff cells with a large amount of basiphilic cytoplasm and the collagen never shows the intensely eosinophilic, wax-like, rigid appearance of the "Fruhinfiltrat" The cells are frequently arranged in a coronal fashion around the interlacing collagen fibres, but sometimes are distributed between the fibres. The lesions vary in size and shape sometimes consisting of only a few cells grouped round a tiny central focus of altered collagen, and sometimes

of large amounts of altered collagen and numerous cells. In many specimens the cellular exudate overshadows the collagen alteration.

The cells found in these lesions vary in the pro--portions of types present. Sometimes the bulk of the cells present have recognisable Aschoff nuclei, but in others only a few recognisable Aschoff cells may be present, lymphocytes and mononuclears predominating. Sometimes the cells are forced into rows between the altered collagen and this is especially the case in the endocardium. Large and small Aschoff cells are present and not infrequently multinucleate cells are encountered with the same type of nuclei. Very occasional polymorphs are noted in some lesions but mast cells (Toluidine blue and P.A.S.) are rarely encountered. In some of the larger Aschoff cells the cytoplasm is less basiphilic and on occasions the nuclei are poorly stained - the "ghost" nuclei described by Gross and Ehrlich (figs. 8 - 30) show the variations in these types of lesion.

The altered collagen in the lesions varies in amount and in appearance. It is usually more eosinophilic than normal collagen and may consist of rounded masses or tiny portions of swollen altered collagen which retain their outline. The collagen may be fused or in some lesions single swollen fibres may be present. In some the altered collagen has a smooth eosinophilic hyaline appearance. In

others the collagen is intensely eosinophilic and granular. Again in others it may stain to the same dull pink with eosin as the surrounding collagen and in this form may be either hyaline or granular. In more florid types of lesions where large amounts of I.H.S. are present the swollen collagen fibres may be slightly basiphilic possibly due to condensation of I.H.S. on the surfaces of the fibres. In some specimens if the section is cut in the long axis of the swollen fibres, collagen can be traced into a lesion and abruptly change its appearance. The cells are sometimes palisaded at right angles to the fibres and this is noted especially in the more diffuse types of lesion described below. In many specimens the collagen appears to be fragmented into small or larger rounded masses but care has to be taken in the interpretation of fragmentation because groups of swollen fibres cut transversely may give such an appearance of fragmentation.

The altered collagen usually stains red with the acid fuchsin of the Van Gieson stain but on occasions yellowish staining is noted. The nature of the changes in the collagen will be more fully discussed later. With the phosphotungstic acid haematoxylin stain no fibrin staining component is recognised.

Between the cells and the altered collagen and also within the surrounding spaces is a variable amount of I.H.S. In the earlier lesions e.g. in the small cell coronal types

the amount of this material is greatest. In the more fully developed type it is not such a prominent feature and in some is barely recognised.

The majority of these lesions are rounded or ovoid but in some the lesions are more elongated. The commonest situation is in the subendocardium and in the myocardial septa at the junction with the subendocardium but similar lesions are present in the endocardium proper and sometimes the lesions are situated at the boundary between the subendocardium and the endocardium.

It should be noted that in many of the lesions in addition to Aschoff cells with recognisable nuclei other cells identical in appearance have deeply staining nuclei, the details of which are difficult to make out. On occasions a mantle of lymphocytes is present and especially when the lesions are in the endocardium the subendothelial layer overlying the areas may be infiltrated with lymphocytes and show extensive I.H.S. With Ehrlich's haematoxylin the cytoplasmic streamers or cell process are well demonstrated. Spindle cells resembling fibroblasts but also with deeply basiphilic cytoplasm are not infrequently found in these lesions.

In this group of lesions described polarisation is not a prominent feature, and the polarised and fibrillar types of lesion will be described separately.

(b): Diffuse lesions:

In addition to the focal lesions described above there

are other types of lesions essentially similar in structure in which long stretches of collagen show the characteristic alteration. These lesions are found in the endocardium and the subendocardium. In the endocardium the swollen collagen bands are found between the elastic lamina and the cells may be forced into rows. In others the cells are palisaded with their long axis at right angles to the collagen band. Multinucleate cells are found in these lesions in a pro--portion of cases. (Figs. 31 - 34).

The collagen is usually more eosinophilic and hyaline and on occasions is deeply eosinophilic. It usually stains red with the Van Gieson stain but on occasions parts of the swollen collagen stains yellow. With the phosphotungstic acid haematoxylin stain no fibrin staining component was detected.

Closely allied to lesions of the type described above ~~are~~ is a small group in which collections of large Aschoff cells are found, sometimes connected together with cyto--plasmic processes, in which the collagen is present in fine normal looking fibres. This is an uncommon type of lesion and corresponds to the description of the syncytial type (Gross and Ehrlich 1934a). It was found in only 6 specimens. (Figs. 35 and 36).

B: Polarised and fibrillar lesions:

In the group described above there is little evidence of polarisation in the lesions, but in a small number of

specimens polarised lesions are found. In general they correspond to the description given by Gross and Ehrlich. The lesions are usually elongated in a direction corresponding to the general direction of the collagen fibres. In the majority there is a mosaic pattern. The collagen within the lesions is usually present in elongated strips and it is difficult to know if the collagen in some of these lesions is broken up into separate portions. The cells are elongated and many of them have a spindle shape resembling in appearance fibroblasts. (Figs. 37; 38 ). Only 12 specimens showed lesions of this type.

Closely allied to the above group is a group of polarised fibrillar lesions. This is not a very common type being found in only 6 specimens. The collagen within the lesions consists usually of parallel delicate fibres in which bulbous or swollen areas are recognised. The cells are elongated and the majority of them resemble fibroblasts, but some still have recognisable Aschoff nuclei. In some of these lesions a small amount of I.H.S. is present but in others it is absent. (Figs. 39 and 40).

Along with this group I have included a group of lesions in which spindle shaped cells resembling fibroblasts but with very basiphilic cytoplasm are found usually arranged in a radiate manner with cell process extending towards the centre. Within the centre of these cells the collagen is

either found in a small rounded or elongated focus staining dull pink with eosin and red with Van Gieson stain or a small tangle of delicate fibrils of collagen. They may be situated either in the endocardium or sub--endocardium but are more commonly found in the former. They are distributed around the endocardium in a focal manner and resemble the arrangement of coronal lesions (Fig. 41). This type of lesion is not very common, being found in seven specimens. In four of these specimens focal lesions of the first type described were found and in three others were the sole type of lesion present. These lesions are described by McKeown (1953) and she suggests that they represent a different method of healing from that described by Gross and Ehrlich. Sometimes similar cells are found palisaded along a strip of thick collagen when this is cut in its long axis and if cut across would almost certainly give such a radiate arrangement of spindle cells (Fig. 42). Some of these lesions contain I.H.S. but in others it is not noted. Diffuse lesions of fibrillary type were not recognised in any specimen.

C: So far the lesions described have been developed lesions in which collagen alteration is associated with a distinct cellular exudate. Other changes are present in which collagen alteration is present associated usually with a large amount of I.H.S. but in which the cellular exudate is very poorly developed or even absent.

In some specimens small focal areas of altered collagen are present in which there is little or no cellular reaction. In the surrounding tissues there is a variable amount of I.H.S. which is more intense in the immediate vicinity of the altered collagen. The altered collagen may show an intense, deeply staining eosinophilic appearance with a slightly granular appearance or it may be eosinophilic and hyaline. On occasions it has the same dull appearance as normal collagen. This may occur in separate focal areas or there may be several areas of altered collagen close together. In four specimens the collagen showed an intensely eosinophilic fused appearance with no cellular exudate. In others there is a slight increase in cells usually lymphocytes or mononuclears with deeply staining oval or round nuclei. In addition to the focal areas of altered collagen, in some specimens long stretches of collagen are involved. Sometimes a single long swollen eosinophilic bundle is seen and in others several adjacent bundles are involved. (Figs. 43 - 54).

Since this type of lesion is considered to be a very early stage in the development of rheumatic lesions it will be discussed more fully in connection with the changes in the collagen. (Chapter 5).

It must be emphasised that the distinction between lesions of this type and those in which there is a more

distinct cellular reaction is not clear cut. They have been divided somewhat arbitrarily according to the prominence of the cellular component.

In sixteen cases focal lesions of this type were observed and in four specimens diffuse lesions were found.

Group 2 lesions:

So far the lesions I have described are lesions in which collagen alteration is noted, and they include I believe most of the types of lesions described by Gross and Ehrlich in the myocardial Aschoff body modified in appearance not only by the presence of thicker collagen and much elastica but also by the involvement of thicker bands of collagen in the rheumatic process in the subendocardium and endocardium.

In addition to the focal or more diffuse lesions described other changes are present in the subendocardium and endocardium.

Between the recognisable rheumatic lesions the subendocardium and endocardium may show a diffuse cellular exudate the cells consisting of lymphocytes, mononuclears and occasional recognisable Aschoff cells. This exudate may be present in the subendocardium or endocardium but it is usually more prominent in the former. This cellular exudate is almost invariably associated with a diffuse amount of I.H.S. in the tissues. The degree of the cellular exudate is very variable sometimes a very moderate increase is noted and in others the exudate is more intense.

As has already been described, intimately associated with the developed or developing lesions there is a variable amount of I.H.S. Sometimes this I.H.S. extends around the whole circumference of the auricular appendage and is most concentrated in the subendocardium. It frequently extends into the myocardial septa and between the muscle fibres. These extensive collections of I.H.S. are usually associated with the less organised types of lesions. In other specimens some areas of the appendage show discrete or diffuse collections of I.H.S. with or without a moderate cellular exudate which appear to be separated from the Aschoff type lesions by intervening areas of endocardium or subendocardium which show no alterations of this type (Figs. 55 - 58).

Of the 103 specimens in which Group 1 lesions were found, areas of I.H.S. with or without a moderate cellular increase were present in the tissues between the developed lesions in 63 specimens.

In nine specimens the subendocardium and less frequently the endocardium showed diffuse collections of I.H.S. some--times with a moderate increase in lymphocytes and mono--nuclears but in others little or no cellular increase was noted. The I.H.S. extended completely round the section in six of these specimens and in three, diffuse stretches were involved but the process was not continuous around the

specimen.

In six of these cases there was a definite increase in cells which was usually fairly evenly distributed around the subendocardium. In the remaining three cases the cellular exudate was indefinite or absent.

In 10 specimens in which organising thrombus was present there was an infiltration of small lymphocytes and collections of fibroblasts in the subendocardium beneath the thrombus. In some of these specimens there was a small amount of I.H.S. associated with the cellular exudate and usually the thrombus also showed I.H.S. and an active organising process. This cellular exudate was confined to the area beneath the thrombus and did not extend beyond it although in some specimens lymphocytic infiltration and I.H.S. were present in the endocardium, especially the subendothelial layer, at a distance from the thrombus. The localisation beneath the thrombus and the presence of active organisation of similar appearance within the thrombus suggested that in these cases the cellular infiltration of the subendocardium was associated with the organisation process and not with active rheumatism.

To give an overall estimate of the numbers of cases showing lesions of the types described is very difficult.

Frequency of changes described.

Group 1 lesions were found in 103 specimens and in 63 of these, Group 2 changes were also present. Group 2 lesions

were found in 9 specimens in the absence of Group 1 lesions making a total of 112 specimens showing lesions which I believe are evidence of active rheumatism.

Of the 103 Group 1 cases 93 showed lesions of the first type described, 3 showed polarised lesions and 4 fibrillar lesions. 3 cases showed lesions in which altered collagen and I.H.S. were present with only a slight cellular exudate. As mentioned in the text of the descriptions, lesions of the polarised and fibrillar types and lesions showing only collagen alteration and I.H.S. were found in specimens which showed other types of developed lesions.

Group 2 lesions were found associated with Group 1 lesions in 63 specimens and in 9 specimens were the sole type present.

Changes in the myocardium of the left auricular appendage.

The myocardium of the left auricular appendages shows changes which, for descriptive purposes are divided into three groups.

A: Fibrosis which is possibly the result of previous rheumatic damage..

B: The presence of lesions suggesting active rheumatic lesions.

C: Changes in the muscle fibres.

A): Fibrosis is present in the majority of specimens and usually consists of thickening of the myocardial septa especially towards the endocardium and around the blood

vessels. In addition there is sometimes a more diffuse, delicate fibrosis, thickened strands of collagen passing between individual fibres. The extent of these changes varies from specimen to specimen and in different parts of the same specimen. (Fig. 7).

B): Active rheumatic lesions are frequently found where the myocardial septa join the endocardium and these lesions are included with those of the endocardium. In addition to these lesions there is a small number of cases (4 cases) where nodular Aschoff lesions are present in the septa or near blood vessels at some distance from the endocardium. Where these lesions are present, similar lesions are found in the endocardium. In addition to these 4 cases, a further type of change was seen. In the more diffuse types of lesion in the endocardium, the I.H.S. extends into the myocardium for a variable distance along the myocardial septa and also between the muscle fibres. The cells of the septa and between the muscle cells are prominent, the nuclei and cytoplasm staining deeply with haematoxylin and in some cases there appears to be a moderate increase in cells. This change was noted in 22 cases. (Figs. 56; 59). In six of these cases the muscle fibres adjoining the endocardium were widely separated by I.H.S. and showed shrinkage and occasionally loss of striation strongly suggestive of damage to the fibres. (Fig.60 ). This appearance is very similar to that frequently described

around early Aschoff nodules in the myocardium of the ventricle. Lendrum suggests that these changes are due to "toxic" radiation from the Aschoff nodule but in the auricular appendages the appearances suggest that this type of damage is probably due to changes in the interstitial tissues around the muscle fibres.

C): Apart from these changes to the muscle fibres described above, other changes are found, the significance of which is not clear. The nuclei are frequently enlarged and aberrant in shape, and the fibres are hypertrophied in the majority of cases. Vacuolation of the cytoplasm is almost invariable. Some of these changes are probably due to hypertrophy and others to artefacts due to immediate fixation of the specimens. No special study has been made of these changes in the muscle fibres.

Changes in the pericardium.

Apart from occasional collections of lymphocytes of doubtful significance there were no changes suggestive of active rheumatism in the pericardium.

Distribution of lesions in auricular appendages.

Although it is difficult to give a clear indication of the frequency of lesions in one specimen and their distribution from one part of a specimen to another, it is important to know if the incidence of cases with lesions would be affected by the amount of tissue examined. As has already been stated, the amount of tissue received varied considerably and in the

first 100 cases all the tissue received was embedded. In the appendix the number of blocks examined and the number showing lesions is indicated for each specimen. For examination of autopsy specimens and because certain chemical estimations were contemplated it was important to find out how many blocks of tissue would be necessary to give reliable evidence on the incidence of lesions.

Fig. 62 shows the distribution in a diagrammatic form of lesions in tissues examined from the first 75 specimens.

It can be seen that in cases with lesions if one block had been examined there was a possibility of missing 11 cases, with two blocks 3 cases may have been missed and with three blocks 2 cases may have been missed.

Since serial sections were not considered practicable in view of the large numbers of cases involved in this investigation it was decided to examine three blocks from the auricular appendages in autopsy cases and if possible two blocks of tissue from biopsy specimens when chemical or other investigations were being carried out on the remainder of the tissue.

It should be noted that there is a difference in the numbers of blocks of tissue examined in those without lesions and in those with lesions, e.g. 20% of patients without lesions had only one block and 4 per cent had 6 or more blocks of tissue. In those with lesions 12 per cent

had only one block and 24 per cent had 6 or more blocks of tissue. As 10 out of 12 of those with active lesions in which 6 or more blocks of tissue were examined showed lesions in every block, it is not considered that many cases would be missed by this difference.

In the first 75 cases the number of blocks of tissue examined was due to the size of the specimen received and there was no other "selection" factor.

## CHAPTER 2.

### THE RELATIONSHIP OF ACTIVE RHEUMATIC LESIONS IN THE LEFT AURICULAR APPENDAGE TO ACTIVE RHEUMATIC LESIONS ELSEWHERE IN THE HEART.

To investigate the rheumatic nature of the lesions described in the left auricular appendages of patients undergoing valvotomy and the relationship of these lesions to lesions elsewhere in the heart, three series were collected from autopsies on patients with rheumatic heart disease:-

Series A - autopsies on patients dying after mitral valvotomy.

Series B - autopsies on patients dying in the Queen Elizabeth Hospital and General Hospital, Birmingham between 1952 and 1955 in which the heart showed macroscopic evidence of rheumatic disease.

Series C - because of the changes described as Group 2 changes in the auricular appendages of the valvotomy series , a control series of 25 hearts from patients up to the age of 50 which showed no macroscopic evidence of rheumatic involvement was also collected. This was in addition to the 90 left and right auricular appendages previously examined.

Method of examination.

After being opened in the usual manner the hearts were

fixed in 10 per cent formol-saline for several days. Blocks of tissue were taken from the areas suggested by Gross, Antopol and Sacks (1930) but in addition 3 blocks were taken transversely across the left and the right auricular appendages and additional tissue was taken from the posterior wall of the atrium and from the left ventricular myocardium.

A total of 20 blocks of tissue was examined from each heart in all three series.

The tissues were embedded in paraffin and sections cut at 7$\mu$ were stained with Ehrlich's haematoxylin and eosin, and Van Gieson's stain. Other stains were employed where necessary as in the study of the biopsies of the auricular appendages.

In addition to "Aschoff bodies", a search was made for changes in the myocardium similar to those described as Group 2. in the auricular appendages of the valvotomy cases.

Series C.

The auricular appendages of the control series showed no differences from the previous control series described. Haematoxyphil material was found in the valves, especially on the right side in approximately half of the specimens. The amount present varied considerably.

No haematoxyphil material was present in the myocardium except in one case in association with an organising infarct. No lesions resembling Aschoff bodies were detected and

although in a few instances there appeared to be a vague increase in cellularity of the interstitial tissues there were no lesions similar to the Group 2 lesions and no cellular aggregates. In several specimens isolated cells with "lattice" nuclei were observed.

Series A.

Fifteen post-mortem examinations were carried out on patients who died in the post-operative period. A further three cases died after surviving 8½ - 18 months and are reported separately.(Chap.12).

In the Appendix brief summaries of the relevant post-mortem findings are given. (Cases 167 - 181).

A brief description of the lesions in the auricular appendage and the rest of the heart is given in those cases in which lesions were detected.

Case 167.

The biopsy shows several focal lesions in one of four sections consisting of elongated lesions with large types of Aschoff cell arranged in rows. Only a trace of I.H.S. is present. (Fig. 63).

Heart: There is an intense suppurative pericarditis and polymorphs are infiltrating along the septa from the pericardium.

The left atrial wall shows focal collections of mononuclear cells some of which have recognisable Aschoff nuclei.

Occasional active lesions are present in the left ventricular myocardium. They consist of closely packed mononuclear cells, some with Aschoff nuclei. The collagen between has a fibrillar appearance. The valves show no evidence of a valvulitis. (Fig. 64).

Case 170.

The biopsy shows numerous lesions in the subendocardium. Some of these lesions consist of small round or oval cells grouped around swollen eosinophilic collagen and in other places diffuse lesions are present. Occasional focal lesions show larger types of Aschoff cells and occasional areas of swollen eosinophilic and fused collagen associated with scanty oval and round cells and I.H.S. Between the lesions there are diffuse areas of I.H.S. (Fig. 65.).

Heart: Left atrium shows focal and diffuse collections of I.H.S. with a moderate increase in mononuclears. No focal lesions are detected.

Scanty Aschoff nodules are present in the left ventricular myocardium. These consist of groups of larger Aschoff cells arranged around and between swollen collagen. They are present in the adventitia of vessels. (Fig. 66).

Case 171.

The biopsy shows lesions in the subendocardium and organising thrombus is present in the lumen. The lesions consist of focal Aschoff lesions in which occasional mutlinucleate cells are present. Several other spindle

celled areas are present which may be late fibrosing lesions. (Fig. 67).

Heart: Only the left ventricular myocardium was examined in this specimen.

Numerous coronal mosaic and fibrillar lesions are present. In the adventitia of some of the vessels there are diffuse collections of I.H.S. associated with cells which resemble lymphocytes. (Fig. 68).

Case 172.

Biopsy. Focal and diffuse lesions are present, some with multinucleate Aschoff cells. Between the lesions there is a diffuse amount of I.H.S. which extends into the muscle. Large areas of dull pink collagen are present in one portion associated with I.H.S. and mononuclear cells. (Fig. 69).

Heart: Numerous mosaic and fibrillar lesions are present in the myocardium of the left ventricle. (Fig. 70).

Case 174.

The biopsy shows focal and diffuse lesions with lymphocytes and mononuclears grouped around swollen eosinophilic collagen. In addition diffuse areas of I.H.S. and lymphocytes are present. (Fig. 71).

Heart: The left atrial wall shows similar changes to the auricular appendage but they are not so numerous. The I.H.S. is very poorly stained.

The mitral valve shows an infiltration of mononuclear and Aschoff cell not related to the site of the split. A

similar cellular exudate is present in the aortic valve.

Occasional small Aschoff nodules are present in the left ventricular myocardium. (Fig. 72).

Case 179.

Organising thrombus is present in the lumen of the biopsy specimen and no active rheumatic lesions are detected.

The mitral valve is almost completely acellular. In association with the vessels in the myocardium there are small cellular collections including Aschoff cells distributed throughout the myocardium. These lesions are small but prominent.

Case 180.

The left auricular appendage shows mosaic and fibrillary lesions. (Fig. 73)

Heart: Lesions similar to those in the biopsy are present in the left atrial wall.

Occasional small coronal lesions are present in the left ventricular myocardium. (Fig. 74).

Case 181.

The biopsy specimen contains organising thrombus and no active lesions are detected.

Heart: Moderate numbers of polarised mosaic nodules are present in the left ventricular myocardium. (Fig. 75).

The biopsy specimen for case 176 was not received. No active lesions were detected in the heart.

Of the remaining 14 cases, in which a biopsy was

received, 6 showed active lesions in the left auricular appendage and in these six cases active lesions were also present in the ventricular myocardium. In two cases active lesions were not found in the left auricular appendage but were present in the ventricular myocardium. Six cases did not show lesions in the biopsy specimens or elsewhere in the heart.

It is noteworthy that only one case showed an inflam--matory reaction in the valves.

This series fails to cast any light on Group 2 lesions since no patient died in which lesions of this type only were present in the left auricular appendage.

Series B.

The plan to be followed in the selection of the type of case for comparison with the biopsy series was drawn up before the investigation commenced so that any results obtained would not be influenced by the findings in the biopsy series.

It is, of course, obvious that no autopsy series is really comparable with the biopsy series except perhaps a group of cases with valve lesions and symptoms similar to those in the valvotomy series who had been killed accident--ally or who had died from some cause totally unrelated to their rheumatic heart disease. This idealistic series is unlikely ever to be obtained except perhaps on a nationally organised basis.

The scheme adopted as a compromise was to collect all

hearts at autopsy in the Queen Elizabeth and General Hospital, Birmingham which showed macroscopic evidence of rheumatic involvement. Series C was collected at the same time and no markings were put on the sections to indicate whether they were from rheumatic hearts or from the control series. No clinical details of the patients were known before microscopic examination was carried out.

The object of collecting the series was two-fold.
(a) To examine the hearts to determine if the lesions of various types described in the auricular appendages could be identified in autopsy material in the auricular appendages and elsewhere in the heart. In this case changes other than those of "Aschoff nodules" were sought in an effort to prove that lesions I have described as Group 2 lesions are part of the rheumatic process.

For this purpose the whole series of all age groups and varying valve lesions was used. A total of 61 cases was examined.

(b) The second object was to compare the incidence of active rheumatic lesions in the valvotomy series with a post-mortem series as similar as possible to the valvotomy cases in age distribution and extent of valvular damage. For this comparison it was decided to reject from the original series the following types:-

a): All cases in which there was no clinical information.

b): All cases of 50 years and above.

c): All cases of aortic valve disease in which there was little or no damage to the mitral valve.

d): All cases which showed bacterial endocarditis in addition to rheumatic damage.

The series showed the following distribution of cases:-

Total number of cases of rheumatic heart disease 61.

Cases rejected from series:-

| | |
|---|---|
| No clinical information..... | 3 cases |
| Patients 50 years and above.....(including 2 cases of aortic stenosis) | 24 cases |
| Aortic valve disease with little involvement of mitral valve. | 2 cases |
| Sub-acute bacterial endocarditis..... | 3 cases |
| Acute bacterial endocarditis..... | 1 case |
| Total rejected..... | 33 cases |
| Patients left in series..... | 28 cases. |

It is to be noted that selection of cases apart from age was made on a pathological basis and no further clinical subdivision was made for the following reasons:-

a): The majority of these patients died from their heart disease and consequently are not in this respect comparable to the patients who have undergone valvotomy.

b): Many of these patients were admitted in severe congestive cardiac failure and died shortly after admission often before complete investigations could be made or were too ill to be fully investigated.

c): Whereas it was known that in the valvotomy series the patients were not suffering from acute or sub-acute rheumatic fever and had all been investigated from this point of view, in the majority of patients in the autopsy series the severe congestive failure completely overshadowed all other considerations and it is not possible to assume that other clinical manifestations of acute or sub-acute rheumatism were not present. This post-mortem series therefore may include cases of acute or sub-acute rheumatic fever and in three cases joint pains were present before death.

In the Appendix summaries of the case histories and post-mortem examination findings are given of those used in the clinical comparison.

Of the 61 cases examined, 12 showed lesions of the types I have described.

Case 189.

Left auricular appendage. Several focal Aschoff nodules with central zone of altered collagen and a cellular reaction of cells with and without recognisable Aschoff nuclei. In addition there are long swollen bands of altered collagen in the endocardium and sub-endocardium. Sometimes these bands have lymphocytes between them but in others there is little or no cellular reaction. Most of the swollen bands are smooth and hyaline in appearance and slightly more eosinophilic than normal collagen. In places

the bands are much more eosinophilic and granular. The material in the smaller nodular lesions stains red with Van Gieson's stain and the long bands stain a mixture of red and yellow. No fibrin staining component is detected with the P.T.A.H. stain. In the tissue spaces and especially in association with the altered collagen there is a small amount of poorly staining granular I.H.S. (Fig. 76).

Around a small vessel in the myocardium there is an infiltration of polymorphs, lymphocytes and larger mono--nuclear cells.

Left atrial wall. The subendocardium is diffusely infiltrated with lymphocytes and swollen hyaline bands of collagen are widely separated by I.H.S. No focal lesions are present in the endocardium or subendocardium. (Fig. 77).

Left ventricle. Occasional myocardial reticular Aschoff nodules are present and the collagen has an intensely eosinophilic, wax-like, refractile appearance. The altered collagen stains blue with the P.T.A.H. stain. In addition to these occasional focal lesions in which there is a moderate cellular reaction, the myocardial septa are widened and oedematous and there are small focal collections of round cells and polymorphs. The most striking feature is the presence of an intense panarteritis. In the intima, the media and the adventitia there is deposited a bright red eosinophilic material which in the adventitia appears to be affecting individual collagen fibres. A cellular

reaction of polymorphs, lympocytes and Aschoff cells is seen but the latter are not prominent. The eosinophilic material stains orange-red with the Van Gieson stain and blue with the P.T.A.H. stain. The changes in the vessels correspond to numerous descriptions of rheumatic arteritis (Von Glahn and Pappenhiemer 1926; Klinge 1933; Lendrum 1941).

The mitral and aortic valves show recent vegetations and a valvulitis.

The right ventricle shows changes similar to those described and the tricuspid valve is involved.

The right atrial wall shows lymphocytic infiltration of the endocardium but the right auricular appendage shows nothing of note.

Although there is obvious oedema in the areas mentioned, apart from the left atrial wall and left auricular appendage, I.H.S. is not demonstrated in association with the lesions in the ventricles or valves. (Figs. 78 - 82).

Case 190.

Left auricular appendage. Small focal Aschoff lesions are present in the subendocardium and between these lesions there are diffuse collections of I.H.S. which extend into the myocardium. Within these areas of I.H.S. are swollen areas of collagen. (Fig. 83).

Left atrial wall. Lesions similar to those in the left auricular appendage are present in the posterior wall of the left atrium.

Mitral valve. A diffuse valvulitis is present, the cells being mainly lymphocytes and polymorphs. No vegetations are noted.

The left ventricle shows widening of the myocardial septa and there is a moderate amount of I.H.S. especially around blood vessels. The I.H.S. is very poorly stained. Occasional small coronal lesions are present in the sub--endocardium of the left ventricle and small fibrillar lesions associated with vessels. (Fig. 84).

Case 192.

Left auricular appendage. Dense organising thrombus. No active lesions detected.

Left atrial wall. Dense organising thrombus with areas of calcification.

Mitral valve. Deposits of bright red eosinophilic material are present within the valve cusps. No vegetations are seen, and no cellular reaction.

Left ventricle. Extensive oedema of myocardium with large amounts of I.H.S. mainly around vessels but also extending diffusely along the septa and between the muscle fibres. There is a diffuse increase in cells mainly lymphocytes and small cells with Aschoff nuclei and these are sometimes congregated in groups especially around vessels. In addition there is focal swelling of collagen sometimes associated with cells but sometimes in areas which show only I.H.S. In addition occasional polarised Aschoff nodules

are also present. (Figs. 85 and 86).

The aortic valve shows a deposit of eosinophilic material at the base of one cusp.

No changes are noted in the right side of the heart.

Case 197.

Left auricular appendage. The endocardium shows diffuse I.H.S. with a moderate increase in lymphocytes. In addition small focal lesions are present with a focus of altered collagen surrounded by a few Aschoff type cells. Several areas of fused, brightly eosinophilic collagen are present.

These areas stain a mixture of yellow and red with Van Gieson's stain. There is no cellular reaction in association with these areas but there is diffuse I.H.S. which is poorly stained. (Fig. 87).

The left atrial wall shows similar lesions.

Ventricle. Occasional coronal and mosaic lesions are present. In addition, in several areas the collagen appears to be fused and eosinophilic but it is difficult to be certain of this. I.H.S. is not noted in the ventricles.

Lesions are not seen on the right side of the heart or in the valves. (Fig. 88).

Case 198.

Left auricular appendage. Organising thrombus is present. In addition there is diffuse I.H.S. in the sub--endocardium and this extends into the myocardium along the septa. Focal collections of small round cells are present

in the subendocardium, but the reaction in the subendo--cardium cannot be dissociated from the organising thrombus.

Left atrial wall. A thick layer of calcified thrombus is present. Mitral and aortic valves show a diffuse valvulitis.

Left ventricle. The endocardium of the interventri--cular septum especially towards the valve ring shows a focal infiltrate of round cells and polymorphs. The myocardium shows oedema, not stainable with Ehrlich's haematoxylin, and a slight increase in cells especially around vessels. In addition there is an intense infil--tration of polymorphs, lymphocytes and larger mononuclear cells around several vessels. No altered collagen change is noted. (Fig. 89).

Similar changes are present in the right ventricle.

Case 204.

Left auricular appendage. Extensive diffuse I.H.S. is present in the subendocardium associated with a moderate increase in cells, mainly lymphocytes. I.H.S. is also present in the myocardium. No focal lesions are found. (Fig 90)

Similar changes are present in the endocardium and myocardium of the left atrial wall and in the mitral valve.

Left ventricular myocardium shows very little fibrosis. The myocardium is oedematous, the muscle fibres being widely separated, but the oedema does not stain with Ehrlich's

haematoxylin. No other lesions are detected in the heart.

Case 206.

Left auricular appendage. Numerous nodular lesions are present in the subendocardium and these are of several types. All are associated with swollen collagen but some appear to be at a more advanced stage than others. (Fig. 91).

In addition to the focal lesions there are more diffuse lesions with swollen collagen separated by I.H.S. and small round cells.

Between these lesions there is diffuse I.H.S. which extends into the myocardium.

Left atrial wall. Lesions similar to those in the auricular appendage are present in this region.

Mitral and aortic valves show diffuse valvulitis more marked towards the bases of the cusps.

Left ventricle. Several developed Aschoff bodies are present in the myocardium and endocardium and in addition several fibrillar Aschoff nodules are noted. No I.H.S. is detected in association with these nodules. (Fig. 92).

Right ventricle. I.H.S. is present in the endocardium of the right ventricle towards the tricuspid valve.

The right atrium, tricuspid and pulmonary valves show no special features.

Organising thrombus is present in the right auricular appendage.

Case 210.

Left auricular appendage. Extensive I.H.S. and

lymphocytic infiltration of subendocardium. Occasional formed Aschoff lesions. (Fig. 93).

Left atrium. Diffuse collections of I.H.S. plus slight increase in lymphocytes. No lesions detected with altered collagen.

Left ventricle. Moderate numbers of Aschoff nodules. (Fig94

Right ventricle. Occasional myocardial Aschoff nodules. Aortic and mitral valves vascularised and calcified. Bacterial vegetations on the mitral valve.

Case 211.

Left auricular appendage. Diffuse collections of I.H.S. and a moderate increase in lymphocytes. There are no Aschoff nodules. Within the areas of I.H.S. the collagen appears to be swollen and more eosinophilic than usual. (Fig. 95).

The left atrial wall shows similar changes.

The mitral valve shows a deposit of brightly eosinophilic material within the cusp. There is no cellular reaction.

The aortic valve is sclerosed and vascularised.

Left ventricle. In addition to scarring there is a moderate focal cellular infiltrate around vessels and in the ventricular endocardium below the insertion of the cusp of the mitral valve. No Aschoff nodules are noted in the heart. (Fig. 96).

Case 212.

Left auricular appendage. Numerous Aschoff nodules are present in the subendocardium. In addition there are areas

of I.H.S. and moderate cell increase. (Fig. 97).

Left atrial wall. Similar to left auricular appendage.

Mitral valve - valvulitis. Bacterial vegetations.

Left ventricle. Moderate numbers of coronal and mosaic Aschoff bodies. (Fig. 98).

No lesions detected on the right side.

Case 213.

Left auricular appendage. Numerous nodular lesions are present in the subendocardium with only a trace of I.H.S. The lesions are frequently polarised. Organising thrombus is present. (Fig. 99).

Left atrial wall. Moderate numbers of Aschoff nodules similar to above. No I.H.S. associated with these lesions.

Mitral and aortic valves show no evidence of active rheumatism.

Left ventricle. Numerous polarised and fibrillar Aschoff nodules. (Fig. 100).

No lesions detected on the right side.

Case 214.

Left auricular appendage. Diffuse infiltrate of mononuclear cells and lymphocytes with large amounts of I.H.S. Within these areas there are small focal areas of swollen fused eosinophilic collagen. The collagen alteration is overshadowed by the intense cellular infiltrate. Organising thrombus is also present. (Fig. 101).

Left atrial wall. Similar to above.

Mitral valve. Valvulitis with vegetations.

Left ventricle. Diffuse myocarditis with a tendency to more intense cellular aggregations around the vessels. The cells are lymphocytes, mononuclears and Aschoff cells and in some areas collagen alteration can be detected.(Fig.102)

The aortic valve is also involved.

The right side of the heart was not examined.

Of 61 cases examined 12 showed active lesions of the types I have described in the biopsy specimens and of these 12 cases 10 showed lesions in the auricular appendages, i.e. the total incidence of all lesions described (Group 1 and Group 2) in this series is 20 per cent. If auricular appendages only are considered the incidence is 16 per cent.

In all except one case (Case 204) when lesions were present in the left auricular appendage they were also found in the ventricular myocardium. Two cases (204 and 211) show Group 2 lesions only in the left auricular appendage and these will be discussed later ( Chap. 3. ).

For comparison with the biopsy series i.e. patients below the age of 50, with mitral disease and without bacterial endocarditis the incidence of active lesions at any situation in the heart is 7 cases out of 28 i.e. 25 per cent, and of these 7 cases 5 showed lesions in the auricular appendage i.e. 18 per cent. This compares with 64 per cent for the biopsy series.

# CHAPTER 3.

## EVIDENCE FOR THE RHEUMATIC NATURE OF THE LESIONS DESCRIBED IN THE LEFT AURICULAR APPENDAGES OF THE VALVOTOMY SERIES.

The changes described in auricular appendages as representing active rheumatism have been divided into two categories:- Group 1 lesions which contain certain diagnostic features of rheumatic disease and Group 2 which are non-specific. The evidence that these two groups are part of the rheumatic process is therefore discussed separately.

Group 1.

a): Evidence from the control series. Series C.

In the control series of 90 auricular appendages and 25 non-rheumatic hearts, lesions of this nature were never encountered.

b): Evidence from the autopsy series.

In six cases in series A, where Group 1 lesions were present in the left auricular appendage, lesions - Aschoff nodules - were found in the myocardium. These lesions have already been illustrated (figs. 63-74) and as can be seen are of several patterns. Some of these cases showed diffuse lesions.

In autopsy series B. in 8 cases Group 1 lesions were present in the left auricular appendage and in the ventric--ular myocardium. (Figs. 76 - 102).

Two of these cases are of special interest from the point of view of lesions consisting of altered collagen and I.H.S. without cellular reaction. Case 189 shows, in addition to focal nodular lesions in the auricular appendage, long stretches of altered collagen without cellular reaction. This collagen stains red with Van Gieson's stain except the lesion illustrated in fig. 76 which stains a mixture of red and yellow, and does not stain blue with the P.T.A.H. stain. This case is an undoubted case clinically and pathologically of acute rheumatic fever and shows reticular Aschoff bodies in the myocardium which contain a fibrin-staining component.

Case 197 shows, in the left auricular appendage, small focal coronal lesions and in addition shows long stretches of eosinophilic altered collagen surrounded by I.H.S. without any cellular reaction. The altered collagen in this case shows yellowish staining areas with the Van Gieson stain although the bulk of it stains red. It stains a brownish-orange colour with the P.T.A.H. stain. (Fig. 87).

The type of lesion described consisting of radially arranged spindle shaped cells was not encountered in the auricular appendages of any specimen at autopsy but in one case radially arranged shrunken spindle cells were found associated with vessels in the myocardium. In several specimens lesions of this type in the biopsy series were present in specimens showing more characteristic features of rheumatic disease.

c): Evidence from the literature.

The bulk of the literature on the pathology of rheumatic disease is devoted to descriptions of lesions in the myocardium, in the adventitia of vessels and in the valves and valve rings, but there are several publications describing changes in the left atrial wall. The most important are those of MacCallum (1924); Von Glahn (1926); Shaw (1929); Klinge (1933); Gross (1935); Lendrum (1941); Koletsky (1945) and McKeown (1945). In addition to focal lesions which correspond to the types I have described, these publications also describe the diffuse type of lesions. These are variously called banded lesions, elongated Aschoff nodules, elongated coronal Aschoff nodules and longitudinal Aschoff nodules. Von Glahn's description of the long bands of swollen collagen correspond almost exactly with what I have described in some specimens.

The types of lesion I have described as consisting of altered collagen and I.H.S. with little or no cellular reaction correspond to the descriptions of Gross and Ehrlich (1934 a and b) as the stage preceding the development of Aschoff nodules. This will be discussed more fully in a further section (Chapter 5).

From a study of the written descriptions and of the photomicrographs or diagrammatic drawings of these publications I believe that the lesions I have described correspond to the descriptions of rheumatic lesions by the authors stated.

In more recent publications since valvotomy began there are numerous illustrations and descriptions of different types of lesion and they correspond to my own observations. It should be noted however that usually only florid, well formed lesions are illustrated owing to the demands of publication and it is difficult to know in the less florid lesions what is in the author's mind. Occasional elongated lesions are illustrated but most publications show lesions of the focal type only.

In my own series I have described the intimate association of I.H.S. with these lesions, a factor which has not been noted in publications from other centres with the exception of Clark and Anderson (1955). With the use of Ehrlich's haematoxylin it has been possible to pick up small lesion which may otherwise have been overlooked.

While most authors describing lesions in auricular appendages have accepted the rheumatic nature of the lesions there have been expressions of doubt in several papers. Enticknap (1953) for example describes "possible" and "probable" lesions depending on whether the lesions conform to the classical picture of swollen altered collagen and Aschoff cells. He illustrates his "probable" and "possible" lesions but unfortunately the "possible" lesions have reproduced very badly and it is not possible to analyse them. His main objections to the rheumatic nature of these lesions are (1) that there is no "fibrinoid". Enticknap was

unable to demonstrate any fibrin staining component and was unable to show argyrophilic fibres within the altered collagen. (2) That the fragmented collagen shows "simple dissolution of continuity", and (3) that the clinical picture is not that of "acute" rheumatic fever. Tedeschi et al (1955) believe that the bulk of the lesions are "senescent" for reasons similar to those put forward by Enticknap.

I have also been unable to demonstrate a fibrin staining component by the use of the P.T.A.H. stain and the reticulin stains in my hands have not been specific enough to draw any conclusions about the presence or absence of silver staining fibrils in the altered collagen. It is perhaps sufficient at this stage to state that the views expressed in the literature on a fibrin-staining component in the lesions of rheumatic fever are conflicting. While it is not denied by most authors that a fibrin staining component is sometimes found in certain types of lesion e.g. the reticular Aschoff body, in valves, blood vessel walls, pericardium, etc., the early coronal lesions do not stain with the fibrin stains and the altered collagen usually stains with the collagen stains. This is the view put forward by Gross and Ehrlich and Lendrum, and Giepel (1906) described the material in the centre of the "Aschoff body" and stated that it stained with the collagen stains. Since at this stage the question of what constitutes "activity" is not under discussion but only the rheumatic nature of

the lesions, further consideration of this aspect is postponed until a later section (Chap.12).

Other autopsy series on deaths following valvotomy and also autopsy series of acute rheumatic fever, or valvular disease of the heart (Thomas et al 1953; McKeown 1953) have also shown a fairly close correlation between the lesions in the auricular appendages and in the ventricular myocardium.

The evidence at present available shows that the lesions I have described as Group 1 lesions conform to the lesions described in the heart in rheumatic fever and are similar to those described by other authors in the auricular appendages of patients undergoing valvotomy.

Group 2.

This second group of changes I have described consisting of collections of I.H.S. with or without an increase in lymphocytes or mononuclear cells are in a different category from Group 1 lesions because they lack the collagen damage and the cellular collections diagnostic of rheumatic heart disease. The evidence that these changes are probably part of the rheumatic process is based on the same three sources as above but in addition it is possible to use internal evidence from the biopsy specimens themselves.

a): Evidence from the control series. Series C.

In the large number of cases studied I.H.S. was found in only four specimens in the subendocardium and endocardium

of the left auricular appendages and never in the right auricular appendages. To recapitulate, in two of these specimens I.H.S. was found diffusely in the subendocardium of the left auricular appendage and in one of these the left atrial wall was also involved. In two others small focal collections were found at the junction of the myocardium and the subendocardium. Similar material was frequently found in the heart valves of the control hearts and occasionally this extended for a short distance into the valve rings. It was not found in the myocardium of any control specimen except in relation to an organising infarct. There was no cellular increase associated with the I.H.S. in any of these specimens.

The control specimens were not of course derived from "normal" hearts but were obtained from patients dying from a variety of diseases. The only control specimen removed during life showed no I.H.S. in the subendocardium or endocardium.

b): Evidence from autopsy series.

The evidence from autopsy series A is not very helpful. None of the cases showed Group 2 lesions only in the auricular appendage. Case 171 in addition to polarised Aschoff nodules in the myocardium showed a diffuse increase of lymphocytes and I.H.S. around several vessels.

Autopsy series B contains several helpful cases. In addition to formed lesions in the auricular appendages many

showed areas of diffuse cellular exudate of lymphocytes and mononuclears associated with I.H.S. Case 197 for example shows collagen alteration and occasional coronal type lesions and the whole subendocardium and endocardium contains I.H.S. in this case with little or no increase in cells. Case 189, a case of acute rheumatic fever shows in the auricular appendage in addition to more diagnostic lesions, areas of I.H.S. and lymphocytes or areas of I.H.S. alone. In the myocardium in addition to the formed reticular Aschoff bodies and an arteritis small focal cellular collections of mononuclears, lymphocytes and occasional polymorphs are present.

Case 192 in addition to polarised lesions in the left ventricular myocardium shows extensive areas of I.H.S. between muscle bundles and around vessels associated with a moderate increase of lymphocytes and mononuclear cells. These lesions are difficult to illustrate but under the microscope are very striking and are identical to the lesions described as Group 2 in the auricular appendages. The auricular appendage and atrial wall showed dense organising thrombus with no evidence of rheumatic lesions.

Case 211 furnishes further proof. In this case the main valve lesion was aortic stenosis - non-calcific and the mitral valve showed thickening of the chordae tendineae and the valves. Histologically the base of the posterior mitral cusp showed a deposit of highly eosinophilic altered

collagen within the cusp unassociated with any cellular reaction. The left auricular appendage and left posterior atrial wall showed extensive I.H.S. with a very slight increase in cells. The myocardium of the left ventricle showed focal collections of lymphocytes and poorly stained I.H.S. most marked towards the valve ring. The presence of the eosinophilic material, "fibrinoid", within the valve cusp suggests that these lesions are early changes of rheumatic fever.

In Case 204 although macroscopically there was mitral incompetence with thickening of the cusps and chordae tendineae, the patient died in uraemia from chronic nephritis and consequently it is not considered a suitable case to be used as evidence.

c): Internal evidence from the biopsy specimens.

It is assumed in this argument that it has been established that Group 1 lesions are rheumatic.

In the descriptions of lesions of Group 1 type the intimate relation of I.H.S. to many of these lesions has been stressed. In 63 specimens, in addition to the nodular or diffuse lesions of Group 1 type, areas of I.H.S. with a variable cellular increase were noted between these lesions. Sometimes this change was very extensive and in others was more localised.

These changes are unlikely to have resulted from operation trauma since they were frequently focal in nature,

occurred mainly in the subendocardial region and were found in autopsy specimens in the absence of interference. They were also absent in more than half of the specimens.

d): Evidence from the literature.

Much of the earlier literature is devoted to proving or attempting to disprove that lesions of the Aschoff type in the myocardium are specific for rheumatic fever and although mention is made of earlier stages in the development of these lesions these do not often receive the same attention as the more characteristic lesions. This weighted consideration of developed lesions is not however entirely due to the non-diagnostic nature of the earliest changes. The numbers of patients dying in a first attack of rheumatic fever is very small and when death does occur it does not usually occur in the first week. Consequently the opportunities for studying the earliest lesions for each investigator is very small. In cases dying in subsequent attacks of acute rheumatic fever the same applies. In patients with valvular disease of the heart who die in congestive cardiac failure without clinical evidence of acute rheumatic fever the incidence of lesions in most reported series is of a very low order.

However most authorities are agreed that changes occur before the development of Aschoff nodules and these are variously described as oedema, and/or cellular infiltrations of lymphocytes, mononuclears or polymorphs.

The descriptions of the earliest type of change not only vary from author to author but usually each author gives a fairly variable range of changes. The estimate of the time after the onset of acute rheumatic fever that Aschoff nodules can be detected varies from 2 weeks (Klinge 1933) - 3 weeks (Talalajew, 1929). Giepel (1906) noted the presence of coronal Aschoff bodies 5 weeks after the onset of the disease. The important feature is that most authors describe changes preceding the development of the Aschoff nodule and what is even more important preceding the development of the alteration in the collagen. These are described by Talalajew as "mucoid oedema" especially of the endocardium but also of the myocardium. Klinge describes in detail that the first change noted is oedema with changes in the cells - shrinkage "possibly due to water loss" before the changes in the collagen are noted. To these descriptions could be added numerous others - Coombs (1911), Sacks (1925), Gross and Ehrlich (1934a) and most of the standard text-books in pathology. In the majority of these publications "oedema" is mentioned but "mucoid oedema" is rarely mentioned.

Gross and Fried (1936) examined the A. V. conducting system and described lesions consisting of cellular infiltrations and oedema.

It must be remembered that all haematoxylins do not stain connective tissue mucins and it is possible that this "oedema" may have been stainable if a haematoxylin such as

well ripened Ehrlich's haematoxylin had been employed. In a later section it will be shown that autolytic changes occur which result in the loss or diminished staining quantities of I.H.S.

More recently Altshuler and Angevine (1949) have demonstrated metachromasia in association with Aschoff nodules and I.H.S. also stains metachromatically. They also describe metachromatic material in the valves and coronary arteries of rheumatic hearts.

Other evidence for the occurrence of I.H.S. in acute rheumatic fever can be found in Klinge's reference to chromotrope substance in the blood vessels in rheumatic fever and by Kasner and Bayliss (1934) in the description of a higher incidence of chromotrope substance in the coronary vessels in rheumatic heart disease as compared with non-rheumatic hearts.

So far the evidence taken from the literature has been from rheumatic disease. Since Klemperer and his co--workers (1941; 1942) popularised the term "diffuse collagen diseases" intensive study has taken place of the diseases placed in this group, for example, disseminated lupus erythematosus, rheumatoid arthritis, rheumatic fever, scleroderma, dermato-myositis and polyarteritis nodosa.

According to Altshuler and Angevine (1949; 1954) there is a certain pattern of initial reaction in these diseases.

They describe oedema as the first noticeable finding

followed by the appearance of a metachromatic substance. Asboe Hansen (1954) also believes that the initial disturbances in this group of diseases is in the "mucinous system" of the connective tissues. Pagel et al (1949) illustrate in their fig. 5 the oedema occurring in the tissues of the tongue in dermatomyositis. The appearance of this oedema is very similar to what I have described. They do not state if it stained with haematoxylin but I have seen similar appearances in cases of dermatomyositis where the oedema was well stained with Ehrlich's haemato--xylin.

From consideration of all these factors it is I believe a reasonable deduction that the changes I have described as Group 2 changes are part of the rheumatic process, although not by themselves diagnostic. In the presence of other evidence of rheumatic disease, in this case mitral valve disease, the occurrence of these changes is strong presumptive evidence of some stage in the rheumatic process and the evidence points to this being an early stage. For this reason the 9 cases showing only changes of this nature are considered to show evidence of active rheumatic disease as defined and have been used in the clinico-pathological correlation.

## CHAPTER 4.

## NATURE OF THE INTERSTITIAL HAEMATOXYPHIL SUBSTANCE.

Material similar to this is found normally in many situations and in various pathological conditions. It is found e.g. in embryonic mesenchymal tissues, in heart valves, in aorta, in granulation tissue, in blood vessels in certain conditions, in various tumours and in association with altered collagen in the so-called diffuse collagen diseases. This is the substance which is frequently called "ground substance" but the latter term is used very loosely and has been avoided so far in descriptions.

A series of histochemical and enzymatic reactions has been carried out to determine as far as possible the nature of the material associated with rheumatic lesions and to compare it with similar material found in other situations.

These studies have been carried out mainly in the biopsy specimens of auricular appendages but they have been checked on post-mortem material.

The materials used for comparison were:-

Heart valves from non-rheumatic hearts..... 4 cases

Auricular appendages from non-rheumatic hearts.. 4 cases

Aorta from non-rheumatic patients..... 4 cases

Organising thrombus in biopsy specimens of

auricular appendages..... 4 cases
(In two of these cases rheumatic lesions were also present in the same sections)

Granulation tissue from skin wound..... 1 case

Skin from non-rheumatic patients..... 4 cases

In all these situations except two of the auricular appendages from non-rheumatic hearts and normal skin, interstitial haematoxyphil substance was noted on staining with Ehrlich's haematoxylin.

A considerable amount of work has been done on these substances in recent years. The most frequently used methods for demonstrating them in sections have been metachromatic dyes and of these toluidine blue has been most frequently employed.

The methods of staining with toluidine blue have varied considerably and there is little agreement on the most satisfactory method. The following are some of the methods recommended by various authors:-

Aqueous solutions in various concentrations and for varying lengths of time, examination of sections in a watery mounting medium (Pearse 1953); rapid dehydration in alcohol (Lison 1935) or acetone (Lillie 1948; Brewer 1950) and examination in Canada balsam. Alcoholic staining solutions have been recommended by Mowry (1954) and buffered solutions by Highman (1945). In addition, various permanent preparations have been described (Hess and Hollander 1947).

To add to the difficulties, different batches of dye vary in their staining properties. Several batches of dye from different sources were tested and it was found that the variations were even greater than one had supposed. One batch for example stained muscle fibres metachromatically. Others stained the thick collagen bundles of the dermis pink while other batches stained them blue.

A batch was selected which in a 0.5 per cent aqueous solution for 2 hours stained I.H.S. in rheumatic lesions, granulation tissue, heart valve and aorta metachromatically, stained thick collagen bundles of the dermis blue and the papillary layer a faint pink. Mast cells granules were stained red. Sections were first examined in water, blotted dry, rapidly dehydrated with acetone, cleared in xylene and mounted in Canada balsam. The sections were examined on the same day. Fading rapidly occurred. Between the stage of examination in water and in xylene there was a considerable loss of metachromasia. For all histochemical purposes the same batch of dye was used and the same technique rigidly employed. To ensure uniformity all sections were stained by myself.

Throughout the investigations with toluidine blue the same lighting system and microscope was used. A code system indicating sections was used so that the nature of the specimen and its treatment were not known to me.

Staining reactions of the I.H.S. in rheumatic lesions.

All sections showing I.H.S. contained metachromic material on staining with toluidine blue. The metachromasia was usually more extensive than the haematoxyphil material and it was noted that fine fibres including fine collagen fibres stained metachromatically in addition to interstitial material. Sometimes these differences were easy to detect when for example I.H.S. was present in large amounts but in other cases it was impossible to be certain if there was metachromatic material between the fibres. (Fig.103). It was also found that metachromasia could be detected in areas of sections where no I.H.S. was seen and also in some sections where I.H.S. was not detectable. In a proportion of non-rheumatic auricular appendages metachromasia was detected, usually to a lesser degree. The distribution of metachromasia in non-rheumatic and rheumatic hearts has been more fully investigated and will be discussed later. (see p. 80).

Similar results were obtained with alcian blue (Steedman 1950). I.H.S. stained blue but in addition areas in which I.H.S. were not detected also stained blue. This is a very unsatisfactory method since staining has to be stopped at an arbitrary level or staining of collagen and other tissue components occurs.

I.H.S. also stained with Hale's dialysed iron method (1946) and Hale positive material was found where no

I.H.S. was detected (fig.104). The disadvantages of this method lie in the diffuse blue background staining which makes interpretation extremely difficult in many cases. Curran (1953) found it a useful method but I have not found it so in these studies.

The methylene blue extinction was measured according to the method of Pearse (1953). This was found to be below pH 4.

The periodic-acid Schiff reaction carried out by the method of Jarrett and Roberts (1950) (unpublished) showed only a faint pink staining or no staining of I.H.S. This absence of staining of "connective tissue mucins" by the P.A.S. reaction has been discussed by Pearse (1953).

These reactions have been confirmed by other workers on similar material in other situations. Variable results have been reported with the P.A.S. reaction but my findings agree with those of Pearse i.e. that the connective tissue "mucins" stain very weakly and doubtfully with the P.A.S. reaction.

Although there is considerable disagreement in the exact substance or substances being demonstrated by any one of these methods, taken together they are generally accepted as indicating acid mucopolysaccharides (McManus, 1954).

A series of enzymatic reactions was carried out to attempt to define still further the nature of the I.H.S. in rheumatic lesions and to see if it differed from that in

other situations.

It was hoped to use Ehrlich's haematoxylin and eosin and toluidine blue as indicators but it was found that after incubation for 3 hours at 37 C Ehrlich's haematoxylin and eosin staining was unsatisfactory. The haematoxyphil material was still identifiable but was reduced in amount and the staining lacked the clear blue appearance of untreated sections. For this reason toluidine blue was used.

The enzymes were tested for activity and controls were treated in the appropriate solvent - saline or buffer solution for the same time. Sections were stained with the same batch of toluidine blue and were examined in water and in xylene after treatment as described before. The controls and treated sections were examined without prior knowledge of their method of treatment. The methods used were from Pearse (1953).

Hyaluronidase, usually of testicular origin, has been frequently employed in studies of this nature.

Hyalase (Benger) 1000 U/cc. and

Wydase (Wyeth) 150 T.R. units/cc. were used in this study.

Incubation for 3 hours at 37°C greatly reduced the metachromasia in all situations examined and abolished it in non-rheumatic auricular appendages and skin. The action on the metachromatic material in the aorta agrees with

results obtained by Pearse (1953) but not with those of Grishman (1948). The latter found it resistant to testicular hyaluronidase.

I have been unable to confirm the observation of Altshuler and Angevine (1949) that the metachromatic material associated with later type lesions is more resistant to the action of hyaluronidase than that associated with early lesions.

Trypsin (B.D.H.) 0.1 mg./ml. in 0.05 M phosphate buffer at pH 6.0 for 1 hour at 37°C. No difference was noted in the metachromasia of the controls and the treated sections.

Pepsin. (B.D.H.) 2 mg./ml. in 0.02 N HCl at pH 1.6 for 3 hours at 37°C.

In control and treated sections metachromasia was abolished.

Pectinase. (Pectozyme. Norman Evans and Rais Ltd.) 0.8 Gm. in 100 ml. acetate buffer at pH 4.2 for 48 hours.

Metachromasia was reduced in the treated sections.

Ribonuclease. (Armour) 0.1 mg./ml. in glass distilled water for 1 hour at 37°C.

No difference was noted in the metachromasia of the control or the treated section.

The action of testicular hyaluronidase confirms the mucopolysaccharide nature of the I.H.S. in rheumatic fever.

No differences were noted in the staining reactions or behaviour towards enzymes in I.H.S. found in rheumatic

lesions or in the other situations examined.

The connective tissue mucins have been the subject of numerous investigations especially since the discovery of the "spreading factor" by Duran-Reynals (1928). Other discoveries have stimulated interest in these substances especially the association of these substances with lesions in the "diffuse collagen diseases" and the response to cortisone therapy in this group of diseases.

Much tissue chemistry has been carried out especially by Meyer who has isolated various mucopolysaccharides from various situations. The most important of these are hyaluronic acid and chondroitin sulphate. Meyer has isolated three types of chondroitin sulphate which differ in their opitcal rotations. These he has called chondroitin sulphates A. B. and C. These mucopolysaccharides have been found together in varying proportions in different situations e.g. hyaluronic acid and chondroitin sulphate B. have been isolated from skin and chondroitin sulphates B. and C. have been isolated from heart valves and aorta.

At one time it was believed that the enzyme in testicular preparations acted only on hyaluronic acid but it is now recognised that chondroitin sulphate is also affected. Interpretations of the individual components has varied from author to author depending on whether the action of testicular hyalurinidase is considered to be on hyaluronic acid or on a group of mucopolysaccharides.

The evidence at present available suggests that the haematoxyphil material associated with rheumatic lesions is a sulphated acid mucopolysaccharide possibly chondroitin sulphate B. or C., with or without hyaluronic acid.

According to Meyer these compounds probably exist as mucopolysaccharide - protein complexes but little is known of the protein component.

A protein component of the interfibrillary substances in connective tissues was reported by Day (1949).

## Effect of autolysis on I.H.S.

It was noted in post-mortem series A and B that I.H.S. was not such a prominent feature in relation to lesions as in the biopsy series. In addition to being less prominent or absent, it frequently appeared granular and stained badly appearing as a rather muddy looking material instead of the clear blue staining in the biopsy specimens. A few experiments were carried out to determine the effect of autolysis.

Specimens of auricular appendages were received unfixed from the operating theatre and trimmed into blocks in the usual manner. One was placed in 10 per cent formal-saline immediately and the remainder were put into a container with a loosely fitting lid, were slightly moistened with saline and left at room temperature. Each day a block was fixed in 10 per cent formol-saline. The blocks were paraffin embedded and stained with the same batch of Ehrlich's

haematoxylin in a comparable manner.

It was found that after 24 hours there was considerable reduction in the amount of I.H.S. After 48 hours it was barely detectable. In addition to the loss of I.H.S. the cytoplasm of the cells in the lesions became less prominent and the nuclear structure more prominent. After 4 days cytoplasm was barely detectable.

When metachromasia was used as an indicator, the staining became less pink after 24 hours and after 72 hours was still detectable when Ehrlich's haematoxylin was no longer showing I.H.S. The colour of the metachromasia changed from reddish pink to reddish purple.

Because of these findings i.e. alteration in the appearance of I.H.S. in post-mortem material, the disappear--ance of this material on autolysis and the fact that metachromasia could still be detected when there was no staining with Ehrlich's haematoxylin, an investigation into the distribution of metachromasia in non-rheumatic and rheumatic hearts was carried out.

### Distribution of metachromasia in rheumatic and non-rheumatic hearts.

The 28 cases in series B were used and 14 non-rheumatic hearts from the control series were compared with them.

Sections from all blocks were taken, mixed together and stained in batches of 20 sections as described before. Comparison was made after the sections had been blotted dry, dehydrated in acetone, cleared in xylol and mounted

in Canada balsam. Sections were examined on the day they were stained. The same batch of toluidine blue was used throughout.

Because of the variations in the colour of the meta--chromasia four grades of colour were noted - red or pink, reddish-purple (i.e. red with a faint blue tinge), bluish purple (i.e. blue with a faint red tinge) and blue. The first two grades were counted as showing definite meta--chromasia.

It was not known at the time of examination of the sections which were from rheumatic or non-rheumatic hearts but it must be confessed that it was relatively easy to recognise those from rheumatic hearts.

The results are set out in tabular form (Fig. 105).

The difference between the rheumatic and non-rheumatic groups is very striking in the left and right auricular appendages and atrial walls and less so in the ventricles. In both series the valves show metachromasia in the majority of cases.

In the rheumatic series 17 out of 28 cases show meta--chromasia of the left auricular appendages and 15 of the left atrial wall as compared to one case in the non-rheumatic group. $I_n$ the ventricular myocardium only 8 cases showed metachromasia in the rheumatic group and none in the control series. In the ventricles the metachromasia was detected in association with cellular lesions in a few cases and also in

the adventitia of blood vessels and diffusely in the septa but some cellular lesions showed no metachromasia. In Case 189, a case in which reticular Aschoff nodules and arteritis was present, no metachromasia was detected in association with the lesions in the ventricles.

A surprising feature was the presence of metachromasia in the right auricular appendages of rheumatic hearts in 10 cases. The majority of these cases also showed meta--chromasia in the left auricular appendage.

The same technique was applied to a comparison between the metachromasia in biopsy specimens and in the left auricular appendage control series.

In the control series of 90 left auricular appendages metachromasia was found in 10 cases (11 per cent).

In the biopsy series, of the 112 cases showing evidence of active rheumatic lesions, all but 11 cases i.e. 90 per cent showed metachromasia. Of the remaining 63 cases with no evidence of active rheumatic lesions 12 cases i.e. 19 per cent showed metachromasia.

Metachromasia is of course frequently encountered in organising thrombus but this was not included in the figures given.

Because of autolytic changes in the post-mortem cases these two series are not really comparable to one another.

As has already been explained metachromatic dyes are very variable in their behaviour but as all cases in these

series have been treated in a standardised manner, it is leitimate to compare them.

It appears from these studies that in biopsy specimens, the great majority of cases showing active rheumatic lesions, using the criteria I have described, show metachromasia but in a further 20 per cent there is metachromasia in the absence of other evidence of active rheumatic lesions.

Similarly in autopsy series B metachromasia was found in all cases except one in which active lesions were present but in addition metachromasia of the left auricular appendage was found in 10 out of 23 cases in which there was no histological evidence of rheumatic activity.

The interpretation of these results presents great difficulty. As has already been shown, the metachromatic material imtimately associated with rheumatic lesions does not differ in its behaviour from similar substance found in various situations in the connective tissues and chemical analysis of connective tissues shows that there is normally a mucopolysaccharide component in these tissues. Under certain conditions this is demonstrable by metachromatic staining.

The explanation for this difference in the presence of metachromasia in the left auricular appendage and left atrium of cases of mitral disease as compared with non--rheumatic cases may lie in two considerations: (a) that this results from the rheumatic disease process or (b) that

some alteration in the mechanics of the blood flow due to valvular disease, hypertrophy of the atrial wall, or the presence of congestive cardiac failure may account for the difference.

(a): There are two opposing factors to be considered in this connection. As has already been discussed the earliest lesions in rheumatic disease consist of oedema or according to Talalajew "mucoid oedema". As has already been stated the mucoid material stains with toluidine blue. The question as to whether "oedema" occurs before I.H.S. appears is difficult to answer. In the biopsy specimens this does not appear to be the case, although it would be very difficult to prove.

In my own autopsy series I have seen oedema in rheumatic hearts which did not stain with Ehrlich's haematoxylin, but in view of the effect of autolysis there is a possibility that it may have stained if fresh tissue had been obtained.

The fact that in most descriptions in the literature oedema is mentioned without reference to its stainibility with haematoxylin may be due to the types of haematoxylin employed or to autolysis. It remains a possibility that toluidine blue staining detects an earlier change than that described as "mucoid oedema" in the literature or as I.H.S. by myself. On the other hand it is possible that meta-chromasia persists in the tissue after healing of the lesions has occurred. Bunting (1950) states that he found

old rheumatic scars in the myocardium to show metachromasia. In a few cases in my own series this was the case but in the majority no metachromasia was noted. As has already been described with I.H.S., in older lesions metachromasia was much less prominent than in fresh lesions and in 11 cases showing developed lesions metachromasia was not found. These were all freshly fixed specimens and the question of autolysis does not enter into this.

In the rheumatic series B the right auricular appendage and right atrial wall showed metachromasia in a number of cases in which the left auricular appendage and left atrial wall also showed metachromasia. This could be considered as further evidence that a more widespread change occurs in the tissues in rheumatic disease than the subsequent development of nodular lesions would lead one to believe.

(b): It must be remembered that in all the rheumatic cases considered - autopsy and biopsy series - there is damage to the mitral valve leading to altered conditions in the left atrium e.g. alterations in pressure. Furthermore, in cases developing congestive cardiac failure similar changes occur in the right atrium. It is possible that this is a factor in producing the difference between rheumatic hearts showing no evidence of activity and the control series. The absence of metachromasia in the left auricular appendage and atrial wall in half of these rheumatic cases might be due to autolytic changes. However,

80 per cent of biopsy specimens showing no evidence of activity also showed no evidence of metachromasia and autolysis is not a factor in this case.

Death in congestive cardiac failure was the rule in rheumatic heart disease and it is possible that the increase in metachromasia in those cases showing no evidence of activity is due to this. In the control series approximately half of the patients died in congestive cardiac failure and the organs showed chronic venous congestion without any evidence of metachromasia in the right or left atrial endocardium.

In the presence of so many variables - the behaviour of the dye, the varying times between death and fixation of tissues with the proven loss of metachromasia on autolysis, the differences in the mode of dying, the variations in the degree of valvular damage, and the difficulty of knowing if metachromasia persists after healing of rheumatic lesions makes further speculation unprofitable. The possibility remains, however, that a higher proportion of patients dying from rheumatic heart disease may be in an active phase of the disease than is revealed by standard histological procedures.

As a diagnostic method, toluidine blue staining appears to be of little or no value.

# CHAPTER 5.

## THE NATURE OF THE CHANGES IN THE COLLAGEN.

In the lesions described in auricular appendages several morphological appearances of the altered collagen have been noted in what appear to be the earliest stages of the process, and these have been divided somewhat arbitrarily according to the degree of eosinophilia.

The altered collagen found in the earliest forms of lesion associated with little or no cellular increase and large amounts of I.H.S. may be intensely eosinophilic, hyaline or slightly granular, or it may be less eosinophilic and hyaline but more eosinophilic than normal collagen or it may have a dull hyaline appearance staining to the same degree as normal collagen. (Figs. 45 - 54; 60; 76).

In the more developed lesions the collagen is usually either moderately eosinophilic or stains in the same way as normal collagen and sometimes in the latter type the collagen may be amorphous or granular. In developed lesion the intense eosinophilic appearance is not recognised. (Figs. 8, 11, 12, 22, 23).

In all these grades of change, single or multiple fibres may be involved in a focal fashion or long stretches of collagen may be affected, a variable degree of fusion of adjacent fibres being present.

Apart from the eosinophilia these types of altered collagen show a fairly close similarity in their staining reactions.

In the majority of cases the altered collagen stains with the collagen stains e.g. it usually stains with the acid fuchsin of the Van Gieson stain (Fig.61), the blue or green of the Mallory or Masson trichrome stains and stains brown with the phosphotungstic acid haematoxylin stain. On occasions and especially when the collagen is dull pink and granular, fragments may show yellowish staining with the picric acid component of the Van Gieson stain. In some of the larger fused areas, focal yellow staining may be present within the altered collagen, the bulk of which stains red with the red fuchsin giving a red and yellow pattern to the area (figs.46: 87). Van Gieson's stain was employed in every case and only on occasions was yellow staining of the collagen noted.

The most commonly employed fibrin stain is Mallory's phosphotungstic acid haematoxylin (P.T.A.H.) and this was carried out in every specimen. In addition selected sections were stained with Lendrum's acid picro-Mallory and eosin--phloxine-tartrazine stains, and Weigert's Gram method. The advantage of the P.T.A.H. stain is that it requires no differentiation and has therefore a great advantage over the other methods which depend on differentiation.

In none of the biopsy specimens was a fibrin staining

component detected in the altered collagen. In some of the more florid lesions small fibrils staining blue were noted in P.T.A.H. preparations. These would often be traced to the cytoplasm of cells and appeared to be cell processes. They were not demonstrable by other fibrin stains.

It is perhaps worth while mentioning that on occasions the cell cytoplasm and nuclei stain almost uniformly dark blue with the P.T.A.H. stain and it is difficult to recognise these structures as cells. Other staining methods e.g. the eosin-phloxine-tartrazine method showed these structures to be cells. Another source of possible error is the presence of smooth muscle fibres in the endocardium.

In only one autopsy specimen, Case 189, was a fibrin staining component detected in the lesions. This was present in the reticular Aschoff bodies in the myocardium, in the lesions around vessels, in the vessel walls and in the valves and pericardium. (Figs. 81 and 82).

The band of altered collagen in the left auricular appendage did not stain with the fibrin stains. The fibrin staining fibres stained orange-red with the Van Gieson stain, and the left auricular lesion stained a mixture of red and yellow.

Certain histochemical methods were employed to try to define the differences between the various morphological types of altered collagen and normal collagen.

Sections were taken of auricular appendages which showed the various types of change described. Owing to the small size of many of the lesions and the large numbers of sections required for staining by various methods and for controls, all the methods could not be carried out on the same lesions. The results here are based on a large number of cases in which each method was employed. Controls of non-rheumatic auricular appendages, valvotomy specimens without lesions and skin were used.

Sections were taken from autopsy specimens especially from Case 189, the lesions of which showed a fibrin staining component.

Toluidine blue was employed in every specimen and gave consistent results. The sections used were the same as those for I.H.S.

On examination in water the altered collagen sometimes stained a light pink. After dehydration in acetone and clearing in xylol the altered collagen stained light blue. Fine fibres within the lesions frequently stained reddish-pink.

The periodic acid Schiff reaction was also employed in every case. With the method used the unaffected collagen stained a light pink as did the collagen in the controls.

The eosinophilic hyaline altered collagen stained a deeper red than normal collagen. (fig. 106). The intensely eosinophilic hyaline or slightly granular material stained

deep red and the duller pink hyaline or granular material stained to the same degree as collagen or slightly more intensely. On occasions in the larger areas of intensely eosinophilic fused material parts stained more intensely with the P.A.S. than the remainder.

The Millon reaction for tyrosine occasionally produced faint orange staining of the altered collagen but this was of less intensity than the staining of the muscle fibres. In most cases the reaction was negative.

The altered collagen proved to be resistant to the action of hyaluronidase, trypsin, pepsin, ribonuclease, and pectinase. After treatment with these enzymes the staining reactions of the altered collagen with eosin, Van Gieson stain, the P.T.A.H. stain and the P.A.S. stain were unaltered.

The results obtained with pectinase differ from those reported by Glynn and Loewi (1952) and Pearse (1953). These workers were able to abolish the P.A.S. reaction in the "fibrinoid" of rheumatic skin nodules with pectinase. Glynn and Loewi used a pectinase from onion root. In the biopsy specimens glycogen was quickly removed by the pectinase and there was a reduction in metachromasia but the P.A.S. reaction of normal and altered collagen remained unaffected even after treatment for 5 days.

In my description of rheumatic lesions the change in the connective tissues has been called "altered collagen".

This term has been deliberately employed to avoid the use of the very frequently employed terms "fibrinoid change", "fibrinoid necrosis" or "fibrinoid change of the ground substance. These terms are not only applied to the changes in rheumatic fever but are applied to morphologically similar materials found in other diseases e.g. disseminated lupus erythematosus, rheumatoid arthritis, the substance in the floor of peptic ulcers and in the walls of bursae, polyarteritis nodosa, scleroderma and malignant hypertension. If the term were restricted to one set of morphological appearances there could be little objection but in rheumatic fever for example it is employed to describe the intensely eosinophilic fibres in the reticular Aschoff body (the rheumatic "Frühinfiltrat" of Klinge), the homogenous material of the auricular lesion, the moderately eosinophilic hyaline or amorphous material of the early coronal Aschoff body or the dull pink granular or hyaline material in other lesions. This to my mind makes for confusion especially when no description is attached to the term.

This confusion is well illustrated in the discussion on Bennett's paper in the First Conference on Connective Tissues of the Josiah Macy Foundation (1950).

The term "ground substance" is often linked to that of "fibrinoid" and the phrase "fibrinoid change of the ground substance" is the one most frequently employed in the more recent literature. This second term "ground substance" is

also confusing to my mind as it is frequently used to indicate substances or hypothetical substances which have different anatomical locations. It is used to indicate the cement substance of collagen fibres i.e. the substance in collagen fibres which lies between the fibrils, and the material which is supposed to lie in the tissue spaces between the fibres, or to both. Klinge (1933) uses it in both senses. Most often no indication is given. The term "fibrinoid degeneration of the ground substance" at least in its application to rheumatic fever may therefore mean a variety of morphological changes.

The publications on the auricular appendages in mitral valvotomy, illustrate very clearly the confusion which arises as the result of such nomenclature. A few examples will suffice.

Enticknap (1953) is of the opinion that the lesions either may not be rheumatic or that they are inactive because there is no fibrinoid.

McKeown (1953) illustrates and names the altered collagen as "fibrinoid change of the ground substance".

Tedeschi et al (1955) draw a distinction between the altered collagen and "fibrinoid degenration of the ground substance". They are of the opinion that only 8 cases in their series of 400 show "active" rheumatism. Of these 8 cases 4 showed alterations of the collagen only but in 4 others there was in addition "fibrinoid change of the

ground substance".

Although the introduction of the term "fibrinoid" is attributed to Neumann (1896), it came into common usage at least in connection with rheumatic diseases after Klinge's very intensive investigations.

The ideas put forward by Klinge (1933) are based on his study of the rheumatic process in the heart and in other situations in acute rheumatic fever.

According to Klinge the earliest changes are oedema of the connective tissues followed or accompanied by swelling of the connective tissue fibres which become eosinophilic and wax-like and stain with the fibrin stains - but not always. "Apparently a threshold damage has to be present to get a positive fibrin stain".

In Klinge's view the change occurs initially within the collagen fibres and on p.34 he says "these histological findings can only be interpreted as acute swelling and a chemical change of the ground substance which surrounds the fibrils..... It is easily demonstrable that the fibrinoid masses lie within the connective tissue fibres and not between or in the meshes of the tissues. Later on the meshes are filled with the same substance and thus frequently described fibrin masses are found". He then goes on to say that the chemical identity of the substance within the fibres and that in the tissue spaces is uncertain but that histologically they appeared to be the same.

In this early stage there is no increase in connective tissue cells but there may be an exudate of lymphocytes and polymorphs which in the heart may be of such intensity as to overshadow the "oedematous phase".

This early stage he calls the exudative-degenerative phase after Talalajew (1929).

Following this phase there is proliferation of connective tissue cells giving rise to the "Aschoff nodule".

The "fibrinoid" gradually becomes absorbed, the material staining a dull pink with eosin and later in the "scarring" stage staining in the same way as normal collagen.

Klinge however qualifies this general description by stating that in the heart the exudative-degenerative phase was not well developed but the proliferative phase was well developed, in contrast to skin nodule where the exudative-degenerative phase was well developed and proliferative phase minimal.

Gross and Ehrlich (1934 a and b) take a different view. They believe that a fibrin staining component is rare in rheumatic fever in the heart and when it occurs it is usually found in the "reticular" Aschoff body, the appearance of which from their photographs correspond to what Klinge calls the "Frühinfiltrat". They reported that the reticular Aschoff body is most commonly found in first acute attacks of rheumatism and less commonly in recurrences. They also believe that what they describe as early coronal lesions is

another form that early rheumatic lesions take. Klinge thought that the reticular Aschoff body developed into the coronal type by the filling in of the spaces between the fibres by material similar to that in the reticular Aschoff body. Gross and Ehrlich were unable to show any transitions between the two forms. Lendrum took a similar view but illustrated one lesion suggesting a transition.

It is possible I believe to reconcile these two views, not so much from the photographs of these publications but from the descriptions in the text and the interpretations put on these descriptions. The stage preceding the coronal stage is a mass of eosinophilic collagen which does not usually stain with the fibrin stains but this mass of eosinophilic collagen could have arisen from fusion in the manner described by Klinge although it has not gone through the stage of the intense eosinophilia of the "reticular" Aschoff body.

The importance of determining the earliest types of changes in the collagen becomes obvious in the auricular appendages of valvotomy specimens. I have not seen in my own series nor have I seen illustrated the intensely eosinophilic refractile, latticed appearance of the collagen illustrated by Klinge as the "Frühinfiltrat". The earliest changes present are similar to those described by Gross and Ehrlich, as the stage preceding the development of early coronal type lesions and there can be little doubt that

these changes are early phases in the process.

There is a similar divergence in view between Gross and Ehrlich and Klinge in the interpretation of what is happening within the areas of altered collagen.

Both Klinge and Gross and Ehrlich described silver staining fibrils in the lesions which Klinge believed were collagen fibrils denuded of their normal "ground substance". He describes these silver staining fibrils passing through the altered collagen but Gross and Ehrlich took a more cautious view. They were unable to satisfy themselves that these silver staining fibrils were passing through the altered collagen and furthermore they described fragmentation of collagen. Klinge's view was that the fibrils were preserved the change occurring between the fibrils or as he describes it in the "ground substance" of the collagen fibres. As the lesions retrogressed these fibrils became non-silver staining and were re-converted as it were to collagen fibres. Klinge put forward the view that destruction of the collagen fibrils was rare in the heart in rheumatic fever but sometimes occurred in skin nodules.

Lendrum (1941) was of the opinion that the fibrin like material was deposited on the surface of the fibres and permeated through them in places.

The question of the role of collagen in the formation of "fibrinoid" and the chemical nature of the alteration in one which is still unsolved. Various histochemical, chemical

and biophysical techniques have been emplcyed but the evidence is conflicting. Most of this work has been done on skin nodules of rheumatic fever or of rheumatoid arthritis. In view of the morphological differences occurring in early lesions of rheumatic fever it is doubtful if results obtained from skin nodules can be directly applied to lesions in the heart. Also it is perhaps open to question if results obtained from another disease, e.g. rheumatoid nodules, can be applied. Gueft and Laufer (1954) have shown that the "fibrinoid" in the connective tissues in disseminated lupus erythematosus is a break down product of nucleo-protein and a disorder of nucleo-protein is known to be present in disseminated lupus erythematosus but not in other diseases.

There are three research tools available which may provide an answer to the question of the preservation of collagen fibrils. These are X-ray diffraction studies, electron microscopy and polarisation microscopy.

X-ray diffraction studies have been carried out by Kellgren et al (1951) on rheumatoid nodules and by Feitelberg (1954) on rheumatoid nodules and endocardial vegetations of disseminated lupus erythematosus. They found the diffraction pattern to be different from that of collagen and distin-guishable from fibrin. Studies of this nature have not been done on lesions in the heart in rheumatic fever.

Electron microscopy yields conflicting results. Most of the electron microscopy of collagen and "fibrinoid" has

been done on teased preparations and is open to the objection that if the fibrils are damaged they may not be recognised. Rich et al (1953) reported that in fibrinoid changes in the Arthus reaction the collagen fibrils showed degenerative changes. Kellgren et al (1951) reported that an amorphous substance was present in rheumatoid nodules and the proportion of collagen fibrils was variable in different areas. Gale (1951) found no alteration in the collagen fibrils.

Polarisation microscopy studies do not appear to have been carried out on "fibrinoid". Normal collagen shows positive birefringence and on examination of the altered collagen in rheumatic lesions of the heart it was found that birefringence could be demonstrated within the altered collagen. This examination can only be carried out if there is a long enough straight stretch of material. Figs. 107-111 show the birefringence of the altered collagen in rheumatic lesions in the heart. This can be demonstrated in the earliest types of lesion and in more developed stages. No attempt was made to carry out detailed studies on the polarisation microscopy of the altered collagen as this is beyond the scope of this work. The presence of birefringence in the altered collagen suggests an orientated structure similar to that of collagen but it does not necessary mean that the collagen fibrils are intact. In rheumatoid nodules even in the very loosened granular

areas birefringent fibres can sometimes be seen.

An investigation of the polarisation microscopy of the altered collagen in conjunction with electron microscopy of sections is planned but in view of the focal nature of the changes and the variations in the microscopy this investigation is likely to prove a very long term procedure. It is felt that electron microscopy of sections rather than teased preparations is more likely to yield information since localisation of the change is impossible with teased preparations. This work is planned in conjunction with Dr. D. B. Brewer of this department who is making a study of the polarisation microscopy of various tissue components.

In addition to biophysical methods employed, various histochemical, enzymatic and chemical investigations have been carried out. Apart from histochemical studies most of this work has again been carried out on skin nodules in rheumatic fever and rheumatoid arthritis. At a histochemical level there is agreement that "fibrinoid" is P.A.S. positive and that there is also a protein component. Most authors believe it is possible to distinguish this material from fibrin by the action of trypsin which has little effect on fibrinoid but rapidly destroys fibrin. (Glynn and Loewi, 1952). The P.A.S. reaction is not of value in distinguishing these substances. On a histochemical basis "fibrinoid" is thought to be a carbohydrate-containing protein. On the

basis of the eosinophilia the protein has been considered by Altshuler and Angevine (1949; 1954) to be a basic protein. They put forward their theory that "fibrinoid" consists of acid mucopolysaccharide and basic protein possibly fibrinogen or a break down product of some constituent of the connective tissues. They believe this results from an interaction of the protein with the "ground substance". In a diagram (1955) they clearly indicate that what they call "ground substance" is in the tissue spaces.

Chemical estimations are conflicting. Consden et al (1950) reported that chemical estimations of rheumatic skin nodules showed that "fibrinoid" consisted of collagen plus excess mucopolysaccharide and a tyrosine containing protein. On the other hand Ziff et al (1953) reported that fibrinoid contained little or no collagen. In rheumatic lesions as seen in the heart it would be very surprising if collagen could be separated from the material which, if not related to collagen protein, is so intimately related to collagen fibres.

It is perhaps again worth while stressing that in rheumatic lesions in the heart the earliest changes show a variation and that apart from eosinophilia and a more intense P.A.S. reaction the altered collagen frequently stains with the collagen stains, a fact which has not been satisfactorily explained in any of the investigations quoted.

My own observations confirm the opinions of Gross and

Ehrlich (1935 a and b), and Lendrum (1941) that the early changes in the connective tissues of rheumatic lesions in the heart may show different morphological appearances. Histochemically they show variations, especially in the intensity of the P.A.S. reaction. This may merely represent a variable degree of damage but it would be unwise to assume that results obtained in one type of change can be applied to the other.

# CHAPTER 6.

## CHEMICAL ESTIMATION OF THE HEXOSAMINE/HYDROXYPROLINE RATIO IN BIOPSY SPECIMENS OF AURICULAR APPENDAGES.

Although it has been shown that there is a muco--polysaccharide material in the tissue spaces around and within the rheumatic lesions and also a carbohydrate component in the altered collagen, this may represent an alteration in the physical state of normal components of connective tissues e.g. the state of polymerisation or hydration of the tissues rather than an actual increase. Because of the mixture of tissues in auricular appendages total quantative measurements are of no value but since the mucopolysaccharides in the connective tissues are closely related to collagen it is possible that an increase in one component would be reflected in an alteration in the ratio of one component to the other.

As an index of mucopolysaccharides hexosamine has been used by various workers (Sobell et al 1953; Loewi 1953; Matthews 1952) and this can be estimated in tissues. Hydroxyproline is found mainly in collagen and the amount of hydroxyproline in tissue estimations has again been used as a measure of the collagen content. The ratio of hexosamine to hydroxyproline may therefore be an index of the proportion of mucopolysaccharide to collagen. Other

factors being equal, an increase in the ratio would represent a relative increase in mucopolysaccharides.

Because of the extreme variations in the proportions of various tissues, the variations in the chemical estimations and the elastica content of the endocardium (which also contains hydroxyproline) it was realised that only very wide differences would be of any significance.

The processing of the tissue and chemical estimation were carried out by Dr. D. Hamer of the Department of Cancer Research, Birmingham University.

The estimations were carried out on auricular appendages removed from valvotomy cases. Because of the autolytic changes which have been shown to occur, control specimens were also cases from valvotomies which showed no evidence of rheumatic lesions or of I.H.S. The tissue was collected fresh in containers surrounded by ice, one or two blocks were removed for histological examination and were fixed in ten per cent formal-saline. The remainder of the tissue was minced and dried in a desiccator over $P_2O_5$ in vacuo and stored in the desiccator until required.

The estimations were all referred to 100 gm nitrogen of this material to allow for variations in the fat and residual moisture.

Estimation methods.

Nitrogen. Kjeldahl combustion followed by Nesslerisation.

Hexosamine. Method of Elson and Morgan (1933) with

modifications suggested by Rienits (1953).

Hydroxyproline. Method of Neumann and Logan (1950),

Tyrosine. Method of Undenfriend and Cowper (1952) using 1 - nitroso - 2 - naphthol.

The latter estimation was done as a guide to non--collagen protein in the tissues.

Estimation of hexosamine. 100 mg. tissue hydrolysed in sealed tube with 2 cc. 6 N HCl. for 4 hours, filtered with charcoal and made up to 10 ccs.

For estimation of amino-acids 100 mg. tissue hydrolysed in sealed tube for 18 hours with 6 N. HCl., evaporated to dryness, taken up in water and filtered with charcoal.

The results of amino-acid determinations were referred to nitrogen content of hydrolysate. Hexosamine was evaluated from nitrogen content of dried material.

The results given in Fig. 112are given on the basis of gm/100Gms tissue nitrogen.

The histological examination shows the presence of I.H.S. and rheumatic lesions and is arbitrarily graded according to the extent of the changes. Grade + means occasional lesions, ++ moderate numbers of lesions with moderate amount of I.H.S. and +++ refers to extensive lesions practically involving the whole endocardium.

There is no significant difference in the ratio of hexosamine to Hydroxyproline in the group showing active lesions and those without.

Two specimens contained organising thrombus (specimens 6 and 7). This is likely to have interfered with the results by introducing a further factor of organising tissue in which mucopolysaccharides are frequently present. In one of these specimens a consider--able amount of I.H.S. was present and both showed meta--chromasia within the thrombus. If these cases are omitted there is still no significant difference between the groups with and without lesions. However it should be noted that there is a marked difference in the number of observations (10 and 3) in the two groups. In those without lesions the highest hexosamine/hydroxyproline ratio is 3.6 and only two specimens with lesions (specimens 6 and 14) have ratios below this level.

If the number of observations in specimens without lesions and without organising thrombus had been increased it may have been conclusive.

Although the results are not statistically significant they raise the possibility of a relative increase in mucopolysaccharides in specimens with active lesions.

# CHAPTER 7.

## CHANGES IN TISSUES OTHER THAN HEART.

In acute rheumatic fever lesions are found in situations other than the heart e.g. joints, subcutaneous tissues and blood vessels and it has been postulated that in addition to focal lesions there is a diffuse alteration in the connective tissues e.g. in the skin. (Bywaters et al 1951; Ansell et al 1953). It was decided to examine skin and muscle, the only readily available tissues, from patients undergoing valvotomy.

The specimens were removed during operation from the skin incision and were fixed in 10 per cent formal saline. The tissue was embedded in paraffin and sections were stained with H and E, Van Gieson and toluidine blue. In one of the specimens there was a slight amount of I.H.S. in the skin but no changes were noted in the others. 40 specimens were examined with toluidine blue and no alteration was noted in the metachromasia of the papillary layer as compared with skin from non-rheumatic patients.

# CHAPTER 8.

## OBSERVATIONS ON THE DEVELOPMENT AND RETROGRESSION OF LESIONS IN AURICULAR APPENDAGES.

Various attempts have been made in the past to describe the development and retrogression of rheumatic lesions in the heart and the studies of Gross and Ehrlich (1934 a and b) are probably the most detailed and useful. This work has been confirmed by McKeown (1945). Other authors have given various estimates of the time interval between the beginning of an acute attack of rheumatic fever and the appearance of lesions: i.e. Giepel states that the coronal Aschoff body (which he illustrates) was present 5 weeks after an attack. Talalajew (1929) gave 3 weeks as the interval after which the proliferative phase was recognisable. Klinge (1933) gave 2 weeks.

The difficulties in determining cycles of this nature in a disease such as rheumatic fever are very obvious. Unless a definite interval is known between the beginning of the lesions and the time of examination and the lesions all follow the same course of development the problem becomes insoluble. In rheumatic fever the exact beginning of the illness is often difficult to determine and in some patients in which lesions are found at autopsy there is no evidence of an acute attack of rheumatic fever. If, as Klinge

believed, the lesions may heal in various ways sometimes directly from the initial stages without the intervention of a proliferative phase, only those lesions which progress and develop beyond a certain stage will be evident at any period of examination apart from the initial phases. In other words after a certain time the lesions still remaining may not represent the extent of the changes present at the beginning of the process.

It should be noted that Gross and Ehrlich (1934 a and b) and Gross (1935) made no attempt to describe in detail a cycle of events in the endocardium and sub-endocardium of the left atrial wall, or around blood vessels similar to that of the myocardial Aschoff body. According to these workers the presence of large amounts of collagen and of elastica and the extensive nature of the lesions made the changes difficult to follow but they believed that the cells went through a similar type of progression to those in the myocardial Aschoff body.

In their system, Gross and Ehrlich starting from reticular and coronal types of Aschoff bodies traced a development through mosaic, polarised and fibrillary stages leaving a fibrillar scar. Sometimes the fibrillar collagen formed into thick collagen fibres.

A search for cycles in auricular appendages of valvotomy specimens is not a very profitable procedure since there is no clinical evidence of the beginning of

the disease. Reliance has to be placed on the descriptions and opinions of others who used the beginning of an acute attack of rheumatic fever and the time of autopsy. This has not been carried out in auricular appendages. The method of applying the general pathological principles of exudative lesions preceding proliferative lesions and tracing developments of one form to another while possibly applicable to extremes may be very misleading. However, in certain instances the latter method is useful if used in conjunction with the former method.

It can readily be shown as McKeown (1953) has done that lesions corresponding in type to what are seen in myocardial Aschoff bodies can be detected in auricular appendages of valvotomy bases, but this is not the same as saying that all the lesions go through such a process. Some of the lesions in which thickened collagen bands are present especially the elongated strip-like lesions suggest that the thickened bands remain intact lose their eosinophilia, look identical to thick collagen fibres and remain as such without the intervention of stages corresponding to the fibrillar stages.

The early phases of the process described as the exudative degenerative phase, are well shown in some of the biopsy specimens. This has already been described but a brief resume is given to link more systematically the sequence of events as I see them.

The subendocardium and endocardium shows extensive collections of I.H.S. which may extend throughout all the tissues of the endocardium and subendocardium, into the myocardial septa and between the muscle fibres. Isolated foci may also be found within the myocardium. Muscle fibres may show wide separation. This change may or may not be accompanied by an exudate of lymphocytes and mononuclears. (Figs.56,90 ). Sometimes a very florid round cell exudate is present. The collagen at this stage especially the thinner fibres may be slightly basiphilic possibly due to the condensation of I.H.S. on the surfaces. Within these areas of I.H.S. or "mucoid oedema" the collagen swells, shows varying degrees of eosinophilia and fusion between adjacent fibres is seen. (Figs.43-45 ). The extent to which these changes occur is very variable, sometimes small focal areas are involved and in others long stretches of collagen are affected. The patterns formed by the altered collagen appear to depend on the direction and thickness of the fibres, the amount of collagen involved, the degree of fusion, the position in the endocardium or subendocardium and the intensity of the initial reaction. The cells at this stage may be small and shrunken with dark staining oval nuclei or if there is a cellular exudate of lymphocytes and mononuclears these may be focally arranged in the area in which the collagen shows these alterations or they may be more loosely and diffusely arranged. Sometimes they are

forced into rows between thick fibres in the elastica lamina. The superficial layers of the endocardium and the sub-epithelial layer may show mucoid oedema and an exudate of lymphocytes. Between the areas of altered collagen in areas where the collagen appears undamaged there may also be cellular infiltrations associated with I.H.S. It is emphasised that the changes in the connective tissues more especially the "mucoid oedema", is more extensive than the subsequent development of Aschoff body-like lesions would suggest.

Cells collect between and around the altered collagen giving rise to a number of patterns which correspond loosely to the coronal and mosaic lesions described by Gross and Ehrlich. In some the collagen has a reticular pattern and occasionally in some lesions at the points of intersection of the fibres small rounded foci of eosino--philic material are present. Although the pattern is similar to that described as reticular the fibres lack the intensely eosinophilic wax-like rigid appearance of the reticular Aschoff body. It should be noted that the pattern in many of these specimens appears to be mosaic from an early stage. The cells may be small mononuclear cells with a narrow rim of basiphilic cytoplasm or larger cells may be present. The cells of the lesion vary much in size and shape but they correspond to the forms described by Gross and Ehrlich. Sometimes multinucleate cells are found.

Within these lesions the collagen is often less eosinophilic and stains the same as normal collagen. What happens after this is difficult to follow. Polarised and fibrillar lesions can be detected in some specimens.

In some lesions a coronal arrangement of cells which bear a resemblance to fibroblasts is seen and I agree with McKeown (1953) that this may represent another form of healing.

In some developed lesions the collagen inside the lesions looks identical to the collagen outside in staining, fibre thickness and arrangement and fibres can be traced through lesions which suggests to be that a fibrillar stage may be omitted in some cases. (Figs. 113, 114) This is especially noticeable in the larger lesions where in some the long bands of thick collagen with cells palisaded along them look exactly like thick collagen bands such as are sometimes seen in specimens without lesions. On the other hand occasional fairly extensive fibrillar lesions are sometimes found in the subendocardium. This is of course not open to any type of proof but the appearances of the collagen within many lesions suggests that thick fibres may be the end result of the process without a fibrillary type of change. As has already been discussed fragmentation of collagen may also not occur in many lesions.

Aschoff (1939) described similar appearances of collagen fibres passing through lesions and put this forward

as proof that the lesions could develop without a preceding "fibrinoid" change of the "ground substance". From my own observations I think it more likely that these fibres or the cement substance of the fibres have undergone some change of insufficient intensity to alter the general arrangement of the fibres.

What is the significance of the collections of I.H.S. with or without round cell collections which lie between developed lesions in auricular appendages and also in the ventricular myocardium? Do these areas represent developing lesions or do they represent areas in which the initial alteration is so slight that it does not proceed beyond a certain stage? These are questions it is impossible to answer but again it must be emphasised that in some specimens with what appears to be more developed lesions the changes are less extensive than in specimens in which the earliest lesions are found. It should also be borne in mind that the methods of recognising the alterations in the collagen are extremely crude and it is possible that there is unrecognised alteration to the collagen in these areas.

With regard to the relative development of lesions in each specimen, usually when the earliest forms of lesions are present there are more developed cellular focal lesions present in addition. In the bulk of specimens it would be almost impossible to decide if the lesions are of the same age. In some there is a marked distinction in pattern and

these cases suggest lesions of different ages. This has also been found in the myocardium and McKeown (1945) remarks that fairly frequently lesions of different stages of development are found. If some of the areas between the developed lesions showing I.H.S. with or without cellular collections are developing lesions then in a large proportion of cases there is an "overlap".

Klemperer takes a very dynamic view of the "collagen diseases" and he suggests that lesions may frequently occur, some advance only to certain stages and retrogress and others proceed on to the later stage of fibrosis. This would provide a satisfactory solution to the interpretation of changes in the left auricular appendages of patients with mitral valve disease but it must remain in the realms of speculation.

To sum up these considerations.

The changes described by previous workers on the heart on the type and course of lesions in rheumatic disease can be seen in auricular appendages of valvotomy cases and also in the auricular appendages of patients dying from mitral valve disease. It is suggested that the sequence of events may not be as regular as that suggested by Gross and Ehrlich for the myocardial Aschoff body in that some lesions may not develop beyond a certain stage and that other lesions may leave thick collagen fibres instead of fibrillar scars.

Lesions of different "ages" may be present in a large proportion of specimens.

# CHAPTER 9.

## CLINICO-PATHOLOGICAL CORRELATION OF PATIENTS UNDERGOING VALVOTOMY.

The patients selected for operation at the Queen Elizabeth Hospital, Birmingham came from three sources.

1: Those selected by the physicians of the Birmingham United Hospitals and referred to the cardiac surgeons.

2: Those selected by physicians of other hospitals in the Midlands (i.e. non-teaching hospitals) and referred to the cardiac surgeons.

3: Those selected at the surgical cardiac out-patient clinic by the cardiac surgeons from patients sent direct from general practitioners.

All operations were carried out by Mr. Collis and Mr. d'Abreu of the Queen Elizabeth Hospital.

The selection of types of patients from different sources varies considerably depending on the criteria adopted by individual physicians and surgeons.

On the whole (personal communication from Mr. d'Abreu) the physicians appear to be more conservative than the surgeons.

The patients ranged from those who were seriously ill, unable to walk for more than 100 yards, orthopnoeic,

suffering from congestive cardiac failure and auricular fibrillation and who had a long history of severe cardiac disability to patients who were dyspnoeic on exertion but who were in sinus rhythm and had no congestive cardiac failure. The prognosis without operation must have varied very widely from patients who had an expectation of life of only a few weeks or months to those with a moderately good prognosis of several years.

The selection of patients therefore covered a wide range of different degrees of disability but all had in common a variable degree of dyspnoea and involvement of the mitral valve. Some patients had valve lesions additional to mitral valve disease.

The clinical data were derived from the hospital case notes and these varied considerably in value. The interpretation of the case notes was done entirely by myself and I accept full responsibility for this inter--pretation. Because the information was derived from case notes and was not organised beforehand, only the usual clinical and laboratory findings were used in the analysis since this information was available in most of the histories.

The histological and clinical data were compiled separately and the information was transferred to punch cards and analysed.

## Clinical data.

Patients' History:

Age

Sex

Dates of first and subsequent attacks of rheumatic fever and chorea, if any.

Duration of symptoms.

History of congestive cardiac failure at any time before admission to hospital for operation.

Clinical examination:

Temperature range.

Pulse range.

Presence or absence of auricular fibrillation before operation. In the majority of cases this was based on electrocardiograph findings.

Presence or absence of signs of congestive cardiac failure on admission prior to operation.

Presence or absence of clinical involvement of valves in addition to the mitral valve lesion.

Laboratory investigations:

Haemoglobin.

Erythrocyte sedimentation rate.

White blood count.

Treatment:

The administration of digitalis, neptal or salicylates before admission to hospital and also prior to operation.

Operation notes:

Presence or absence of calcification of the valve.

Presence or absence of stenosis or regurgitation.

The first 175 cases were analysed in this way. Short case summaries are given in the Appendix to give an indication of the type of patients submitted to operation.

In all cases except one the temperature was within normal limits and the pulse rates in those not receiving digitalis were also within the normal range.

None of these patients showed clinical evidence of acute or sub-acute rheumatism although in a few cases there were grounds for suspecting this, for example, a persistently raised E.S.R. or a pulse rate remaining at the top range of normal or perhaps a fairly rapid development of congestive cardiac failure. Rheumatic nodules were not noted in any patient and joint pains and skin manifestations were absent in all cases.

All patients showing signs of congestive cardiac failure prior to operation received medical treatment - rest in bed, low salt diet, digitalis and mercurial diuretics.

The 175 cases were analysed and the data outlined above were correlated with the presence or absence of active rheumatic lesions corresponding to the histological criteria given in Chapter 1.

For brevity and clarity, patients showing active rheumatic lesions will be "positive" (+) and those showing

no such evidence will be negative (-).

In all cases a separate analysis of males and females was made. Since this rarely showed any significant differences, only total results will be given in some cases.

I: There were 106 females and 69 males. The ages distribution of patients is shown in Fig.115, the range being 12 - 53 years.

There is little difference in the age grouping of the sexes and it will be noted that all except 25 cases were between the ages of 25 and 49 years.

112 cases out of the total of 175 i.e. 64 per cent showed histological evidence of active rheumatism. These were divided between the sexes in equal proportions. (Females 64.2 per cent; males 63.8 per cent.).

II: Fig.116shows the age distribution with respect to the presence or absence of active rheumatic lesions. The patients were divided into 5 year age groups.

At all age groups, except 50 and over, the numbers of patients showing active rheumatic lesions exceeds those showing no evidence of rheumatism. Up to age 35 - 39 there is an increasing proportion of cases showing no evidence of active lesions and thereafter it remains fairly constant. It was surprising to find two cases of 50 and over with active lesions. The same distribution of cases is found in both sexes.

III: 94 patients (53 per cent) gave a history of

rheumatic fever or chorea. The proportion of females giving a rheumatic history was 60 per cent as compared with 43 per cent of males, a difference which is statistically significant ($\chi^2 = 5.5$. $P = .02$).

55 per cent of "positive" cases and 51 per cent of "negative" cases gave a history of rheumatic fever or chorea.

IV: In Fig.117 is shown an analysis of various clinical data taken from the case notes. In each case the analysis is with respect to the total incidence of active rheumatic lesions.

Only erythrocyte sedimentation rates of over 10 mm. in 1 hour (Wintrobe) for males and 20 mm. in 1 hour for females were taken as abnormal. These levels were taken in an attempt to render a raised level more indicative of "activity".

The most outstanding feature of this analysis is the marked difference in the incidence of active rheumatic lesions in patients in sinus rhythm and those with auricular fibrillation. Of the patients in sinus rhythm 88.5 per cent showed histological evidence of active rheumatism and only 33 per cent of patients with auricular fibrillation showed active lesions. This difference is highly significant.

In none of the other data considered is any significant difference noted. The E.S.R. for example appears to be of little value by itself as an index of activity.

Note the number of patients with raised E.S.R. who have no evidence of histological activity.

From these considerations it would appear that there are no simple clinical or laboratory findings or combination of findings which lead one to suspect the presence of active rheumatic lesions in patients with mitral stenosis who do not display the usual features of acute or sub-acute rheumatism.

The difference in the incidence of lesions in patients in sinus rhythm and those with auricular fibrillation has been further investigated. The following factors have been considered:-

1. The possibility of some factor in the auricular appendages of patients with auricular fibrillation which would obscure histologically the presence of active lesions.

2. The age of the patients.

3. Length of history of the disease.

4. Length of history of symptoms i e. dyspnoea.

5. The administration of drugs e.g. salicylates, digitalis or possibly mercurial diuretics.

1: The most obvious of the differences between those fibrillating and those with regular pulses is the presence of organising thrombus in the former.

Organising thrombus was noted in 50 cases and 46 of these were fibrillating.

Of the 46 cases 11 showed active lesions and 35 showed

no evidence of active lesions.

Of the 4 cases in sinus rhythm, 3 showed active lesions and 1 no evidence of activity.

As has been pointed out before, the subendocardium beneath an organising thrombus is frequently not involved in the organisation process although the endocardium itself is involved. Also in the majority of cases the thrombus is not found encircling the lumen of the appendage but is localised to one area. Because of these two observations it is not considered that the presence of organising thrombus is obscuring the tissue reaction of the rheumatic process in many cases. In 6 cases a very florid reaction was present within the thrombus, in the endocardium and subendocardium beneath the thrombus and in the endocardium of the surrounding unaffected areas.

2: The age distribution of patients in sinus rhythm and those with auricular fibrillation is shown in Fig. 118.

The proportion of patients with auricular fibrillation rises until the age group 30 - 34 years and remains fairly constant in the older age groups.

In Fig.119 the age distribution of patients in sinus rhythm and auricular fibrillation is shown with respect to the presence or absence of active rheumatic lesions.

In all age groups the number of patients in sinus rhythm showing active rheumatic lesions exceeds those in which no active lesions are found.

When patients with auricular fibrillation are considered, the proportion of patients showing no evidence of active rheumatism (i.e. negative patients) rises with age until age group 35 - 39 years beyond which the rise is not maintained.

From this graph it can be seen that age by itself is not a sufficient explanation for the difference between patients in sinus rhythm and those fibrillating.

3: Length of history of the disease.

The total length of history of the rheumatic disease was not known in the majority of cases but it was considered that the date of the first acute attack in those patients giving such a history could be used to compare the incidence of lesions with the length of history of the disease. The date of the first acute attack was known in 72 patients. Of these patients 36 were fibrillating and 36 were in sinus rhythm, an alteration in the proportions as compared to the whole series which should be borne in mind in interpreting the following groups.

Fig.120 shows this relationship. Up to 14 years from the first attack practically all patients have active lesions. Beyond this the proportions are approximately equal.

In Fig.121 the relationship of cardiac rhythm to the length of the history of the disease is shown. In this graph it can be seen that there are no patients of less

than 14 years history with auricular fibrillation. Beyond this the proportion of patients in auricular fibrillation increases and from 20 years onwards the numbers fibrillating exceed those in sinus rhythm.

Fig.122 shows the relationship of length of history, the presence or absence of rheumatic lesions and the cardiac rhythm. This graph illustrates that although the bulk of the patients in sinus rhythm give a shorter history of the disease than those fibrillating, there is no evidence that within the group showing auricular fibrillation the presence or absence of active lesions is related to the length of history.

These graphs (figs.120 - 122) do not take the age of the patients into account and in Fig123 a break down into age groups is shown. Because of the small numbers the patients have been grouped in ten year age periods.

There is a tendency, and it cannot be put stronger than that, for patients who are fibrillating to have a longer history than those in sinus rhythm in each age group and also for those with no active lesions to have a longer history. The numbers are, however, too small in most age groups to draw any definite conclusions.

4: Length of history of symptoms.

In the majority of cases a history was obtained of the approximate time of onset of dyspnoea and the time interval between the onset of symptoms and the date of

operation was related to the presence or absence of rheumatic lesions and the presence or absence of auricular fibrillation. For various reasons this analysis is based on 139 patients.

Fig.124 shows the length of history related to the number of patients, patients in sinus rhythm and those with fibrillation being shown separately. The bulk of the patients had histories of less than 14 years of symptoms. After 9 years of symptoms the proportion of patients with auricular fibrillation increases rapidly.

In Fig.125 the relationship of length of symptoms to the presence or absence of rheumatic lesions is seen, the result being indicated separately for sinus rhythm and auricular fibrillation. This graph shows a tendency which is not very marked for the proportion of cases with auricular fibrillation showing no active lesions to increase as the length of symptoms increases.

There is, of course, an age factor involved in the length of symptoms as it might be expected that older patients would have had symptoms for a longer period.

A further set of graphs (fig.126 ) shows the relation--ship between length of history of symptoms, the presence or absence of active lesions and the relationship with fibrillation in each ten year age group.

These graphs show that for each age group the same conclusions can be drawn as for the whole series namely that

there is a tendency for the proportion of patients in fibrillation to have had their symptoms longer than those in sinus rhythm and the proportion of patients in fibrillation showing no evidence of activity increases with the longer duration of symptoms.

5: Administration of drugs.

This investigation has been difficult to carry out. Salicylates were not administered to any patients except as mild analgesics on occasions and none of the patients were being regularly treated with full salicylate therapy. The same considerations apply to mercurial diuretics. In a small number of patients in congestive cardiac failure mercurial diuretics were administered but no difference was noted in those receiving mercurials.

When digitalis preparations are considered there is difficulty in getting sufficient information from the case notes as to whether or not the patients were taking digitalis regularly before admission for operation. It cannot be assumed that patients were not taking digitalis because no mention of this is made in the case notes. Definite information was given in 73 cases.

Of these 73 cases 58 were taking digitalis regularly before admission and 15 were stated as not taking digitalis.

Of the 58 patients taking digitalis 28 had active lesions and 30 had no evidence of activity. Of the 15 patients not taking digitalis 13 had lesions and 2 had

no lesions.

At first glance it looks as if there is a considerable difference in incidence of active lesions in those taking digitalis and those not taking digitalis but as might be expected there is a marked difference in the proportions of patients in sinus rhythm and auricular fibrillation taking digitalis.

If these are considered separately the difference in the incidence of active lesions between patients taking digitalis and those not taking digitalis disappears.

Sinus rhythm:

Information on 26 cases, 24 with active lesions and 2 without lesions.

Of the 24 cases with active lesions 12 were taking digitalis and 12 were not taking digitalis.

Two cases without lesions were not taking digitalis.

Auricular fibrillations:

Information on 47 cases, 17 with lesions and 30 without lesions.

Of the 17 with lesions 16 were taking digitalis and 1 was not. 30 cases without lesions were all taking digitalis.

If these figures are compared to the total number of cases with auricular fibrillation in the series 16 out of 26 cases showing lesions were known to be taking digitalis and 30 out of 50 without lesions were known to be taking digitalis.

It is evident from these figures that digitalis is very unlikely to have any effect in the incidence of lesions.

Digitalis and thrombosis in the left atrium.

There is conflicting evidence in the literature as to whether digitalis has an effect in increasing the liability to thrombus formation.

Askey and Neurath (1945) and Peters et al (1946) suggest that thrombo-embolic phenomena are increased in patients with myocardial infarcts receiving digitalis, and the latter stated that the increase could be prevented by the administration of dicumarol. De Takats et al (1944) found heparin to be less effective in the presence of digitalis. Others have come to the conclusion that there is no significant effect on humans; (Levin and Ruskin (1949); Cathcart and Blood (1950), Sutton (1950).).

If organising thrombi in auricular appendages of valvotomy cases are considered with respect to digitalis it is found that of 58 patients known to be taking digitalis preparation 27 had organising thrombi.

Of 50 patients with organising thrombi in the auricular appendages 27 were known to be taking digitalis.

4 of these 50 patients were in sinus rhythm and 46 were fibrillating.

Furthermore, of 12 patients in sinus rhythm taking digitalis, none had organising thrombi.

It appears likely that auricular fibrillation is the main factor and not the digitalis preparations. If a combined factor of digitalis and auricular fibrillation is operating to promote thrombus formation, the information available in this series is unsufficient to permit separation of these factors.

# CHAPTER 10.

## COMPARISON OF THE VALVOTOMY SERIES WITH AN AUTOPSY SERIES OF RHEUMATIC HEARTS OF COMPARABLE AGE DISTRIBUTION AND EXTENT OF DAMAGE TO THE MITRAL VALVE.

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As has already been explained the original autopsy series of 61 cases has been reduced to 28 to provide a reasonable comparison with the biopsy series.

The age distribution of the whole original series of 61cases is given in Fig.127. The age was known in 59 cases. Note the high proportion of patients over the age of 50.

Fig. 128 shows the age distribution of the 28 cases used for comparison with the biopsy series. There is a noticeable difference in the two series. In the autopsy series the largest number of patients is found in the 40 - 49 age group whereas in the biopsy series the largest number is in the 30 - 39 age group. (Fig.115).

There were 15 female and 13 males, a reduction in the proportion of females.

Biopsy series Females : males 1.53 : 1

Autopsy series Females : males 1·15 : 1

7 out of 28 i.e. 25 per cent showed active lesions as compared with 64 per cent in the biopsy series. 5 of the 7

cases had lesions in the left auricular appendage i.e. 18 per cent.

The remaining data are given in Fig.129. The information is often incomplete and only positive findings are given.

The most outstanding difference between the two series is in the proportion of patients showing auricular fibrillation. In the biopsy series the ratio of sinus rhythm/auricular fibrillation was 1 : 0.80 and in the autopy series 1 : 3.65.

The numbers of cases in sinus rhythm is very small as compared with the numbers in auricular fibrillation and the proportion showing active lesions is not significantly higher. When the total autopsy series of 61 cases is considered the following figures are obtained:-

| | No. of cases | + | - |
|---|---|---|---|
| Sinus rhythm | 12 | 6 | 6 |
| Auricular fibrillation | 47 | 6 | 41 |
| Not known | 2 | | 2 |
| Total No. of cases | 69 | 12 | 49 |

In the whole series the incidence of lesions in those with sinus rhythm is significantly higher than those in auricular fibrillation. ( $\chi^2 = 8.2$ $P < .01$).

It is to be noted that roughly the same proportions of patients in sinus rhythm are present in the whole of the series as in the selected portion and the incidence of

of lesions is the same.

It should be remembered that all cases of rheumatic heart disease are included in the series and at least 3 cases were though on clinical grounds to have a recrude--scence of rheumatic fever in their last illness.

This, I believe, may explain in part the difference between the high incidence of lesions in the biopsy series and the low incidence in post-mortem series. It is unlikely to be the whole explanation since Graham et al (1951) describe a series of 101 cases in which 40 patients were in sinus rhythm and 61 had auricular fibrillation. 43 cases were below the age of 50. The incidence of Aschoff bodies in the whole series was 10 per cent.

This incidence in post-mortem series B is not strictly comparable with the figures given in most series, but in view of the small numbers of patients (3) with clinical recrudescence at the time of death as compared with the large number (56) which were not believed to have clinical evidence of rheumatic fever the totals can I believe be compared directly with other series in which there was no clinical evidence of activity.

In most of the series published no clinical details are given and it is not possible to compare them from the point of view of auricular fibrillation.

The incidence given by various authors in the literature shows a considerable variation. This variation is, I believe,

due partly to the pathological criteria used for the diagnosis of active rheumatism, partly to the different age distributions and partly to the fact that clinical criteria for the diagnosis of active rheumatism in the final illness has varied. Because of this latter factor in my own series I have made no effort to split off the group of those considered on clinical grounds to be "active".

The incidence of rheumatic lesions, or more correctly of Aschoff nodules in post-mortem studies of clinically quiescent cases has been reported from many sources. In few cases is there sufficient clinical data to draw any comparison with my own series.

Coombs (1924) was, I believe, the first to draw the negative association between auricular fibrillation and rheumatic activity. In his clinical investigations he noted clinically active rheumatism in only 9 cases out of 58 cases of auricular fibrillation shown in his table IX and only 1 case in 12 post-mortem examinations of patients with rheumatic heart disease who were fibrillating.

In my reading I have not come across another post-mortem series giving this information although it can be inferred from studies on thrombosis in the auricular appendage. For example, Weiss and Davis (1933) found extensive auricular thrombosis in 28 cases out of 164 cases. Of these 28 cases the rhythm was known in 25 and of these

25, 22 were fibrillating.

Rheumatic activity (a combined clinico-path. approach) was found in only 5 cases with thrombi i.e. 18 per cent as compared with 43 per cent in the general series. This is, however, a special series in which thrombus formation was being investigated in relation to rheumatic activity.

Clawson, Bell and Hartzell (1926) in their group of "Old healed valves" found 3 cases out of 25 with Aschoff nodules in the myocardium in cases under 50.

Gross, Antopol and Sacks (1930) give a figure of 15 per cent in clinically quiescent cases of rheumatic heart disease coming to autopsy.

Klinge gives an incidence of 15 per cent in his series of clinically inactive cases.

Rothschild, Kugel and Gross (1933) using a combined gross pathological and histological method found active rheumatism in 106 cases out of 161 i.e. 66 per cent in all age groups.

From their table I it can be seen that between the ages of 21 - 50 there were 67 cases of which 40 were active (60 per cent).

Their figures for the decades corresponding to my own series are as follows:-

| | No. of cases | No. active | per cent |
|---|---|---|---|
| 21 - 30 | 16 | 11 | 78 |
| 31 - 40 | 30 | 21 | 70 |
| 41 - 50 | 21 | 8 | 38 |

These figures are very much higher than in my series in which histological criteria alone were used and my own figures do not bear out their findings that death in congestive cardiac failure up to the age of 50 in patients with rheumatic heart disease is closely correlated with rheumatic activity.

It is interesting to note that the ages of the patients in their series coming to autopsy show an almost complete reversal of the age grouping in the patients in my series. In my total series of 59 cases half were above the age of 50. Even excluding the 66 patients below the age of 20 in Rothschild's series only 28 cases were above the age of 50 as compared with 67 between the ages of 21 and 50. No information is given in this paper of the state of pulse or whether or not the patients were believed to have clinical evidence of activity. In this connection it should be borne in mind that the management of patients has improved and possibly the use of antibiotics and other measures is now resulting in patients with rheumatic heart disease living for longer periods. Many other factors may be involved such as the type of hospital and the area in which the hospital is situated. It is also possible that rheumatic heart disease has been changing its character during this century. In view of the close relationship of acute rheumatic fever and streptococcal infections this would be in keeping with the change in

diseases such as scarlet fever and acute nephritis which are now much less severe.

# CHAPTER 11.

## REVIEW OF HISTOLOGICAL STUDIES OF VALVOTOMY SPECIMENS.

It would perhaps be most useful at this stage to discuss the results and opinions of other people who have published their observations on valvotomy specimens. For easy reference to the variation in results fig. 130. shows the total results in various series published mostly in the English language. In the majority of cases it should be noted that the incidence is that of "Aschoff nodules" and there is considerable variation in the criteria used in the diagnosis of "Aschoff nodules".

The first published report of Aschoff nodules was that of Ellis and his co-workers (1951). In a paper concerned with the physiologico-pathological correlation of mitral stenosis they stated that four cases had shown Aschoff lesions in the left auricular appendage. They stated that autopsies on two of these cases revealed no active lesions elsewhere in the heart. No illustrations are given of the lesions in the auricular appendages.

Pinniger (1951), the first British series, showed Aschoff nodules in 10 of 15 cases. He illustrated fairly florid lesions, and some less well formed lesions including a band of altered collagen. He found occasional small areas of fibrin staining using the Weigart Gram method. One case

with lesions died and nodules were found in the myocardium of the left ventricle . Six cases out of 19 autopsy specimens showed myocardial lesions but the left auricular appendages were not examined. He believed the lesions represented sub-clinical rheumatism.

Kuschner et al (1952) showed four cases with definite Aschoff nodules. Of the remaining seven in their series 4 showed thrombi and all four were fibrillating.

They believe these findings may explain in part the development of typical rheumatic heart disease in patients who have never had clinically detected rheumatic fever and also may explain the progressive cardiac damage in patients who show no clinical evidence of recurrences of activity.

Catto, Taylor and Smith (1952) showed lesions in 15 of 25 cases. They describe "sub-endocardial cell formations of the Aschoff body type in an oedematous subendocardium infiltrated with mononuclear cells", and they were usually centred in swollen or fragmented hyaline collagen. Although no photomicrographs are given, their verbal descriptions correspond to what I have described. They describe "Aschoff cells" with characteristic nuclei and basiphilic cytoplasm with indefinite edges, lymphocytes, larger mononuclears and "sometimes a radial arrangement of endothelioid cells in the bodies". They do not define endothelioid cells.

No relationship was noted in their series between activity and thrombus formation. In the cases with thrombi

the endocardium sometimes showed lymphocytic infiltration. The subendocardium in appendages not showing activity showed dense fibrosis sometimes with whorled areas suggesting healing of miliary granulomas.

Of 3 cases dying after valvotomy, 2 showed lesions in the auricular appendages and both showed myocardial lesions.

They expressed the view that the selection of patients with mitral stenosis may be the cause of the high incidence of rheumatic lesions in operative specimens and also are of the opinion that rheumatic inflammation may proceed in the absence of clinical activity gradually producing a progressive fibrosis and fresh bouts of clinical activity may be associated with a more acute exudative reaction.

They also state that in concentrating on the Aschoff body they may have minimised or overlooked changes of greater functional significance.

Sabiston and Follis (1952) found lesions in 32 of 43 cases.

They used Aschoff nodules as their criteria and describe the lesions as consisting of "stellate" cells with characteristic basiphilic cytoplasm arranged as small foci or as large aggregations of such cells, intermixed with lymphocytes".

In the cases with auricular fibrillation 12 of 15 showed lesions and 20 of 28 cases in sinus rhythm also

showed lesions. 13 cases with thrombi showed lesions in seven cases.

The magnification of their illustrations is usually too low to show details but they resemble my Group 1 lesions.

They express the opinion that it is fairly certain that the lesions are retrogressing.

Biorck, Winblad and Wulff (1952) found 8 of 18 cases with Aschoff nodules and 4 cases with "lymphocytic endocarditis". The latter was present with and without thrombi.

The anti-streptolysin titres showed no difference in those showing lesions.

4 patients died who showed no lesions and none were found elsewhere in the heart.

Waaler (1952) showed lesions in 3 of 12 cases of biopsy specimens. In 2 acute cases of rheumatic fever he found similar lesions in the ventricular myocardium and the auricular appendage.

The author believes that the lesions are sub-acute.

Janton et al (1952) give an incidence of active lesions in 14 of 78 cases.

Entricknap (1953) described changes in the auricular appendages in terms of probable and possible rheumatic lesions.

Of 71 cases he found 12 probable and 17 possible rheumatic cases. 8 had "cellular foci".

Organising thrombus was present in 31 cases and probable lesions were present in 4 of these and "possible" in 6 i.e. 10 cases out of 31 showed lesions. This compared with 8 probable and 11 possible i.e. 19 cases out of 40 cases without thrombi.

Enticknap doubts the significance of these lesions. He is of the opinion that the minute structure of the lesions differ from that described by Gross and Ehrlich in the myocardium.

In the probable lesions fragmentation of collagen was seen but this resulted "from simple loss of continuity of the fibrils" and was unassociated with the deep red amorphous appearance characteristic of fibrinoid when stained by eosin. Silver impregnation failed to reveal any argyophil fibres.

"It may then be emphasised that in no case was typical fibrinoid change of collagen seen".

He also states that the endocardial distribution of the lesions is unusual and that the absence of the lesions in the myocardium of the auricular appendage is probably a significant difference.

His conclusions are that the lesions in auricular appendages did not have the typical structure of Aschoff nodules and were not distributed in the usual manner. In addition, these lesions were found in patients who had no clinical evidence of acute rheumatic fever. From this he

concludes that the results do not justify redefining acute rheumatic fever. He suggests these findings should be regarded as new findings to be elucidated only by prolonged clinico-pathological investigation. In his photomicrographs the possible lesions show groups of cells in what appear to be oedematous areas of the subendocardium.

Decker, Hawn and Robbins (1953) give an account of a series comparable in size to my own and it will be examined in some detail for comparison with my own series. The clinical aspects were published later by McNeely et al (1953).

They used "Aschoff nodules" as the sole criteria and state that reticular and mosaic from were present. In addition, there was focal lymphocytic collections in the endocardium, myocardium and epicardium which seemed in their view to be related most frequently to organising thrombus.

They found 83 of 183 specimens had Aschoff nodules. Thrombus was present in 71 cases and in only 4 of these were Aschoff nodules detected.

4 of 21 autopsy cases showed lesions in the auricular appendage and showed lesions elsewhere. In one case showing lesions in the ventricular myocardium there were no lesions in the auricular appendage.

2 cases of 11 post-mortem of rheumatic heart disease not subjected to valvotomy showed lesions in the left

auricular appendage and the myocardium.

The clinical aspects provide an excellent comparison with my own series since the numbers are roughly equal. (183 as compared to my own 175).

The age distribution of their series given in decades is very similar except that in my own series there are more cases below the age of 20 and few above the age of 50. Otherwise there is a good comparison between the series.

The incidence of fibrillating patients is higher in their series.

86 of 183 patients i.e. 47 per cent were in sinus rhythm as compared to 97 of 175 i.e. 56 per cent in sinus rhythm in my series.

Their figures for incidence in relation to the cardiac rhythm is:

| | | No. with lesions | per cent |
|---|---|---|---|
| Sinus rhythm | 86 | 65 | 76 |
| Aur. fib. | 95 | 16 | 17 |

Compared with my own series of 88 per cent with lesions in sinus rhythm and 33 per cent in fibrillation.

It should be noted that the decrease in incidence with age which they show in their series is largely the result of the increase in the numbers of patients with auricular fibrillation. In the fifth decade in their series the number of patients with auricular fibrillation constitutes a much higher proportion ( 80 per cent) than in my series ( 52 per cent).

They found no correlation between any other clinical findings.

In 8 of their patients with fibrillation who had active lesions the duration of fibrillation was known and it varied from 2 years to 20 years or longer.

They also found no correlation with the length of time from last acute attack and relationship of lesions. They do not attempt a correlation with first acute attack of rheumatic fever. No seasonal variation was noted.

Other differences from my own series are the numbers with thrombi (71) and the number of patients with aortic diastolic murmurs (76).

The selection of patients for operation in their series and that of the Birmingham United Hospitals are difficult to compare but there appears to be wider range of selection in this area.

They conclude that there is no evidence to prove or disprove a relationship between Aschoff lesions and a continuing rheumatic state.

McKeown (1953) described Aschoff bodies and illustrated various types of lesion representing stages from the early lesions to the fibrillary lesions. She also described lesions consisting radially arranged spindle shaped cells which she believed represented a different pattern of healing in the endocardium. Active lesions were found in 24 of 53 cases.

In a series of post-mortem cases which showed no clinical evidence of activity before death she found active lesions in 24 per cent of 90 cases. Her series was partially selected in that the relationship of thrombosis and rheumatic activity was being studied when the first part of her series was being collected.

No clinical information is given.

Thomas et al (1953) used Aschoff nodules as their criteria and found these lesions in 22 of 40 cases ( 55 per cent). In a post-mortem series of 40 cases of acute fulminating rheumatic fever, they found Aschoff nodules in 72 per cent and lymphocytic infiltration in 95 per cent. No clinical information is given in this paper. The authors believe from their examination of the left auricular appendages in acute rheumatic fever that the lesions are identical to those in the biopsy series.

Denst et al (1954). This paper is mainly devoted to changes in the pulmonary vessels in mitral stenosis but the authors summarise the findings in auricular appendages of 75 cases. 28 per cent showed Aschoff nodules and 28 per cent showed "chronic non-specific myocarditis".

They showed a decline of incidence with age but no mention is made of the cardiac rhythm.

Thrombus was present in 36 per cent of cases and only one showed Aschoff nodules.

Iuse et al (1954) found active lesions in 32 of 77

cases (41.6 per cent). The highest incidence was found in the age group 20 -29 (64 per cent) and the lowest incidence in the group 50 - 54 where no lesions were found. They mention "mucoid change of collagen".

In a post-mortem series of 28 non-operative cases of mitral stenosis they found lesions in three.

Manchester et al (1955) in an analysis of 35 cases showed "Aschoff nodules" in 13 cases. They define an Aschoff nodule as a focal accumulation of histiocytes associated with swollen eosinophilic fragmented collagen. Among the histiocytes were cells with abundant somewhat basophilic cytoplasm and a nucleus with a distinct nuclear membrane.

9 other cases showed "non-specific inflammation" consisting of lymphocytes and histiocytes. 3 of these cases showed focal fragmented collagen changes but were not included because the changes were so small.

1 in 6 cases of auricular fibrillation showed "Aschoff nodules" and 12 of 29 in sinus rhythm.

Following operation 12 cases were considered to have a recurrence of their rheumatism and 8 of these had shown no Aschoff nodules.

They found no clinical correlation and no seasonal incidence.

The criteria used in their series are for developed Aschoff nodules. If their non-specific group is added the total incidence of lesions is 65 per cent. They

express the opinion that these lesions indicate sub-clinical rheumatism.

Tedeschi et al (1955). Since this paper takes the opposite viewpoint of most of the published series it will be considered in some detail later but in this section only the histological and incidence criteria will be discussed.

They divide their lesions into two categories "active" lesions and healed or healing rheumatic carditis.

Their "active" lesions were defined as an exudative inflammatory reaction when the characteristic cells of the nodule could be well made out, when the collagen fibres and ground substance were altered and when the myocardial fibres showed degenerative changes.

8 cases out of 400 showed lesions of this type.

"Besides the disorganisation of the fibrous tissue within the nodule with swelling, eosinophilia and granular degeneration of collagen fibres which was noted in all 8 cases, in three instances fibrinoid alteration of the ground substance was detected in the endocardial and myocardial nodules". The 8 cases showed co-existent fibrosis indicating a previous attack.

67 cases showed "senescent" Aschoff nodules. Metachromasia of the ground substance was often observed without fibrinoid alteration. Within the nodule the collagen fibres were swollen, fragmented or fused together in an amorphous mass of dull eosinophilic material in which

were embedded lymphocytoid cells and large mononuclear cells of the Aschoff type.

The latter rarely showed the characteristic owl eye nucleus. The nucleus was more often pyknotic or vesicular and resembled in many respects the "ghost" nuclei described by Gross and Ehrlich and interpreted by them as indicating senescent change.

In the thickened endocardium the collagen fibres for long stretches in some specimens showed a bright eosinophilic staining with loss of the natural wavy appearance which the authors interpreted as evidence of regressive change.

In 40 cases the endocardial elastosis and collagen--isation was accompanied by increased cellularity. "Large basophilic cells with ragged edges and darkly staining nuclei either sparse or irregularly aligned was noticed in a few cases in the thickened endocardium."

Endocardial and less often myocardial infiltration by lymphocytes was found in 65 cases and in every case there was concurrent thrombosis.

These inflammatory cells were regarded as a non-specific reaction elicited by the thrombi.

A clinical summary is not given but it should be noted that the 8 cases in which "active" lesions were found did not show any different features from the other cases. The authors attribute this to treatment with

antibiotics and steroids although it is not stated that these patients were receiving steroids at the time of operation.

Several features may be pointed out at this stage. The "active" lesions which they use as synonymous with "acute" lesions are nearly all well developed lesions in the proliferative phase.

The use of the term fibrinoid degeneration of the ground substance in a manner, not according to my interpretation, used by Talalajew, Klinge, or Gross and Ehrlich i.e. separating it off from changes in the collagen.

Their mention of long eosinophilic fibres which they interpreted as regressive changes.

They show graphically that the age of distribution of their "active" lesions is slightly less than that of those with "senescent" lesions but it should be observed that the age grouping in both categories is expressed in decades as percentage of total showing these lesions and the "active" group only contains 8 cases. This appears to be of little or no value.

Clark and Anderson (1955). Of 78 cases examined 39 (50 per cent) had granulomata. This paper is the only one published so far in which mucoid oedema is well described. This was the commonest finding, being found in 52.6 per cent of cases. It was found in association with Aschoff nodules and also in the intervening tissue and stained

metachromatically with toluidine blue. Fibrinoid change of the collagen was sometimes seen in the absence of cellular reaction. Basophil degeneration was found unassociated with granulomas in 19 cases and 16 cases showed Aschoff nodules without basophil degeneration. The two were associated in 23 cases.

They considered the possibility that the basophilic degeneration might be due to the surgical procedure or to the increase in pressure in the left atrial wall but came to the conclusion that it was probably not related to these factors.

Chiari (1955). found Aschoff bodies in 27 of 53 cases. Ten others had non-specific lesions. The author makes a brief reference of mucoid changes which he found most frequently in the subendocardium.

Elster and Wood (1955) found Aschoff nodules in 7 of 20 cases submitted to valvotomy. They found no correlation with the duration of the disease, age, white blood count, erythrocyte sedimentation rate or electro--cardiographic findings. 4 patients with active lesions had raised anti-streptolysin - O titres as had 3 patients without active lesions. C reactive protein was detected in 2 patients with active lesions and in 4 without active lesions. The authors express the view that in patients showing active lesions in the left auricular appendages who have no C reactive protein in the blood, the degree of

rheumatic activity may have little or no clinical significance.

Gil et al (1955) studied the effect of cortisone on the lesions found in the auricular appendages of patients undergoing valvotomy. In a group of 60 patients, 14 of which had been treated with cortisone, they found active lesions in 36 cases and healing lesions in a further 9 cases. They found a decrease in the incidence of active lesions in the cortisone treated group and an increase in the proportion of healing and healed lesions.

# CHAPTER 12.

## DISCUSSION OF RESULTS.

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It is clear from the short reviews given that there is a considerable variation in the histological criteria employed and in the interpretation of the findings. There are several points of interest in these papers which I have reviewed. In the majority of cases the sole criterion used has been "Aschoff nodules" and the descriptions employed have usually been of the rather monotonous reiteration of eosinophilic, swollen or fragmented collagen between or around which are cells of various descriptions. Some authors use the term Aschoff cell in a restricted sense to indicate a cell with characteristic "owl eye" or "fibrocytoid" nucleus and basophilic cytoplasm. Others include cells with round or oval dark staining nuclei and basophilic cytoplasm as Aschoff cells. Some refer to histiocytes, others to mononuclears. The importance of the description of the cells is that some authors do not accept some varieties of lesion because there are no Aschoff cells. It should also be noted that to some, e.g. Enticknap, only fragmented collagen is acceptable. Manchester and his co-workers reject three cases because the amount of

fragmented collagen was small and the cells were not Aschoff cells. To the best of my knowledge no one has illustrated swollen eosinophilic collagen and mucoid changes in the absence of cellular reaction. McKeown illustrates one early lesion but in the photomicrograph there is already a fairly obvious cell collection. None of these authors, except Clark and Anderson (1955), have made anything more than a brief reference to the changes in the spaces between the collagen fibres. Usually the reference has been made in terms of oedema. Occasionally metachromasia is mentioned (Tedeschi et al, 1955) but no studies appear to have been made on this aspect.

One point is clear and that is that the swollen eosinophilic collagen, unless it is formed into rounded, easily identifiable masses, or is surrounded by cells, is not readily identified. From descriptions I believe that in many instances what I have interpreted as swollen collagen bands probably in the earlier phases of the cycle have been interpreted as normal or as previously damaged because the collagen fibre pattern has been maintained, e.g. Tedeschi and his co-authors refer to these bands as showing "regressive changes". By virtue of using a haematoxylin which stains the material in the tissue spaces blue it has been possible to identify and interpret lesions in a manner not possible with haematoxylins which do not

stain the connective tissue mucins. In addition the collections of I.H.S. so characteristically associated with the more developed lesions are also associated with what I consider to be the earliest diagnostic lesions and also are found in the absence of detectable collagen alteration. On the basis of evidence already stated I believe that these are earlier manifestations of rheumatic activity than the developed lesions, and all the papers quoted concern lesions at least developed to a stage with recognisable diagnostic features of rheumatic disease although there is considerable variation in what is considered diagnostic.

A strict comparison of my own series from the histological point of view is therefore not possible in view of the divergent criteria and descriptions employed. The photomicrographs published are usually well developed lesions.

There also appears to be some variation in the type of patients subjected to valvotomy in different centres and the biggest variation would appear to be in the numbers with auricular fibrillation. As has been shown by McNeely and his associates and by myself, there is a marked difference in incidence between the two groups and this would also lead to variations in the incidence of reported lesions.

In view of the experience in so many different centres it is evident that there are changes present in the auricular appendages of patients undergoing valvotomy which indicate

that an active disease process is occurring although there is considerable variation in the interpretation of the relationship of this process to the natural history of the disease rheumatic fever.

In order to avoid confusion, in the section on definitions I define activity in terms of a tissue process and avoided its use from the clinical point of view, preferring to employ the terms acute, sub-acute and sub-clinical rheumatic fever. The validity of this separation has not however been discussed and in view of the divergence of opinion expressed in publications and at scientific meetings, it is necessary to go into the question of "activity". Much of the confusion in medical literature is due to the use of ill-defined terms and the literature on rheumatic fever is an outstanding example.

What does "activity" mean in a clinical sense and how is this judged in a disease such as rheumatic fever?

If one considers the symptomatology of acute rheumatic fever it becomes evident that there is a very wide range of clinical appearances. There is a variable degree of pyrexia or it may be absent, joint pains occur in some patients but not in others. The same applies to practically every other clinical phenomenon associated with rheumatic fever. It may be a very mild disease or it may on rare occasions kill in its first attack. It may commence with chorea.

In the days before laboratory aids were known special

attention was paid to pure clinical observation. When joint pains, pyrexia, sweating, etc. had disappeared the patient was still considered to have active rheumatism if the pulse rate remained high. When laboratory tests became available other standards were now employed. The patient had no joint pains, no pyrexia, no sweating, normal pulse rate but the E.S.R. remained raised. Therefore the patient's disease was still active. As more and more tests become available the same situation is perpetuated. The patient has no pyrexia, no joint pains, normal pulse, no sweating, good appetite, normal E.S.R. - but the anti-streptolysin titre is still raised therefore the patient still has active rheumatism. It is quite evident from considerations such as these that the word "activity" used in the clinical sense has a very indefinite meaning. All these measures are non-specific methods of estimating the presence of various abnormalities and it is not known whether the abnormalities are due to the presence of the disease or to some changes associated with the reaction of the patient to the disease.

We have now reached the stage in the process of diagnosing "activity", of having a piece of the patient's heart and the argument now is: the patient has no clinical symptoms directly attributable to the disease, the non-specific laboratory tests show no abnormality - the E.S.R. is normal, the W.B.C. is normal, the anti-streptolysin titre is not raised, the C reactive protein and mucoprotein levels show

little change, but the auricular appendage shows histological evidence of a rheumatic disease process. At this stage there is considerable hesitation on the part of some authors to relate this to "activity". This reluctance is due in some measure to an idea about the disease rheumatic fever which is not, I believe, that taken up by most investigators, clinical or pathological. From the literature it is almost commonplace to find statements that the clinical diagnosis of "active" rheumatism cannot be made with certainty. Coombs (1924) from his long study of patients stated that this was frequently impossible. The quotation at the beginning of this thesis sums up the situation from the clinical point of view.

The hypothesis that the majority of the lesions in auricular appendages are not indicative of "active" rheumatic disease is summed up in the paper by Tedeschi, Wagner and Pani (1955).

Reduced to essentials their argument appears to be as follows:-

In most diseases there is a close correlation between clinical "activity" and histological appearances.

In acute rheumatic fever certain lesions are found in the hearts of patients who die from their disease.

In patients undergoing valvotomy certain lesions are detected.

These patients do not have acute rheumatic fever

therefore these lesions are not "active".

The criteria for "activity" adopted by Tedeschi and his co-workers is as follows:- "The rheumatic process was thought to be active when an exudative type of inflammatory reaction was detectable in the nodule, in the endocardium or in the myocardium (independently from mural thrombosis), when the structure of the characteristic cells of the nodule was well made out; when the collagen fibres and the ground substance were altered and when the myofibres showed degenerative change".

The proof of this hypothesis would be either a) that lesions corresponding to what they describe as the lesions of acute rheumatic fever are never found in auricular appendages of patients undergoing valvotomy or b) that if lesions of this nature are found then the patients should have acute rheumatic fever (note: acute rheumatic fever - not a raised E.S.R. or other laboratory tests).

These workers in my opinion disprove their own case by finding eight patients in 400 who had lesions of acute rheumatic fever by their definition but who did not have acute rheumatic fever clinically. These patients did not differ from the other patients in the series.

The premises on which Tedeschi and his co-workers base their argument are open to dispute on practically every aspect.

The first premise has already been discussed in some

respects but as they illustrate their argument by tuberculosis it would perhaps be worth while enquiring into its validity.

While it is true that in acute phases of tuberculosis, e.g. miliary tuberculosis, the patient has symptoms and histological examination of the tissues will probably show tubercles, and also it is true that in calcified tuberculosis foci tubercles may not be seen and the patients have no symptoms, it would, in my opinion, be entirely wrong to presume that in a patient with pulmonary tuberculosis who has no general symptoms, tubercles will be absent from the affected portion of lung. It would also be wrong to assume that a patient who has tubercles in his lung does not have an active disease because he has no general symptoms. The physician in change of any case of chronic disease of this nature is frequently in doubt as to whether he should consider the disease active or not and few would declare such a patient free from active disease because he has no general symptoms.

It is standard teaching in most text books of pathology that the process of repair or healing cannot be completely separated from that of the inflammation. If rheumatic fever were a disease with a fixed type of onset, a fixed course and a series of very characteristic symptoms and signs it might be possible to say by clinico-pathological correlation that at a certain stage of development or retrogression of the lesions there are no clinical signs

or symptoms of the disease. This is not the case in rheumatic fever. Sometimes the clinical features of the disease are of short duration and sometimes much longer. When the clinical features subside certain laboratory tests may remain positive. The significance of many of these tests is not known.

To add to the difficulties of such a clinico-pathological correlation is the very important fact which has been overlooked, that this examination is not possible unless the patient dies and death in an acute attack of rheumatic fever is not a very common occurrence. Death in a first acute attack is extremely rare and death in subsequent acute attacks is not very common compared to the total number of patients with rheumatic heart disease. It could be argued that the lesions in patients who die in a first acute attack of rheumatic fever are likely to differ from those in patients who survive. Even now there is no means of determining this since patients subjected to valvotomy do not have acute rheumatic fever.

This is however only one aspect of "activity". Sometimes this term is used to indicate the presence of the initiating stimulus. In this respect again there can be no answer in rheumatic fever because the initiating stimulus is not known and the mechanism of production of lesions, symptoms and signs is not understood.

I agree with Tedeschi et al that if the earlier type

of histological change is noted then it probably indicates that whatever the initiating factor might be, it is operating to produce fresh lesions. If this can be shown then the disease may rightly be called sub-clinical if in the presence of these fresh changes there are none of the signs and symptoms of acute rheumatic fever.

Tedeschi and his co-workers adopt certain criteria which have been described as occurring in the hearts of patients dying from acute rheumatic fever but some of the lesions illustrated are already in the proliferative phase. With their criteria I have little disagreement except that they omit a great variety of changes also described in acute rheumatic fever. They ignore the early changes described by Talalajew and Klinge which sometimes take place in the absence of cellular reaction. The rheumatic "Frühinfiltrat" illustrated by Klinge would not be covered by their definition of "activity".

I believe I have shown lesions earlier than those described by Tedeschi et al.

Having proved that, according to their own criteria, the earliest rheumatic lesions can be demonstrated in auricular appendages of valvotomy cases, they do not then take the logical view that this is proof of sub-clinical rheumatism. They suggest that the disease has been altered in some way by anti-biotics or steroids. They do not state

if these patients were receiving steroids or anti-biotics. In my own series none of the patients were on prolonged anti-biotic or steroid therapy.

The point of view of those who are unwilling to accept the idea of sub-clinical rheumatism or who believe that the lesions in auricular appendages are not "active" rests on two hypotheses (a) that these lesions are the result of a previous attack of acute rheumatic fever with the inference that if the patients had been examined at the time of the supposed acute attack clinical evidence of "activity" would have been present or (b) that these lesions are not those of rheumatic fever. This second hypothesis is bound up with the idea that rheumatic fever is not a single entity but a group of diseases with similar histological appearances.

(a): With regard to the first hypothesis it has been shown by McKeown, Tedeschi et al, Clark and Anderson and myself that lesions of the earliest type described in rheumatic heart disease are found in auricular appendages of valvotomy specimens and the patients with these early lesions do not differ from those with more developed lesions or those without lesions. This, I believe, furnishes proof of sub-clinical rheumatism. Furthermore, an examination of the case histories and of the method of selection of patients for valvotomy in this centre makes the hypothesis of "residual" lesions unlikely.

As has already been stated, the patients are selected by physicians and surgeons at this centre. Some patients are

examined and assessed as out-patients initially, put on the waiting list, admitted to hospital and re-assessed before operation. Others are admitted to hospital, investigated and assessed and are put on a waiting list and discharged. They are re-admitted for surgical treatment. Other cases are admitted for assessment and undergo valvotomy during this admission. The time spent on the waiting list is very variable and may be up to six months. During this time and also prior to being put on the waiting list the majority of these patients have been under close medical supervision and it is unlikely that an acute attack of rheumatic fever would be overlooked. Of course, there is no absolute proof of the time taken between the development of lesions and the stage of complete healing. Various estimates of up to 9 months have been given for the ventricular myocardium but nothing is known of the duration in the left auricular appendage. Comparison of the valvotomy series with post-mortem series B would not support the view that these lesions are "residual" since they are found in very small numbers in autopsy specimens.

(b): The second hypothesis put forward as a possibility by Enticknap and Tedeschi et al is one which has been discussed for many years especially the idea that rheumatic fever may not be a specific disease.

From the histological point of view there can be little doubt that the lesions in the auricular appendages

of patients with mitral disease are similar to those found in some patients who die from acute rheumatic fever. This has been shown by various workers recently and their views have already been summarised. I do not understand the statement by Enticknap that these lesions differ from those of rheumatic fever in that there is "simple loss of continuity of the fibres" in the lesions in auricular appendages.

The view that rheumatic fever is not one disease but a group of diseases with similar histological appearances is one which has been discussed for many years but more recently it has received more attention in view of the concept of the "collagen diseases" put forward by Klemperer. It should be noted that this term is now applied in a manner not intended by Klemperer and in a recent review (1954) Klemperer repudiates the idea that these diseases are interchangeable.

The statement is frequently made that connective tissues can only react in a certain manner to various stimuli so that histological examination may not be able to distinguish lesions due to different diseases. Some support for this view is found, for example, in the finding of lesions indistinguishable from Aschoff nodules in the heart of a patient with disseminated lupus erythematosus (Ferguson and Milne 195?), and in the close similarity of arterial lesions in scleroderma, disseminated lupus erythematosus,

polyarteritis nodosa and rheumatic disease. However, in the present state of knowledge there is no evidence that the disease known as rheumatic fever is not a specific disease and the lesions found in the auricular appendages appear to be those of the lesions described for rheumatic fever. Over many years it has been established by autopsy studies that if lesions are found in hearts of patients with mitral valve disease these lesions are those of rheumatic heart disease. Klemperer and his co-workers have separated off the collagen changes in disseminated lupus erythematosus by the demonstration that the haematoxyphil bodies and the "fibrinoid" material are derivatives of nucleo-protein. Until the chemical identity of the substances involved in the lesions of rheumatic disease is known it would be better to view them as being part of one disease. It is my belief that the development of mitral valvotomy has offered no evidence to support the view that rheumatic heart disease is a group of diseases.

The application of the results of examination of auricular appendages to the natural history of rheumatic heart disease is not easy. While the views expressed in the past that rheumatic fever can be sub-clinical have been confirmed the magnitude of the incidence of lesions in valvotomy series from different centres is more difficult to explain.

Various suggestions have been put forward to explain this high incidence as compared with most autopsy series.

Kuschner and his associates suggested that the left auricular appendage is a site of election. In one respect this is the case in that most cases showing lesions in the myocardium also have lesions in the auricular appendage. It does not seem to be the case that lesions occur in the auricular appendages with any greater frequency than elsewhere in the heart. This has been shown by Thomas et al, McKeown, and myself. It should, however, be noted that the intensity of the rheumatic process in the auricular appendage is frequently greater than in the rest of the heart. Lesions in the auricular appendages can be very readily found, often in large numbers, where lesions in the myocardium in some cases are few and not easily found even in the "sites of election" as described by Gross, Antopol and Sacks.

Catto, Taylor and Smith expressed the view that the selection of patients with mitral stenosis may lead to selection of a group where the disease is falling most heavily on the left atrium. In the present series the size of the orifice in the mitral valve appears to have been very variable and many were incompetent. The numbers of patients in my autopsy series without severe stenosis is too small to show any difference but there is not a high incidence of lesions in patients with severe mitral stenosis. Although this explanation appears unlikely such a factor

may play some part in boosting the incidence of lesions in the left auricular appendage.

At the Pathological Society (London, 1953) I put forward the suggestion that the patients may have been selected for mitral valvotomy because their symptoms have become worse and this worsening of their condition may be the result of active rheumatism. On examining the case histories and the method of selection there is no evidence that this is the case.

As has been shown there is a very marked difference in incidence in patients in sinus rhythm and in patients with auricular fibrillation. It is possible that different factors are involved for each group. In patients in sinus rhythm the mechanical effect of the valve lesion in addition to active rheumatic disease may be producing symptoms whereas in the bulk of patients with auricular fibrillation the valve lesion and the cardiac arrhythmia may be the combined factors producing symptoms. If this is the case, in view of the very wide selection of patients with differing degrees of disability the selection factor must be one that is operating with great accuracy in patients in sinus rhythm. It is, of course, possible that the symptomatology of the disease in these patients is due entirely to the valve lesion and the effect on the pulmonary vasculature in which case the conclusion is

inevitable that in a very high proportion of patients with mitral disease at any given period there is an extremely high incidence of patients with active lesions and in the group in sinus rhythm, in order to produce such a high incidence(McNeely 76 per cent, this series 88.8 per cent) there must either be an overlapping of "attacks" of rheumatism, very short intervals between "attacks", or the disease may be continuously active.

From the histological point of view there is evidence in a proportion of cases of early definite rheumatic lesions and more developed lesions co-existing in the one specimen. If some of the Group 2 lesions found in specimens with Group 1 lesions also represent developing lesions then the proportion of cases with lesions of different ages would rise. However, in view of the very variable appearances of lesions and the differences even in the earliest lesions it is difficult to be certain if the lesions are of the same "age". McKeown (1945) noted that in the myocardium lesions of different stages of development could be found in the same specimen and this was the case in some of my own specimens. In some specimens the lesions do appear to be at the same stage of development and it appears likely the disease occurs in phases.

If one attempts to apply the results obtained to the natural history of rheumatic fever one is up against the difficulty of not knowing how great is the degree of

selection of patients undergoing valvotomy. Figures are not available in this centre of the total number of patients referred to hospital with rheumatic heart disease and the proportion of these patients selected for valvotomy. Even if the total figures were known it would still not show the extent of the selection because many of these patients are referred to this centre from a wide area and presumably only those patients with a certain degree of disability are referred.

Figures are available from Edinburgh in a paper by Fraser and Turner (1955) on auricular fibrillation:-

Of 500 patients with mitral disease studied over a period of 5 years, 250 were treated surgically. 115 were regarded as unsuitable because their condition was too mild and 135 because it was too severe or because some other complicating factor was predominant e.g. mitral incompetence, aortic valve disease or systemic hypertension. (Auricular fibrillation occurred in 4 per cent of the mild cases and 80 per cent of the severe cases). The incidence of active lesions is not given . In the series of 250 cases submitted to valvotomy 42 per cent were suffering from auricular fibrillation i.e. in this one centre (Edinburgh) half of the patients seen who were suffering from mitral disease were submitted to valvotomy.

If a similar state of affairs is in operation at this centre it would appear that in a very large proportion of

cases of mitral stenosis there is at any one time histological evidence of rheumatic activity in the absence of clinical evidence.

It is difficult to escape the conclusion that acute attacks of rheumatic fever are rare episodes in the course of the disease and that repeated episodes of sub-clinical rheumatic fever plays a more important part in the production of the damage to the heart than the occasional acute attack of rheumatic fever. This hypothesis explains more satisfactorily the extent of the damage produced in the heart, the occurrence of mitral disease in the absence of any history of rheumatic fever and the high incidence of lesions in auricular appendages of valvotomy cases.

The high incidence in patients with sinus rhythm as compared with patients in auricular fibrillation is not readily explained. The disease appears to die out or "attacks" become much less frequent when fibrillation is present and it is possible that these two factors are related quantitatively. Auricular fibrillation may develop as the result of a certain degree of damage to the myocardium and "immunity" to the disease may also be related to the amount of previous damage. In other words a certain amount of damage may be necessary to produce auricular fibrillation and "immunity" and the two "amounts" may be similar. This hypothesis is of course not open to proof and until a satisfactory explanation is found for the

aetiology of auricular fibrillation, this problem is likely to remain unanswered.

If the hypothesis of repeated sub-clinical rheumatism is correct, what is likely to be the effect of this on the split valve? Are these patients likely to develop stenosis again? The factor of organising thrombus enters into this but in addition it should be noted that in the patients who died in the post-operative period, lesions were found in some specimens in the myocardium and left atrial wall but in only one case was a valvulitis present. There is a possibility that the tissues of the valves are already so altered that further involvement in the rheumatic process may not be possible.

Autopsies were obtained in three patients who survived for periods of 8½ months to 30 months following valvotomy.

In all three cases the split was noted at operation to have been unsatisfactory. In all three cases there was a tight stenosis of the mitral valve at autopsy. In one of the cases the split could be recognised as a linear scar. In two others the split could not be detected and in one of these (case 72) it was the second attempt at a split.

In case 50, the biopsy specimen showed active lesions and 8½ months later at autopsy active lesions were not found in the heart.

Case 107 showed active lesions in the biopsy specimen and 11½ months later at autopsy active lesions were found

in the posterior wall of the left atrium and the endo--cardium of the right ventricle close to the pulmonary valve. In this case the mitral, aortic and tricuspid valves were involved macroscopically.

Case 72 showed no active lesions in the biopsy and none were found in the heart 2½ years later.

Since the original split was noted to be unsatisfactory these cases do not add evidence of what is likely to happen to a well split stenotic valve.

The role of organising thrombus in the production of stenosis is not clear but it has been suggested by Magarey (1951) that there is a considerable possibility of stenosis recurring after valvotomy due to organising thrombus. This will always remain difficult to evaluate because the extent of the split in valves produced by valvotomy is very variable and there is no good method of estimating this factor, as can be seen in case 72 where after the second attempt at valvotomy no split was detected at autopsy. In one case dying 11½ months after valvotomy the line of the split could be recognised and had healed by organisation of what appeared to be platelet thrombus.

Tweedy (1956) extended the work of Magarey and he expresses the opinion that the bulk of the valvular deformity and thickening in rheumatic heart disease is due to organising thrombus. It is difficult however to agree with his opinion that the mucoid oedema and the fibrin-like material deep in the valves in cases of acute rheumatic

fever are due to organising thrombus, since in many cases the whole valve is oedematous.

Numerous follow-up studies have been published (Janton et al 1952; Baker et al 1952; and 1955; Wood 1952; Wade et al 1954.), and all are agreed that there is no difference in the results in those showing histological evidence of active rheumatism and those in which there is no evidence of activity. Baker, Brock and Campbell (1955) however found that patients in fibrillation in their series appeared to benefit more from valvotomy that those in sinus rhythm, an observation which may be of some significance in view of the high incidence of active rheumatism in patients in sinus rhythm in this centre. They state that the pathologist who reported the histology of their series takes a cautious view of the lesions in auricular appendages. His views have already been discussed. (Enticknap 1953).

## SUMMARY AND CONCLUSIONS.

In a group of 175 with mitral valve disease submitted to valvotomy, changes suggesting an active disease process were present in 64 per cent of cases. Of the patients showing active disease 23 per cent showed lesions which do not appear to have reached the stage of developed Aschoff type lesions. In a proportion of patients (8 per cent) the lesions are of the earliest type described in rheumatic disease as mucoid oedema, and 15 per cent show lesions in which the earliest type of change in the collagen is present. The changes in the collagen correspond to the changes described by Gross and Ehrlich as preceding the formation of the coronal type of Aschoff body and differ in appearance from the reticular Aschoff body which I believe corresponds to the rheumatic "Frühinfiltrat" of Klinge.

A fibrin staining component was not detected in any of the auricular appendages, reliance being placed on Mallory's phosphotungstic acid haematoxylin stain which requires no differentiation. Preceding any detectable alteration in the collagen there is an accumulation of acid mucopolysaccharide in the tissue spaces and this persists but in reduced amount to the later types of lesions. The altered collagen appears

to contain a variable amount of periodic-acid-Schiff positive material and possibly a tyrosine-containing protein. The staining reactions of the altered collagen in most cases are similar to those of collagen. Preservation of the fibrils is suggested by the preservation of bire--fringence in the altered collagen and the configuration of the material within some of the lesions.

The healing process described by Gross and Ehrlich can be recognised but it is suggested that healing can occur with retention of the radiate arrangement of cells found in coronal lesions and also that a fibrillary stage may not occur in some cases, thickened collagen fibres being left in place of fibrillary scars.

The early exudative phase appears to be much more extensive than the developed lesions would suggest.

The differences between acute and sub-clinical rheumatic fever may lie in the extent of the exudative-degenerative phase and also in the intensity of the alteration to the collagen.

A close correlation was found between the presence of active lesions in the left auricular appendage and the ventricular myocardium.

Skin and muscle from patients with active rheumatic lesions in the left auricular appendages showed no abnormality.

In an autopsy series of 61 cases of rheumatic heart

disease, active lesions were found in 12 cases. In 28 of these patients in the same age group and with valve lesions comparable to the biopsy series, 7 cases (25 per cent) showed active rheumatism.

As compared with a control series of non-rheumatic hearts, a large proportion of patients with rheumatic heart disease showed metachromasia in the auricular appendage and the left atrial wall.

In a clinico-pathological correlation it has been shown that there is a marked difference in the incidence of lesions in patients with sinus rhythm and auricular fibrillation. The explanation for this has not been found but it applies at all age groups above the age of thirty.

No evidence of clinical activity was found in the valvotomy cases and because the earliest changes of rheumatic disease can be found in some specimens this is put forward as proof that sub-clinical rheumatism is an entity and present clinical and laboratory methods are inadequate to detect this.

The incidence of active rheumatism in the valvotomy series and the histories of these patients suggest that the acute attack of rheumatic fever is a rare occurrence in the course of the disease and that the bulk of the damage to the heart is the result of repeated episodes of sub-clinical rheumatic fever which may overlap, or to a continuous

rheumatic process.

One major difference is detected between the autopsy series and the valvotomy series. There is a marked change in the proportion of patients in auricular fibrillation and it is suggested that this factor may account at least in part for the low incidence of active lesions in the autopsy series. The majority of patients with rheumatic heart disease who die in this centre die in auricular fibrillation and show no histological evidence of active rheumatism. It is tentatively suggested that the increase in metachromasia in the hearts of patients with valvular disease who die with no evidence of rheumatic activity may be the result of early rheumatism.

The results of chemical estimations of the hexosamine/hydroxyproline ratio in auricular appendages showing active lesions and without active lesions were inconclusive.

# CHAPTER 13.

## EXPERIMENTAL ATTEMPT TO PRODUCE RHEUMATIC-LIKE LESIONS IN THE HEARTS OF RABBITS BY REPEATED INNOCULATIONS OF GROUP A BETA HAEMOLYTIC STREPTOCOCCI INCUBATED IN A SOLUTION OF CHONDROITIN SULPHATE PRIOR TO INJECTION.

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The relationship of antecedent Group A beta haemolytic streptococcal infections to acute rheumatic fever has been firmly established by the work of Coburn (1930, Collis (1931) Coburn and Pauli (1932) and many others, but the mechanism of the production of lesions is not known. It has been postulated that the lesions of rheumatic carditis are due to the presence of organisms within the lesions. In 1900 Poynton and Payne isolated an organism which they claimed was specific for the disease. Various attempts to produce the disease experimentally in animals by streptococcus viridans were made (Bracht and Wachter, 1909, Jackson 1912, Coombs et al 1912, Clawson 1945) but the lesions produced in the myocardium were not generally accepted as being rheumatic. The relationship to streptococcal infections is, however, closely established with Group A beta haemolytic streptococci and all Lancefield types have been reported from the throats of patients in the antecedent infection except types 4 and

22 (Committee on Rheumatic Fever 1950, quoted by Baggenstross 1953). Green (1939) reported the isolation of Group A beta haemolytic streptococci from the hearts of eight out of nine patients who died from acute rheumatic fever. Blood cultures were negative in these patients. This was confirmed by Collis (1939) who isolated Group A beta haemolytic streptococci from lymph nodes in addition to the heart.

It has been shown by Coburn and Pauli (1939) that after an acute streptococcal infection the maximum anti-haemolysin titre is usually reached in three weeks, whereas in rheumatic subjects the concentration of antibody may go on rising even up to six months after the infection. In view of their work on the production of chronic Group A beta haemolytic streptococcal infections by injections of streptococci embedded in agar, they believed that this phenomenon indicated the presence of continuing streptococcal infection in the rheumatic subject.

However, the general opinion at present is that rheumatic disease is due to hypersensitivity and various experiments have been carried out using foreign protein injections into animals. Rheumatic-like lesions have been described by Klinge (1929 - 1930), Rich and Gregory (1943), (1944), Fox and Jones (1944), McKeown (1947) and Kirschner and Howie (1952), using horse serum and other foreign protein. This, and other experimental work on rheumatic disease has

been recently reviewed by Murphy (1952).

Other investigators have postulated the formation of antibodies to the patient's own tissues and Cavelti (1947) put forward the view that the formation of autogenous antibody takes place as the result of a reaction in which streptococci or streptococcal products combine with tissue components of the host making the latter antigenic. This antigen stimulates the formation of antibody which in turn precipitates the rheumatic lesions by a reaction with the antigen in the patient's own tissues. Cavelti based his theory on a series of experiments in which emulsions of various tissues were mixed with Group A beta haemolytic streptococci and the mixtures were injected into animals of the same species. He describes anti-bodies to heart, skeletal muscle and connective tissue (1947) and to kidney (Cavelti and Cavelti 1945 a). They also claimed the production of nephritis by utilising this mechanism (Cavelti and Cavelti 1945 b), and Cavelti (1947) also produced lesions in the hearts of rats by a similar mechanism which be believed resembled rheumatic lesions "in a broad sense". This work on nephritis was not confirmed by Humphrey (1948).

It has been shown by Landstiener (1945) that the antigenicity of a protein may be altered by chemical combination with various non-protein substances and polysaccharides are one of the group of non-protein substances. Antibodies to agar, a plant polysaccharide,

have been produced by combination of this polysaccharide with various types of bacteria and Glynn and Holborrow (1952 a) reported that Group A beta haemolytic streptococci were particularly active in endowing agar and sodium alginate with antigenic properties. In the same year (Glynn and Holborrow 1952 b) they reported the production of anti-body to chondroitin sulphate by incubating Group A streptococci with this substance and injecting them into rabbits. Histological evidence of arthritis was found in five of six rabbits injected with killed Group A streptococci which had been incubated in a solution of chondroitin sulphate prepared from human rib. The chondroitin sulphate was not found to be antigenic when injected alone.

Attempts to produce rheumatic disease experimentally in animals by means of Group A streptococci have not had much success. Hypersensitivity to Group A streptococci in animals was produced by Lancefield (1928), and Angevine (1939) but the first definite reports on the production of rheumatic-like lesions in experimental animals by inoculation of Group A streptococci were made by Murphy and Swift (1949, 1950). These workers described rheumatic-like lesions in the hearts of a proportion of rabbits subjected to repeated skin inoculations of living Group A beta haemolytic streptococci, different serological types being used in successive injections. This work was confirmed by Kirschner and Howie (1952).

In view of the widespread changes in the mucopolysaccharide

component of the connective tissues in rheumatic disease, an experiment was designed utilising the findings of Glynn and Holborrow (1952 a and b) and Murphy and Swift (1949).

A group of rabbits received repeated intra-dermal injections of different serological types of Group A beta haemolytic streptococci which had been incubated in a solution of chondroitin sulphate. Half of the animals received living organisms and the other half received killed organisms. A similar number of rabbits received intra-dermal injections of the same types of organisms which had not been incubated with chondroitin sulphate, half of the animals receiving living organisms and the other half killed organisms.

Methods and Materials.

Chondroitin sulphate of rabbit origin was not available and because of the difficulty of preparing a sufficiently pure extract, a preparation of chondroitin sulphate from bovine cartilage was obtained by the courtesy of Dr. W.J.C. Dyke of Evans Biological Institute, Runcorn, Cheshire. This was stated to be an extremely pure preparation, containing no detectable protein.

Preparation of injections.

Group A beta haemolytic streptococci of types 4 (strain R.50 2662), 5 (strain R.51. 779), 9 (strain R.51.2), 12 (strain R.51. 178), 15 (strain T.15, Stubbs), 18 (strain R.50.710), 19 (strain R.51.453), 22 (strain 11300), 23 (strain

R.54.320), 26 (Strain R.54.877), 29 strain R.53.1919), all of which had been isolated from human throats, were obtained by the courtesy of the Colindale Reference Laboratory.

The dry cultures were suspended in glucose-broth and sub-cultured several times on blood-agar plates. Matt or mucoid colonies were sub-cultured into Todd-Hewitt broth and incubated for twenty-four hours. The twenty-four hour culture was centrifuged, washed in saline and re-suspended in saline to the original culture volume. The culture was divided into two parts:- (1). One part was centrifuged and suspended in a one per cent chondroitin sulphate solution and incubated for one hour. The culture was washed once in saline to remove surplus chondroitin sulphate, re-suspended in saline to its original volume and diluted with saline to the required amount. The diluted culture was separated into two parts, one of which was injected immediately and the other was killed by heating for one hour at 56°C. before injection.

(2): The second part of the original Todd-Hewitt twenty-four hour culture was diluted to the required amount and divided into two parts. One of these was injected immediately and the other was killed by heating for one hour at 56°C. before injection.

Both cultures of the various injection suspensions were carried out as a control on the viability of the

culture. In every case a positive culture was obtained from the "living" injections and none from the "killed" injections.

Commencing with dilutions of $10^{-6}$ of the original Todd-Hewitt broth cultures, injections of 0.2 cc. were given into the clipped skin of buttock or back, and every three to four weeks an injection of a different serological type was given. The dilution was decreased ten-fold in each injection until an undiluted culture was being given. A different area of skin was selected for each injection. After eleven injections the serological types used at the beginning of the experiment were repeated. After nineteen injections given over eighteen months the experiment was terminated and the survivors killed by intravenous nembutal. Post-mortem examinations were carried out immediately after death, and the heart, lungs, spleen, liver, kidneys and knee joint were fixed in 10 per cent formal saline.

Forty black and white young Dutch rabbits obtained from the same breeding source were divided into five groups of eight. All were kept in the same animal house and were fed the same diet. There were approximately equal numbers of both sexes in each group.

Course and Results of the Experiment.

Tests for antibodies to chondroitin sulphate were carried out at approximately three-monthly intervals by the capillary tube method of Swift et al (1943) which had been

employed by Glynn and Holborrow, but no antibodies were detected in any of the animals.

Before the experiment was terminated the anti--streptolysin titre was measured, the control being serum from a convalescent case of rheumatic fever. In only one rabbit was any titre detected and this was 1x12. The control showed a titre of 1 : 256.

None of the rabbits showed any evidence of an illness such as that described by Murphy and Swift (1949) in their experiment.

Group I. Repeated inoculation with living Group A beta streptococci previously incubated with chondroitin sulphate.

Skin abscesses were consistently produced after the second injection. The skin at the injection sites became red and inflamed and after the fifth to the seventh day discharged pus. The size of the abscesses varied from animal to animal and with different injections. Healing was usually complete before the next injection.

Five of the eight rabbits survived the experiment.

Of the three rabbits who failed to survive, one was killed following an injury after receiving four injections, one was killed because of a severe intractable middle ear infection after eleven injections, and one died with a Pasteurella bronchopneumonia after twelve injections. No lesions were detected in the hearts of these animals.

None of the five survivors showed any evidence of an illness such as that described by Murphy and Swift (1949) at any time during the course of the experiment.

Histological Examination.

In two cases small focal infiltrations of cells resembling lymphocytes were present in the myocardium. These were usually located close to the pericardium, bore no relation to the blood vessels or the septa and were distributed between muscle fibres. No alteration was noted in the collagen and I.H.S. was not detected in or around the lesions. The valves, endocardium and vessels showed no changes. In one of these cases a focal pyelonephritis was present.

Two rabbits showed focal lesions of a different type. In one of these the lesion was wedge-shaped with its base in the pericardium and the apex deep in the myocardium. The lesion consisted of cellular collections of polymorphs, lymphocytes and larger mononuclear cells, with open vesicular nuclei. Damaged and sometimes necrotic muscle was readily identified in the lesion and nuclear debris was present. There was no recognisable alteration in the collagen and no I.H.S. was detected. Gram stains showed no identifiable organisms. (Fig. 131).

The second rabbit showed one focal lesion in the left ventricular myocardium essentially similar in structure to the lesion described in the left auricular appendage but

with less necrosis.

In both of these rabbits the lesions were solitary and no lesions were noted in the valves, endocardium or blood vessels.

Group II. Repeated inoculation of killed Group A beta haemolytic streptococci incubated with chondroitin sulphate.

A papule was produced at the inoculation sites which varied in size but rarely ulcerated. Healing was complete before the next injection.

Six rabbits survived the experiment.

One was killed after twelve injections because of a severe suppurative panopthalmitis due to a Gram negative bacillus. One died with a bronchopneumonia due to a Gram negative bacillus after the eighteenth injection.

No lesions were detected in the hearts or joints of either of these two rabbits.

Of the six survivors two showed tiny focal collections of lymphocytes in the myocardium of the ventricles, similar to those already described in Group I rabbits. (Fig. 132)

One rabbit showed a valvulitis in one cusp of the mitral valve and in addition tiny focal areas of lymphocytic infiltration were present in the myocardium. The lesion in the cusp showed spindle cells and mononuclear cells, some of which were aligned in the direction of the long axis

of the cusp. There was no evidence of collagen alteration or I.H.S. The endothelium was intact and no vegetations were present. (Fig. 133).

Group III. Repeated inoculations of living Group A beta haemolytic streptococci.

The lesions produced at the skin inoculation site were similar to those described in Group I.

All the animals survived the experiment.

One animal showed focal lymphocytic collections in the myocardium similar to those already described. Similar lesions were present in the kidneys. Focal myocardial scarring was present in one animal and pyelonephritis was also present. (Fig. 134).

Group IV. Repeated inoculations of killed Group A beta haemolytic streptococci.

The skin lesions were similar to those in Group II animals.

Seven animals survived the experiment. One died with a Gram negative bacillus bronchopneumonia after the fifth injection. One cusp of the tricuspid valve showed intensely eosinophilic material ("Fibrinoid"). (Fig. 135).

Three rabbits showed scanty focal lymphocytic infiltration of the myocardium and in two of these pyelonephritis was also present.

Another rabbit showed a lesion in the angle between the mitral valve and the ventricular wall. This lesion

consisted of closely packed large mononuclear cells including multinucleate cells. In addition to these larger cells there were lymphocytes and fibroblasts. A tendency to palisading was noted in the lesions. There was no evidence of collagen damage and no I.H.S. Lesions were not detected elsewhere in the heart. A pyelonephritis was present in the kidneys. (Figs. 136 and 137).

Group V. Control Group.

Five rabbits survived the experiment. One died from a bronchopneumonia and one was accidentally killed. The third died from a middle ear infection. No lesions were detected in the hearts of any of this group, and ten other control hearts from rabbits of various types in the same animal house showed no cardiac lesions.

During the course of the experiment a further supply of chondroitin sulphate was obtained from Dr. Dyke and the experiment of Glynn and Holborrow (1952 b) was repeated. A streptococcus-chondroitin vaccine was prepared using Group A type 4 streptococci according to the method described by Glynn and Holborrow. The dosage used was their schedule A. The streptococcus-chondroitin vaccine was injected intravenously three times weekly beginning with 0.5 ml. and increasing to 1 ml.

Antibodies to chondroitin sulphate were not detected in any of the rabbits and the dosage was increased to 2 ccs.

after two weeks. The experiment was terminated after four weeks. The animals remained well and no lesions were detected post-mortem.

Boake and Muir (1955) also report negative results using a chondroitin sulphate preparation derived from cartilage of rabbits. They suggested that traces of protein in the chondroitin sulphate preparation used by Glynn and Holborrow, which was of human origin, may have accounted for the difference in the results.

Glynn and Holborrow (1955) state that they had obtained antibodies to human chondroitin sulphate preparations in rabbits on several occasions since their original communication and they suggested that the presence of traces of blood group substances in preparations of extract of human cartilage may account for the results they obtained. They suggested that another factor which may influence the response of rabbits is the presence of an "A"-like substance in the tissues of some rabbits. They describe the effect of this factor on the antibody to human blood group A substance in a later paper (Glynn et al 1956).

Discussion of Results.

From the histological view there can be little doubt that the majority of the lesions described in the hearts of the rabbits in this experiment cannot seriously be considered to resemble rheumatic lesions. Most of them resemble the lesions described by Miller (1924) in "normal" rabbits.

In only three cases did the lesions bear any resemblance to rheumatic lesions and in one there was a pneumonia which makes any relationship to the injections doubtful.

One valvular lesion (fig.135) and one endocardial lesion (fig.136) bore a close resemblance to rheumatic lesions but similar lesions have been described as occurring spontaneously (Loewe and Lenke 1940). It should be noted that these two cases were receiving injections of killed organisms.

This experiment differed from that of Murphy and Swift and Kirschner and Howie in several respects. (1). The rabbits were of a different type and recently Murphy (1956) has described a strain of rabbits which produces lesions in a large proportion of cases after skin inoculations of Group A streptococci. (2). The streptococci were also of different types, but if the theory of Murphy and Swift is correct this should not affect the results. (3). One important difference lies in the preparation of the injections. In my experiment the organisms were washed and injected in saline whereas in the experiments of Murphy and Swift (1949) and Kirschner and Howie (1952) the cultures were diluted with Todd-Hewitt broth so that in addition to the organisms, streptococcal products and broth were being injected. In my experiment the organisms were washed before being treated with chondroitin sulphate as a safe-guard against the possible destruction of the chondroitin sulphate

by streptococcal products. It is possible that this accounts for the low or absent anti-streptolysin titres at the end of the experiment.

Conclusions.

A preparation of chondroitin sulphate of bovine origin was not found to be antigenic using the method of Glynn and Holborrow (1952 b).

In a group of rabbits receiving repeated intradermal innoculations of living and killed streptococci treated with chondroitin sulphate prior to injection, and in a control group not treated with chondroitin sulphate, myocarditis was found in a small number of cases. In only two of these cases receiving killed organisms did the lesions resemble rheumatic disease and the relationship of these lesions to the injections is not clear.

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# A P P E N D I X.

Case history summaries and autopsy reports.

## Arrangement of Appendix.

The cases are arranged in groups and as far as possible in chronological order. Departmental reference numbers are given in brackets.

Biopsy series.....,.Cases 1 - 175
Autopsy series A.....Cases 167 - 181
Cases in autopsy series B used for comparison with the biopsy series.....Cases 182 - 209

Of the remaining 31 cases in autopsy series B case history summaries and autopsy reports are given in cases which showed active lesions.....Cases 210 - 214.

## Abbreviations.

M. Male
F. Female
Rh.F. Rheumatic Fever.
S.R. Sinus Rhythm.
A.F. Auricular Fibrillation.
C.C.F. Congestive Cardiac Failure.
Gp 1 and Gp 2 refer to the type of lesion as described in Chapter 1. A rough indication of the extent of the lesions is given in terms of "+".
N. Number of blocks of tissue examined.
P. Number of blocks of tissue showing lesions.

Case 1. (C.1694/51) M. Age 33. Coal miner.
Rh.F. age 23 while in services. Discharged.
Cough and dyspnoea on exertion since then.
Gave up work as miner 5 yrs ago. Dyspnoea
has become worse during last 6/12 yrs.
O/E: S.R. Mitral stenosis. No.C.C.F. E.S.R.20.
Operation: Stenosis. Calcification of valve.
Histology: Gp 1. + N 2 P 1.

Case 2. (C.1695/51) M. Age 33. Labourer.
Chorea age 9. Dyspnoea on exertion 12 yrs
becoming progressively worse. Can now walk
50 yrds on the flat and has difficulty in
climbing stairs. Several haemoptyses 1 yr ago.
No history of C.C.F. Taking digitalis regularly.
Has been off work for 1 yr.
O/E: A.F. No C.C.F. Mitral stenosis and aortic
regurgitation.
Operation: Mitral regurgitation. Calcification
of valve.
Histology: No active lesions. N 1.

Case 3. (C.1793/51) M. Age 45. Polisher.
Rh.F. age 25. Haemoptysis two years later.
Dyspnoea on exertion for 10 yrs. Gave up work
5 yrs ago and has been twice in hospital.
Treated with digitalis. No history of previous
attacks of C.C.F. Can walk 1 mile on the flat

but has difficulty in climbing stairs.

O/E: Orthopnoeic. A.F. No C.C.F. Mitral stenosis. E.S.R. 21.

Operation: Mainly regurgitation.

Histology: No active lesions. N 1.

Case 4. (C.1904/51) F. Age 37. Housewife.

Chorea age 9. Dyspnoea on exertion for 12 yrs but has had two pregnancies during this period. Dyspnoea has become worse during last few years. Now has difficulty in climbing stairs. No history of C.C.F. Taking digitalis regularly.

O/E: Orthopnoeic. No C.C.F. A.F. Mitral stenosis.

Operation: Mitral stenosis with considerable regurgitation. Calcification.

Histology: Gp 1. ++

Gp 2. +

Organising thrombus. N 2 P 2.

Case 5. (C.2361/51) F. Age 38. Housewife.

No history of Rh.F. Dyspnoea for 10 yrs, recently becoming worse. No history of C.C.F. Can walk 200 yds on the flat.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Mitral stenosis.

Histology: Gp 1. +

Gp.2. + N 1.

Case 6. (C.2573/51) M. Age 42. Company Secretary. Rh.F. age 21. Dyspnoea for 2 yrs becoming steadily worse. Palpitations. Can walk slowly on flat but has difficulty in climbing stairs. Haemoptysis 1 yr ago. Not taking digitalis.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Severe stenosis. Not calcified.
Histology: Gp 1. +++
Gp 2. + N 2 P 2.

Case 7. (C.2728/51) F. Age 21. Dress-maker. Rh.F. at 4 and 6 yrs. After second attack was in a school for rheumatic children for 2 yrs. No symptoms during school age. Dyspnoea began at age 14 and has progressively become worse. Can now walk 1 mile slowly on the level. No attacks of C.C.F. or haemoptyses.
O/E: S.R. Mitral stenosis. No C.C.F. E.S.R.20.
Operation: Stenosis.
Histology: No active lesions. N 1.

Case 8. (C.3342/51) M. Age 48.
Rh.F. age 13 yrs. Dyspnoea for 4 yrs. Grade IIIA disability. Not taking digitalis. No history of C.C.F.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: No active lesions. N 3.

Case 9. (C.3501/51) F. Age 31. Shop assistant.
No history of Rh.F. Dyspnoea for many years. Occasional haemoptysis. Swelling of ankles. Admitted following collapse at work.
O/E: A.F. Early C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: No active lesions. Organising thrombus. N 2.

Case 10. (C.3569/51) M. Age 28.
No history of Rh.F. Dyspnoea for 7 yrs gradually becoming worse. Can walk moderate distances on the level but has difficulty in climbing stairs.
O/E: S.R. No C.C.F. Mitral stenosis and aortic valve disease.
Operation: Stenosis. Calcification.
Histology: Gp 1. +++
Gp 2. + N 2 P 2.

Case 11. (C8/52) M. Age 21.
No history of Rh.F. Dyspnoea since school age. Unable to play games. In hospital with C.C.F. two years ago.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: Gp 1. ++ N 4 P 4.

Case 12. (C.44/52) F. Age 37.

No history of Rh.F. Swelling of ankles at age 16 yrs. Dyspnoea for 9 yrs, gradually increasing in severity. Sleeps with 2 pillows.

O/E: S.R. Early C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: Gp. 1. ++

Gp. 2 + N 3 P 3.

Case 13. (C.76/52) F. Age 46.

No history of Rh.F. Dyspnoea for 14 yrs, gradually becoming worse. No history of C.C.F. Taking digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions. Normal auricular appendage. N 3.

Case 14. (C.82/52) F. Age 27.

Rh.F at 13 and 21 yrs. Increasing dyspnoea for 1 yr. Haemoptysis on one occasion. No history of C.C.F. Can walk fairly well on the level but becomes breathless on climbing stairs.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis with considerable regurgitation.

Histology: Gp 1. ++ N 2 P 2.

Case 15. (C.111/52) F. Age 38. Housewife.
Rh.F. at 9 yrs. Dyspnoea for 13 yrs, gradually becoming worse. C.C.F. 9 yrs ago. Has been confined to bed for 1 yr.
O/E: A.F. No C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: No active lesions. Organising thrombus. N 3.

Case 16. (C.304/52) M. Age 35.
No history of Rh.F. Dyspnoea for 18 yrs, gradually becoming worse. Can walk ½ mile on the level without dyspnoea but cannot climb hills.
O/E: A.F. No C.C.F. Mitral stenosis and aortic regurgitation.
Operation: Stenosis.
Histology: No active lesions. Organising thrombus. N 4.

Case 17. (C.380/52) M. Age 22. Office worker.
No history of Rh.F. Dyspnoea for 4 yrs, gradually becoming worse. Has now given up work. Uses 3 pillows at night.
O/E: S.R. No C.C.F. Mitral stenosis and aortic regurgitation.
Operation: Stenosis.
Histology: Gp 1. +++
Gp 2. + N 3 P 3.

Case 18. (C.522/52) F. Age 30. Viewer.
Rh.F. at 13 yrs. Dyspnoea on exertion for several years. Can now walk only 50 yds. Not taking digitalis.
O/E: S.R. Mitral stenosis. No C.C.F.
Operation: Tight stenosis.
Histology: Gp 1. + N 2 P 2.

Case 19. (C.848/52) F. Age 40.
No history of Rh.F. Dyspnoea on exertion for 5 yrs. Oedema of ankles for 4 yrs. Two previous admissions to hospital for treatment of C.C.F. Taking digitalis.
O/E: S.R. Early C.C.F. Mitral stenosis and aortic regurgitation.
Operation: Stenosis. Calcification.
Histology: Gp 1. ++
Gp 2. + N 3 P 1.

Case 20. (C.1041/52) M. Age 29.
Chorea at age 12. Dyspnoea for 2 yrs gradually becoming worse. No history of C.C.F.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Stenosis. Calcification.
Histology: Gp 1. +++
Gp 2. + N 6 P 5.

Case 21. (C.1043/52) F. Age 27. Housewife.
No history of Rh.F. Dyspnoea on exertion for 5 yrs. Nocturnal dyspnoea. Now able to walk only 20 yds on the level. Has never had C.C.F. Haemoptysis on one occasion. Taking digitalis.
O/E: S.R. No C.C.F.
Operation: Stenosis.
Histology: Gp 1. +++
Gp 2. ++ N 7 P 7.

Case 22. (C.1157/52) M. Age 37 Labourer.
Rh.F. at 9 yrs. Chorea between 11 and 14 yrs. Two cerebral emboli 5 yrs and 6 mths ago. Dyspnoea on exertion for 5 yrs, gradually becoming worse. Can now walk only 250 yds on the level.
O/E: A.F. Early C.C.F. Mitral stenosis.
Operation: Mainly regurgitation. Calcification.
Histology: No active lesions.
Organising thrombus. N 7.

Case 23. (C.1210/52) F. Age 31. Clerkess.
Rh.F. at 21 yrs. Dyspnoea for 1 yr. No history of C.C.F. Difficulty in climbing hills and stairs.
O/E: S.R. No C.C.F. Mitral stenosis.
W.B.C. 12,500.
Operation: Stenosis.
Histology: Gp 1. +++
Gp 2. ++ N 7 P 5.

Case 24. (C.1221/52) F. Age 50. Housewife.
No history of Rh.F. Dyspnoea for 20 yrs gradually becoming worse. Oedema of ankles for 2 - 3 yrs.
O/E: A.F. No C.C.F. Mitral stenosis.
Operation: Moderately tight stenosis.
Histology: No Gp 1. lesions.
Gp 2. ++ N 3 P 3.

Case 25. (C.1290/52) F. Age 29. Housewife.
No history of Rh.F. Dyspnoea for 7 yrs, gradually becoming worse. Several haemoptyses. Can walk slowly on the level, and is still working part-time. Taking digitalis regularly.
O/E: S.R. No C.C.F. Mitral stenosis.
W.B.C. 13,000.
Operation: Stenosis.
Histology: Gp 1 ++
Gp 2 + N 4 P 3.

Case 26. (C.1429/52) F. Age 42.
No history of Rh.F. Dyspnoea for 1½ yrs. Occasional attacks of nocturnal dyspnoea. Can walk only a few yds and has been unable to do housework for 1 yr. Developed hemiplegia 13 yrs ago. Sterilised 6 yrs ago following a pregnancy.
O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. ++

Gp 2. ++ N 7 P 6.

Case 27. (C.1465/52) M. Age 45 Labourer.

No history of Rh.F. Dyspnoea for 5 yrs. Mitral disease diagnosed at age 17. Off work for 1 yr. 4 yrs ago in hospital 7 weeks at this time. In hospital 1 yr ago. Has not worked for 8 mths. Can walk only 100 yds on the level.

O/E: S.R. No C.C.F. Mitral stenosis. ? aortic valve disease. E.S.R. 16 mm.

Operation: Stenosis with marked regurgitation.

Histology: Gp 2. ++. In one section is a fully organised thrombus not related to the areas with lesions. N 5 P 4.

Case 28. (C.1776/52) M. Age 41. Factory worker.

No history of Rh.F. Dyspnoea for 14 yrs which commenced with haemoptysis. Has gradually become worse. Has been in hospital on numerous occasions with haemoptysis. Has not worked for 4 yrs.

O/E: S.R. Mitral stenosis and aortic regurgitation.

Operation: Stenosis. Calcification.

Histology: Gp. 1. ++ N 5 P 4.

Case 29. (C.1867/52) M. Age 28. Draughtsman.
No history of Rh.F. Dyspnoea for 7 yrs gradually becoming worse. Recently severe dyspnoea and haemoptysis.
O/E. A.F. No C.C.F. Mitral stenosis and aortic regurgitation.
Operation: Stenosis. Calcification.
Histology: Gp 1. +
Organising thrombus not related to the lesions. N 5 P 4.

Case 30. (C.1961/52) M Age 40. Dog handler.
Rh.F. at 10 yrs. Dyspnoea on exertion for 1 yr. Symptoms began suddenly with an acute attack of dyspnoea. Taking digitalis. Able to walk long distances slowly.
O/E. A.F. No C.C.F. Mitral stenosis.
Operation: Mainly regurgitation. Calcification.
Histology: Gp 1. + N 7 P 7.

Case 31. (C.2121/52) F. Age 45. Housewife.
No history of Rh.F. Dyspnoea on exertion for 10 yrs which has become worse. One small haemoptysis. Ankle oedema for 2 yrs. Can walk slowly upstairs. Occasional attacks of nocturnal dyspnoea.
O/E. S.R. No C.C.F. Mitral stenosis.
Operation: Tight stenosis.

Histology: Gp 1. ++

Gp 2. ++ N 8 P 8.

Case 32. (C.2167/52) M. Age 38.

No history of Rh.F. Dyspnoea on exertion and oedema of ankles for several years. Much worse in last year. Treated with digitalis and mercurial diuretics.

O/E. Orthopnoeic. A.F. C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: Gp 1. +++

Organising thrombus. N 6 P 6.

Case 33. (C.2221/52) F. Age 36 Viewer.

Chorea age 6 yrs. Dyspnoea on exertion for 8 yrs. C.C.F. 2 yrs ago. Treated with digitalis. Can now walk very slowly on the flat.

O/E. A.F. C.C.F. Mitral stenosis.

E.S.R. 22 mm. in 1 hr. W.B.C. 27,400.

Operation: Stenosis.

Histology: Organising thrombus.

No active lesions. N 2.

Case 34. (C.2268/52) M. Age 24.

Rh.F. at 9 yrs. Has been treated in institutions on several occasions. Several haemoptyses. Dyspnoea on exertion from age 9. Orthopnoeic. Can now walk only 100 yds on the level.

O/E: S.R. No C.C.F. Stenosis.

Operation: Stenosis.

Histology: Gp 2. ++ N 2 P 2.

Case 35. (C.2279/52) M. Age 29. Colour matcher.
No history of Rh.F. Palpitations and repeated attacks of haemoptysis. Slight dyspnoea on exertion but can walk long distances on the flat. Can also run upstairs.
O/E.S.R. No C.C.F. Mitral stenosis.
Operation: Slight stenosis. Marked regurgitation.
Histology: Gp 1. +++
Gp 2. ++ N 2 P 2.

Case 36. (C.2343/52) M. Age 34. Porter.
No history of Rh.F. Dyspnoea for 1 yr. Can walk slowly for long distances on the flat. Orthopnoeic.
O/E. S.R. No C.C.F. Mitral stenosis.
Operation: Mainly regurgitation. Calcification.
Histology: No active lesions. Normal looking auricular appendage. N 2.

Case 37. (C.2344/52) M. Age 35.
No history of Rh.F. Dyspnoea for 2 yrs with oedema of ankles. Very breathless on climbing stairs and can walk only 50 - 100 yds on the flat. Taking digitalis regularly.
O/E: A.F. C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: Organising thrombus.
No active lesions. N 3.

Case 38. (C.2569/52) F. Age 31. Housewife.
No history of Rh.F. Dyspnoea on exertion for 14 yrs, gradually becoming worse. Can now walk only 100 yds.on the level with difficulty. Sleeps with 4 pillows.
O/E. S.R. Orthopnoeic. No C.C.F. Mitral stenosis.
Operation: Tight stenosis.
Histology: Gp 1. +++
Gp 2. +++ N 5 P 5.

Case 39. (C.2640/52) F. Age 22. Housewife.
No history of Rh.F. Dyspnoea on exertion during and since school. Can go up one flight of stairs and then becomes breathless. Patient is 20 weeks pregnant. Treated with digitalis for 7 wks prior to operation.
O/E. A.F. No C.C.F. Mitral stenosis.
Operation: Mitral regurgitation.
Histology: Gp 1. ++
Gp 2. ++ N 2 P 2.

Case 40. (C.2660/52) F. Age 28. Housewife.
No history of Rh. F. Dyspnoea for 4½ yrs, started during her first pregnancy and has steadily become worse. Haemoptysis 3 mths ago. Can now walk only 50 yds on the level. Taking digitalis regularly.

O/E. S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Gp 2. ++ N 1 P 1.

Case 41. (C.2702/52) M. Age 13.

Rh.F. at 5 and 10 yrs. Dyspnoea for 3 yrs. In hospital on several occasions. Can now do very little without becoming breathless.

O/E. S.R. C.C.F. Mitral stenosis with possible regurgitation. E.S.R. 22 mm.in one hr.

Operation: Regurgitation. No stenosis.

Histology: Gp 1. +++

Gp 2. +++ N 1.

Case 42. (C.2731/52) F. Age 36. Housewife.

Rh.F. at age 7. Dyspnoea on exertion since then. Much worse in past 2 yrs. Cerebral embolus 1 yr ago. Can walk ¼ mile slowly on the flat.

O/E. A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: Organising thrombus.

No active lesions. N 4.

Case 43. (C.2733/52) F. age 47.

Rh.F. at 9 and 11 yrs. Dyspnoea on exertion for several yrs but her disability is not very marked. Occasional attacks of nocturnal dyspnoea. Taking digitalis regularly.

O/E. A.F. No C.C.F. Mitral stenosis.

Operation: Slight stenosis. Mainly regurgitation.

Histology: $N_0$ active lesions. N 3.

Case 44. (C.2771/52) F. 46 yrs. Sheet metal worker. Rh.F. at 13 yrs. Has been slightly dyspnoeic on exertion since that time but much worse in last 4 yrs. following a cerebral embolus. Oedema of ankles for 4 yrs. Uses 5 pillows at night. Receiving mersalyl injections and digitalis.

O/E. A.F. Early C.C.F. Mitral stenosis.

Operation: Stenosis with considerable regurgitation. Calcification.

Histology: Gp 1. +

Gp 2. ++

Organising thrombus not associated with the lesions. N 3 P 3.

Case 45. (C.2937/52) F. Age 37.

Rh.F. at 18 and 20 yrs. Dyspnoea on exertion for 12 yrs. Oedema of ankle for 1 yr. Attack of C.C.F. 2 yrs ago. Occasional haemoptyses. Patient is very disabled.

O/E. S.R. Early C.C.F. Mitral stenosis with regurgitation. ? tricuspid lesion.

Operation: Tight stenosis.

Histology: Gp 1. +++

Gp 2. +++ N 4 P 3.

Case 46. (C.2972/52) F. Age 48.

No history of Rh.F. Dyspnoea on exertion for 11 yrs, gradually becoming worse. No history of C.C.F. Can walk slowly on the flat.

O/E: A.F. No C.C.F. Mitral stenosis and aortic regurgitation.

Operation: Mitral stenosis.

Histology: No active lesions.

Organising thrombus. N 3.

Case 47. (C.3051/52) F. Age 19 Metal worker.

Rh.F. at age 7. Breathlessness on exertion since then. Could not play games at school. Can climb stairs slowly. Sleeps with 5 pillows. No history of C.C.F.

O/E: S.R. Orthopnoeic. No C.C.F. Mitral stenosis. ? aortic valve disease.

Operation: Slight stenosis. Gross regurgitation.

Histology: No active lesions.

Appendage appears normal. N 3.

Case 48. (C.3162/52) M. Age 32 Gas welder.

No history of Rh.F. Dyspnoea on exertion for 9 yrs. Haemoptysis on two occasions. Mitral stenosis discovered during a routine army medical examination. At present can walk very slowly upstairs and can walk ¼ mile on the flat at normal pace. Sleeps with 4 pillows.

O/E: S.R. No C.C.F. Mitral stenosis.

E.S.R. 28 mm. in 1 hr.

Operation: Stenosis. Following operation patient was thought to have a "rheumatic flare-up".

Histology: Gp 1. +++

Gp 2. +++ N 8 P 8.

Case 49. (C.3190/52) F. Age 22.

Rh.F. at 2 yrs. Dyspnoea on exertion for 6 yrs, gradually becoming worse during last year. No history of C.C.F. Can walk on flat without difficulty but is breathless on climbing stairs. Not taking digitalis.

O/E: S.R. No C.C.F. Mitral stenosis.

W B C 10,000.

Operation: Stenosis.

Histology: Gp 1. ++

Gp 2. +++ N 4 P 3.

Case 50. (C.3216/52) F. Age 28.

No history of Rh.F. Chorea at 4 yrs. Dyspnoea for 6/12 yrs. No haemoptysis. No history of C.C.F. Has difficulty in climbing stairs and becomes breathless after walking short distances.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Gp 2. ++ N 2 P 2.

Response to operation was unsatisfactory. Developed auricular fibrillation which persisted. Re-admitted 8 months after operation in an acute attack of cardiac failure. Patient was jaundiced and died the day after admission.

Post-mortem findings. (E.N. 221/53).

Heart (430 gms). Mitral valve severely stenosed admitting only one finger. Slight calcification. No evidence of a valvotomy split. Other valves n.a.d.

Other organs show chronic venous congestion.

Histology: Active lesions were not detected in the heart.

Case 51. (C.3243/52) F. Age 33.

No history of Rh.F. Recurrent oedema of ankles for 17 yrs. Dyspnoea on exertion for same period. Can walk up one flight of stairs without stopping but is breathless at the top. Can walk fairly long distances on the flat. Taking digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: No active lesions.

Organising thrombus.

Case 52. (C.3299/52) F. Age 45. Housewife.
Rh.F. at age 15. Chorea at age 12. Dyspnoea on exertion for 9 yrs, gradually becoming worse. Can no longer do her housework. No history of C.C.F.
O/E: No C.C.F. Mitral stenosis. ? aortic disease.
Operation: Stenosis.
Histology: No active lesions. N 7.

Case 53. (C.3313/52) F. Age 30.
Rh.F. at age 10. Dyspnoea on exertion for 16 yrs. Worse in last 6 yrs. No haemoptysis or C.C.F. Can go up one flight of stairs slowly and can walk long distances on the flat.
O/E: A.F. No C.C.F. Mitral stenosis.
Operation: Tight stenosis.
Histology: No active lesions. N 10.

Case 54. (C.3377/52) F. Age 39.
Rh.F. at age 8. Dyspnoea on exertion for several years but more noticeable in past 2½ yrs. No history of C.C.F. Now has difficulty in climbing stairs.
O/E: A.F. No C.C.F. Mitral stenosis.
Operation: Mitral regurgitation.
Histology: Gp 1. +
Gp 2. + N 3 P 3.

Case 55. (C.3433/52) F. Age 41. Housewife. Chorea at 8 yrs. No Rh.F. Dyspnoea on exertion for 12 yrs. Several haemoptyses. Can walk ¼ mile on the flat before becoming breathless. Sleeps with several pillows. Taking digitalis regularly.
O/E: A.F. No C.C.F. Mitral stenosis and aortic regurgitation.
Operation: Tight stenosis. Calcification.
Histology: Gp 1. +
Gp 2. + N 4 P 1.

Case 56. (C.3505/52) M. Age 25. Chocolate marker. Rh.F. as a child. Dyspnoea for 12 yrs, but much worse in past 4 yrs. No history of C.C.F. Has difficulty in climbing stairs and becomes breathless after walking short distances.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Stenosis. Calcification.
Histology: Gp 1. +++
Gp 2. +++ N 3 P 3.

Case 57. (C.3603/52) F. Age 36. Housewife. Rh.F. at 14 yrs. Dyspnoea for 17 yrs. Worse during last 4 yrs. Has had 5 twin pregnancies, the last being terminated at 7 mths four years ago. Can now climb only ten stairs. No history

of C.C.F. Taking digitalis regularly.

O/E: A.F. Orthopnoeic. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: No active lesions.

Organising thrombus. N 2.

Case 58. (C.3616/52) F. Age 43. Supervisor.

No history of Rh.F. Chorea at 11 yrs. Dyspnoea on exertion for 10 yrs. Cerebral embolus 1 yr ago. Ankle oedema on several occasions. Able to walk on the flat but breath--less on hills or stairs. Taking digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Slight stenosis and regurgitation.

Histology: No active lesions. N 5.

Case 59. (C.3822/52) F. Age 41. Housewife.

Rh.F. at age 19 and 25. Chorea as a child. Dyspnoea on exertion for 16 yrs. Worse during last 3 yrs. No history of C.C.F. Can now walk only 20 yds on the flat. Has been in bed for 1½ yrs. Has been in hospital on several occasions with fainting attacks.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions. N 4.

Case 60. (C.3825/52) M. Age 39. Moulder.
No history of Rh.F. Dyspnoea on exertion for 8 yrs. Discharged in 1943 from R.A.F. with "heart trouble". Has had several haemoptyses since 1948. No history of C.C.F. Sleeps with 6 pillows. Taking digitalis regularly.
O/E: S.R. Orthopnoeic. No C.C.F. Mitral stenosis.
Operation: Tight stenosis.
Histology: Gp 1. +++
Gp 2. ++ N 1 P 1.

Case 61. (C.27/53) M. Age 42. Factory worker.
Joint pains at age 16. Passed A 1 for military service at age 31. Discharged after 4 yrs with dyspnoea and defective hearing. Remained slightly dyspnoeic on exertion until age 37 yrs when he had a haemoptysis. Treated since then with digitalis. Has remained dyspnoeic on exertion but continued to work until admission to hospital for operation.
O/E: S.R. Mitral stenosis. No C.C.F.
Operation: Stenosis.
Histology: Gp 1. +
Gp 2. +++ N 2 P 2.

Case 62. (C.64/53) M. Age 37. Grinder.

No history of Rh.F. Dyspnoea on exertion for 8 yrs. Stopped work shortly after dyspnoea began. Attack of C.C.F. 3 yrs ago. Several haemoptyses in last 2 yrs. Can walk upstairs without difficulty.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Organised thrombus. N 2 P 1.

Case 63. (C.153/53) F. Age 39. Factory worker.

No history of Rh.F. Dyspnoea on exertion for 5 yrs. Now gets breathless after walking 100 yds or climbing one flight of stairs. Taking digitalis.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 1. +++

Gp 2. +++ N 7 P 7.

Case 64. (C.155/53) M. Age 23.

No history of Rh.F. Dyspnoea on exertion for 2½ yrs, gradually becoming worse. Paroxysmal nocturnal dyspnoea. Taking quinidine.

O/E: S.R. No C.C.F. Mitral stenosis and aortic regurgitation.

Operation: Slight stenosis.

Histology: Gp 1. +++ Gp 2. ++ N 3 P 3.

Case 65. (C.172/53) F. Age 24.

Rh.F. at 11 and 24 yrs. Dyspnoea for 10 yrs. Several haemoptyses. Can now walk slowly for short distances on the flat.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Gp 2. +++ N 2 P 2.

Case 66. (C.223/53) F. Age 35. Housewife.

No history of Rh.F. Dyspnoea on exertion and palpitations for 4 yrs. Unable to do her own housework. No history of C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: Gp 1. +++

Gp 2. ++ N 2 P 2.

Case 67. (C.384/53) F. Age 30.

Rh.F. and chorea at 5 and 18 yrs. Following the second attack she began to be breathless and this has continued. Now unable to climb stairs. C.C.F. on several occasions. Taking digitalis regularly.

O/E: A.F. Early C.C.F. Mitral stenosis and aortic regurgitation.

Operation: Stenosis. Calcification.

Histology: No active lesions.

Fully organised thrombus. N 3.

Case 69. (C.584/53) F. Age 35. Dietician.

? Rh.F. at 8 yrs. Dyspnoea for 10 yrs gradually becoming worse. Haemoptyses on two occasions in past 1½ yrs. Can walk 100 yds on the flat before becoming breathless. Difficulty in climbing stairs.

O/E: S.R. No C.C.F. Mitral stenosis. ? aortic regurgitation.

Operation: Tight stenosis.

Histology: Gp 1. ++

Gp.2. +++ N 7 P 7.

Case 70. (C.634/53) M. Age 34. Labourer.

No history of Rh.F. Dyspnoea on exertion for 12 yrs. Several attacks of C.C.F. Taking digitalis regularly. Difficulty in climbing stairs, and can walk only short distances on the flat.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Organising thrombus. N 1.

Case 71. (C.635/53) F. Age 42.

Rh.F. at age 30. Dyspnoea for 5 yrs gradually becoming worse until she is now unable to do

her housework. No history of C.C.F. or haemoptyses.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: Gp 1. +++

Gp 2. ++ N 4 P 4.

Case 72. (C.671/53) M. Age 34. Bricklayer.

Rh.F. at 11 and 16 yrs. Rejected for military service and worked as a bricklayer until 3 yrs ago when he became breathless and developed C.C.F. Has been unable to work for 1 yr and spends a lot of time in bed.

O/E: A.F. Early C.C.F. Mitral stenosis. Aortic stenosis.

Operation: Stenosis. Valve dilated but not split.

Histology: No active lesions.

Organising thrombus. N 1.

Discharged April 1953 from hospital and resumed work. Continued to take digitalis. 10 mths later admitted as an emergency in C.C.F. Treated with methyl thiouracil. Improved but unable to resume work. Re-admitted Sept.'55 as an emergency having had C.C.F. for 2 wks.

Operation: Mitral valve dilated but not split. Ventricle opened and aortic valve dilated.

Developed C.C.F. and died a few days later.

Autopsy: (E.N. 315/55).

Heart 650 gms. Rt and lt ventricular hypertrophy. Mitral and aortic valves are both severely stenosed.

Other organs show C.V.C.

Histology: No active lesions detected anywhere in the heart.

Case 73. (C.695/53) F. Age 29. Housewife.

Rh.F. at 7 yrs. Dyspnoea on exertion for 5 yrs. Haemoptyses on several occasions. Carried on normal life until 1½ yrs ago when she had a sudden attack of dyspnoea. Since then she can only walk ½ mile on the flat with several stops. Can climb one flight of stairs.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis with considerable regurgitation.

Histology: Gp 1. + N 7 P 3.

Case 74. (C.735/53) F. Age 45. Housewife.

No history of Rh.F. Dyspnoea for 5 yrs. Haemoptyses on several occasions. Diagnosed as mitral stenosis in 1937 but had no symptoms for 10 yrs following this diagnosis. Can walk 2 - 3 miles on the flat. Taking digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis. Aortic

regurgitation.

Operation: No stenosis. Regurgitation.

Histology: Gp 1. +

Organising thrombus. N 5 P 3.

Case 75. (C.810/53) F. age 24.

Chorea at age 8, 9 and 11 yrs. Rh.F. at 11 yrs. During a pregnancy 4 yrs before operation she was twice under hospital care. No history of C.C.F. Now able to walk ¼ mile on flat at own pace. Cannot climb hills.

O/E: S.R. No C.C.F. Mitral stenosis.

ESR 23 mms. in 1 hr.

Operation: Stenosis.

Histology: Gp 1. + N 1.

Developed acute rheumatic fevere 4 mths after operation.

Case 76. (C.863/53) F. Age 30. Housewife.

Rh. fever at 7 yrs. Dyspnoea on exertion for 5 yrs. During her second pregnancy 1 yr ago she developed C.C.F. and was sterilised after delivery. Can walk considerable distances on the flat. Able to climb stairs slowly. Uses 1 pillow at night. Not taking digitalis.

O/E: S.R. Mitral stenosis. No C.C.F.

ESR 20 mm. in 1 hr.

Operation: Tight stenosis.

Histology: Gp 1. ++

Gp 2. + N 1 P 1.

Case 77. (C.922/53) M. age 42.

No history of Rh. fever. Dyspnoea on exertion for 12 yrs. Worse during past 3 yrs. Invalided from army. Can now walk slowly on the flat. Takes digitalis regularly.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis with considerable regurgitation.

Histology: Gp 1. +

Gp 2. + N 2 P 2.

Case 78. (C.1054/53) M. Age 36. Engineer.

No history of Rh.F. Dyspnoea on exertion for 5 yrs. Occasional haemoptyses. C.C.F. last year. Takes digitalis regularly. Can now walk only 25 yds on the level without becoming breathless.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 2.

Case 79. (C.1079/53) F. Age 31. Housewife.

Rh.F. at 19 yrs. Dyspnoea and frequent haemoptysis since then. Had one pregnancy 5 yrs ago and was sterilised following delivery.

Following this she was very breathless and was unable to do housework. Several attacks of paroxysmal nocturnal dyspnoea.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 2. ++ N 1 P 1.

Case 80. (C.1108/53) F. Age 40.

Arthritis of knees age 17. Dyspnoea for 11 yrs gradually becoming worse. Able to do shopping but has to go slowly on hills. Not taking digitalis.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 1. + N 1.

Case 81. (C.1197/53) F. Age 25. Machinist.

Rh.F. at 12 yrs. Dyspnoea on exertion for 6 yrs. One haemoptysis 6 yrs ago. Now is unable even to make a bed or cook.

O/E: A.F. Orthopnoeic. Early C.C.F.

Operation: Tight stenosis.

Histology: Gp 1. +++

Gp 2. ++ N 4 P 4.

Case 82. (C.1198/53) F. Age 23.

No history of Rh.F. Dyspnoea on exertion for 1 year. Haemoptysis on one occasion. No history of C.C.F. Now finds difficulty in climbing stairs.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Regurgitation.

Histology: Gp 1. + N 1.

Case 83. (C.1224/53) M. Age 52.

Rh.F. at age 32. Dyspnoea on exertion for several years gradually becoming worse. Haemoptyses on several occasions. Patient is under treatment for diabetes mellitus. No history of C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis. Calcification. Considerable regurgitation.

Histology: Gp 1. +

Gp 2. +++ N 1.

Case 84. (C.1294/53) F. Age 39. Housewife.

Rh.F. at age 36 yrs. Dyspnoea on exertion since then. Treated with digitalis. Has been unable to do housework and now requires assistance to climb stairs. Can walk only 40 yds on the flat.

O/E: A.F. Early C.C.F. Orthopnoeic. Mitral stenosis. W.B.C. 10,800.

Operation: Stenosis. Calcification.

Histology: Gp 1. +

Organising thrombus. N 6 P 3.

Case 85. (C.1339/53) F. Age 41. Housewife.

Rh.F. at age 16 yrs. During her only pregnancy

12 yrs ago she had attacks of dyspnoea which disappeared after the birth of her child. Well until 6 yrs ago when she developed dyspnoea on exertion. In past 6/12 yrs has been almost completely confined to her home. Has great difficulty in climbing stairs. Cerebral embolus 4 yrs ago. Taking digitalis regularly. No history of C.C.F.

O/E: A.F. Early C.C.F. Mitral stenosis.

Operation: Stenosis. Not calcified.

Histology: No active lesions.

Organising thrombus. N 10.

Case 86. (C.1360/53) F. Age 25. Radiographer.

No history of Rh.F. Repeated haemoptyses for 4 mths. One previous attack of C.C.F. Is only moderately dyspnoeic on exertion. Not taking digitalis.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Regurgitation. No stenosis.

Histology: Gp 1. ++

Gp 2. + N 4 P 4.

Case 87. (C.1474/53) M. Age 37.

No history of Rh.F. Dyspnoea on exertion for 9 yrs, gradually becoming worse. Haemoptysis on two occasions. No history of C.C.F. Difficulty

in climbing stairs.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Moderate stenosis.

Histology: Gp 2. +++ N 1.

Case 88. (C.1657/53) F. Age 33.

No history of Rh.F. Dyspnoea on exertion for 8 yrs. 5 yrs ago she became suddenly very breathless and since then has done little housework and no shopping. Has had occasional haemoptyses. Ankles swell at night.

O/E: S.R. No C.C.F. Orthopnoeic. Mitral stenosis.

Operation: Tight mitral stenosis.

Histology: Gp 1. +

Gp 2. ++ N 3 P 3.

Case 89. (C.1781/53) M. Age 32. Bus driver.

No history of Rh.F. Haemoptysis on two occasions 12 yrs and 1½ yrs before operations. Dyspnoea on exertion for 4 yrs. Now unable to climb stairs. Can walk 50 yds on the flat. No history of C.C.F.

O/E: A.F. No C.C.F. Mitral stenosis.

W.B.C. 11,7000.

Operation: Stenosis.

Histology: Gp 1. +

Organising thrombus. N 6 P 3.

Case 90. (C.1821/53) F. Age 29.

No history of Rh.F. Dyspnoea for 11 yrs, steadily becoming worse. Prior to admission for operation she had a cerebral embolus and a haemoptysis. Also C.C.F. at that time. Taking digitalis regularly,

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 3.

Case 91. (C.1923/53) M. Age 18.

"Growing pains" at age 7 yrs with several recurrences of joint pains. Dyspnoea on exertion since age 9. Breathlessness has slowly increased. Can only walk slowly on the flat. Uses 4 pillows at night. Haemoptysis on several occasions.

O/E: S.R. No C.C.F. Stenosis.

Operation: Mainly regurgitation. Slight stenosis.

Histology: Gp 1. +

Gp 2. ++ N 4 P 4.

Case 92. (C.1932/53) F. Age 42. Housewife.

Chorea at age 12 yrs. Rh.F. at age 16. Dyspnoea on exertion for 16 yrs, gradually increasing in severity. Can walk 150 yds on level at own pace. Had an attack of C.C.F. 3 mths before admission.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation:

Histology: Gp 1. +

Organising thrombus. N 3 P 2.

Case 93. (C.1935/53) F. Age 41. Housewife. Chorea at age 13. Rh.F. at age 16. Dyspnoea and palpitations for 5 yrs. Taking digitalis regularly. No history of C.C.F. Can walk ¼ mile on flat. Cannot climb stairs.

O/E: A.F. No C.C.F. Mitral stenosis

? incompetence. Aortic incompetence.

Operation: Gross regurgitation. No stenosis.

Histology: No active lesions. N 1.

Case 94. (C.1986/53) F. Age 40. Canteen worker. Rh.F. at age 30. Dyspnoea on exertion for 3 yrs. Ankle oedema 1½ yrs. Dyspnoea has gradually become worse until she is now unable to do housework or climb stairs.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +++

Gp 2. ++ N 5 P 5.

Case 95. (C.2065/53) F. Age 42.

Rh. F. at age 20. Dyspnoea on exertion for 17 yrs, gradually becoming worse. Swelling of

ankles for 10 yrs, persistent during last 7/12 yrs. Taking digitalis. Is now orthopnoeic and completely incapacitated.

O/E: A.F. C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: No active lesions. N 3.

Case 96. (C.2155/53) M. Age 35. Fitter.

No history of Rh.F. Dyspnoea on exertion for 6 yrs. Recent haemoptysis. Disability is increasing and he can now only walk slowly on the flat and has difficulty in climbing stairs.

O/E: A.F. No C.C.F. Orthopnoeic. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions. N 2.

Case 97. (C.2383/53) F. Age 32. Housewife.

Rh.F. at age 28. Dyspnoea on exertion for 3 yrs following a pregnancy. Can now walk any distance on the flat but is breathless on climbing stairs. No history of C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

W.B.C. 12,000.

Operation: Stenosis with considerable regurgitation.

Histology: Gp 1. + N 8 P 3.

Case 98. (C.2428/53) M. Age 30. Commercial traveller. Rh.F. at age 14. Dyspnoea on exertion for 15 yrs. Worse in last 5 yrs. Cerebral embolus 5 yrs ago. Able to carry on his work and can walk ½ mile on the flat. Dyspnoea on climbing one flight of stairs. Occasional haemoptysis and palpitations. Taking digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Pure regurgitation. No stenosis.

Histology: No active lesions. N 8.

Case 99. (C.2551/53) M. Age 40. Caretaker. Rh.F. at age 21. Dyspnoea on exertion for 4 yrs and several attacks of C.C.F. Able to walk 50 yds on the flat.

O/E: A.F. C.C.F. Mitral stenosis. E.S.R. 12.

Operation: Stenosis with marked regurgitation. Calcification.

Histology: No active lesions. N 1.

Case 100. (C.2633/53) M. Age 29. Rh.F. at age 5. Dyspnoea for 13 yrs with occasional haemoptyses. Difficulty in climbing stairs and can only walk for short distances on the flat. Taking digitalis regularly.

O/E: A.F. C.C.F. Mitral stenosis and aortic regurgitation.

Operation: Moderate stenosis. Marked regurgitation. Calcification.

Histology: Gp 1 +.

Organising thrombus. N 4 P 2.

Case 101. (C.2634/53) M. Age 34. Engine fitter. Rh.F. at 7, 9 and 27 yrs. Haemoptyses 6 yrs ago. Discharged from army in 1943. Not very dyspnoeic on exertion. Can still climb stairs fairly well.

O/E: S.R. No C.C.F. Mitral stenosis. Aortic regurgitation.

Operation: Stenosis with considerable regurgitation. Calcification.

Histology: Gp 1. +++

Gp 2. ++ N 3 P 3.

Case 102. (C.2677/53) F. age 48. Rh.F. at age 10. Dyspnoea for 4 yrs. No history of C.C.F. Finds difficulty in climbing stairs and can only walk short distances on the flat.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +++

Gp 2. ++ N 12 P 12

Case 103. (C.2678/53) F. Age 47. Rh.F. at age 19. Well until 5 yrs ago when she suddenly developed C.C.F. Treated with digitalis.

Since then has had several attacks of C.C.F. and during last 2 yrs she had been in almost permanent failure.

O/E: A.F. C.C.F. Mitral stenosis. Aortic incompetence.

Operation: Stenosis and moderate regurgitation. Extreme calcification.

Histology: Gp 1. +

Organising thrombus. N 6 P 3.

Case 104. (C.2742/53) F. Age 35. Housewife.

? Rh.F. at age 27. Dyspnoea on exertion for 6 yrs which has steadily become worse until now she cannot do her housework. Cannot walk more than 50 yds. Has never had C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

W.B.C. 10,000.

Operation: Stenosis.

Histology: Gp 1. +++

Gp 2. +++ N 4 P 4.

Case 105. (C.2755/53) M. Age 43. Craftsman.

No history of Rh.F. Dyspnoea on exertion for 10 yrs. Gave up work 7 mths before operation because of breathlessness following "influenza". 4 mths ago started office work. Can walk up to 2 miles on the level but finds it difficult to climb hills or stairs. Has never had digitalis.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Gp 2. + N 2 P 2.

Case 106. (C.2838/53) M. Age 27. Factory engineer. No history of Rh.F. Old T.B. arthritis of knee. Dyspnoea on exertion for 4 yrs. Haemoptysis 3 yrs ago. Mitral stenosis diagnosed at that time. Took up light work but dyspnoea increased. Has not worked for 1 yr. Taking digitalis regularly.
O/E: A.F. No C.C.F. Mitral stenosis.
Developed tonsillitis (Beta H.S. not isolated) and had a tonsillectomy. One month later valvotomy was carried out.

Operation: Tight stenosis.

Histology: No active lesions.

Organising thrombus. N 2.

Case 107. (C.2840/53) F. Age 32. Housewife. Rh.F. and chorea at age 13. Dyspnoea on exertion since then. Dyspnoea became worse and has been very bad for 3 yrs. Several attacks of C.C.F. Taking digitalis regularly. Orthopnoeic.
O/E: S.R. Early C.C.F. Mitral stenosis, aortic and tricuspid valves involved.

Operation: Tight stenosis. Calcification. Split unsatisfactory.

Histology: Gp 1. ++ N 2 P 2.

Following operation she remained in C.C.F. Re-admitted 11 mths after operation in severe C.C.F. Died 3 wks after admission.

Post-mortem findings. (E.N. 304/54)

Heart (370 gms). Right and left ventricular hypertrophy. Dilatation and hypertrophy of left atrium. Severe calcified mitral stenosis. No evidence of valvotomy split. Moderate aortic stenosis. Moderate tricuspid stenosis. Pulmonary valve not involved.

Other organs showed C.V.C.

Histology of Heart.

No active lesions found in the left ventricular myocardium but several small nodular lesions present in the left atrial wall and in the sub-endocardium of the right side below the pulmonary cusps.

Case 108. (C.2874/53) M. Age 46. Engineer.

No history of Rh.F. Dyspnoea on exertion for 10 yrs becoming worse during last year. Gave up work 1 yr ago. Has difficulty in climbing stairs. One attack of C.C.F. 1 yr ago. Taking digitalis regularly.

O/E: A.F. No C.C.F. Orthopnoeic. Mitral stenosis. E.S.R. 12.

Operation: Gross regurgitation.

Histology: No active lesions. N 1.

Case 109. (C.2970/53) F. Age 42.

Rh.F. at age 5 and 26. Dyspnoea on exertion for 10 yrs, gradually becoming worse. Occasional attacks of paroxysmal nocturnal dyspnoea. Slight ankle oedema on occasions. Unable to do housework or shopping.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Organising thrombus. N 2 P 2.

Case 110. (C.3018/53) F. Age 22.

No history of Rh.F. Dyspnoea on exertion for 4 yrs. Can walk long distances on the flat but is breathless on climbing stairs.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +

Gp 2. ++ N 5 P 3.

Case111. (C.3169/53) F. Age 19.

No history of Rh.F. Well until 2 yrs ago when she developed dyspnoea on exertion which has gradually become worse. Can still walk upstairs. No haemoptysis or C.C.F. Taking digitalis.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 1. ++

Gp 2. + N 2 P 2.

Case 112. (C.3317/53) F. Age 23. Factory worker. No history of Rh.F. Dyspnoea for 8 yrs gradually becoming worse. No history of C.C.F. Difficulty in climbing stairs but can walk fairly long distances on the flat.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: No active lesions. N 2.

Case 113. (C.3322/53) M. Age 31. Bus driver. No history of Rh.F. Dyspnoea on exertion for 5 yrs, gradually becoming worse. Can now walk only 100 yds before becoming breathless. Has not had C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

E.S.R. 14.

Operation: Stenosis.

Histology: Gp 1. ++ N 1 P 1.

Case 114. (C.3393/53) F. Age 26. Factory worker. No history of Rh.F. Dyspnoea on exertion for 6 yrs gradually becoming worse. Becomes breathless after walking 5 - 10 mins. Can climb stairs with difficulty. Sleeps with 4 pillows. Attacks of

paroxysmal nocturnal dyspnoea in past few weeks.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Mitral stenosis.

Histology: Gp 1. ++

Gp 2. ++ N 2 P 2.

Case 115. (C.3402/53) F. Age 33.

Rh.F. at age 12 and 14. Dyspnoea on exertion for 4 yrs. In hospital on one occasion with C.C.F. Difficulty in climbing stairs. Becomes breathless very quickly when walking. Sleeps with several pillows.

O/E: A.F. C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 2.

Case 116. (C.3432/53) M. Age 43.

No history of Rh.F. Dyspnoea for 6 yrs gradually becoming worse. Can now walk only 500 yds on the flat. Has never had C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis. E.S.R.10.

Operation: Stenosis.

Histology: Gp 1 ++

Gp 2 + N 3 P 3.

Case 117. (C.3500/53) M. Age 30. Labourer.
No history of Rh.F. Dyspnoea on exertion for 10 yrs becoming progressively worse. No history of C.C.F. Several haemoptyses.
O/E: A.F. No C.C.F. Probably mitral regurgitation. W.B.C. 12,000.
Operation: Regurgitation.
Histology: Gp 1. +
Organising thrombus. N 3 P 2.

Case 118. (C.3685/53) F. Age 28.
Chorea at age 7 and 14. Dyspnoea for 2 yrs becoming worse. Can walk 1 mile on the level but has difficulty with hills. Has not had C.C.F.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: Gp 1. +++
Gp 2. +++ N 7 P 7.

Case 119. (C.3686/53) F. Age 45. Shop assistant.
Rh.F. at age 9 and 13. No symptoms until age 25 when she had her first child when she became dyspnoeic. Her symptoms became progressively worse and she has been taking digitalis for 10 yrs. Stopped working 5 yrs ago. Has great difficulty in climbing stairs.

O/E: A.F. No C.C.F. Mitral stenosis. Aortic regurgitation.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 3.

Case 120. (C.3689/53) M. Age 35.

No history of Rh.F. Dyspnoea on exertion for 10 - 14 yrs gradually becoming worse. Can now walk ½ mile on the flat but has difficulty in climbing hills or stairs.

O/E: S.R. No C.C.F. Mitral stenosis. Aortic regurgitation.

Operation: Stenosis.

Histology: Gp 1. +++

Gp 2. +++ N 2 P 2.

Case 121. (C.3748/53) M. Age 33. Shop-keeper.

Rh.F. at age 17. Has been known to have a valvular lesion for 10 yrs but has had dyspnoea on exertion for 5 yrs. Haemoptysis 6 yrs ago. Has not had C.C.F. Can walk quite well on the flat but becomes breathless on climbing stairs. Taking digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis, with considerable regurgitation.

Histology: No active lesions. Organising thrombus. N 1.

Case 123. (C.3756/53) M. Age 43. Grinder.
Rh.F. at age 5, 9, 13 and 19 yrs. Dyspnoea on exertion for 20 yrs. Haemoptysis in 1935. Cerebral embolus 5 yrs ago. Embolus in femoral artery 6/12 yrs ago necessitating amputation of leg. Breathlessness has become more marked but can still walk on the level for long distances. Taking digitalis regularly.
O/E: A.F. No C.C.F. Mitral stenosis. E.S.R. 10.
Operation: Stenosis.
Histology: No active lesions.
Organising thrombus. N 1.

Case 124. (C.11/54) M. Age 26. Factory worker.
No history of Rh.F. Dyspnoea on exertion for 5 yrs. Dyspnoea has persisted and become worse. No history of C.C.F. Has continued with his work until admission for operation.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: Gp 1. ++ N 1.

Case 125. (C.169/54) M. Age 39.
Rh.F. at 9 and 27 yrs. Dyspnoea for several years gradually becoming worse. No history of C.C.F. Now has difficulty in climbing one flight of stairs.
O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 2.

Case 126. (C.213/54) M. Age 40. Factory worker. Chorea at age 12. Dyspnoea on exertion for 16 yrs but disability was not very marked until 6 yrs ago since when it has steadily become worse. Can now walk only 20 yds on the level. Haemoptysis on several occasions.

O/E: A.F. Early C.C.F. Mitral stenosis. Aortic regurgitation. E.S.R. 11.

Operation:

Histology: Gp 1. ++

Gp 2. +

Organising thrombus. N 3 P 3.

Case 127. (C.349/54) M. Age 37. Craftsman. No history of Rh.F. Dyspnoea on exertion for 3 yrs. Worse in last year. Haemoptysis. No history of C.C.F. Working until 3 mths before admission. Able to walk 2 miles on the level. Not taking digitalis.

O/E: A.F. No C.C.F. Mitral stenosis.

E.S.R. 9. W.B.C. 11,200.

Operation: Stenosis. Calcification.

Histology: No active lesions.

Organising thrombus. N 3.

Case 128. (C.370/54) F. Age 42.

No history of Rh.F. Dyspnoea on exertion for 4 yrs, becoming gradually worse until now she can only climb a short flight of stairs slowly. No history of C.C.F. Can walk 300 yds on the flat at own speed.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. ++

Gp 2. ++ N 2 P 2.

Case 129. (C.345/54) F. Age 45.

Rh.F. as a child. Dyspnoea on exertion for 10 yrs. Several attacks of C.C.F. Dyspnoea has slowly increased. Now has difficulty in climbing stairs at home.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +++

Gp 2. ++ N 3 P 3.

Case 130. (C.440/54) M. Age 33.

No history of Rh.F. Dyspnoea on exertion and recurrent haemoptysis for 2 yrs. Dyspnoea has increased and now he has difficulty in walking on the flat.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +++ Gp 2. + N 1.

Case 131. (C.727/54) M. Age 43 Company director. No history of Rh.F. Dyspnoea on exertion for 12 yrs. Ankle oedema for 4 yrs. Treated with mercurial diuretics. Haemoptysis 4 yrs ago. Unable to climb stairs. Can walk slowly for 200 - 300 yds on the flat.

O/E: A.F. C.C.F. Mitral stenosis. E.S.R. 12.

Operation: Tight stenosis.

Histology: No active lesions.

Fully organised thrombus. N 2.

Case 132. (C.728/54) M. Age 53. Cable inspector. Rh.F. as a child. Dyspnoea for 8 yrs gradually becoming worse. Several attacks of C.C.F. Can now walk only 200 - 300 yds on the level.

O/E: A.F. No C.C.F. Mitral stenosis. Aortic incompetence.

Operation: Stenosis. Calcification.

Histology: No active lesions.

Organising thrombus. N 2.

Case 133. (C.756/53) F. Age 30. Housewife. No history of Rh.F. Dyspnoea on exertion for 7 yrs gradually becoming worse. Can walk upstairs without difficulty but is breathless at the top. No history of C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. ++

Gp 2. ++ N 1 P 1.

Case 134. (C.757/54) F. Age 25. Clerkess.

Rh.F. at age 5 and 8. Dyspnoea on exertion for 9 yrs, gradually becoming worse until now is just able to walk 1 mile on the flat. Several embolic episodes and one attack of C.C.F. Takes digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis.

W.B.C. 12,000.

Operation: Stenosis.

Histology: Gp 1. +

Gp 2. ++ N 1.

Case 135. (C.764/54) F. Age 37. Housewife.

No history of Rh.F. Dyspnoea for 30 yrs gradually becoming worse. Can still walk 3 miles on the flat. Sleeps with 4 pillows. Several attacks of "pleurisy".

O/E: A.F. No C.C.F. ? Mitral regurgitation.

Operation: Mitral regurgitation.

Histology: No active lesions. N 2.

Case 136. (C.801/54) F. Age 37.

Rh.F. at age 12. Dyspnoea on exertion for 6 yrs which has steadily increased. Now becomes breathless on making her bed. No history of C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 1. ++

Gp 2. + N 2 P 2.

Case 137. (C. 963/54) M. Age 49. Factory worker. Rh.F. as a child. Dyspnoea on exertion for 8 yrs. Can now walk only 200 yds on the flat. Embolism of femoral artery last year.

O/E: A.F. No C.C.F. Mitral stenosis. E.S.R. 13.

Operation: Stenosis. Calcification.

Histology: No active lesions.

Organising thrombus. N 1.

Case 138. (C.1126/54) F. Age 60.

Rh.F. at age 22. Asthma for many years. Dyspnoea on exertion for 2 yrs which has become progressively worse. Haemoptyses on two occasions. One attack of C.C.F.

O/E: A.F. Orthopnoeic. No C.C.F. Mitral stenosis and aortic regurgitation.

Operation: Stenosis. Calcification.

Histology: Gp 1 +

Organising thrombus. N 2 P 1.

Case 139. (C.1211/54) M Age 19 Machinist.

Rh.F. at age 10. Dyspnoea on exertion and frequent haemoptysis for 1½ yrs. Gave up work 6/12 yrs before operation.

O/E: S.R. No C.C.F. Mitral stenosis with regurgitation. E.S.R. 16.

Operation: Regurgitation. Calcification.

Histology: Gp. 1. + N 3 P 2.

Case 140. (C.1279/54) F. Age 38.

No history of Rh.F. Chorea on three occasions between age 5 and 10. Became breathless during her fourth pregnancy 7 yrs ago. The pregnancy was terminated and she was steralised. Since then she has had increasing dyspnoea and is now only able to do very light housework. No history of C.C.F. Haemoptysis on two occasions.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 2. +++ N 5 P 5.

Case 141. (C.1280/54) M. Age 26. Van driver.

Rh.F. at age 16. Dyspnoea on exertion for 6/12 yrs, becoming much worse. Can now walk only 30 - 40 yds on the flat.

O/E: S.R. No C.C.F. Mitral stenosis with ? regurgitation.

Operation: Regurgitation. Calcification.

Histology: Gp 1. +++

Gp 2. +++ N 6 P 6.

Case 142. (C.1296/54) M. Age 42.

Chorea at age 13. Increasing dyspnoea on exertion for 14 yrs. Several attacks of C.C.F. Becomes breathless on very little exertion.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: No active lesions.
Organising thrombus. N 2.

Case 143. (C.1389/54) M. Age 36.

No history of Rh.F. Dyspnoea on exertion for 6 yrs, increasing in severity. Is now fairly disabled and finds difficulty in climbing stairs. No history of C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: No active lesions. N 7.

Case 144. (C.1465/54) F. Age 38.

Rh.F. as a child. Dyspnoea on exertion for 4 yrs gradually becoming worse. No attack of C.C.F. Now can walk slowly on the flat for some distance but has difficulty with stairs.

O/E: A.F. No C.C.F. Mitral stenosis. E.S.R. 22.

Operation: Stenosis. Calcification.

Histology: No active lesions.
Organising thrombus. N 2.

Case 145. (C.1787/54) F. Age 23.

Chorea at age 14. Joint pains at age 14. Dyspnoea on exertion for 7 yrs, especially bad during last 3 yrs. Haemoptysis on one occasion. Cannot walk upstairs.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Developed joint pains 1 wk after operation. N 3.

Case 146. (C.1835/54) F. Age 28. Housewife.

No history of Rh.F. Dyspnoea on exertion for 1 yr. which is becoming worse. Haemoptyses on two occasions 3 yrs before operation. No history of C.C.F. Still does her own housework and shopping.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +++

Gp 2. ++ N 5 P 3.

Case 147. (C.1836/54) F. Age 48.

No history of Rh.F. Dyspnoea on exertion for 4 yrs. Can now walk ½ mile on the flat at own speed. No history of C.C.F.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 2. +++ N 1.

Case 148. (C.1879/54) M. Age 30.

Chorea as a child. Dyspnoea on exertion for 5 yrs gradually becoming worse. Can now walk only 1 mile at own pace on the flat. Haemoptyses on several occasions.

O/E: A.F. No C.C.F. Mitral stenosis. Aortic regurgitation.

Operation: Stenosis. Calcification.

Histology: No active lesions. N 2.

Case 149. (C.1902/54) M. Age 19. Switch fitter.

No history of Rh.F. Chorea at age 10. Dyspnoea for 9 mths, which is increasing. Can now hardly make any physical effort without becoming breathless.

O/E: S.R. No C.C.F. Mitral stenosis.

W.B.C. 12,200.

Operation: Stenosis. Calcification.

Histology: No active lesions. N 1.

Case 150. (C.1944/54) F. Age 39.

Rh.F. at age 15 and 37. Dyspnoea on effort for 12 yrs. Orthopnoea for several years. Haemoptysis on one occasion and swelling of ankles for several years. Taking digitalis regularly for 10 yrs.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions. N 1.

Case 151. (C.1982/54) F. Age 28. Press operator. No history of Rh.F. Dyspnoea on exertion for 1 yr. Dyspnoea occurred suddenly. One haemoptysis. Disability is not very great.
O/E: S.R. No C.C.F. Mitral stenosis.
Operation: Stenosis.
Histology: Gp 1. ++ N 1.

Case 152. (C.1983/54) F. Age 32. Housewife. Rh.F. at age 5. Dyspnoea on exertion since age 18. Has been in hospital on several occasions usually suffering from upper respiratory infections. Can now barely walk 1 mile.
O/E: A.F. No C.C.F. Mitral stenosis.
W.B.C. 12,100.
Operation: Tight stenosis.
Histology: No active lesions.
Organising thrombus. N 1.

Case 153. (C.1911/54) F. Age 38. Housewife. No history of Rh.F. At age 22 had joint pains. Dyspnoea on exertion for 5 yrs. Sterilised after her first pregnancy 3 yrs ago. Taking digitalis since then. Dyspnoea has become worse during past year. C.C.F. 9/12 yrs ago.

O/E: S.R. Orthopnoeic. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 1. ++

Gp 2. + N 1.

Case 154. (C. 1992/54) F. Age 44.

Rh.F. at 12. Dyspnoea for 10 yrs becoming steadily worse. Haemoptyses on several occasions during past 6 yrs. Patient is an epileptic and a history is difficult to obtain.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 2. +++ N 1.

Case 155. (C.1993/54) F. Age 40. Child welfare worker.

No history of Rh.F. Dyspnoea on exertion for 8 yrs. Can now walk ½ mile on the flat. No history of C.C.F. Taking digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis. Aortic regurgitation.

Operation: Stenosis. Calcification.

Histology: No active lesions.

Case 156. (C.2269/54) M. Age 42. Policeman.

No history of Rh.F. Dyspnoea on exertion for 1½ yrs. Can now walk only 12 steps upstairs. Sleeps with 4 pillows. Not taking digitalis. No history of C.C.F.

O/E: S.R. Early C.C.F. Orthopnoeic. Mitral Stenosis.

Operation: Extreme stenosis. Calcification.

Histology: Gp 1. + N 1.

Case 157. (C.2370/54) F. Age 50.

No history of Rh.F. Increasing dyspnoea for 10 yrs. Occasional attacks of nocturnal paroxysmal dyspnoea. Several attacks of C.C.F. Taking digitalis for 6 yrs.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 3.

Case 158. (C.2736/54) F. Age 45.

No history of Rh.F. Dyspnoea on exertion for 1½ yrs, becoming steadily worse. Can now walk only ½ mile on the flat and climbs stairs with great difficulty.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 1.

Case 159. (C.2795/54) F. Age 46. Housewife.

Chorea at age 16. Rh.F. at age 21. Dyspnoea on exertion for 14 yrs. No history of C.C.F. Can just manage to do her own housework. Has become

worse recently.

O/E: S.R. C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 2. +++ N 1.

Case 160. (C.2864/54) F. Age 43. Housewife.

Rh.F. at age 3, 20 and 28. Dyspnoea on exertion for 3 yrs gradually becoming worse. One episode of C.C.F. Can walk 200 yds on the flat.

O/E: S.R. C.C.F. Mitral stenosis and aortic regurgitation.

Operation: Stenosis.

Histology: No active lesions. N 1.

Case 161. (C.2865/54) F Age 48.

Rh.F. at age 7. Dyspnoea on exertion for 14 yrs. Recently has become worse. No history of C.C.F. Has difficulty in climbing stairs.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Ball thrombus in left atrium. Valve left unsplit.

Histology: No active lesions.
Organising thrombus. N 3.

Case 162. (C.2878/54) F. Age 27.

Rh.F. at age 11. Dyspnoea began during a pregnancy 6 yrs ago. Following delivery she was sterilised. Dyspnoea persisted. Several

haemoptyses. Can still do her own housework and washing but is breathless after climbing stairs.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

One week after operation, joint pains and pyrexia developed.

Histology: Gp 1. +

Gp 2. ++ N 2 P 1.

Case 163. (C.2913/54) F. Age 32.

Rh.F. at age 3. Dyspnoea for several yrs. Swelling of ankles on occasions. Thyroidectomy for thyrotoxicosis in 1940 and 1953. Dyspnoea much worse in past 4 mths.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Moderate stenosis.

Histology: Gp 1. +++

Gp 2. ++ N 1.

Case 164. (C.2926/54) M. Age 32.

No history of Rh.F. Rejected for military service at age 17 because of heart disease but had no symptoms at that time. Dyspnoea on exertion for 4 yrs, gradually becoming worse. Now unable to climb hills but can walk 1 mile on the flat. Not taking digitalis.

O/E: S.R. No C.C.F. Mitral stenosis. E.S.R. 25.

Operation: Stenosis.

Histology: Gp 1. ++

Gp 2. +

Case 165. (C.3001/54) F. Age 22.

No history of Rh.F. Dyspnoea on exertion for 9 yrs. Swelling of ankles for 4 yrs. Can walk well on the flat but is breathless after climbing stairs. Patient is 10 wks pregnant and her dyspnoea has become a little worse.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Tight stenosis.

Histology: Gp 1. +++

Gp 2. +++ N 1.

Case 166. (C.3002/54) M. Age 26.

Rh.F. as a child. Dyspnoea on exertion for 4 yrs. No history of C.C.F. Can walk slowly on the flat but has difficulty in climbing stairs.

O/E: S.R. Mitral stenosis. No C.C.F.

Operation: Stenosis.

Histology: Gp 1. +

Gp 2. ++ N 1.

Case 167. (C.333/52. E.N. 33/52). F. Age 41.

Chorea at age 14 and 16. Dyspnoea for 1 yr. No history of C.C.F. Can now walk for fairly long distances slowly on the flat.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. + N 4 P 1.

Following operation temperature became raised, blood pressure fell and she died 3 days afterwards.

Post-mortem findings:

Heart (435 gms). Pericarditis. Rt ventricular hypertrophy. Tight mitral stenosis. Only a small split present. Other valves not involved.

Other organs. Collapse of left lung.

Histology of heart. Occasional active lesions in left atrium and left ventricular myocardium.

Case 168. (C.588/52. E.N. 57/52) F. Age 26.

Chorea at age 7. Progressive dyspnoea on exertion for several years. Two attacks of C.C.F. 3 yrs and 1 yr ago. Can now walk only 50 yds slowly on the flat.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: No active lesions.

Following operation patient did not recover consciousness and died the same day.

Post-mortem findings.

Heart. (335 gms). Rt ventricular hypertrophy. Tricuspid valve thickened and incompetent. Mitral valve stenosed and calcified. One small recent

split identified. Aortic valve normal.

Other organs show no relevant findings.

Histology of heart. No active lesions detected.

Case 169. (C.2531/52. E.N. 242/52) F. Age 36.

Rh.F. at 15 yrs. Dyspnoea on exertion for 5 yrs which began with an attack of C.C.F. Treated with digitalis which she is still taking. Has not worked since. 1 yr ago had another attack of C.C.F. Can now do no housework. Breathless on climbing one flight of stairs. Patient is 22 wks pregnant.

O/E: A.F. No C.C.F. Mitral stenosis. E.S.R. 32.

Operation: Stenosis.

Histology: No active lesions.

Organising thrombus. N 2.

Patient died on the same day as her operation.

Post-mortem findings:

Heart (430 gms). Rt ventricular hypertrophy. Mitral stenosis, which has been well split. Tricuspid valve thickened. Other valves normal.

Other organs show no relevent features.

Histology of Heart: No active lesions found.

Case 170. (C.434/53. EN. 62/53) F. Age 42. Housewife.

No history of Rh.F. or chorea. Dyspnoea for 6 yrs. Admitted to hospital 1 yr ago with C.C.F. Treated with digitalis, mercurial diuretics etc. Can now

walk only 20 - 30 yds.

O/E: A.F. C.C.F. Mitral stenosis. E.S.R. 40.

Operation: Stenosis. Calcified.

Histology: Gp 1. ++

Gp 2. ++

Organising thrombus. N 4 P 1.

Following operation patient developed haemoptysis and died 3 days later.

Post-mortem findings:

Heart. Gross rt ventricular hypertrophy. Calcified mitral stenosis. Cusps well split. Aortic valve thickened but competent.

Other organs. Lungs bronchopneumonia. Thrombus in right middle cerebral artery.

Histology of Heart: Active lesions in left atrium, and left ventricular myocardium.

Case 171. (C.585/53. EN.83/53) M. Age 31.

Several attacks of Rh.F. as a child and on other occasions since then, the last being 16 yrs ago. Dyspnoea on exertion for several years gradually becoming worse. Can now walk only 100 yds on the flat.

O/E: A.F. C.C.F. Orthopnoeic. Mitral stenosis. Aortic regurgitation.

Operation: Aur. appendage filled with thrombus.

No attempt made at valvotomy.

Histology: Gp 1. +

Organising thrombus. N 3 P 3.

Following operation developed pulmonary oedema and died a few days later.

Post-mortem findings:

Heart: (720 gms). Rt and left ventricular hypertrophy. Severe mitral stenosis. Occasional areas of calcification. Aortic valve shows fusion of cusps. Other valves normal.

Other organs: show no relevant changes.

Histology of heart: Numerous lesions in left ventricular myocardium.

Case 172. (C.2599/53. EN.294/53) F. Age 31.

Rh.F. at age 8, 18 and 27 yrs. Dyspnoea on exertion for 2 yrs becoming progressively worse. Several attacks of C.C.F. in the past and is now in almost permanent failure.

O/E: A.F. C.C.F. Mitral stenosis.

Operation: Stenosis. Calcification.

Histology: Gp 1. +

Gp 2. ++ N 2 P 2.

Following operation she developed massive collapse of lungs and died 3 days after operation.

Post-mortem findings:

Heart (350 gms). Tricuspid stenosis, mitral

stenosis with heavy calcification of valve with two recent splits. Aortic cusps thickened.

Other organs: Collapse of left lung. Liver showed cardiac cirrhosis. Spleen and kidneys showed C.V.C.

Histology of heart: Active lesions in left ventricular myocardium.

Case 173. (C.3150/53. EN. 375/53) F. Age 53.

No history of Rh.F. Dyspnoea for 5 yrs gradually becoming worse. Taking digitalis regularly. Now is unable to climb stairs.

O/E: A.F. C.C.F. Mitral stenosis. WBC. 13,900.

Operation: Tight stenosis. Ball thrombus in left atrium. Valve not split.

Histology: No active lesions.

Following operation she developed an embolus of abdominal aorta. Died 16 days after operation.

Post-mortem findings:

Heart (440 gms). Rt ventricular hypertrophy. Mitral stenosis with calcification. Large ball thrombus in left atrium. Aortic valve thickened.

Other organs. Gangrene of right foot. Thrombus at bifurcation of aorta. Infarcts in spleen and kidneys.

Histology of Heart: No active lesions.

Case 174. (C.1177/54. EN.136/54) M. Age 35. Factory worker. No history of Rh.F. Haemoptyses on several occasions. Dyspnoea on exertion for 3½ yrs. Can now walk 500 yds on the level.

O/E: S.R. No C.C.F. Mitral stenosis.

W.B.C. 11,000.

Operation: Stenosis. Calcification.

Histology: Gp 1. ++

Gp 2. ++

Two days after operation he became cyanosed and unconscious. Died on the 3rd day following operation.

Post-mortem findings:

Heart (460 gms): Rt ventricular hypertrophy. Mitral stenosis. Partially split cusps. Calcification of valve. Aortic valve thickened.

Other organs show no relevant findings.

Histology of Heart: Active lesions in left atrium, mitral valve and left ventricular myocardium.

Case 175. (C.2796/54. EN.314/54) F. Age 36. Housewife. Chorea at age 7. Dyspnoea on exertion for 7 yrs gradually becoming worse but can still walk about 1 mile on the level. Cerebral embolus a few years ago. Takes digitalis regularly.

O/E: A.F. No C.C.F. Mitral stenosis. Aortic

regurgitation.

Operation: Tight stenosis.

Histology: No active lesions.

Organising thrombus.

Patient died on the day after the operation.

Post-mortem findings:

Heart (470 gms). Hypertrophy and dilatation of both ventricles. Mitral stenosis. Valve moderately well split. Aortic valve stenotic and incompetent.

Other organs. Old infarct of right basal ganglion. Recent massive infarct of kidney.

Histology of Heart: No active lesions found.

Case 176. (EN. 112/52) F. Age 39. Housewife.

Rh.F. at age 12. Dyspnoea on exertion for 9 yrs. 3 yrs ago during a pregnancy she became dyspnoeic. Delivered and later sterilised. 10 wks before operation became very dyspnoeic and had several haemoptyses. One previous attack of C.C.F.

O/E: A.F. Orthopnoeic. C.C.F. Mitral stenosis and regurgitation.

Operation: Tight stenosis. Unsatisfactory split.

Histology: The auricular appendage was not received.

Following operation she developed a cerebral embolus and died four days later.

Post-mortem findings:

Heart (360 gms). Mitral stenosis with little evidence of a split. Aortic valve stenotic and incompetent. Tricuspid valve moderately stenosed.

Other organs: Thrombus in right middle cerebral artery. C.V.C. of liver, spleen and kidneys.

Histology of Heart: No active lesions in the left auricular appendage or elsewhere in the heart.

Case 177. (EN. 292/54) F. Age 52.

No history of Rh.F. Dyspnoea on exertion for 2 yrs and haemoptysis on one occasion. Difficulty in climbing stairs.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

2 days after operation patient collapsed and died.

Post-mortem findings:

Heart (360 gms). Rt ventricular hypertrophy. Mitral valve stenotic but recent split present in both commissures. Aortic cusps thickened. Other valves normal.

No other relevant findings.

Histology of Heart: No active lesions.

Case 178. (EN. 108/55) F. Age 41.

No history of Rh.F. Dyspnoea on exertion for

12 yrs. 4 mths ago cerebral embolus. Repeated 3 mths ago.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.

Following operation patient remained unconscious with evidence of cerebral embolus.

Post-mortem findings:

Heart (360 gms). Rt ventricular hypertrophy. Mitral stenosis. Incision in valve and papillary muscle. Other valves normal.

Thrombus in both internal carotids.

No other relevant findings.

Histology of Heart. No active lesions.

Case 179. (C.1990/55. EN. 209/55) M. Age 45.

Rh.F. at age 4. Well until age 29 when he developed dyspnoea on exertion. Several attacks of C.C.F.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Large adherent clot. Valve not split.

Histology: No active lesions.

Organising thrombus.

Patient developed C.C.F. following operation and died a few days later.

Post-mortem findings:

Heart. (670 gms). Mitral stenosis with

calcification. Large mural thrombus in left atrium.

No other relevant findings.

Histology of Heart: Occasional small focal lesions in myocardium.

Case 180. (C.3473/55. EN.13/54) M. Age 50.

No history of Rh.F. Dyspnoea on exertion for 30 yrs, recently becoming worse. Frequent attacks of paroxysmal nocturnal dyspnoea during past 4 yrs. Can walk ½ mile at slow pace on the flat.

O/E: S.R. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: Gp 1. +++

Following operation developed A.F. and C.C.F. Died 4 wks after operation.

Post-mortem findings:

Heart (700 gms). Fibrinous pericarditis with encysted effusion. Severe mitral stenosis with two small incision at commissures. Aortic valve normal. Tricuspid valve relatively incompetent.

Other organs. Bilateral fibrinous pleurisy. Liver, spleen and kidneys show C.V.C. Chronic peptic ulcer of stomach with pyloric stenosis.

Histology of Heart: Lesions similar to those in the auricular appendage in left atrial wall. Small focal lesions in myocardium.

Case 181. (C.418/56. EN. 47/56). F. Age 43.

Rh.F. at 25 yrs followed by progressing dyspnoea on exertion. Normal pregnancy 9 yrs ago. Paralysis of arm and epileptic fits 8 yrs ago. Pneumonia 2 yrs ago followed by worsening of dyspnoea.

O/E: A.F. No C.C.F. Mitral stenosis.

Operation: Stenosis.

Histology: No active lesions.
Organising thrombus.

Did not recover from anaesthetic.

Post-mortem findings:

Heart (420 gms). Tricuspid stenosis. Mitral stenosis with split in one commissure. Aortic and pulmonary valves normal.

Other organs. Brain - old ? cystic softening. Liver C.V.C. Spleen C.V.C. and healed infarcts. Kidneys C.V.C.

Histology of heart: Small focal lesions in the left ventricular myocardium.

Case 182. (EN. 196/52) M. Age 32. Fitter.

Chorea at 11 yrs. Progressive dyspnoea on exertion for 2 yrs. Seen 1 yr ago with a view to valvotomy but was not considered to have sufficient degree of disability. Admitted as

an emergency c/o pain in chest of 24 hrs duration.

O/E: S.R. No C.C.F. T.100.4. Thought to have bronchopneumonia. 2 wks later suddenly became cyanosed and died shortly afterwards.

Post-mortem findings:

Heart (610 gms). Rt and left ventricular hypertrophy and dilatation. Mitral stenosis. No calcification. Aortic incompetence.

Lungs. Massive infarcts. Other organs show C.V.C.

Histology of Heart: No active lesions.

Case 183. (E.N. 198/52) M. Age 16.

Rh.F. at age 4 and 12. Dyspnoea on exertion for several years. Several attacks of C.C.F. during past 4 yrs. Treated with digitalis.

Present admission c/o swelling of joints 4 mths before admission. Oedema of ankles.

O/E: A.F. C.C.F. Mitral and aortic disease. Joints swollen but not tender. E.S.R. 1. W.B.C. 13,100. Died 8 days after admission.

Post-mortem findings:

Heart (655 gms). Rt and left ventricular hypertrophy and dilatation of left ventricle. Mitral incompetence and aortic incompetence.

Other organs show C.V.C.

Histology of Heart: No active lesions.

Case 184. (EN. 209/52) M. Age 42.

Rh.F. at 19. Dyspnoea on exertion and oedema of legs for 3 yrs. Recently much worse and had been in bed for 8 wks prior to admission.

O/E: A.F. C.C.F. Treated with digitalis and mercurial diuretics. Gradually deteriorated and died.

Post-mortem findings:

Heart (850 gms): Hypertrophy and dilatation of both ventricles. Mitral stenosis with calcification of valve. Aortic incompetence.

Other organs show C.V.C.

Histology of Heart: No active lesions.

Case 185. (EN. 313/52) M. Age 49.

Rh.F. as a child. Dyspnoea on exertion for 12 yrs. Severe attacks of C.C.F. during this time. Occasional haemoptysis. Admitted as an emergency in C.C.F.

O/E: A.F. Gross C.C.F. with ascites. Collapsed and died on the day after admission.

Post-mortem findings.

Heart (750 gms): Dilatation and hypertrophy of all chambers. Mitral incompetence. Aortic valve not

involved but small reddish vegetations present on all cusps at the line of closure.

Other organs show C.V.C. The liver shows early cardiac cirrhosis.

Histology of Heart; No active lesions.

Case 187. (EN. 315/52) F. Age 14.

No history of Rh.F. Fleeting joint pains 9 mths before admission. 2 days before admission became orthopnoeic and developed a cough.

O/E: T. 99.5°C. S.R. Mitral stenosis.

W.B.C. 12,100. E.S.R. rose to 53 mm. in 1 hr.

Pyrexia continued and patient became worse. Treated with various antibiotics, aspirin, etc., but deteriorated. Developed C.C.F. and died 3 wks after admission.

Post-mortem findings:

Heart (340 gms): Mitral stenosis ? vegetations on mitral and aortic valve.

Lungs: Bronchopneumonia.

Other organs show C.V.C.

Histology of Heart: No active lesions.

Case 188. (EN. 359/52) F. Age 47 Housewife.

No history of Rh.F. Dyspnoea on exertion for 7 yrs gradually becoming worse. Has had several attacks of C.C.F. Admitted in C.C.F.

O/E: A.F. C.C.F. Mitral stenosis.

Developed pain in legs and chest on the day after admission.

Post-mortem findings:

Heart (570 gms): Extreme dilatation of left atrium. Tight mitral stenosis. Other valves normal.

Other organs C.V.C. Liver shows cardiac cirrhosis. Numerous healed infarcts in kidneys.

Histology of Heart: No active lesions.

Case 189. (E.N. 120/53) F. Age 31. Housewife.

Rh.F. at age 3. Chorea at age 13. Dyspnoea on exertion began 11 yrs ago. After her second pregnancy 5 yrs ago she was sterilised. Admitted to hospital in C.C.F. on two occasions. On second occasion had a small haemoptysis. After her discharge she had "influenza" and was confined to bed.

Present admission. Re-admitted 2 mths after previous discharge c/o pains in joints for a few days and drowsiness for 2 days.

O/E: A.F. Slight C.C.F. Mitral stenosis.

T. 100°C. Joints swollen. Collapsed and died suddenly 3 days after admission.

Post-mortem findings:

Heart (580 gms). Rt vent. hypertrophy. Mitral

stenosis. Other valves normal. Rows of recent vegetations on mitral and aortic valves.

Other organs show C.V.C.

Histology of Heart: Active lesions in left auricular appendage, left atrial wall, mitral and aortic valves and ventricular myocardium.

Case 190. (EN. 170/53) M. Age 29.

Rh.F. at age 9. Dyspnoea on exertion for 7 yrs. Began with haemoptysis and has had several small haemoptyses since then.

Admitted Feb. 1953 c/o oedema of ankles. While in hospital he developed joint pains. Discharged after several weeks.

Re-admitted April 1953 c/o haemoptysis and joint pains.

O/E: A.F. C.C.F. No pyrexia. 3 days after admission had a cerebral embolus. Gradually deteriorated and died 4 wks later.

Post-mortem findings:

Heart (500 gms): Rt vent. hypertrophy. Tight mitral stenosis with gross calcification. Other valves normal.

Brain - cystic softening. Other organs - C.V.C.

Histology of Heart: Active lesions in left auricular appendage, mitral valve and left ventricular myocardium.

Case 191. (EN. 264/53) F. Age 42. Housewife.
Rh.F. at 13 yrs. Slight dyspnoea on exertion for 25 yrs, much worse during past year. 6/12 yrs ago she had an attack of acute Rh.F. and was in hospital for 4 mths. Since this time she has been very breathless and can now walk only 20 yds. "Joints frequently ache".
O/E: A.F. C.C.F. Mitral stenosis. Put on salicylates, mercurial diuretics, digitalis, etc., and given radio-active iodine. Gradually became worse and died 4 wks after admission in C.C.F.
Post-mortem findings:
Heart (450 gms): Rt and left vent. hypertrophy. Mitral incompetence and aortic stenosis.
Other organs show C.V.C.
Histology of Heart: No active lesions.

Case 192. (EN. 279/53) F. Age 35. Housewife.
Rh.F. at age 17. Acute nephritis at age 17. Dyspnoea on exertion for 13 yrs, gradually becoming worse. Haemoptysis on several occasions. Sterilised 7 yrs ago. Can now walk only about 30 yds on the level.
O/E: A.F. C.C.F. Mitral stenosis. E.S.R. 44. Treated with digitalis, mercurial diuretics, etc., but deteriorated and died.
Post-mortem findings:
Heart (480 gms): Rt vent. hypertrophy. Tight

mitral stenosis.

Lungs - multiple infarcts.

Other organs - C.V.C.

Histology of Heart: Active lesions in myocardium.

Case 193. (EN. 280/53) M. Age 39.

Admitted as an emergency (On waiting list for mitral valvotomy).

Rh.F. at age 12 and 21. Dyspnoea for 2 yrs. Began with haemoptysis and has become worse especially during past year. Developed C.C.F. several weeks ago. 1 mth before admission had a pulmonary infarct.

O/E: A.F. Cyanosed. C.C.F.

Died 2 days after admission.

Post-mortem findings:

Heart (650 gms): Hypertrophy and dilatation of all chambers. Gross mitral stenosis with calcification. Aortic stenosis and incompetence.

Lungs - numerous infarcts.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 194. (EN. 283/53) F. Age 36. Housewife.

Rh.F. at age 12 and 18. Dyspnoea on exertion for 5 yrs which has been slowly progressive. Has had ankle oedema for 1 yr and has been confined to bed.

Treated with digitalis and mercurial diuretics.

O/E: A.F. Mitral stenosis. C.C.F. with ascites. E.S.R. 31.

Died 2 wks after admission with acute tachycardia.

Post-mortem findings:

Effusions in pericardium, pleural sacs and peritoneal cavity.

Heart (385 gms): Gross calcified mitral stenosis. Other valves normal.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 195. (EN. 326/53) F. Age 33. Housewife.

Rh.F. and chorea at age 14. Dyspnoea began several years ago during her second pregnancy and has continued. First attack of C.C.F. 3 yrs ago and second attack 1 yr ago. Transferred from another hospital in C.C.F.

O/E: A.F. C.C.F. Orthopnoeic. No pyrexia.

Treated with digitalis, mercurials and low salt diet. Died 2 mths after admission.

Post-mortem findings:

Heart (480 gms): Dilatation of all chambers. Mitral incompetence. Other valves normal.

Other organs - C.V.C. Ascites.

Histology of Heart: No active lesions.

Case 196. (EN. 373/53) M. Age 43.

No history of Rh.F. Asthma for 20 yrs. Dyspnoea on exertion and swelling of ankles for 11 yrs. Now gets breathless after walking 60 yds on the flat. Off work for 10 months. 4 days before admission had embolus of left leg.

O/E: A.F. Cyanosed. Orthopnoeic. C.C.F. Condition deteriorated. Death occurred 2 wks after admission.

Post-mortem findings:

Heart (310 gms): Rt vent. hypertrophy. Mitral stenosis and calcification.

Other organs - C.V.C.

Histology of heart: No active lesions.

Case 197. (EN. 19/54) F. Age 42.

Rh.F. at age 20 and 28. Dyspnoea on exertion for several years. Attacks of C.C.F. 6 yrs and 3 yrs ago when she was given radio-active iodine. The year following the treatment she had another attack of C.C.F. On maintenance dose of thyroxin. Admitted as an emergency following paracentesis as an outpatient.

O/E: S.R. Collapsed. Patient died a few hours after admission.

Post-mortem findings:

Heart (420 gms): Rt vent. hypertrophy. Severe

mitral stenosis. Aortic valve thickened. Recent infarct in I.V. septum.

Other organs C.V.C. No thyroid tissue detected.

Histology of Heart: Active lesions in left auricular appendage and left ventricular myocardium.

Case 198. (EN. 45/54) F. Age 25.

Rh.F. at age 17. Dyspnoea on exertion for 3 yrs. Admitted 1 yr ago in C.C.F. Treated with digitalis and mercurial diuretics. Able to walk to shops. Sore throat 3 wks before admission in C.C.F.

O/E: A.F. C.C.F. Apyrexial. W.B.C. 13,900. Deteriorated and died 8 days after admission.

Post-mortem findings:

Heart (650 gms): Rt vent. hypertrophy and dilatation. Mitral stenosis. Other valves normal. Large thrombus in left atrium and left auricular appendage.

Lungs - numerous infarcts.

Other organs - C.V.C.

Histology of Heart: Active lesions in valves and myocardium.

Case 199. (EN. 67/54) F. Age 49. Housewife.

? Rh.F. as a child. Admitted as an emergency c/o pain in chest for 14 days beginning with a

"cold".

O/E: A.F. C.C.F. Collapsed. Cyanosed. Consolidation of lung.

Died a few hours after admission.

Post-mortem findings:

Heart (350 gms): Tight mitral stenosis. Other valves normal.

Lungs: Rt lobar pneumonia and empyema.

Liver shows C.V.C.

Histology of Heart; No active lesions.

Case 200. (EN. 134/54) M. Age 30.

Rh.F. at age 16. Admitted c/o diarrhoea. No history of dyspnoea or cardiac symptoms. Ulcerative colitis. Colostomy performed.

O/E: A.F. No C.C.F. on admission. Mitral stenosis. Aortic regurgitation. Died 3 wks after admission in C.C.F.

Post-mortem findings:

Heart (550 gms): Rt and left vent. hypertrophy. Mitral stenosis and aortic regurgitation. ? recent vegetations in valves.

Colon - ulcerated colitis.

Other organs - C.V.C.

Histology of heart: No active lesions. Considerable oedema of myocardium. The presence of vegetations was not confirmed.

Case 201. (EN. 139/54) M. Age 20.

Rh.F. at 7. Several recurrences until age 20. Dyspnoea for many years. One attack of C.C.F. last year. Admitted in C.C.F.

O/E: A.F. Mitral stenosis and aortic regurgitation. E.S.R. 14. Cyanosed. Responded to digitalis and mercurial diuretics but 4 wks after admission oedema returned. Condition deteriorated. Death occurred 2 mths after admission.

Post-mortem findings:

Heart (720 gms): Localised fibrinous pericarditis. Mitral stenosis with calcification. Aortic stenosis.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 202. (EN. 186/54) M. Age 42.

Rh.F. at age 8 and 16. Dyspnoea for 14 yrs. Admitted in C.C.F. which had been almost permanently present for 1 yr.

O/E: A.F. C.C.F. Mitral and aortic stenosis. W.B.C. 13,900. E.S.R. 15.

Post-mortem findings:

Heart (1,000 gms): Fibrinous pericarditis. Hypertrophy of rt. vent. Fibrosis of tricuspid.

Mitral stenosis with calcification. Aortic stenosis with calcification.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 203. (EN. 204/54) M. Age 44.

Rh.F. at age 30 and 38. Dyspnoea on exertion for 6 yrs. Developed ankle oedema a few months ago. Treated with digitalis and mercurial diuretics. 4 days before admission became much worse.

O/E: A.F. C.C.F. Ascites. Mitral and aortic valvular disease. Gradually deteriorated and died 4 wks after admission.

Post-mortem findings:

Heart (700 gms): Mitral and aortic stenosis with calcification of both valves.

Lungs - Multiple infarcts.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 204. (EN. 309/54) F. Age 27.

Admitted with chronic nephritis and hypertension. No history of Rh.F. S.R.

Patient died shortly after admission.

Post-mortem findings:

Heart (460 gms): Left vent. hypertrophy and

dilatation. Mitral incompetence. Left atrium hypertrophied.

Lungs - brown induration.

Kidneys - chronic nephritis.

Histology of Heart: Active lesions in left auricular appendage, left atrium and mitral valve.

Case 205. (EN. 393/54) M. Age 23.

Chorea at age 10. 1½ yrs prior to admission had sub-acute bacterial endocarditis which was treated with penicillin. Has had dyspnoea since this illness and it has become worse in last 2 mths.

O/E: S.R. C.C.F. Mitral stenosis.

Five days after admission developed pyrexia and tachycardia. Treated with salicylates. Slowly deteriorated and died 3 wks after admission.

Post-mortem findings:

Heart (750 gms): Mitral stenosis with calcification. Aortic cusps thickened. Other valves normal.

Lungs - Large infarct at apex.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 206. (EN. 35/55) F. Age 25. Housewife.

No history of Rh.F. No symptoms until first pregnancy 6 yrs ago. Became breathless during delivery and was found to have a cardiac lesion.

Recovered and was well until 5 yrs ago when she had a haemoptysis. This was repeated the following year and she has been dyspnoeic ever since. C.C.F. last year and was treated in hospital. Sterilised 4 wks before present admission.

Admitted in C.C.F. and died on day of admission.

O/E: S.R. C.C.F. Mitral stenosis. ? aortic valve disease.

Post-mortem findings:

Heart (490 gms): Rt vent. hypertrophy. Mitral stenosis. Recent vegetations. Aortic valve thickened but competent.

Other organs - C.V.C.

Histology of Heart: Active lesions in left auricular appendage, left atrium, mitral and aortic valves and left vent. myocardium.

Case 207. (EN. 211/55) F. Age 43. Housewife.

Rh.F. at age 12. Dyspnoea on exertion for 13 yrs. Gradually increasing in severity. Ankles swollen for past 6 mths. Admitted as an emergency in C.C.F.

O/E: A.F. C.C.F. Mitral stenosis.

Deteriorated and died 10 days after admission.

Post-mortem findings:

Heart (500 gms): Tricuspid, mitral and aortic

stenosis.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 208. (EN. 233/55) F. Age 41.

Chorea at age 12. Dyspnoea on exertion for several years. Pulmonary infarct 1 yr ago. Admitted as an emergency with cerebral embolus. Died on day of admission.

O/E: A.F. Mitral stenosis. Cerebral embolus.

Post-mortem findings:

Heart (250 gms): Gross mitral stenosis. Thrombus in left auricular appendage. Other valves normal. Thrombus in basilar artery.

Other organs - C.V.C.

Histology of Heart: No active lesions.

Case 209. (B.265/53) M. Age 46.

Rh.F. at 9 and 16 yrs. No symptoms until 2 wks before admission when he became breathless on exertion. On admission he c/o pain in the left shoulder.

O/E: A.F. No C.C.F. Mitral stenosis.

Suddenly developed severe abdominal pain 10 days after admission and died.

Post-mortem findings:

Heart (350 gms): Tight mitral stenosis. Aortic

valve thickened but competent. No thrombus in left auricular appendage.

Infarct of small intestine. Superior mesenteric embolism.

Histology of Heart: No active lesions.

Case 210. (EN. 54/53) F. Age 21.

Rh.F. at age 5 and 15. In hospital for 3 yrs after first attack.

Admitted 21/11/52 c/o dyspnoea and oedema of ankles for 3 wks. Sub-acute bacterial endo--carditis diagnosed. S.R. Treated with penicillin for 6 wks. Gradually deteriorated and died in C.C.F. 4 mths after admission.

Post-mortem findings:

Heart (615 gms): Rt and left vent. hypertrophy. Mitral stenosis and aortic incompetence. Friable vegetations on aortic valve.

Other organs - C.V.C. Healed infarcts in kidneys.

Histology of Heart: Active lesions in left auricular appendage and ventricular myocardium.

Case 211. (EN. 173/53) M. Age 41.

Rh.F. at age 4. Dyspnoea on exertion for 6 wks. Given A.C.T.H. for a short period but this was stopped because it precipitated C.C.F.

O/E: S.R. Aortic stenosis.

Patient died in C.C.F. 6 mths after admission.

Post-mortem findings:

Heart (670 gms): Pericardium adherent. Mitral valve normal in appearance. Aortic valve stenosed but not calcified.

Other organs - C.V.C.

Histology of Heart: Active lesions in left auricular appendage, mitral valve and myocardium.

Case 212. (EN. 219/54) F. Age 17.

1 yr ago had "rheumatic pains" and was febrile.

c/o melaena and loss of appetite.

O/E: S.R. No C.C.F. Mitral stenosis.

Sub-acute bacterial endocarditis. Treated with penicillin. Developed haemoptysis and died.

Post-mortem findings:

Heart (440 gms): Mitral stenosis. Soft, friable vegetations on mitral cusps and chordae tendineae. Aortic valve shows slight thickening of cusps.

Other organs - Brain - cerebral haemorrhage.

Histology of Heart: Active lesions in left auricular appendage and ventricular myocardium.

Case 213. (GH. 83/55) F. Age 73.

Admitted in coma. Cerebral softening diagnosed. No history available.

O/E: A.F. B.P. 200/100. Cerebral softening.

Post-mortem findings:

Heart (320 gms): Slight rt vent. hypertrophy.

Tight mitral stenosis with calcification.

Other organs: Brain - cerebral softening.

Kidneys - chronic pyelonephritis.

Histology of Heart: Active lesions in left auricular appendage and ventricular myocardium.

Case 214. (EN. 252/55) M. Age 71.

Rh.F. at 14 yrs. 8 yrs history of paroxsymal dyspnoea with frequent attacks of C.C.F.

O/E: Mitral and aortic incompetence. A.F. C.C.F.

Died shortly after admission.

Post-mortem findings:

Heart (850 gms): Dilatation and hypertrophy of all chambers. Mitral and aortic incompetence. No calcification.

Other organs - C.V.C.

Histology of Heart: Active lesions in left auricular appendage and myocardium.

## ACKNOWLEDGEMENTS.

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# STUDIES ON RHEUMATIC CARDITIS

## WITH SPECIAL REFERENCE TO SUB-CLINICAL RHEUMATISM

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in which is included an experimental attempt to produce rheumatic lesions in rabbits.

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VOLUME 2

ILLUSTRATIONS, GRAPHS AND TABLES

## Arrangement of Volume 2

As far as possible the figures are arranged in the order in which they first occur in the text. An attempt has been made to show the variations in the types of lesions and some of these are difficult to illustrate. The case number or departmental number is shown and clinical summaries of those with case numbers are given in the Appendix, Volume 1. The type of lesion shown may not be representative of the majority of lesions present in the specimen.

Figs. 107-111 were taken with a 35 mm. adapter on a polarising microscope, without the use of filters.

Fig. 1. Left auricular appendage from non-rheumatic heart. Note the relatively acellular subendocardium. H. and E. X 75.

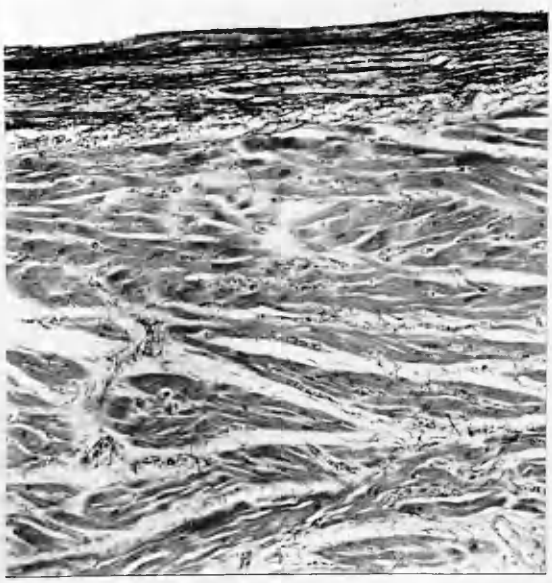


Fig. 2. Elastic stain of same specimen as Fig. 1. Lawson's modification of the Weigert-Sheridan method. X 75.

Fig. 3. From the same specimen as Figs. 1 and 2 to show the interrupted smooth muscle layer. Mallory's phosphotungstic acid haematoxylin. X 75.

Fig. 4. The smooth muscle layer is hypertrophied and the subendocardium is irregularly thickened. Note the thick collagen fibres in the subendocardium.

Case 24. H. and V.G. X 75.

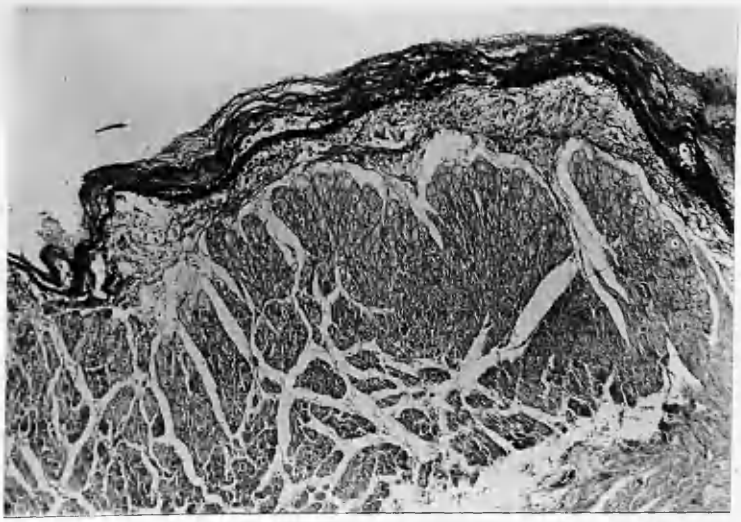


Fig. 5. The elastic layer is thickened and shows dense bands of elastic tissue. Occasional active lesions are present in the subendocardium.

Elastic stain. X 50.

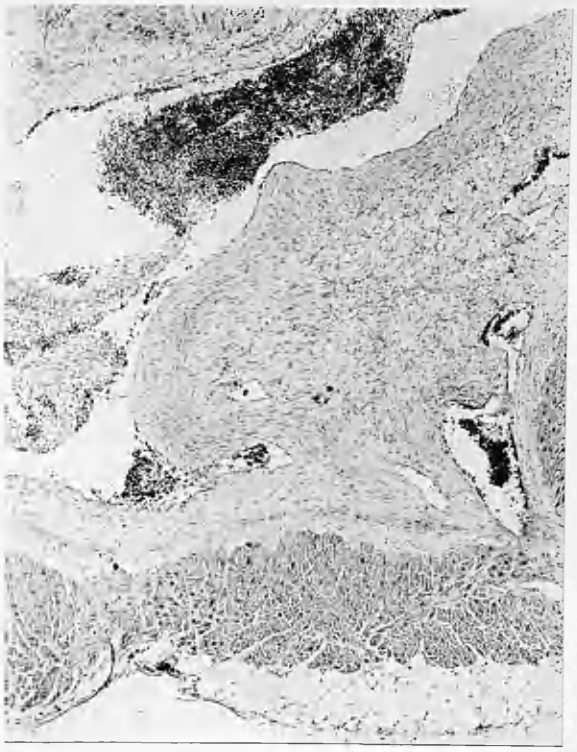


Fig. 6. Organising thrombus. There is no inflammatory reaction in the subendocardium beneath the thrombus.
(C.843/56) H. and E. X 35.

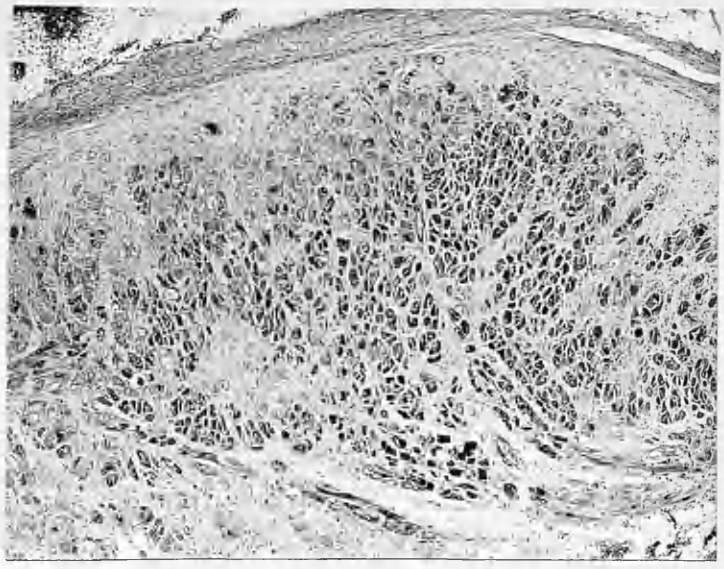


Fig. 7. Gross fibrosis of subendocardium and myocardium. Organising thrombus is present at other areas.

Case 46. H. and E. X 35.

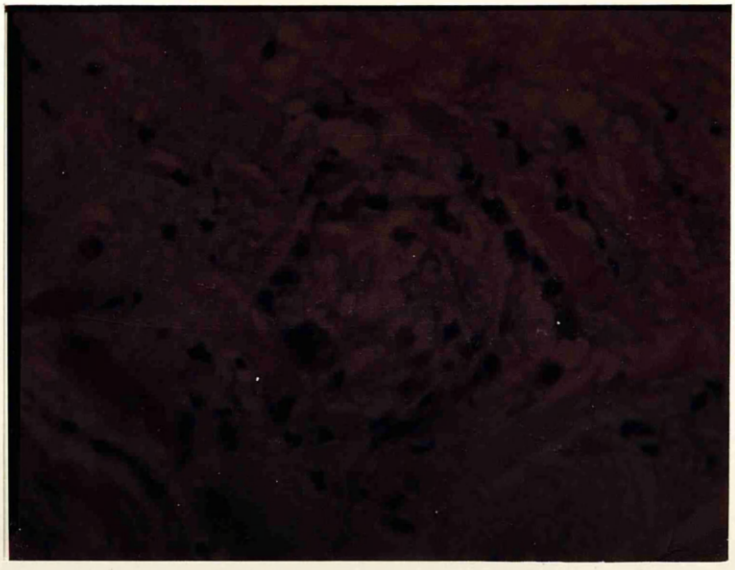


Fig. 8. Aschoff body showing a coronal type of arrangement. The majority of the cells are small but one larger cell with an owl-eye nucleus is present. Note the pattern of the altered collagen and the dull staining with eosin as compared with the muscle. Within the lesion and in the surrounding tissues is a moderate amount of pale staining I.H.S.

Case 48. H. and E. X 300.

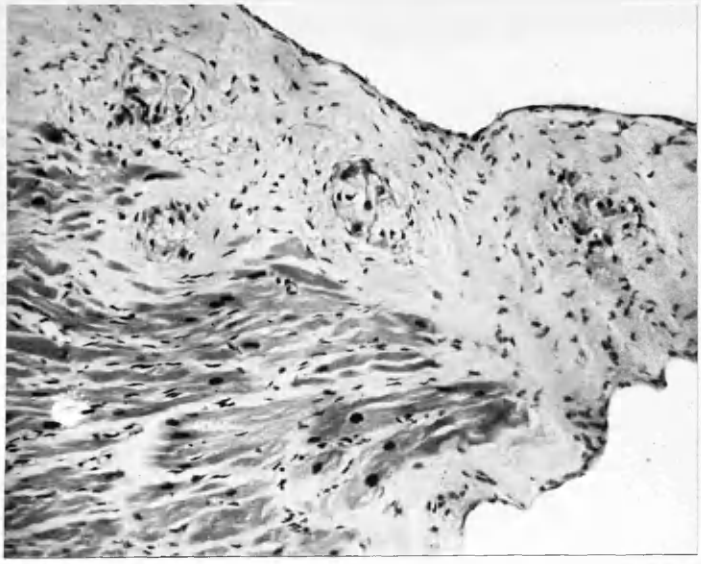


Fig. 9. Four coronal type lesions in the endocardium and subendocardium. Vacuolated I.H.S. is associated with the lesions.

Case 71. H. and E. X 175.

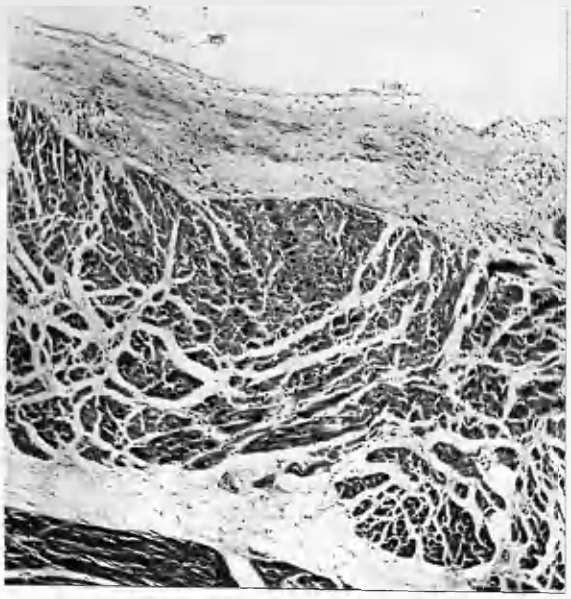


Fig. 10. Several lesions in the endocardium and subendocardium. Some of the lesions show a linear arrangement of cells.

Case 48. H. and E. X 70.

Fig. 11. Coronal Aschoff body. The central mass of altered collagen is hyaline and moderately eosinophilic. Vacuolated I.H.S. can be seen within and around the lesion. Occasional "owl-eye" nuclei can be recognised.
(C.3473/55) H. and E. X 325.

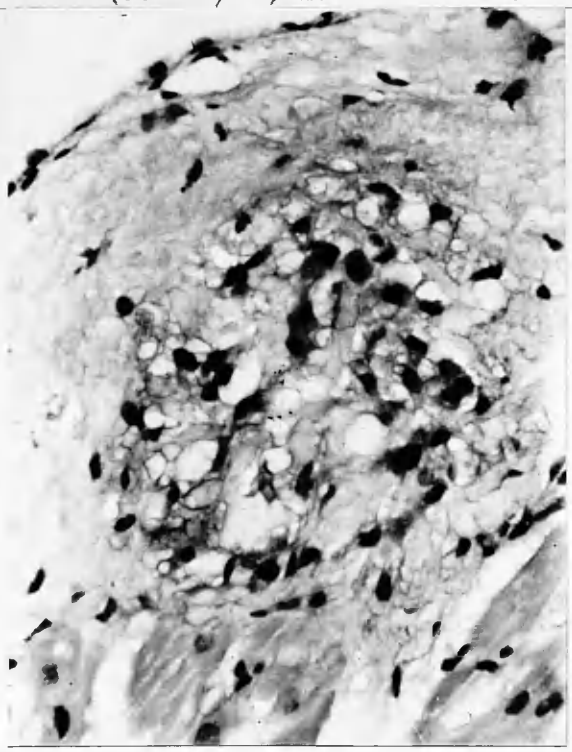


Fig. 12. From the same case as Fig. 11. Note the pattern of the altered collagen within the lesion.
H. and E. X 325.

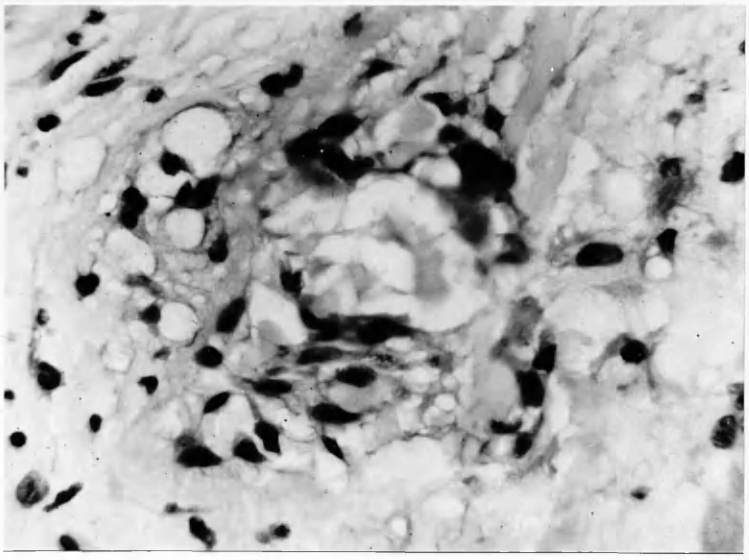


Fig. 13. This lesion shows a complex pattern of cells and altered collagen. In the upper part of the lesion the cells are large and deeply basiphilic. In the lower part the cells are spindle-shaped.

Case 23. H. and E. X 375.

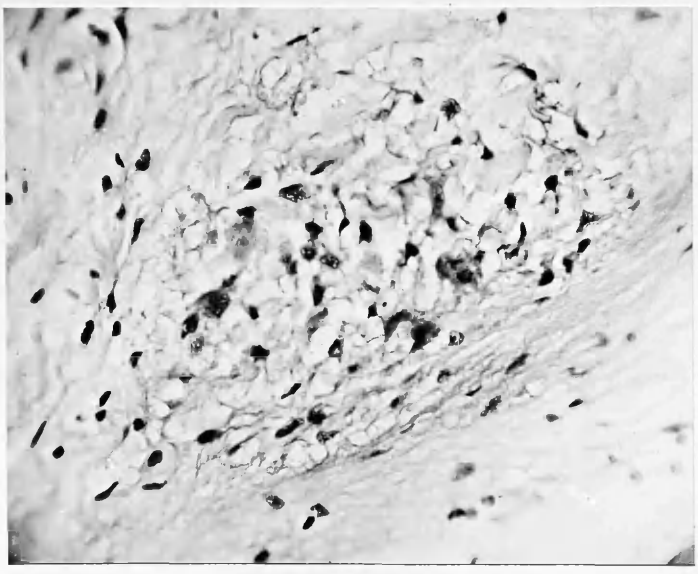


Fig. 14. Mosaic patterned lesion. "Owl-eye" and occasional "fibrocytoid" nuclei are present.

Case 48. H. and E. X 300.

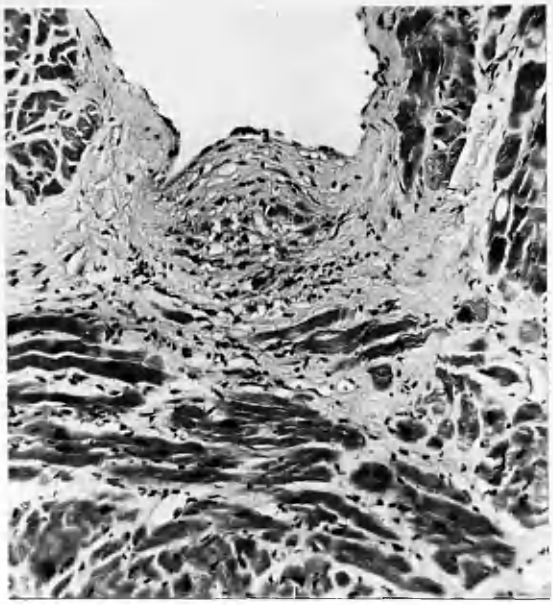


Fig. 15. Lesion showing small and large types of Aschoff cell with a tendency to be arranged in rows. Fibres can be traced through the lesion. A slight round cell infiltrate is present in the surrounding tissues.
Case 124. H. and E. X 150.

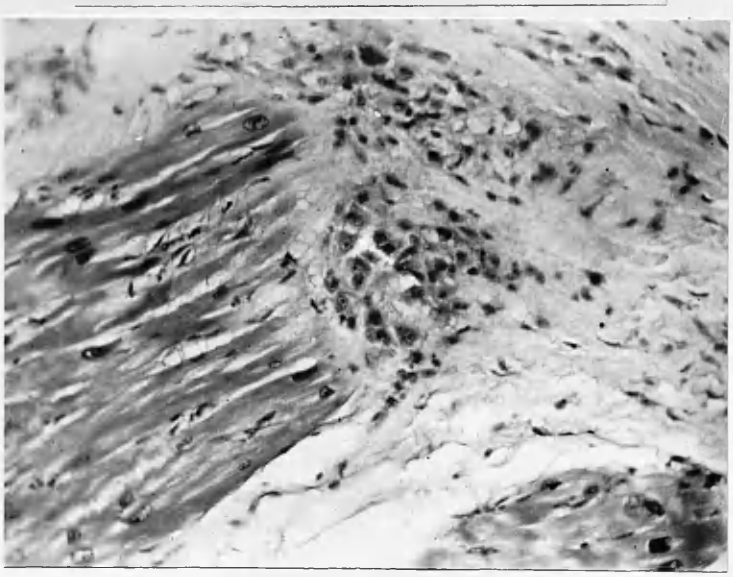


Fig. 16. Mosaic lesion. The owl-eye type of nucleus is present in the majority of cells.
Case 153. H. and E. X 150.

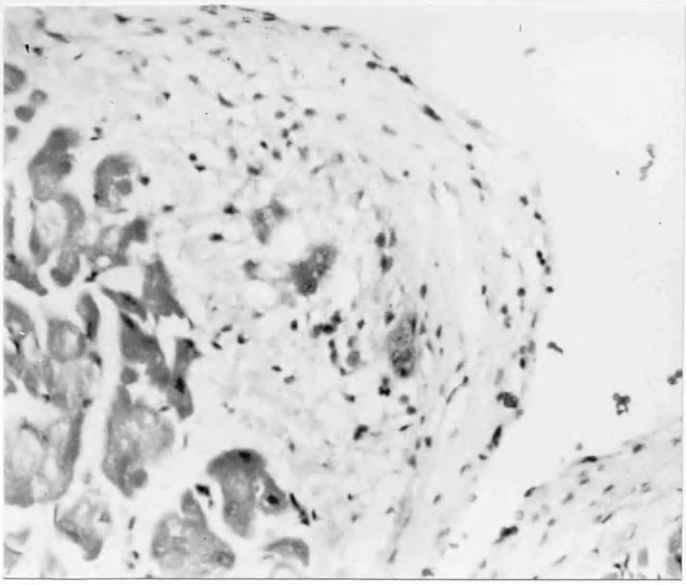


Fig. 17. Lesion with multinucleate cells. The nuclei are owl-eye in type and stain very poorly.

(C.3567/55) H. and E. X 300.

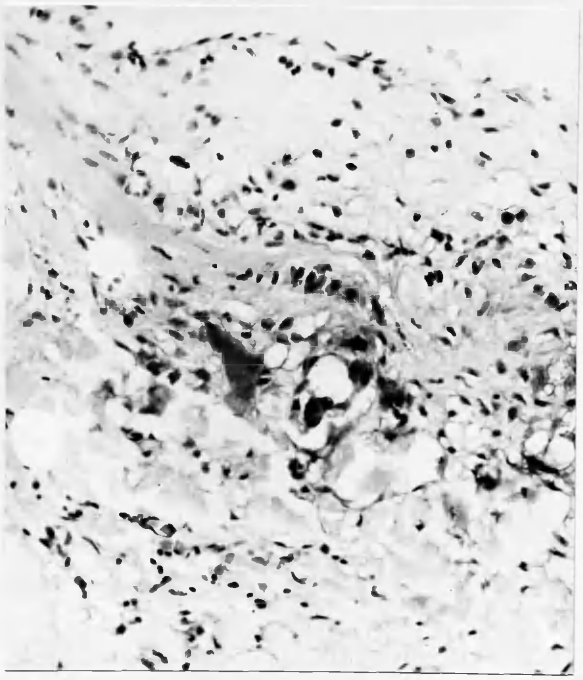


Fig. 18. The large cell shows deeply basiphilic cytoplasm and a very poorly stained nucleus - the "ghost" nucleus. Note the oedematous sub-endothelial layer and the moderate lymphocytic infiltrate.

(C.2697/55) H. and E. X 350.

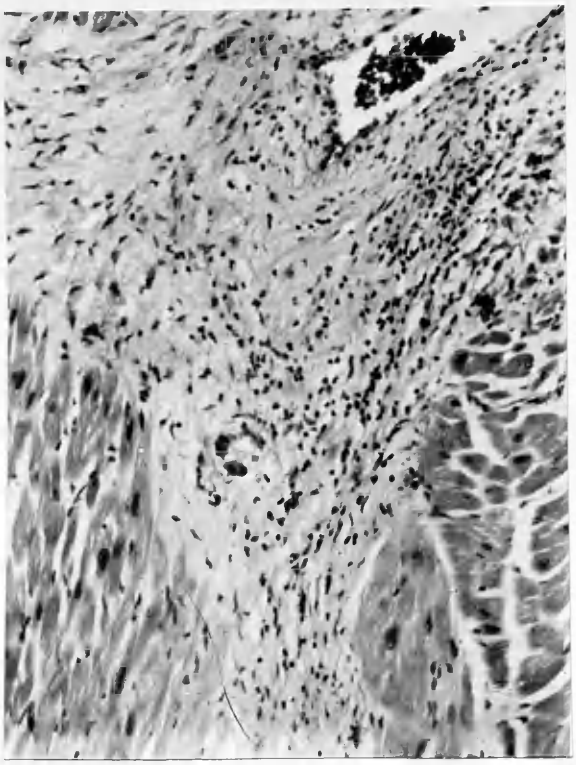


Fig. 19. Extensive lymphocytic infiltration of the endocardium and subendocardium. A small coronal Aschoff body is present in the subendocardium.

(C.419/56) H. and E. X 200.

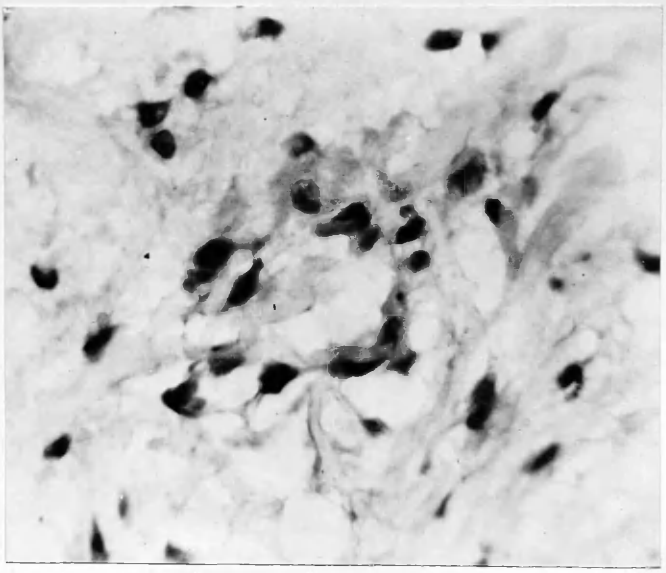


Fig. 20. Small coronal lesion showing a central area of hyaline altered collagen and a ring of elongated, distorted basiphilic cells.

Case 174. H. and E. X 450.

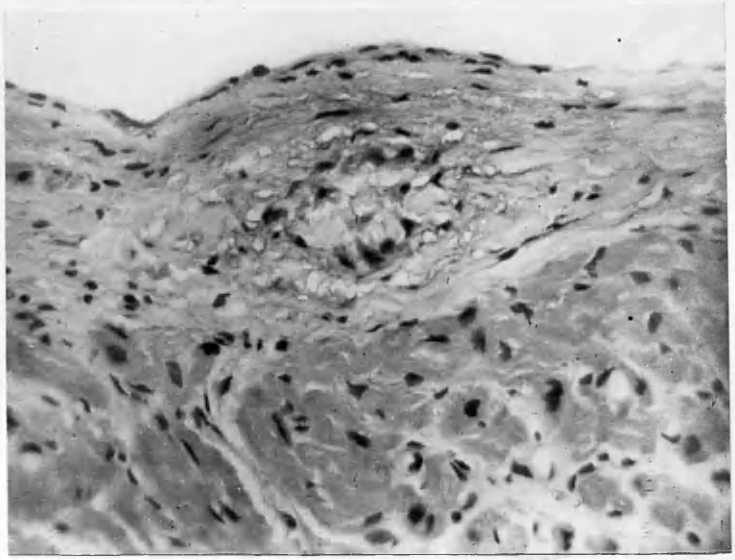


Fig. 21. Lesion showing a large amount of swollen, fused collagen. The cells in the lesion are small and round with occasional elongated cells. The nuclei and cytoplasm stain deeply with haematoxylin. Vacuolated I.H.S. is present around the lesion.
(C.3391/55) H. and E. X 230.

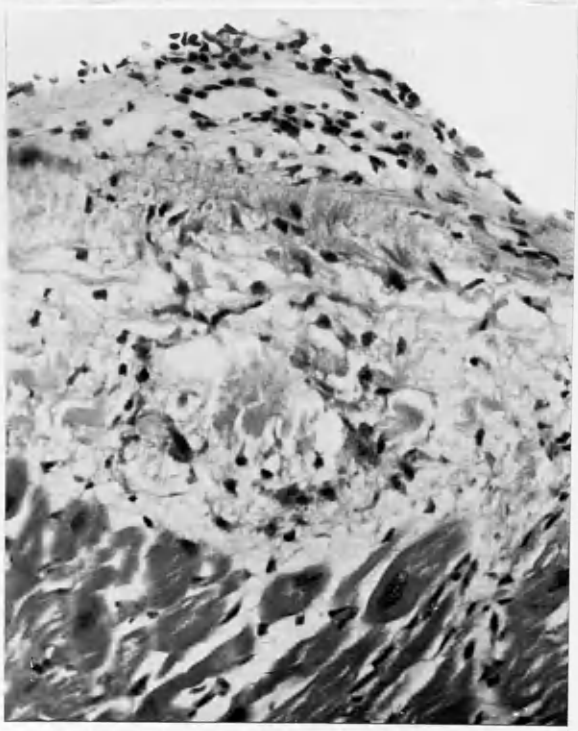


Fig. 22. The altered collagen is granular in appearance and appears to be fragmented. The cells are mainly small round or oval cells with occasional larger mononuclear cells. The sub-endothelial layer shows an exudate of lymphocytes.
Case 113. H. and E. X 250.

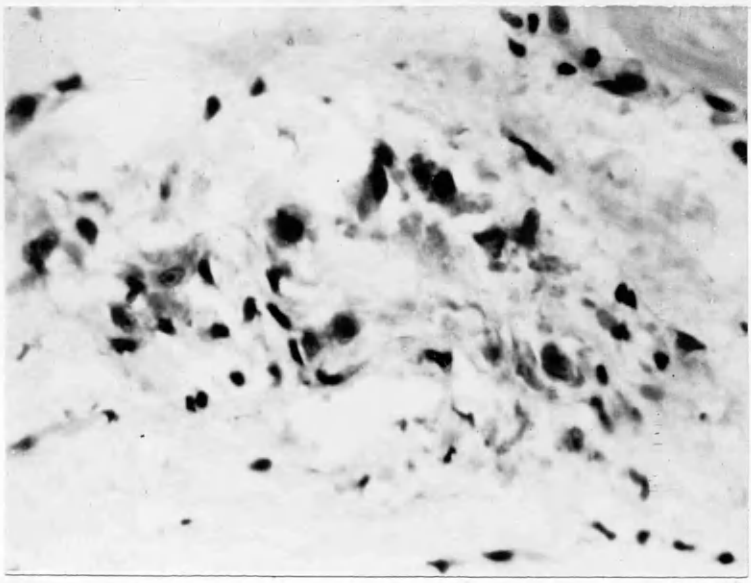


Fig. 23. Elongated lesion showing granular altered collagen and cells of various shapes. Typical "owl-eye" nuclei can be recognised.
Case 14. H. and E. X 450.

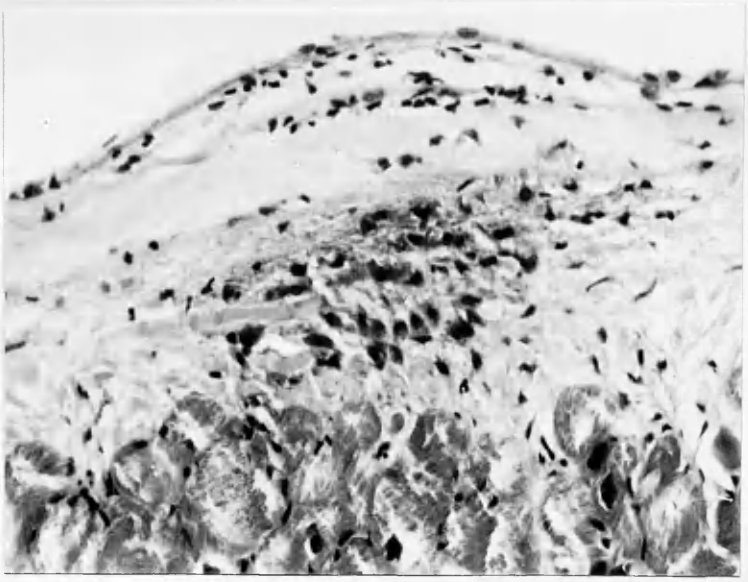


Fig. 24. A thick band of swollen eosinophilic collagen enters the lesion on the left. Within the lesion the collagen fibres have an interlacing pattern. Only occasional cells show recognisable Aschoff nuclei.
Case 71. H. and E. X 250.

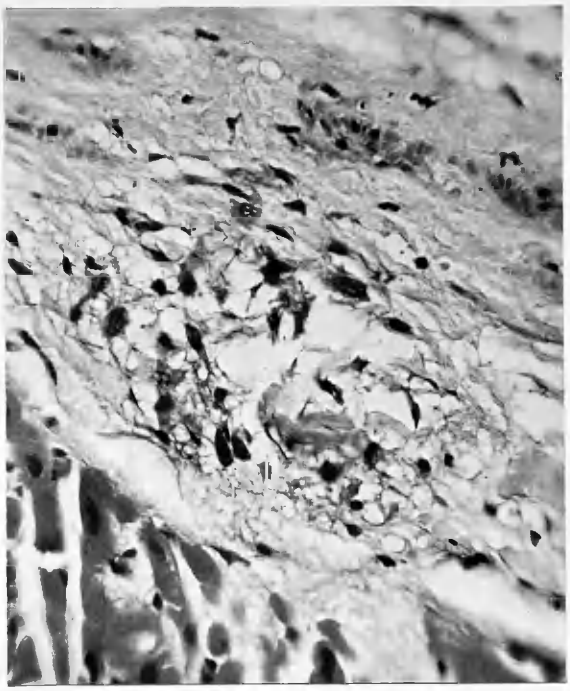


Fig. 25. Most of the cells in this lesion are spindle-shaped and have long processes. Vacuolated I.H.S. is present around and within the lesion.
Case 23. H. and E. X 280.

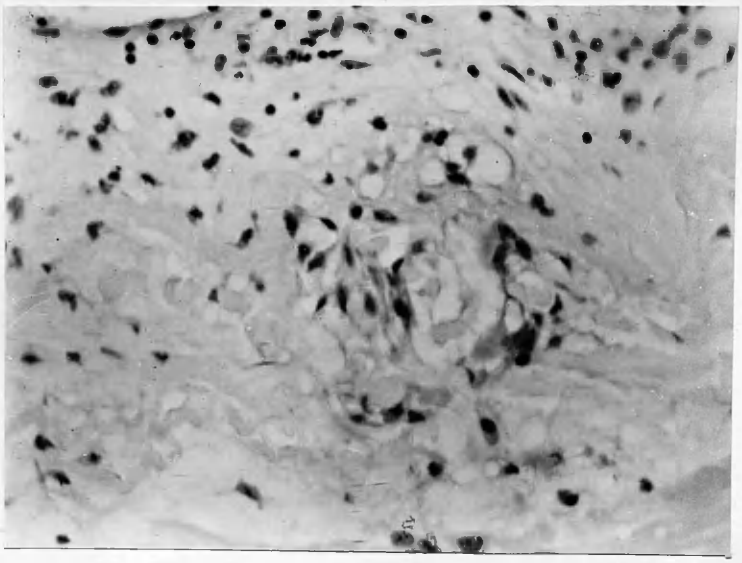


Fig. 26. A radiate arrangement of spindle-shaped cells is present on the left side. Note the cellular exudate superficial to the lesion.
Case 48. H. and E. X 250.

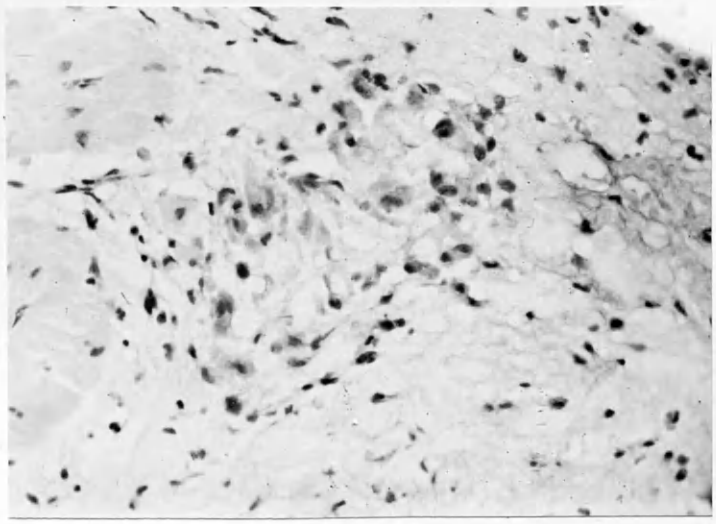


Fig. 27. The altered collagen consists of interlacing fibres and small areas of fused granular material. The cells are mainly mononuclears and lymphocytes but occasional recognisable owl-eye nuclei are present.
(C.419/56) H. and E. X 250.

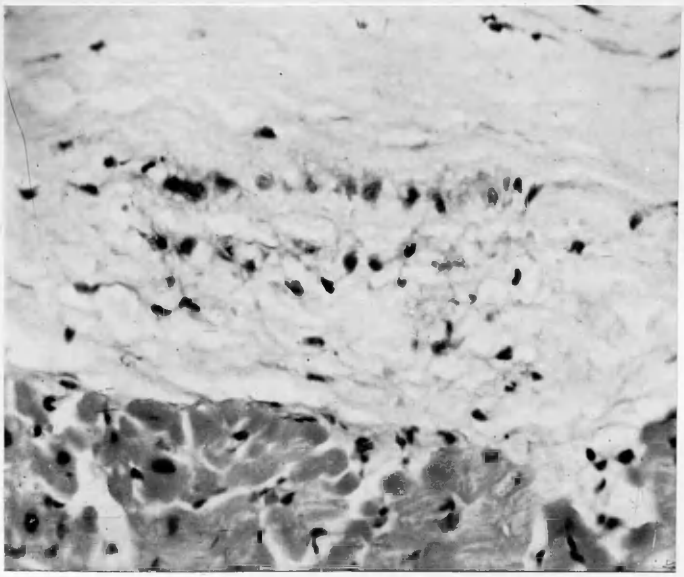


Fig. 28. This lesion consists of a double row of cells, many of which have owl-eye and fibrocytoid nuclei. The collagen between the rows is in delicate fibrils.
Case 141. H. and E. X 250.

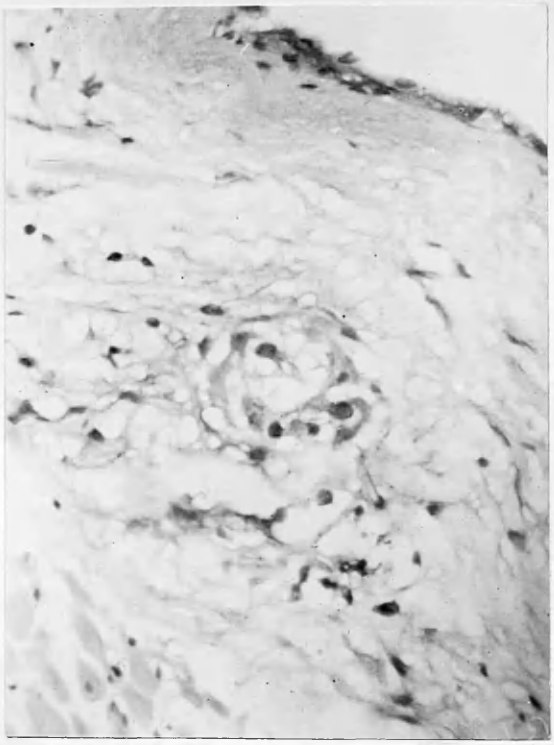


Fig. 29. Small lesion showing brightly eosinophilic collagen and small numbers of mononuclear cells. A large amount of I.H.S. is present within the lesion and in the surrounding tissues. This lesion looks very inconspicuous but numerous similar lesions are present at irregular intervals in other parts of the specimen. Case 71. H. and E. X 250.

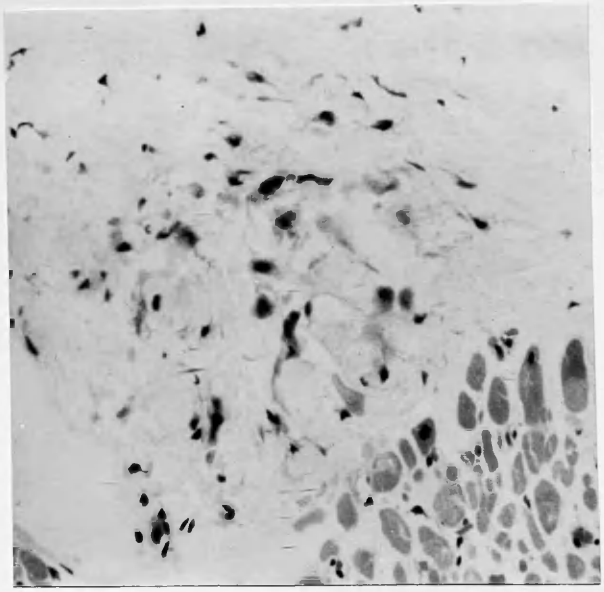


Fig. 30. Small foci of granular collagen with lymphocytes and mononuclears distributed between. None of the cells in this lesion have recognisable Aschoff nuclei.
Case 12. H. and E. X 250.

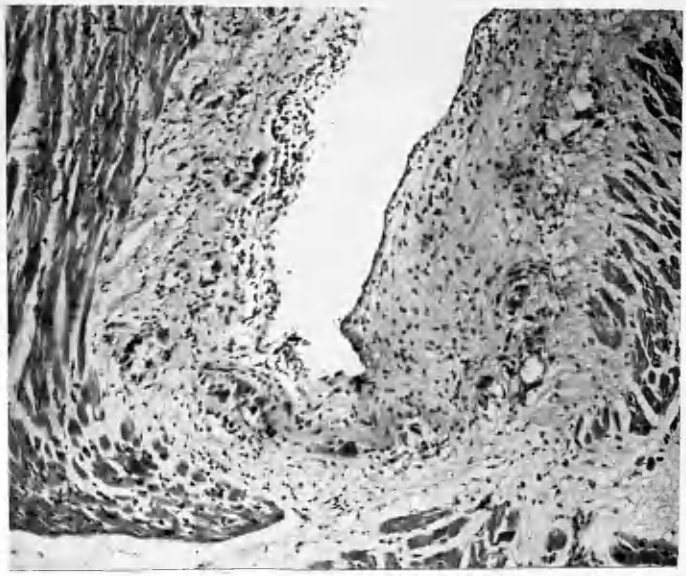


Fig. 31. An elongated curved lesion is present towards the bottom of the field and numerous confluent Aschoff bodies are found on either side. There is diffuse infiltration with lymphocytes around the lesions and in the sub-endothelial layer.
(C.2697/55) H. and E. X 100.

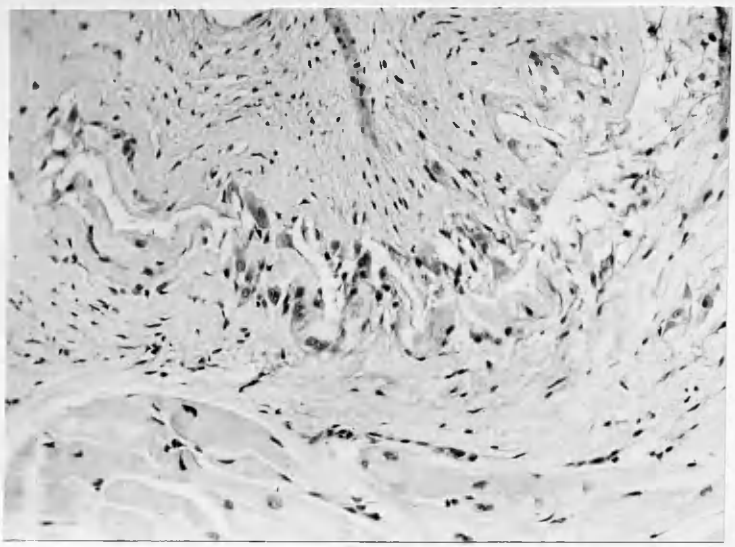


Fig. 32. Elongated coronal type of Aschoff nodule. The thick swollen collagen band is almost continuous within the lesion and there is a tendency for the cells to be orientated with their long axis perpendicular to the altered collagen. Many large basiphilic Aschoff cells are present.
Case 10. H. and E. X 160.

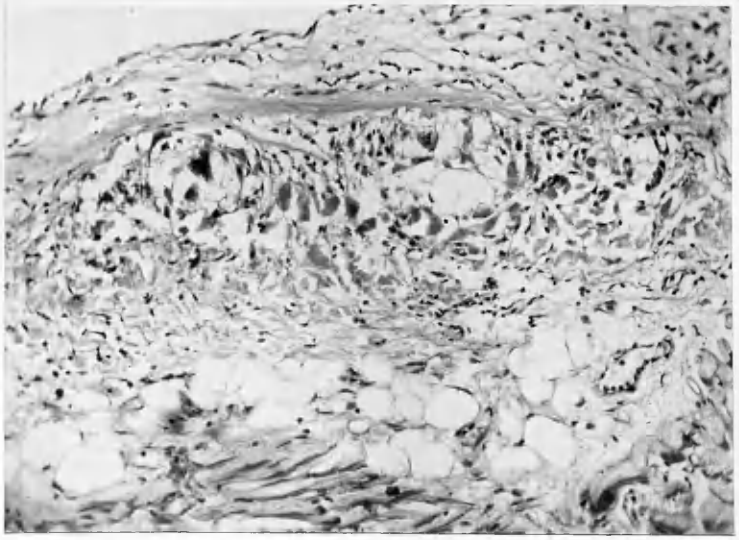


Fig. 33. Extensive mosaic lesion with large amounts of fused collagen.

(C.2697/55) P.A.S. X 125.

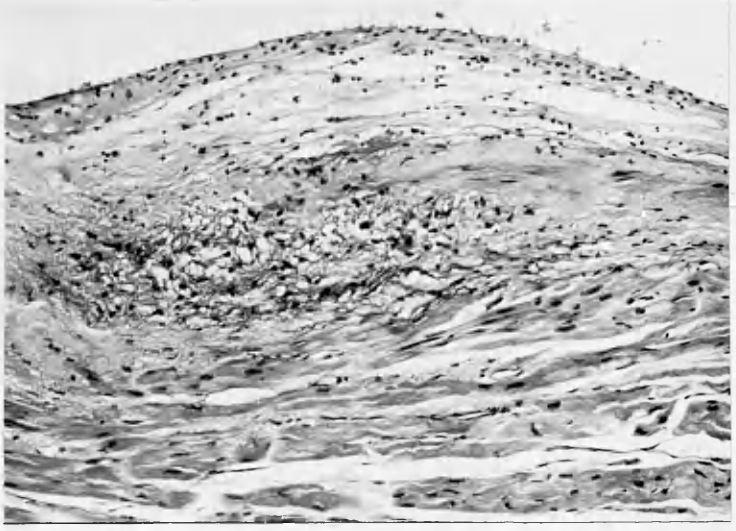


Fig. 34. Diffuse lesion in the subendocardium. The collagen is eosinophilic and has a reticular pattern. The cells are mainly mononuclears and some have oval shaped nuclei. A large amount of I.H.S. is present.

Case 38. H. and E. X 150.

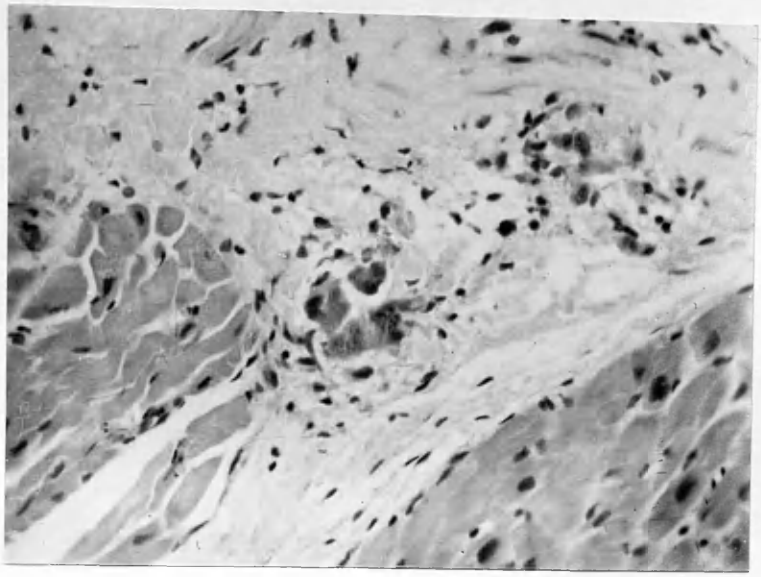


Fig. 35. The lesion in the centre of the field consists of giant cells with several typical owl-eye nuclei. An irregular mantle of lymphocytes is present.
Case 10. H. and E. X 250.

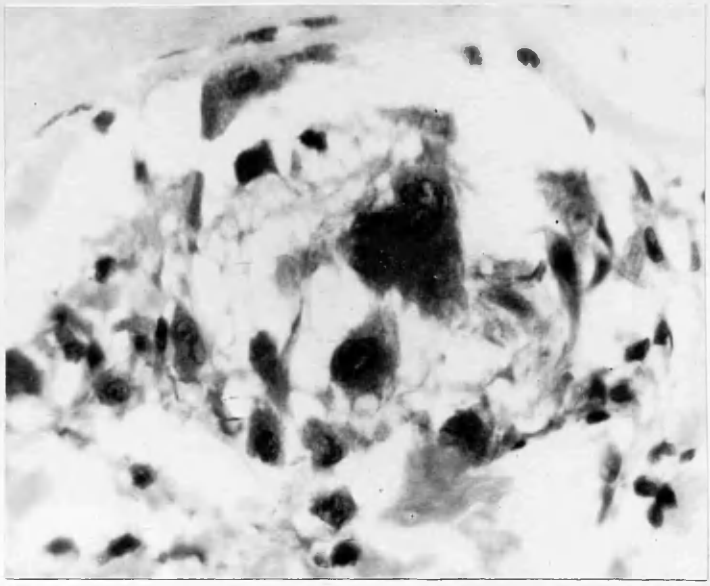


Fig. 36. Aschoff body with larger types of cells. Note the characteristic nuclei, the ragged cytoplasm, and occasional cytoplasmic processes. Little altered collagen is noted in the lesion.
(C.2695/55) P.A.S. X 600.

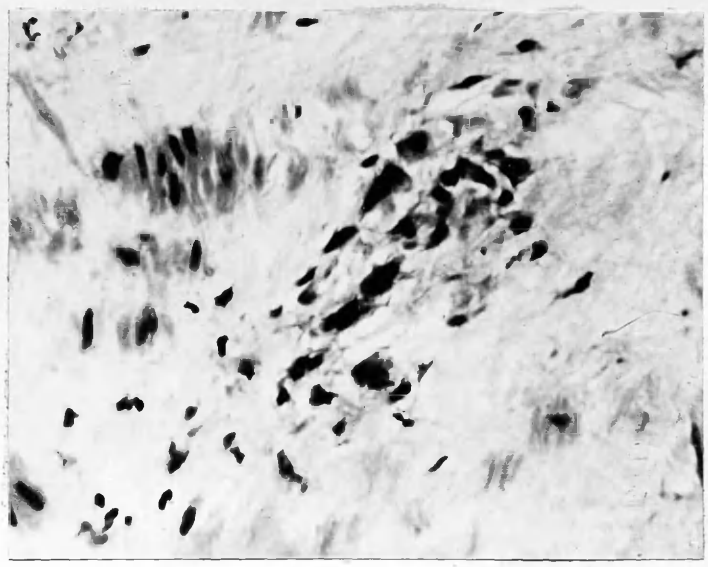


Fig. 37. Polarised lesion in endocardium.
Case 48. H. and E.X 300.

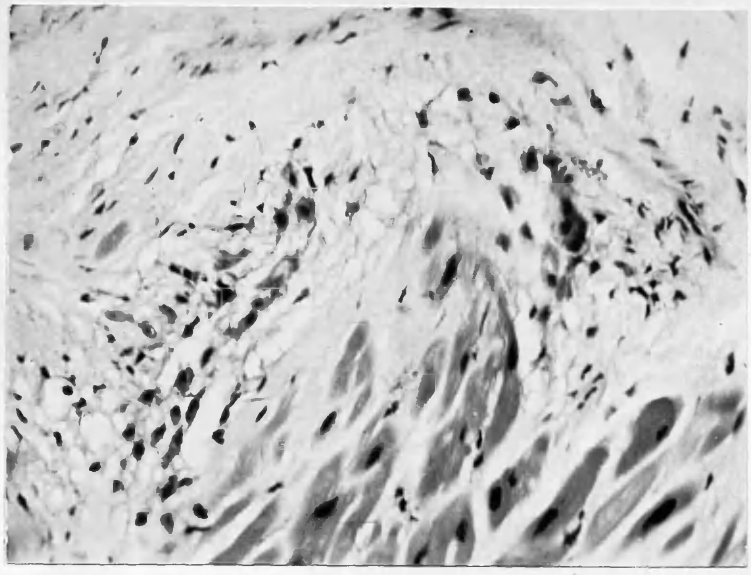


Fig. 38. Polarised fibrillar lesion. The pattern is best seen in the lesion on the left side. Many of the elongated cells have typical Aschoff nuclei.
Case 124. H. and E. X 225.

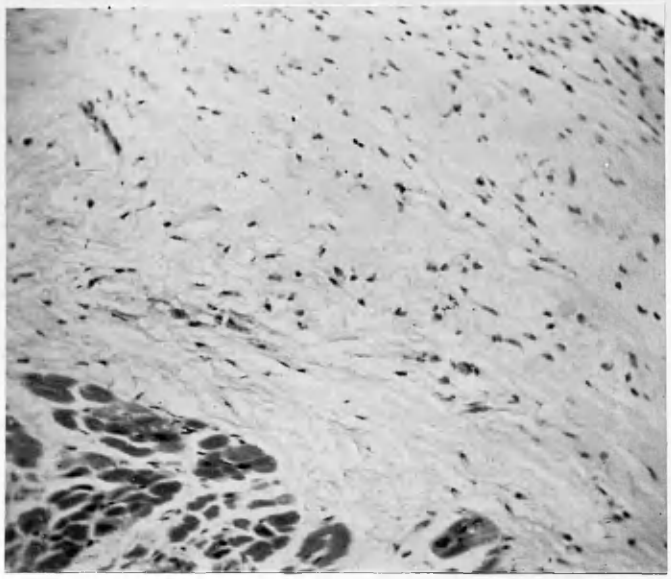


Fig. 39. Low power view of fibrillary lesions in the subendocardium. These lesions also contain cells with recognisable Ascoff nuclei.
Case 50. H. and E. X 150.

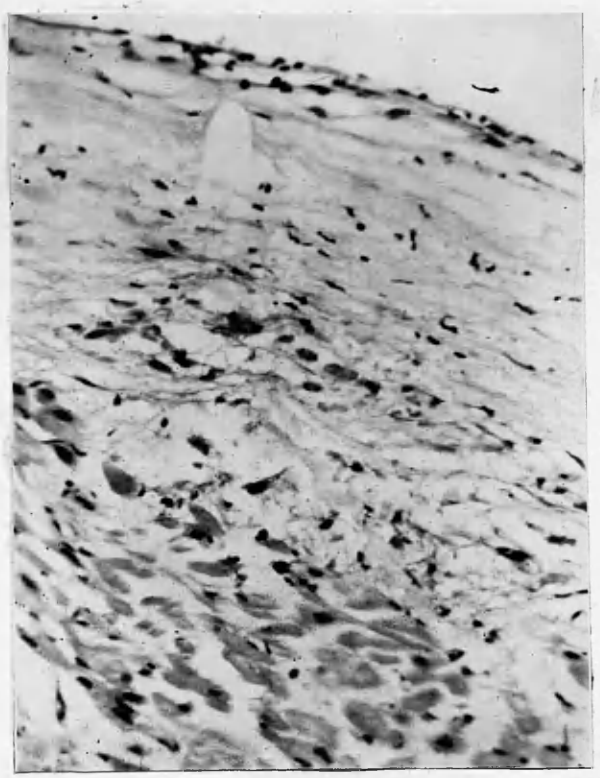


Fig. 40. Fibrillary lesion in subendocardium and endocardium.
Case 48. H. and E. X 250.

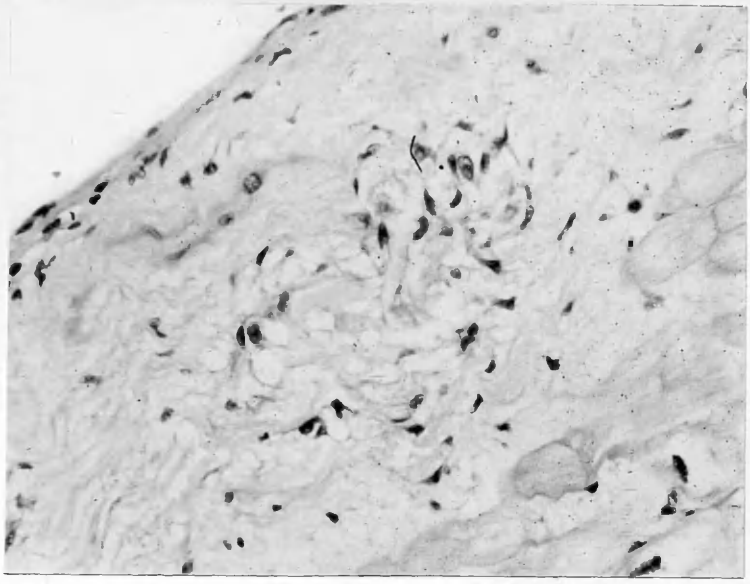


Fig. 41. Note the radiate arrangement of spindle cells. One of these cells shows an owl-eye nucleus. In other lesions of this type the cells consist entirely of spindle cells. Case 6. H. and E. X 250.

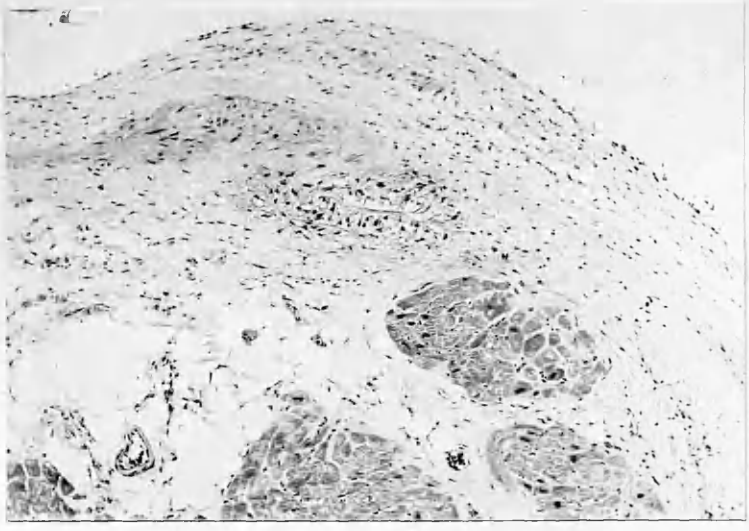


Fig. 42. Spindle-shaped cells aligned along a strip of thickened collagen. The processes of these cells are directed towards the fibre. Case 49. H. and E. X 100.

Fig. 43. Central mass of fused eosinophilic collagen and several small foci of similar altered collagen. There is a moderate amount of I.H.S. in the tissues surrounding the altered collagen but little or no cellular reaction.

(C.1160/56) H. and E. X 150.

Fig. 44. Several areas of swollen fused eosinophilic collagen in an area of vacuolated I.H.S. The I.H.S. extends into the muscle along a septum. Note the differing degrees of eosinophilia in the fused collagen.

Same specimen as Fig. 43. X 150.

Figs. 45 and 46 on next page

Fig. 47. A massive band of pale staining fused collagen is present in the subendocardium. Superficial to this in the area marked there is a focus of fused eosinophilic collagen. A slight cellular reaction of oval-shaped cells is present and the collagen within this area of cellular reaction is showing an interlacing pattern. It is difficult to decide if the very large dull staining band of fused collagen is an early or a healed lesion. This section shows the differing appearances of altered collagen. I.H.S. is present but is not visible in the photograph.

Case 35. H. and E. X 300.

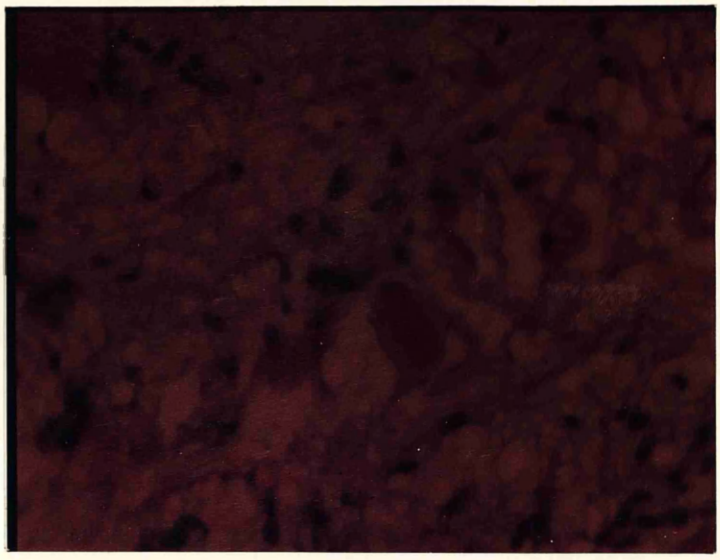


Fig. 45. Central area of swollen eosinophilic collagen with differing degrees of eosinophilia.
Case 153. H. and E. X 375.

Fig. 46. From the same area as Fig. 45 deeper in the block. Note the yellowish staining of part of the fused collagen.
H. and V.G. X 375.

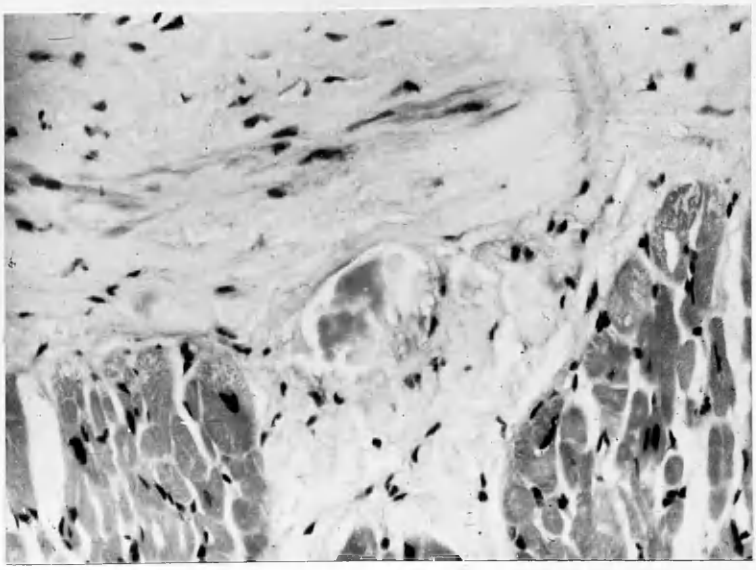


Fig. 48. Mass of fused, granular, eosinophilic collagen. There is no cellular reaction.
(C.2391/55) H. and E. X 300.

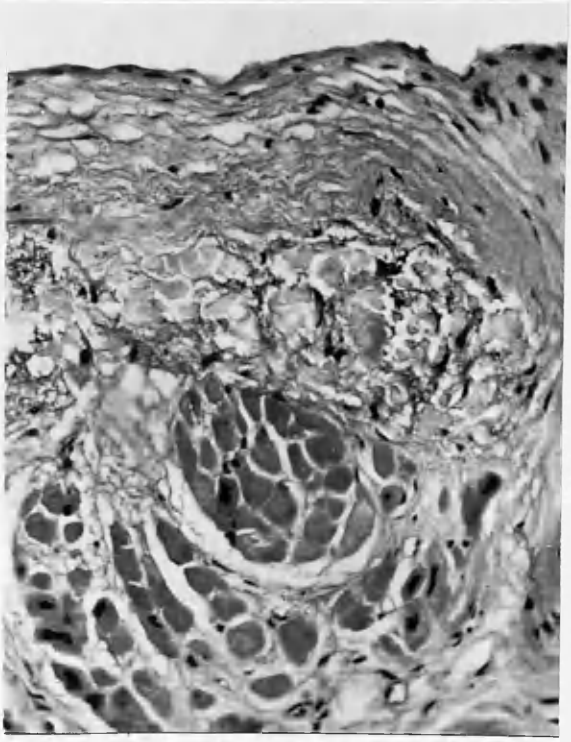


Fig. 49. Masses of fused, moderately eosinophilic collagen with a fragmented appearance. I.H.S. is present between the fused areas, but there is no cellular reaction.
Case 38. H. and E. X 250.

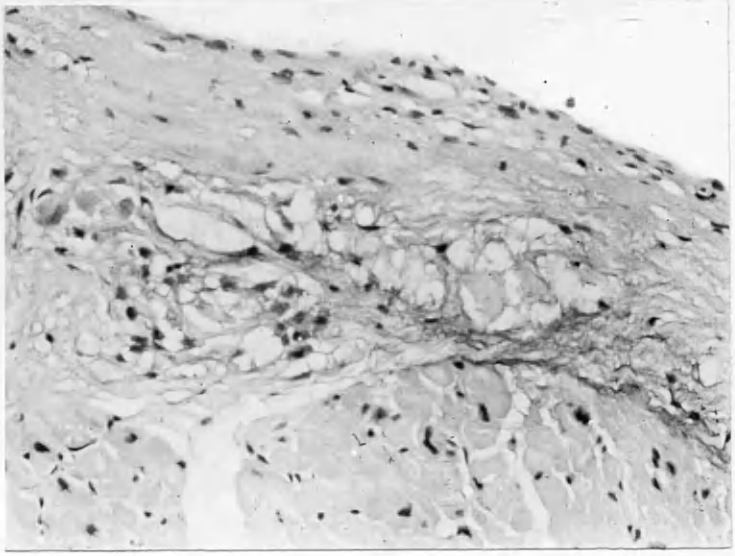


Fig. 50. On the right of the field there is an area of fused hyaline, slightly eosinophilic, collagen. A cellular reaction is present in the lesion on the left.
Case 133. H. and E. X 250.

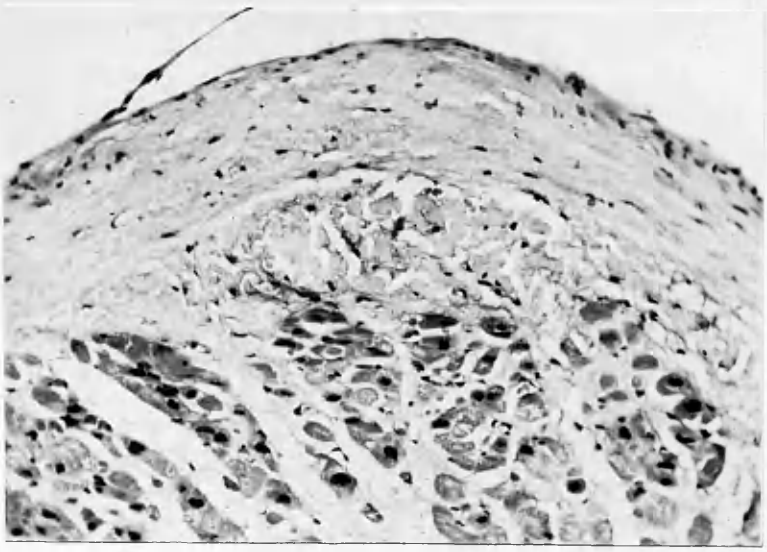


Fig. 51. Areas of fused, dull-staining collagen. A few cells are present between the fused foci. This lesion is similar to Fig. 49 but the collagen is less eosinophilic.
Case 153. H. and E. X 160.

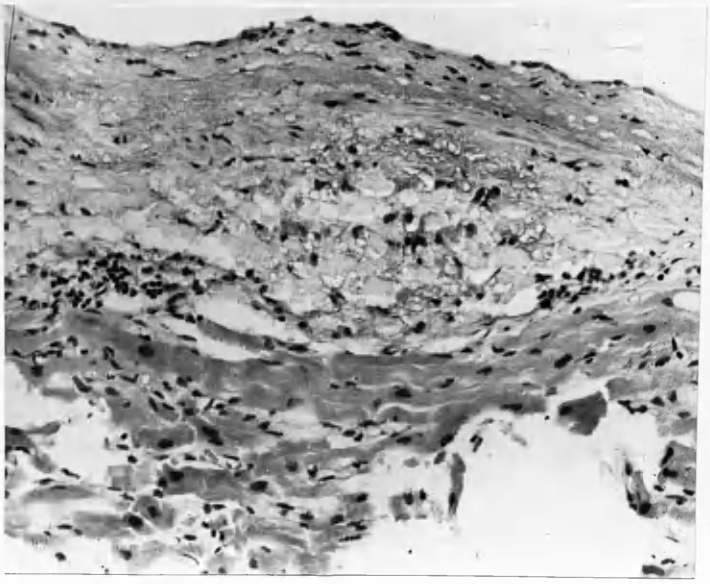


Fig. 52. Large amount of fused, hyaline, dull-staining, altered collagen. A moderate infiltrate of lymphocytes is present.

Case 153. H. and E. X 160.

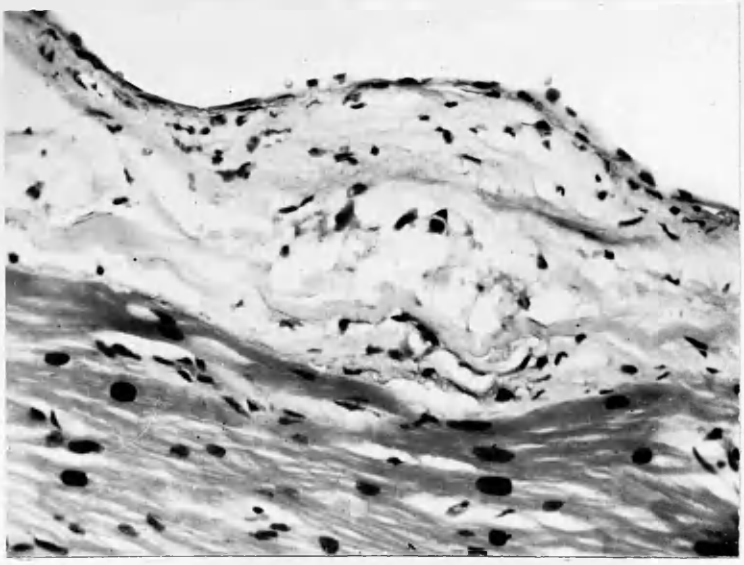


Fig. 53. Long band of swollen eosinophilic hyaline collagen with several smaller fused areas. An early cellular infiltrate is present and there is a large amount of pale-staining I.H.S.

Case 23. H. and E. X 200.

Fig. 54. The endocardium and subendocardium show large amounts of I.H.S. and an infiltrate of lymphocytes. The I.H.S. extends between the muscle fibres. In the centre of the endocardium there is an area of fused eosinophilic collagen indicated by an arrow.
(C.650/55) H. and E. X 100.

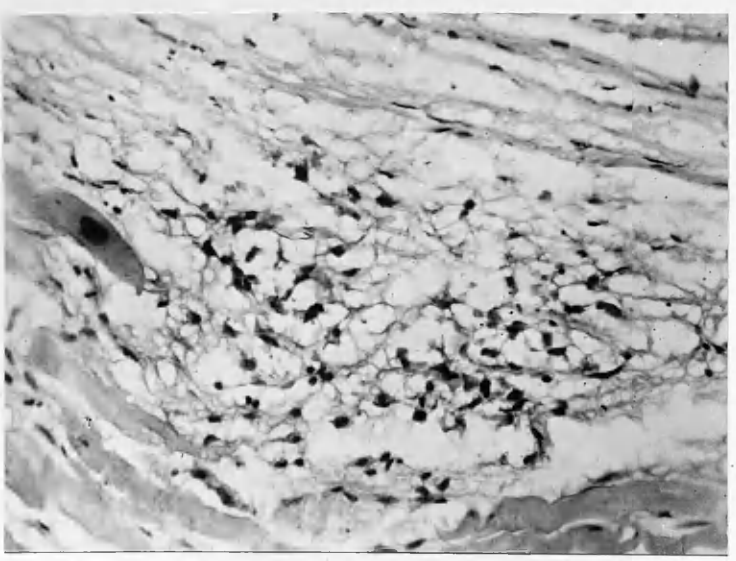


Fig. 55. Area of cellular exudate and I.H.S. The collagen appears normal.

Case 174. H. and E. X 200.

Fig. 56. Extensive mucoid oedema of the endocardium and subendocardium extending into the myocardium. A moderate cellular exudate of mononuclears and lymphocytes is present. There is no evidence of damage to the collagen.

Case 120. H. and E. X 105.

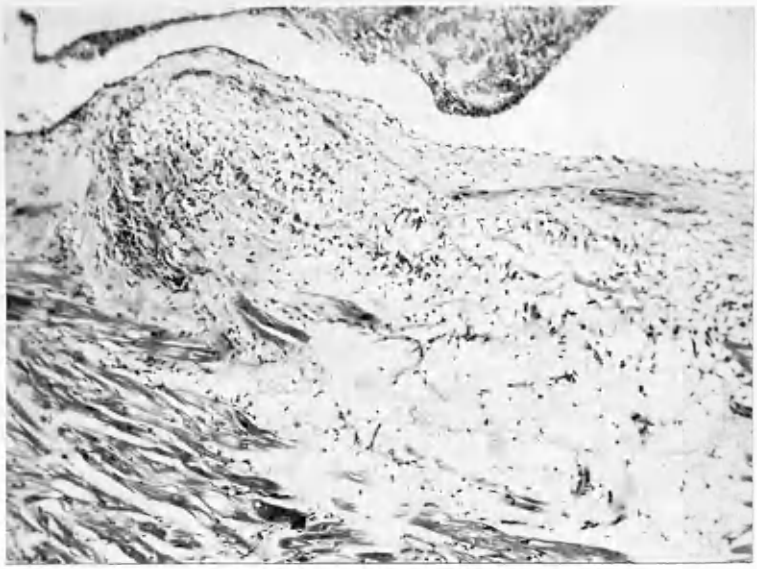


Fig. 57. Extensive amounts of I.H.S. are present in the endocardium and subendocardium. A moderate lymphocytic exudate is present in most of the field and at the left is much more intense. The collagen in places appears to be swollen but it is difficult to be certain of this.

Case 126. H. and E. X 85.

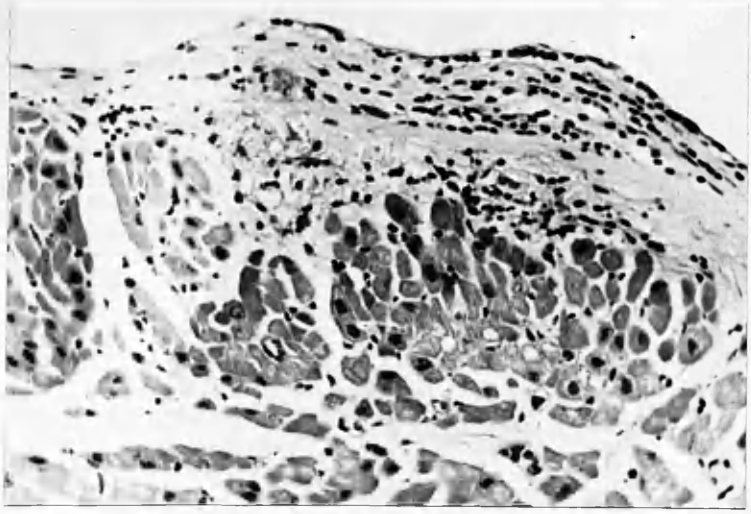


Fig. 58. An infiltrate of lymphocytes is present in the sub-endothelial layer and two focal areas of similar cellular exudate are present in the sub-endocardium. All these infiltrates are associated with I.H.S. There is a suggestion of thickening and granularity of the collagen within the left focal lesion in the subendocardium.

(C.3391/54) H. and E. X 200.

Fig. 59. Mucoid oedema of myocardium. There is no cellular increase.

(C.1160/56) X 250.

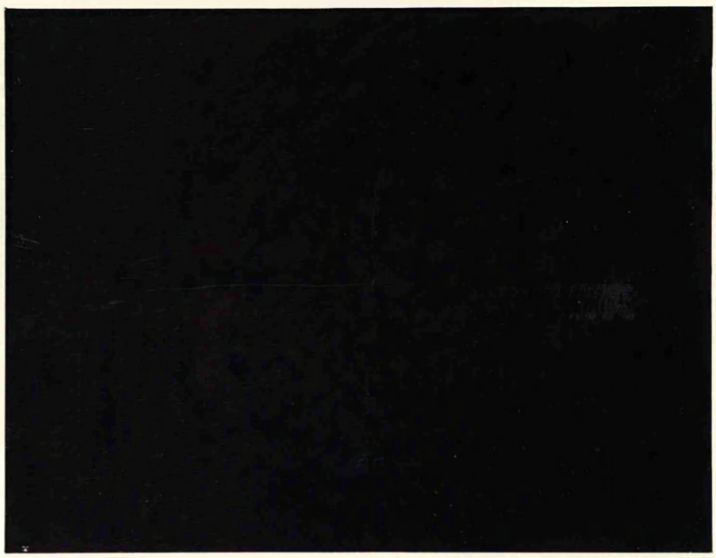


Fig. 60. Early coronal Aschoff lesion with extensive I.H.S. which extends between the muscle fibres. Note the wide separation and the reduction in size of the muscle fibres. Case 133. H. and E. X 230.

Fig. 61. Same section as Fig. 60, decolourised and re-stained H. and V.G. Note the fuchsin staining of the altered collagen.

Case 133. X 230.

Fig. 62. Diagram to show the distribution of active lesions in first 75 biopsy specimens examined.
The diagonal line in the lower diagram indicates the number of cases in which active lesions were found in all blocks of tissue.

RHEUMATIC LESIONS NOT SEEN (24 cases)

−

| No. of blocks of tissue | No. of cases |
|---|---|
| 1 | 5 |
| 2 | 4 |
| 3 | 9 |
| 4 | 3 |
| 5 | 2 |
| 6 & over | 1 |

RHEUMATIC LESIONS PRESENT (51 cases)

+

| No. of blocks of tissue | No. of cases | No. of blocks showing lesions | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 & over |
| 1 | 6 | 6 | | | | | |
| 2 | 14 | 1 | 13 | | | | |
| 3 | 8 | 1 | 1 | 6 | | | |
| 4 | 8 | 2 | - | 2 | 4 | | |
| 5 | 3 | | | | 2 | 1 | |
| 6 & over | 12 | | | | | 2 | 10 |

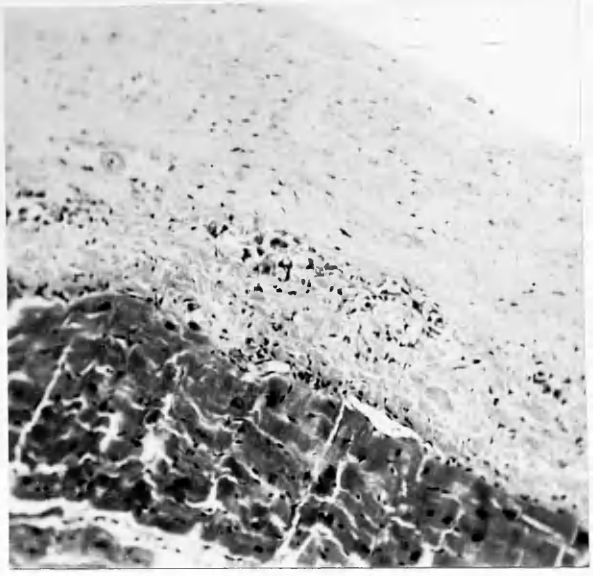


Fig. 63. Elongated lesion in left auricular appendage.

Case 167. H. and E. X 125.

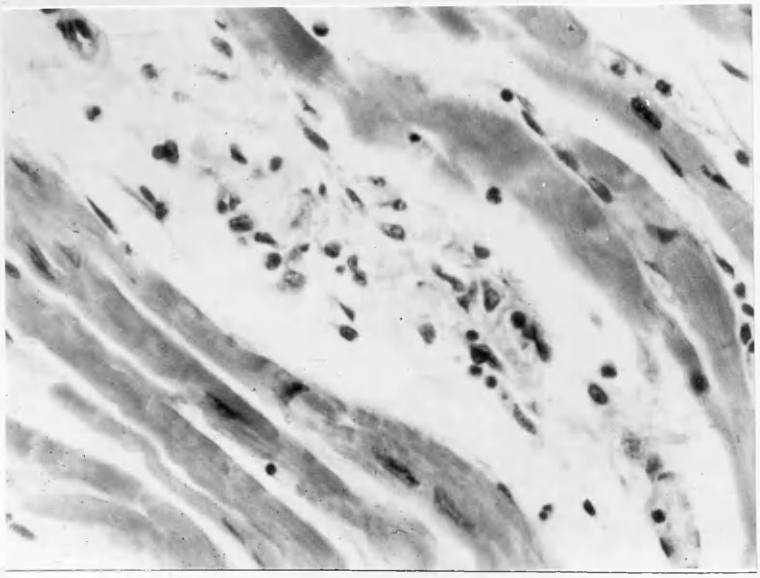


Fig. 64. Small Aschoff body in left ventricular myocardium.

Case 167. H. and E. X 350.

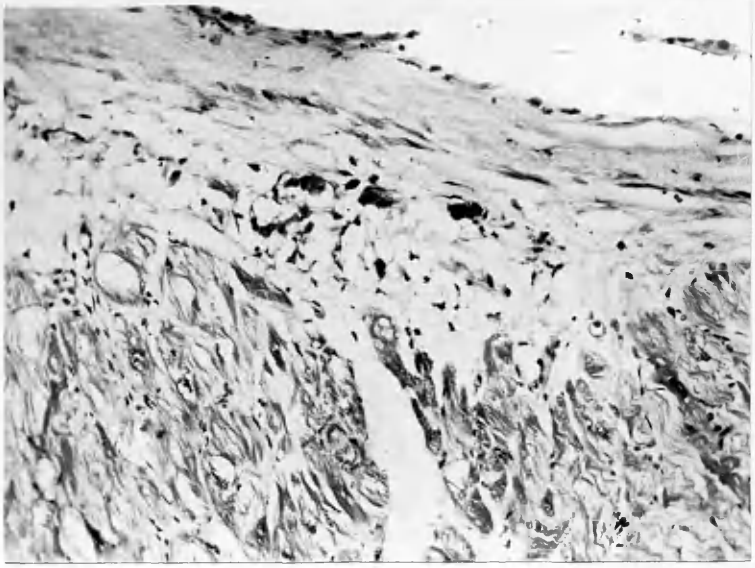


Fig. 65. Lesion in auricular appendage showing large basiphilic Aschoff cells and mucoid oedema.

Case 170. H. and E. X 160.

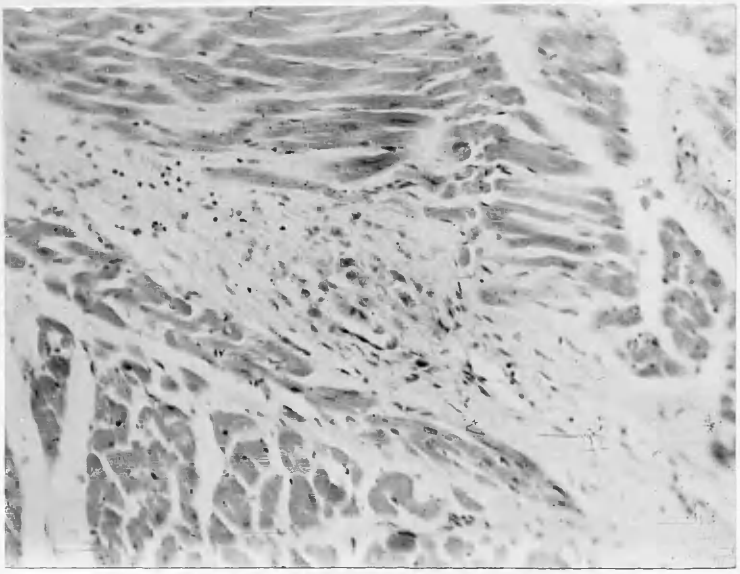


Fig. 66. Aschoff body in the left ventricular myocardium.

Case 170. H. and E. X 160.

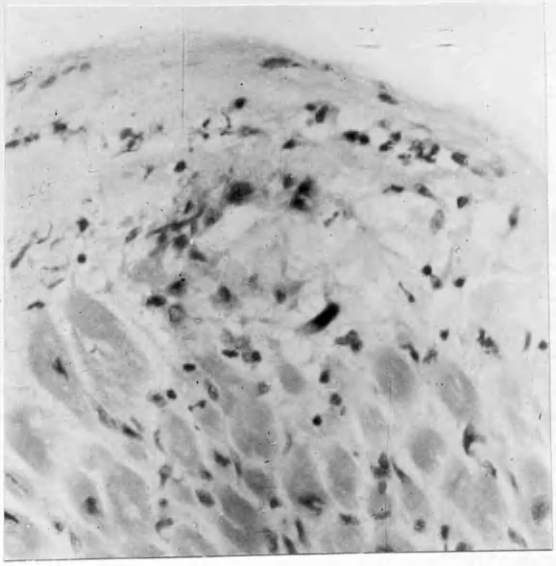


Fig. 67. Small lesion in endocardium and subendocardium of the left auricular appendage. Occasional owl-eye nuclei are present.

Case 171. H. and E. X 300.

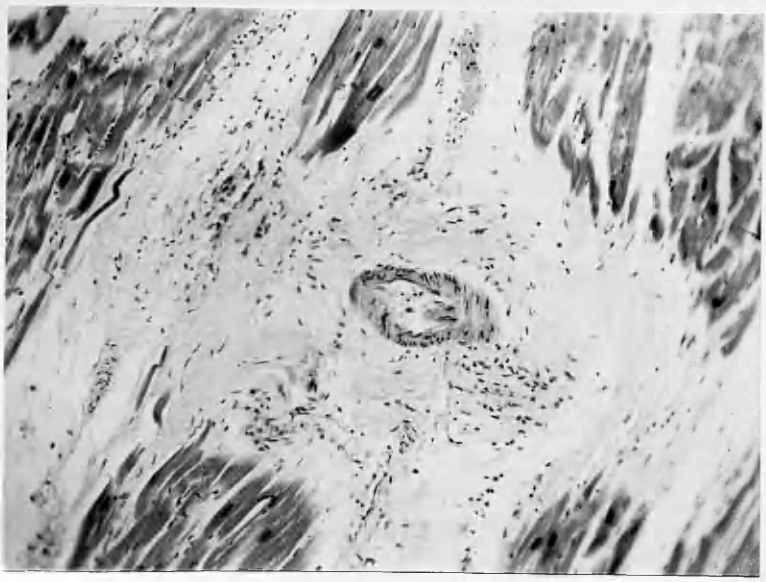


Fig. 68. Group of lesions around a vessel in the left ventricular myocardium.

Case 171. H. and E. X 125.

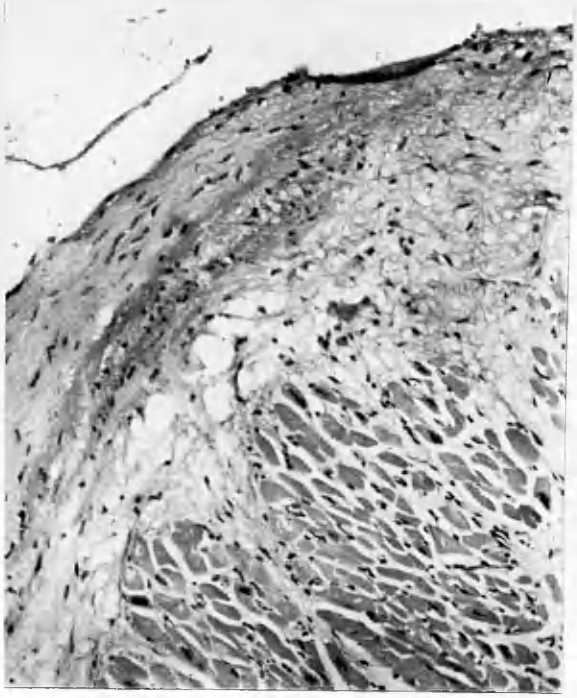


Fig. 69. Extensive area of mucoid change in which there is a cellular exudate including a multinucleate Aschoff cell. The I.H.S. extends into the muscle. Case 172. H. and E. X 200.

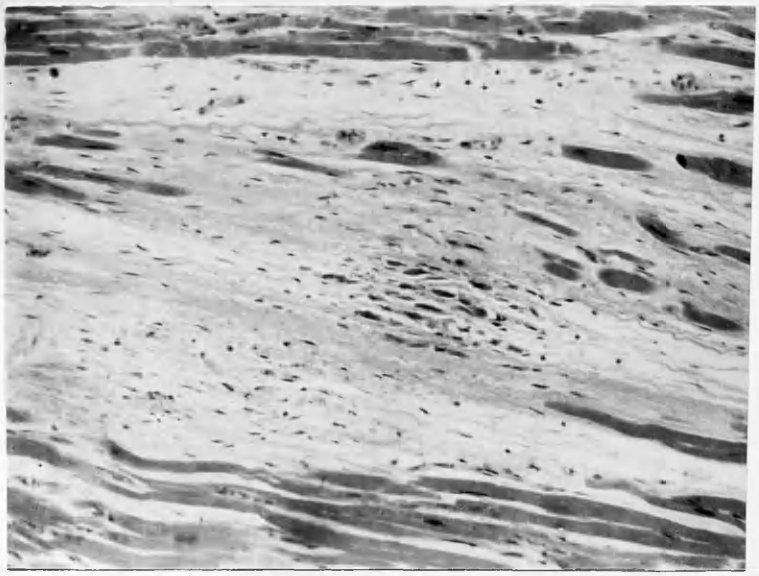


Fig. 70. Polarised lesion in the left ventricular myocardium. Case 172. H. and E. X 200.

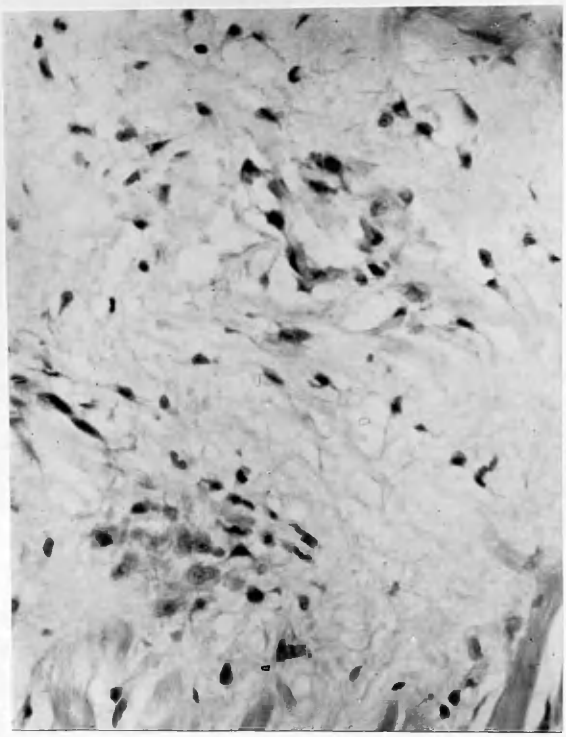


Fig. 71. Mosaic and coronal lesions in the left auricular appendage.

Case 174. H. and E. X 300.

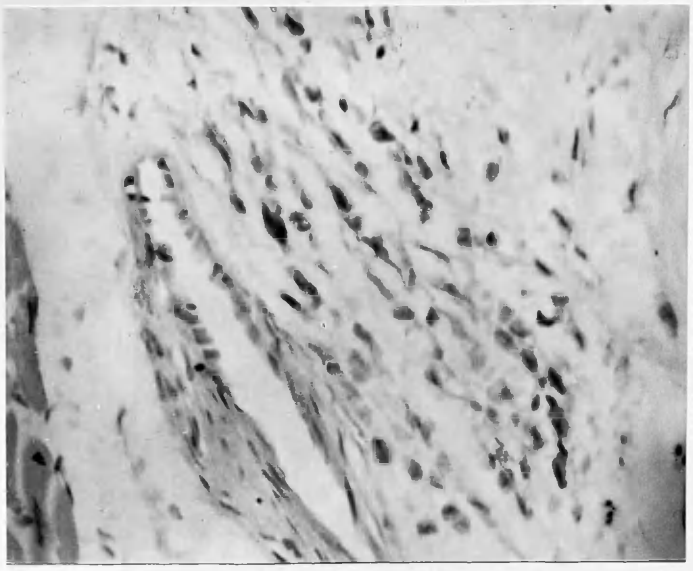


Fig. 72. Lesion alongside a small vessel in the left ventricular myocardium.

Case 174. H. and E. X 300.

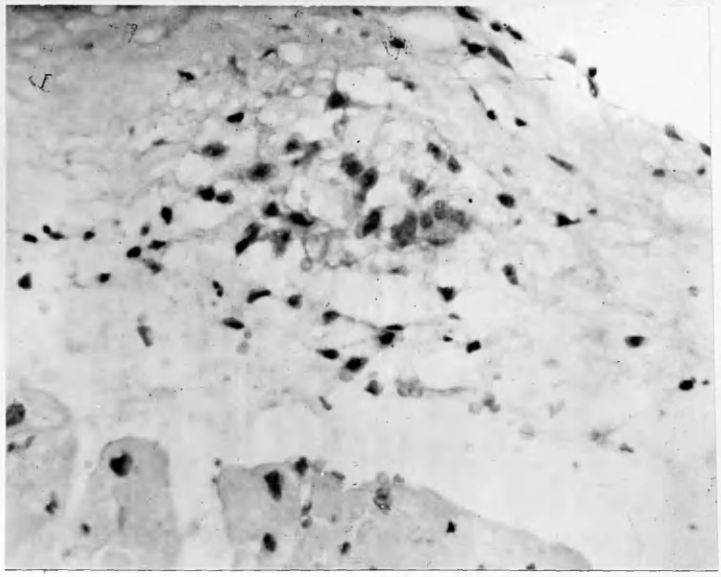


Fig. 73. Small lesion with Aschoff cells and a large amount of I.H.S. in biopsy specimen.

Case 180. H. and E. X 300.

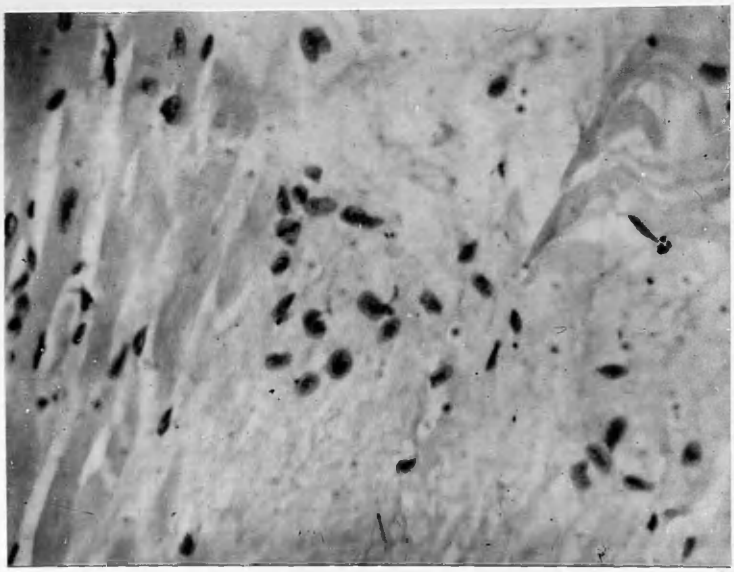


Fig. 74. Small lesion in left ventricular myocardium.

Case 180. H. and E. X 300.

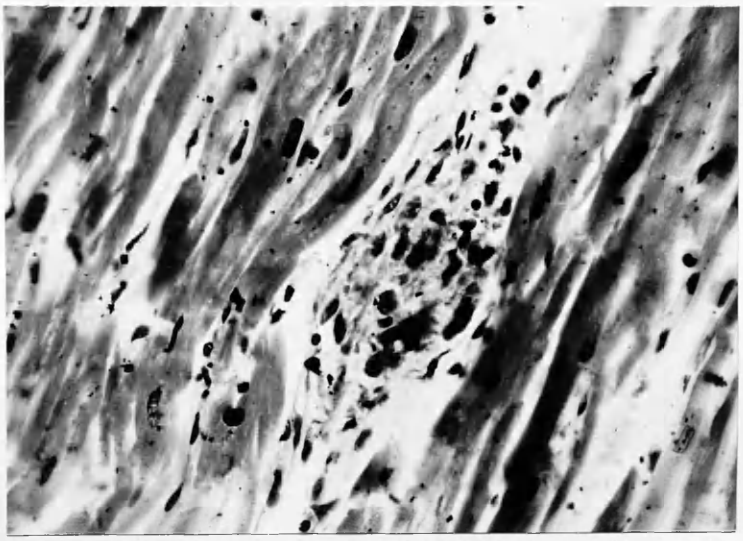


Fig. 75. Polarised mosaic lesion in the left ventricular wall.

Case 181. H. and E. X 360.

Fig. 76. Band of eosinophilic, granular material in the endocardium. Note the infiltration of the sub-endothelial zone, the endocardium and subendocardium with lymphocytes and oval cells.

Case 189. H. and E. X 250.

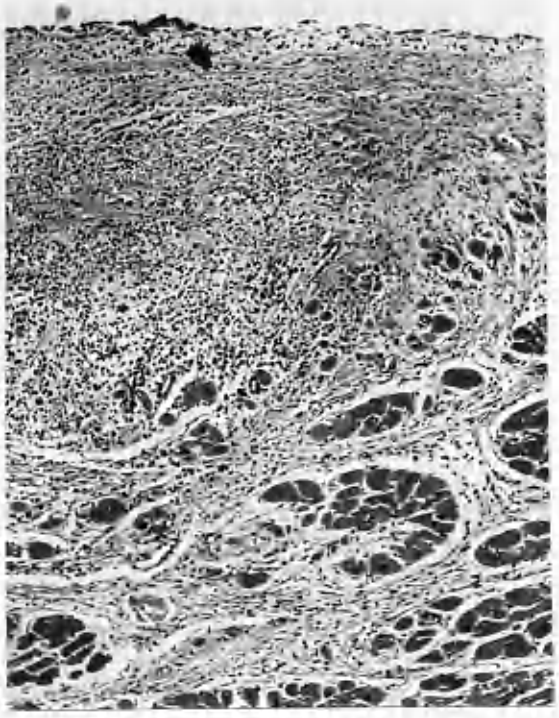


Fig. 77. Diffuse cellular infiltration of left atrial wall. The cells are mainly lymphocytes. The collagen is swollen and rigid in appearance.

Case 189. H. and E. X 100.

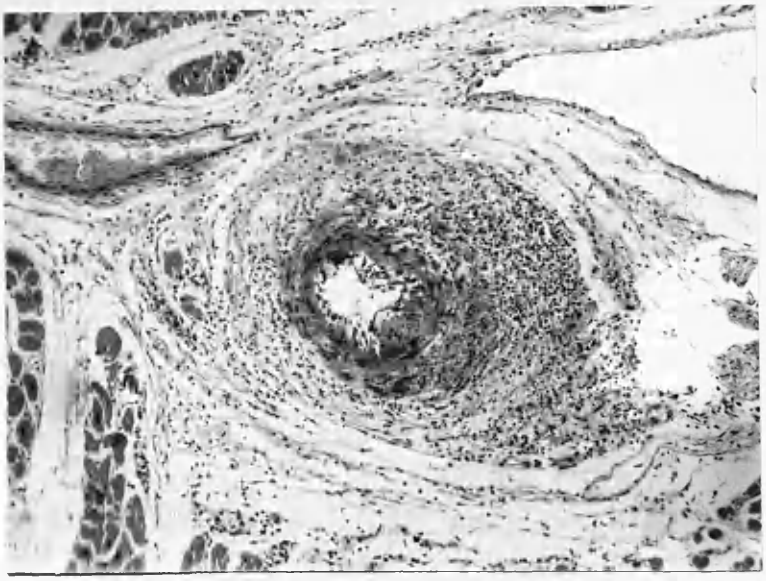


Fig. 78. Intense cellular exudate of lymphocytes and polymorphs around a vessel. Note the deep staining of the collagen on the right hand side of the vessel.

Case 189. H. and E. X 100.

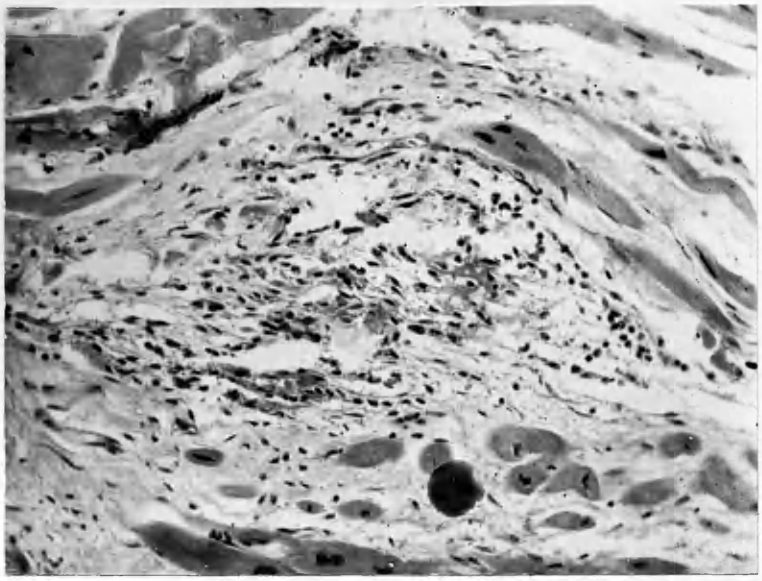


Fig. 79. Reticular Aschoff body in myocardium. Note the oval-shaped cells and the lattice effect of the collagen which is extremely eosinophilic.
Case 189. H. and E. X 180.

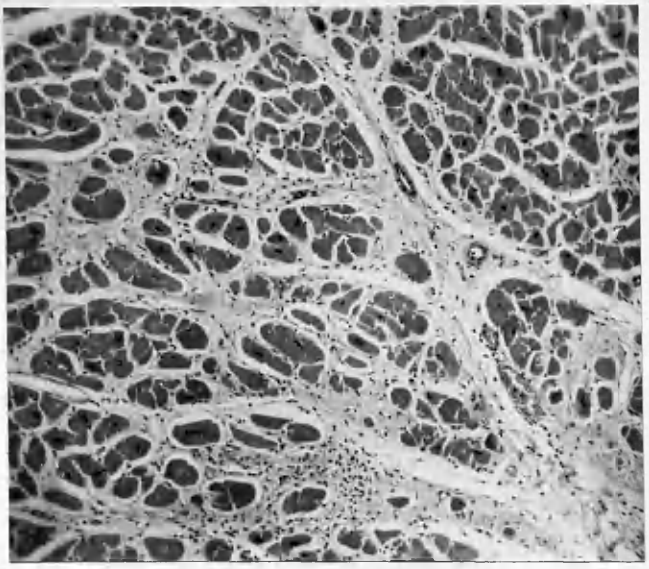


Fig. 80. Diffuse cellular infiltrate mainly of lymphocytes in the myocardial septa.

Case 189. H. and E. X 100.

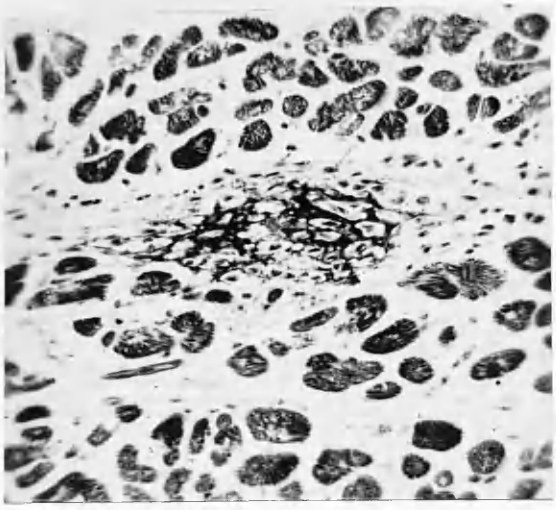


Fig. 81. Reticular Aschoff body.
Note the fibrin-staining reticulum.

Case 189. Mallory's P.T.A.H. X 200.

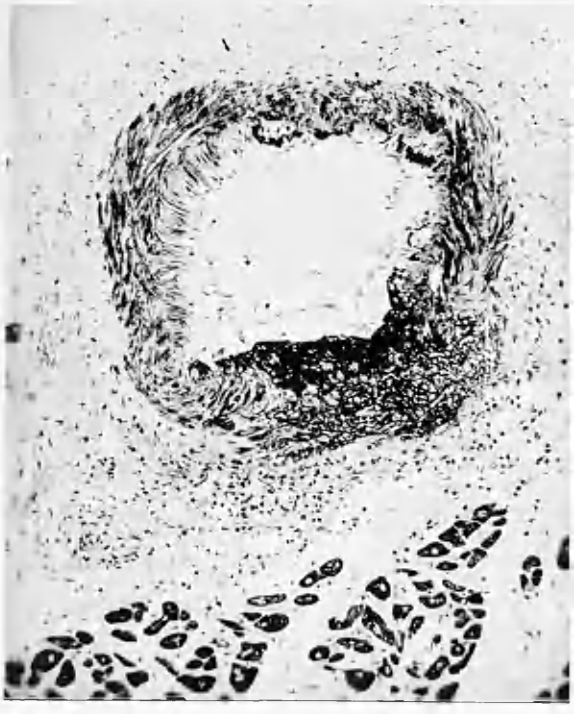


Fig. 82. Rheumatic arteritis.
Note the fibrin-staining material
in the intima, media and adventitia.

Case 189. Mallory's P.T.A.H. X 86.

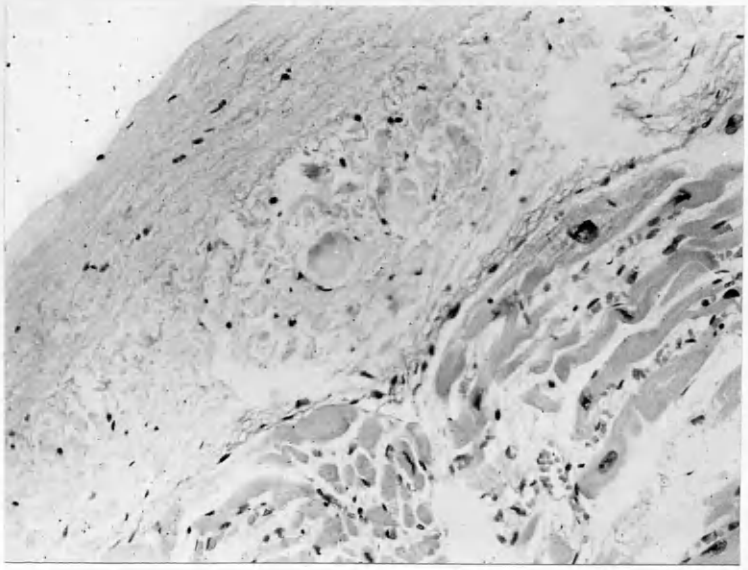


Fig. 83. Mass of fused eosinophilic, slightly granular, collagen in the left auricular appendage.

Case 190. H. and E. X 160.

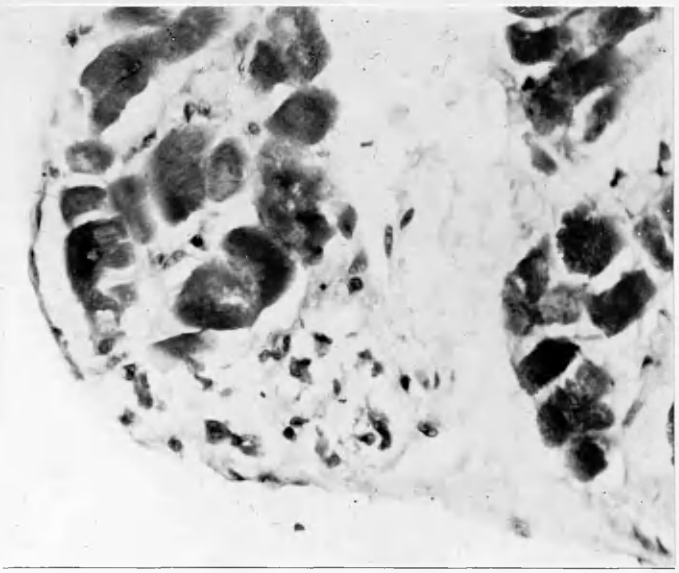


Fig. 84. Tiny lesion in the endocardium of the left ventricle.

Case 190. H. and E. X 300.

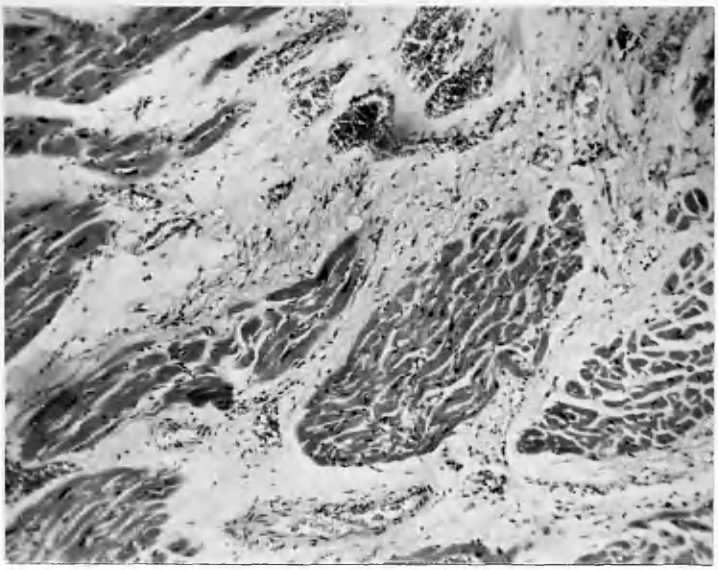


Fig. 85. Extensive mucoid oedema of left ventricular myocardium with a slight infiltrate of lymphocytes.

(Cf. Fig. 59) Case 192. H. and E. X 100.

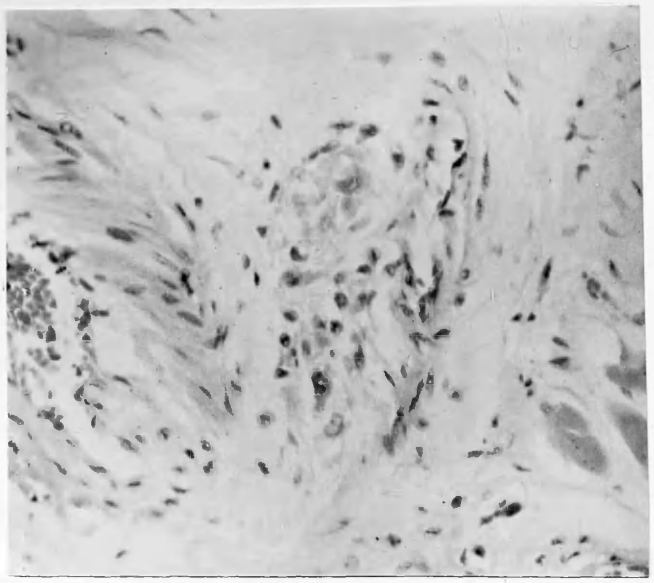


Fig. 86. Small Aschoff body related to a vessel.

Case 192. H. and E. X 250.

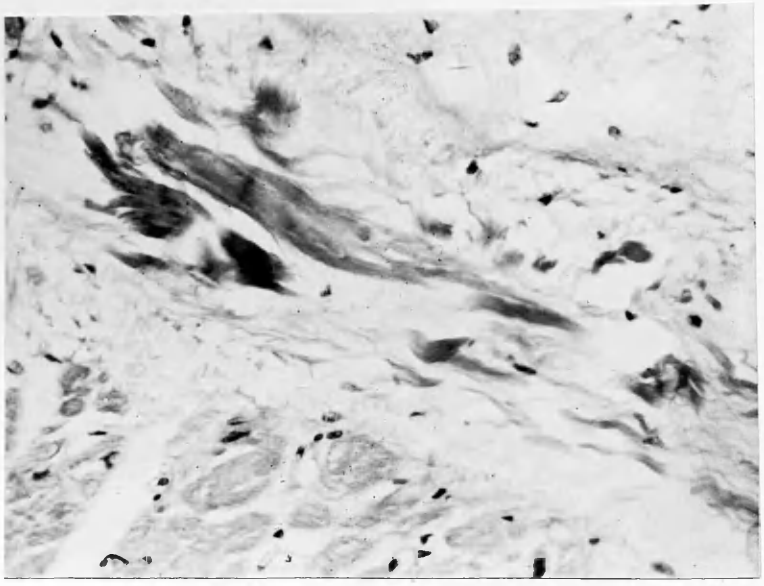


Fig. 87. Stretches of fused collagen staining red and yellow with the Van Gieson stain. Note the absence of cellular reaction and the oedema.

Case 197. H. and V.G. X 200.

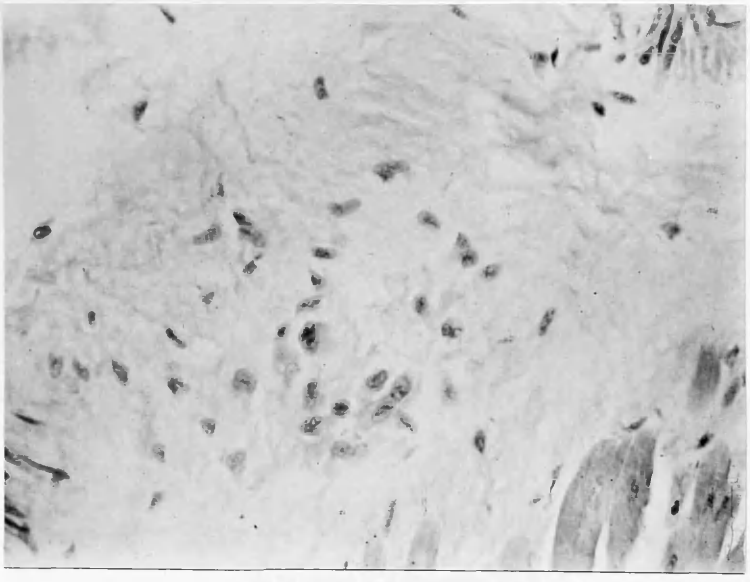


Fig. 88. Lesion in left ventricle. Note the characteristic Aschoff nuclei.

Case 197. H. and E. X 250.

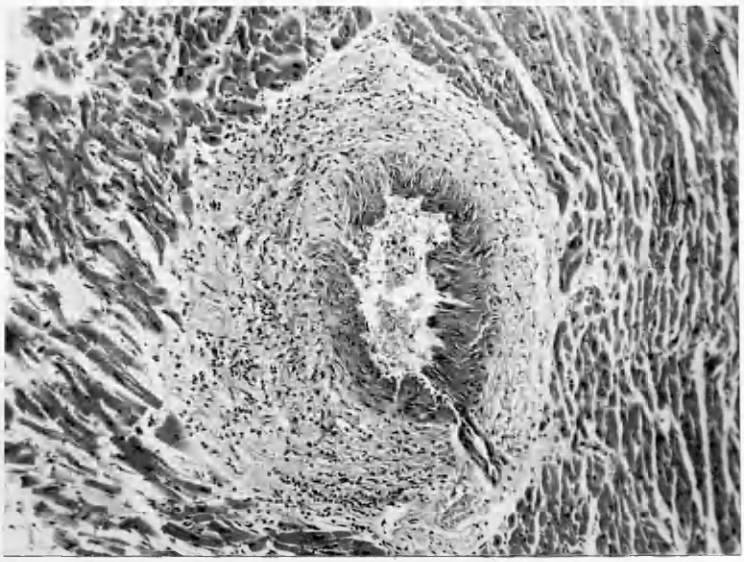


Fig. 89. Exudate of lymphocytes and polymorphs around a vessel in the left ventricle.

Case 198. H. and E. X 100.

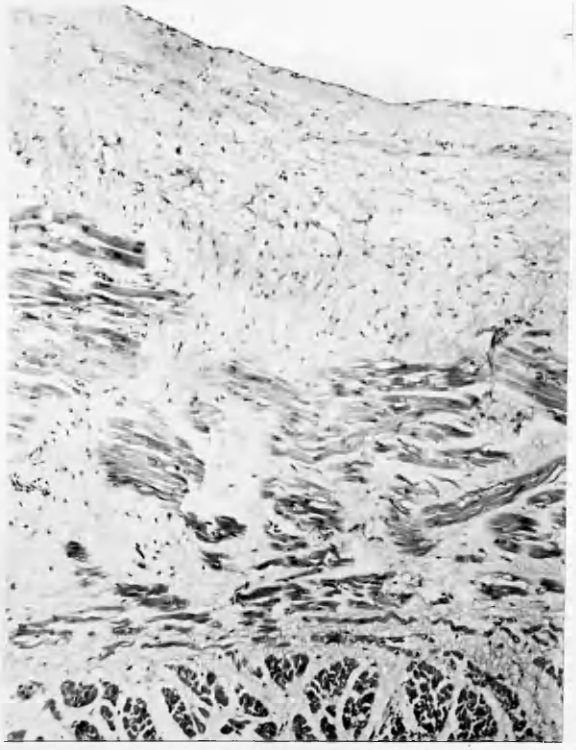


Fig. 90. Extensive mucoid changes in the endocardium and subendocardium extending into the myocardium. Left auricular appendage.

Case 204. H. and E. X 75.

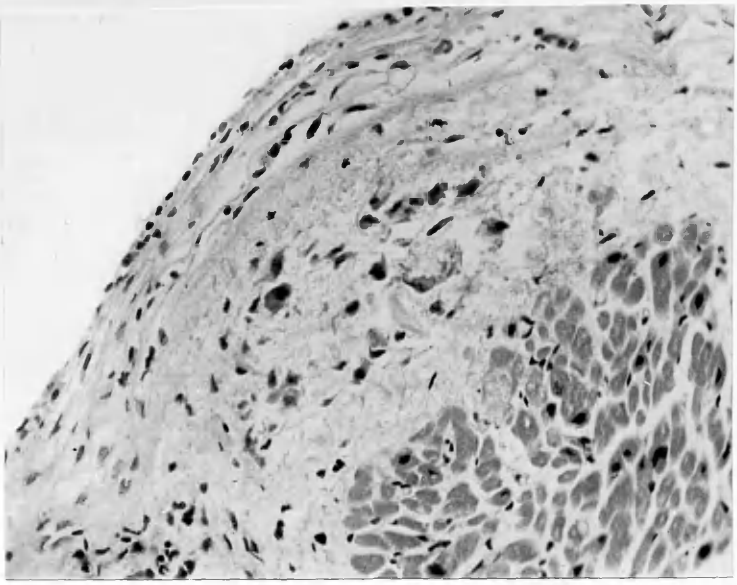


Fig. 91. Mosaic lesion in left auricular appendage.

Case 206. H. and E. X 250.

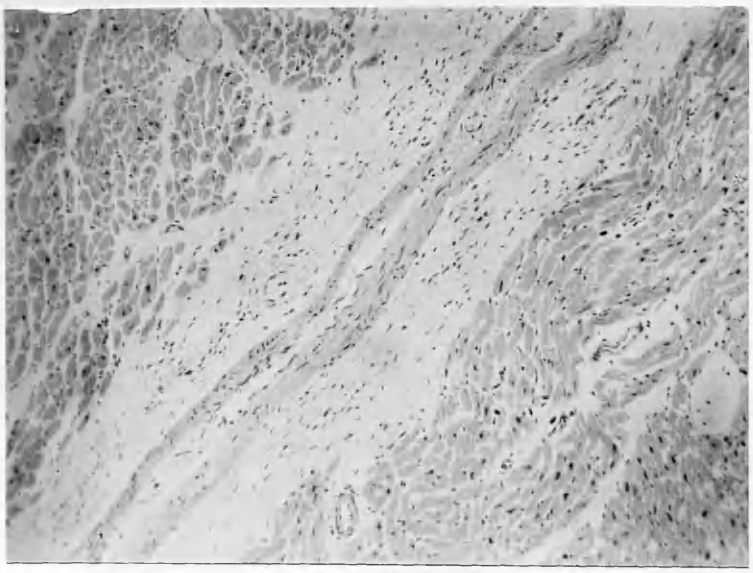


Fig. 92. Numerous fibrillary lesions around a vessel in the left ventricular myocardium.

Case 206. H. and E. X 100.

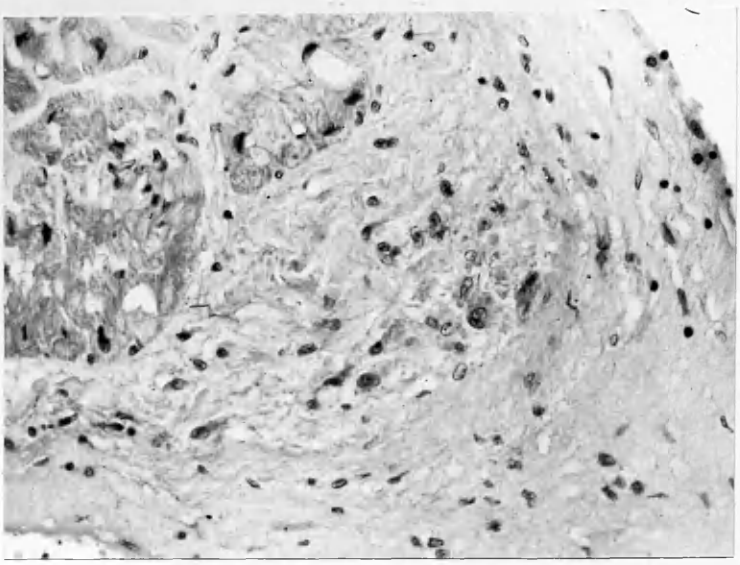


Fig. 93. Lesion in left auricular appendage.

Case 210. H. and E. X 250.

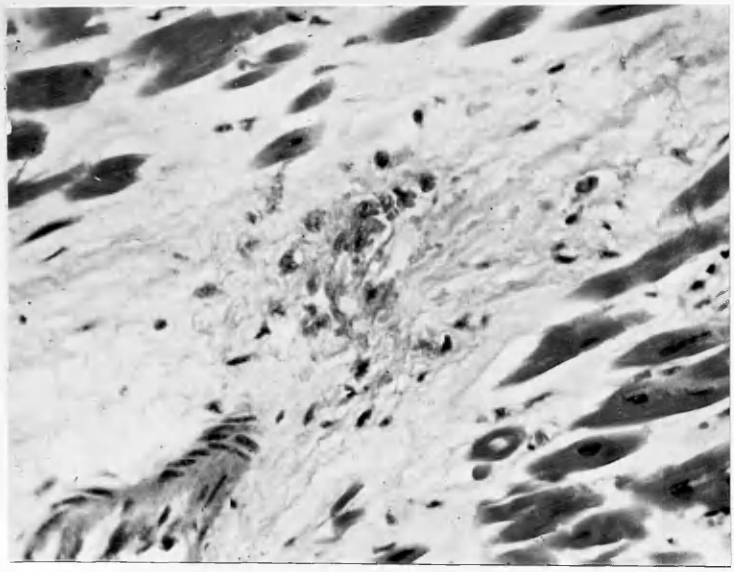


Fig. 94. Similar lesion in left ventricular wall.

Case 210. H. and E. X 250.

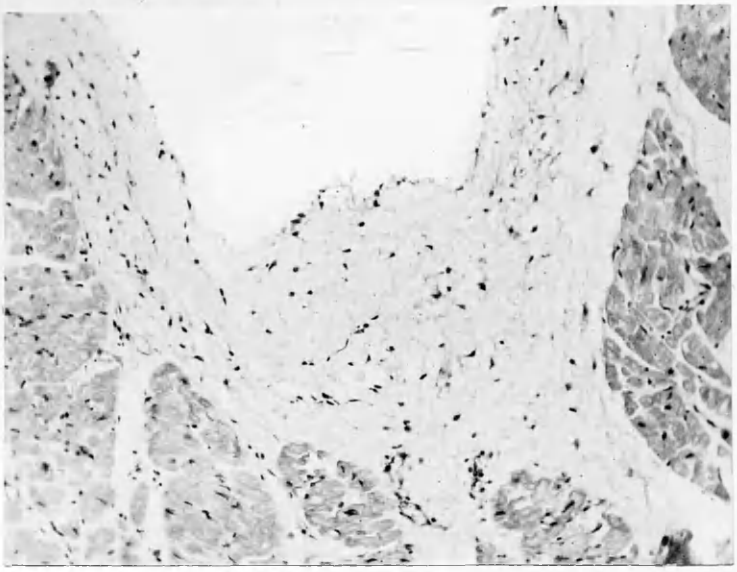


Fig. 95. Diffuse I.H.S. and slight lymphocytic infiltration of the endocardium and subendocardium of the left auricular appendage.

Case 211. H. and E. X 160.

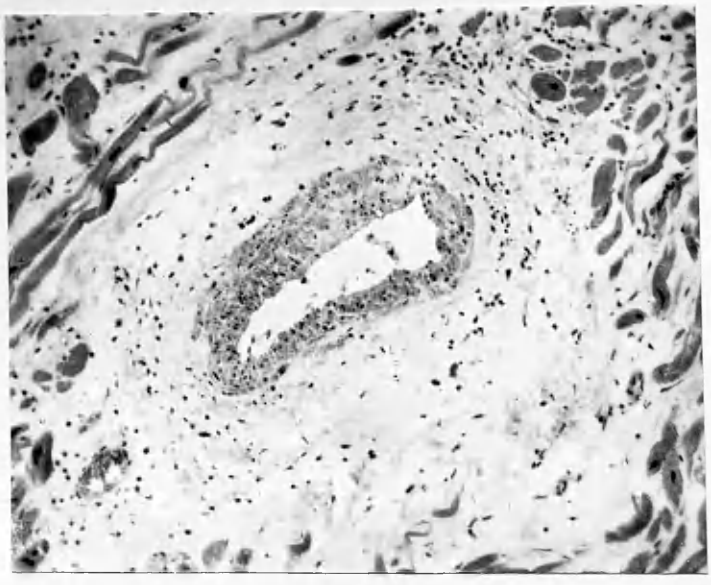


Fig. 96. Moderate infiltrate of lymphocytes and oedema around a vessel in the left ventricular myocardium.

Case 211. H. and E. X 150.

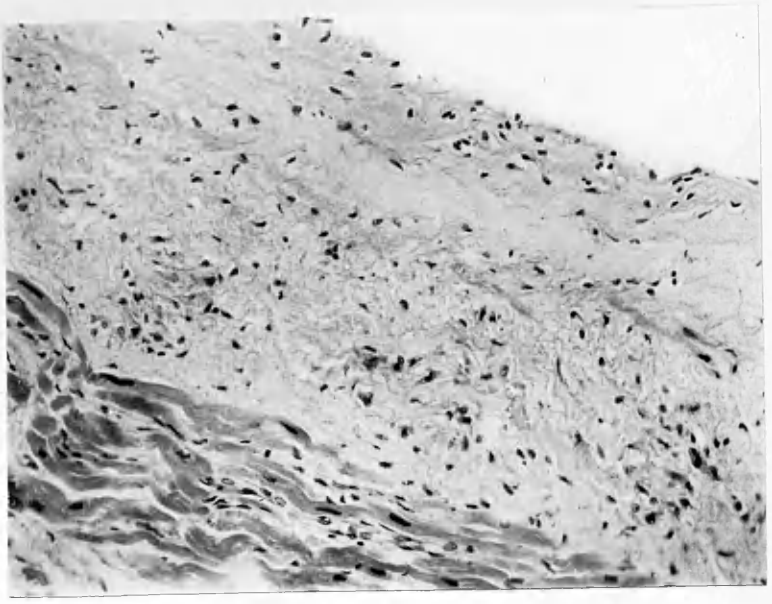


Fig. 97. Numerous Aschoff nodules in the left auricular appendage.

Case 212. H. and E. X 160.

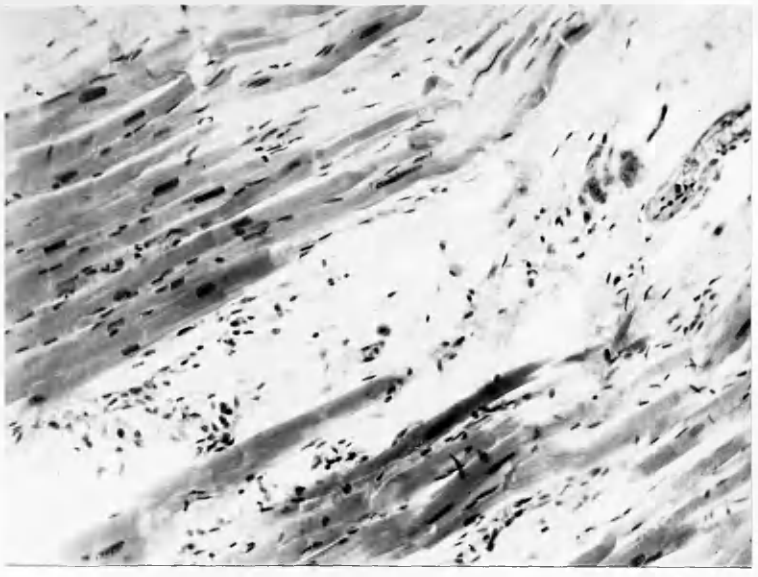


Fig. 98. A small focal Aschoff nodule with large cells is related to a vessel towards the right upper corner. A moderate infiltrate of oval-shaped cells is present in the septum.

Case 212. H. and E. X 160.

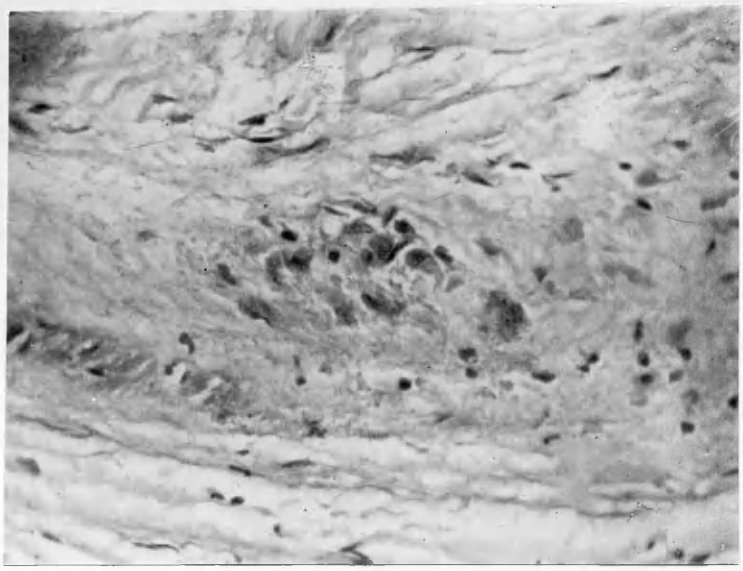


Fig. 99. Mosaic lesion in the left auricular appendage.

Case 213. H. and E. X 300.

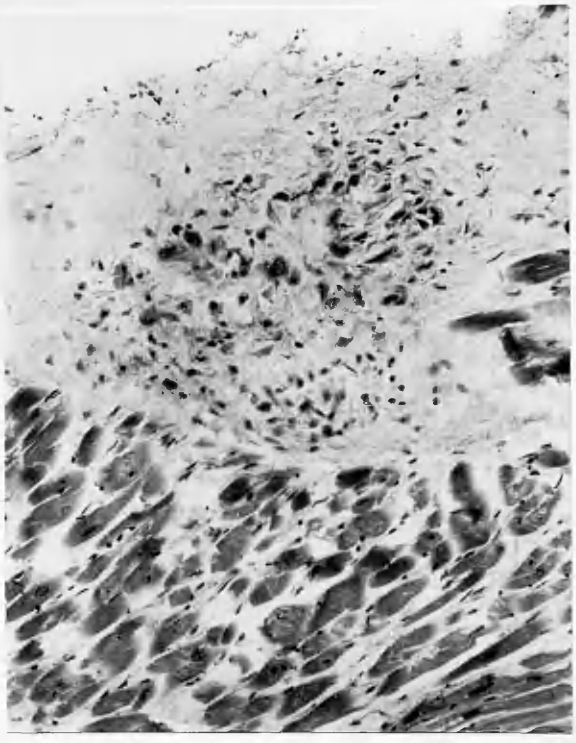


Fig. 100. Mosaic lesion in the left atrial wall.

Case 213. H. and E. X 160.

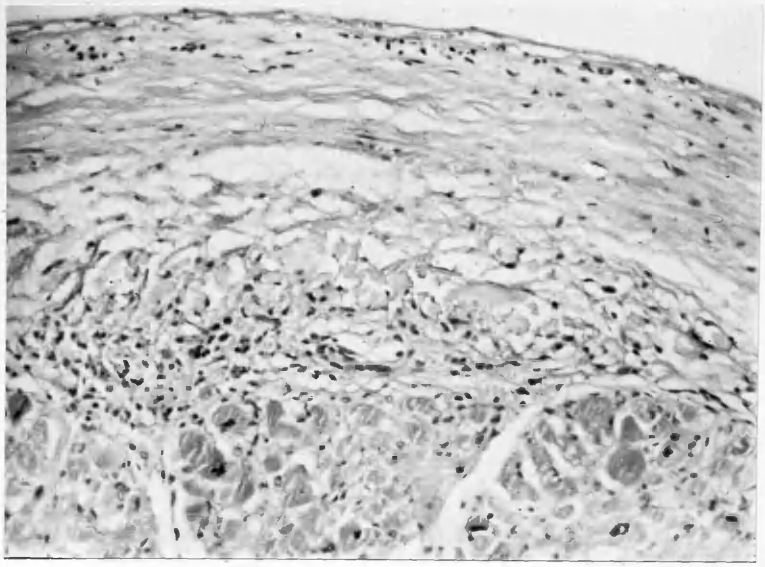


Fig. 101. Left auricular appendage showing swelling of collagen and a diffuse infiltrate of lymphocytes in the subendocardium.

Case 214. H. and E. X 200.

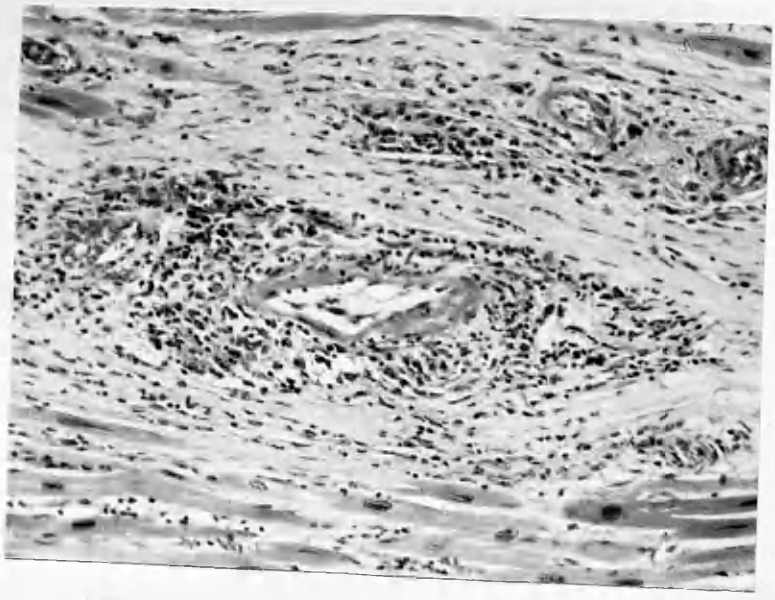


Fig. 102. Intense mononuclear and lymphocytic infiltration especially around vessels. The collagen to the left of the vessel shows granularity and eosinophilia.

Case 214. H. and E. X 200.

Fig. 103. Metachromasia of endocardium extending into myocardium. Several Aschoff nodules are present in the subendocardium. Case 120. Toluidine blue. X 140.

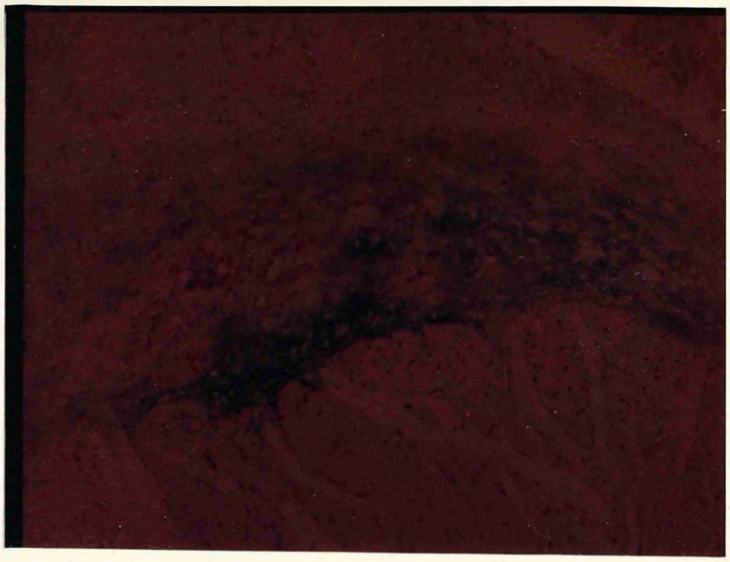


Fig. 104. Hale's dialyzed iron method. Note the collection of Hale positive material in the subendocardium and within small Aschoff nodules. (C.1945/56) Counterstained neutral red. X 150.

Fig.105 Distribution of metachromasia in rheumatic and non-rheumatic hearts

| | NON-RHEUMATIC HEARTS (14 Cases) | RHEUMATIC HEARTS (28 Cases) |
|---|---|---|
| | No. showing metachromasia | No. showing metachromasia |
| Left auricular appendage | 1 | 17 |
| Left atrial wall | 1 | 15 |
| Mitral valve | 10 | 23 |
| Aortic valve | 11 | 17 |
| Left ventricular myocardium | 0 | 8 |
| Right auricular appendage | 1 | 10 |
| Right atrial wall | 0 | 8 |
| Tricuspid valve | 6 | 15 |
| Pulmonary valve | 7 | 16 |
| Right ventricular myocardium | 0 | 5 |

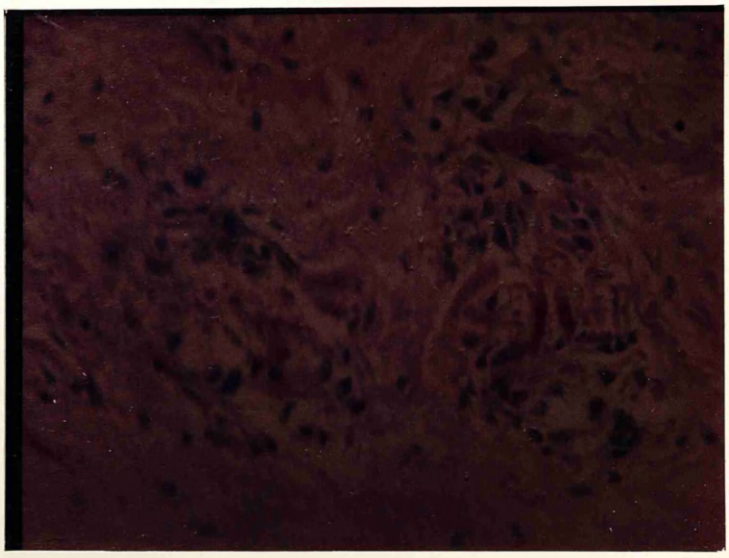


Fig. 106. Note the deeply-staining bands of altered collagen within the lesion on the right and the less intensely stained apparently fragmented collagen in the lesion on the left.

P.A.S. counterstained Haematoxylin. X. 280.

In Figs. 107 - 111 lesions photographed in ordinary light are shown on the left and the same lesions photographed in polarised light are shown on the right.

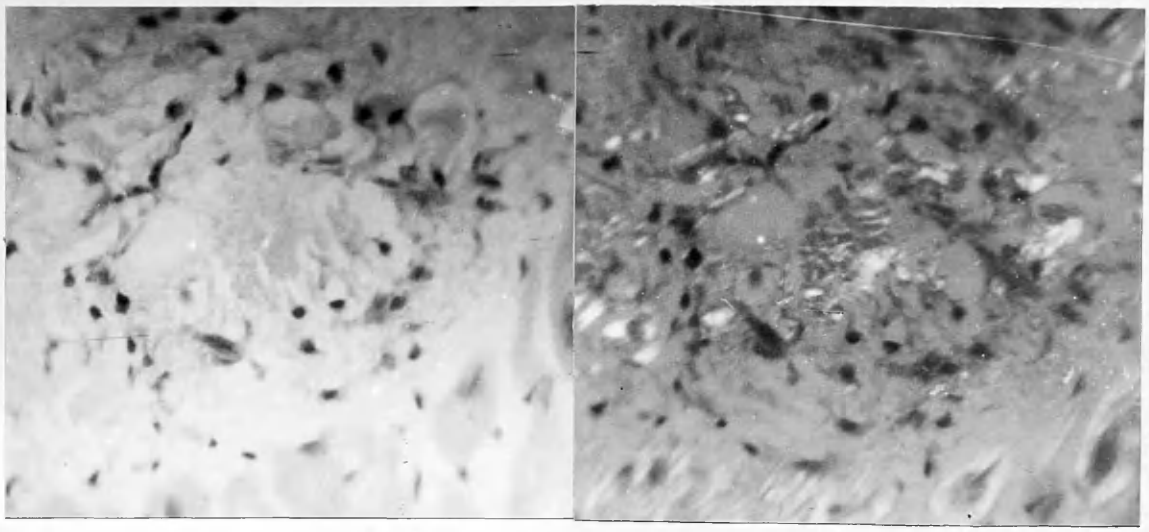


Fig. 107. H. and E. X 350. (See Fig. 22)

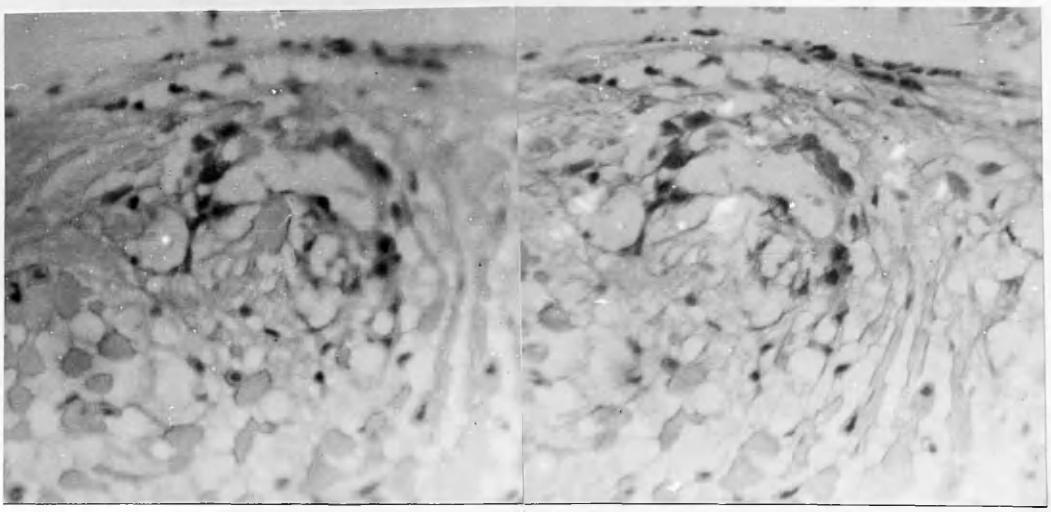


Fig. 108. H. and E. X 350. (See Fig. 60)

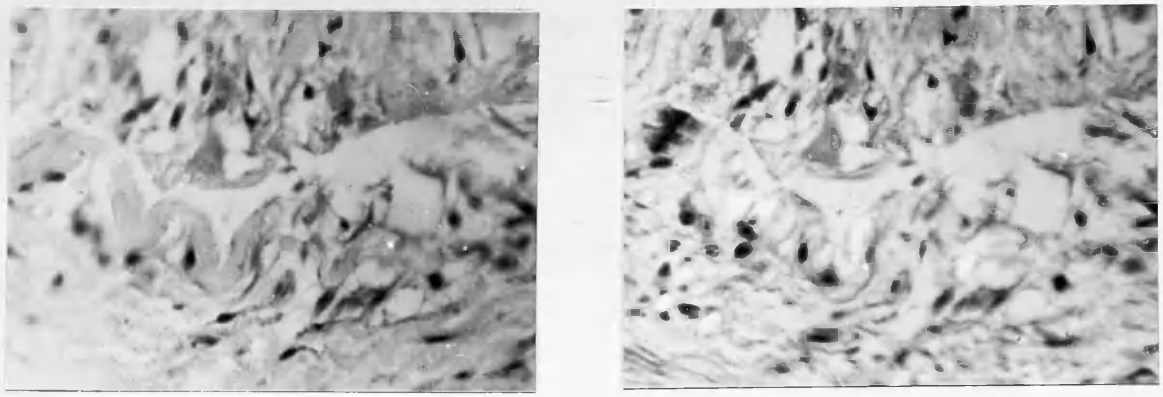


Fig. 109. H. and E. X 350. (See Fig. 32)

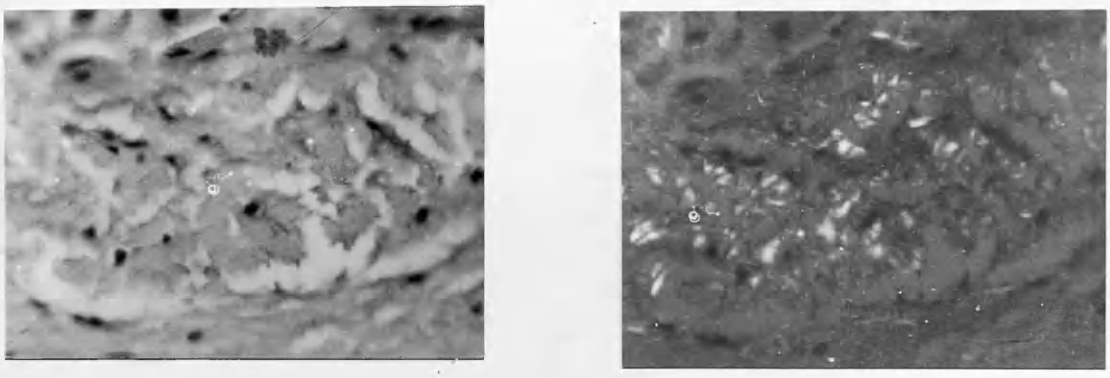


Fig. 110. H. and E. X 350. (See Fig. 51)

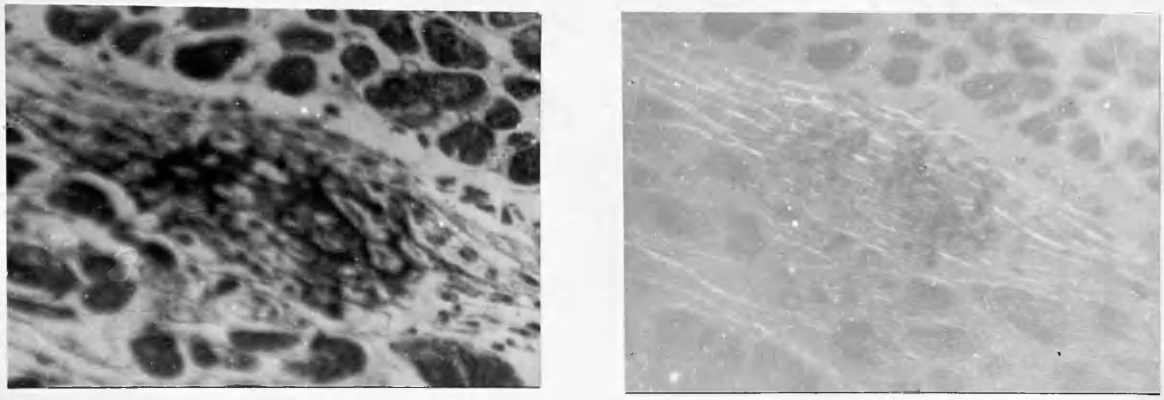


Fig. 111. P.T.A.H. X 350. (See Fig. 81)

Fig.112 Results of chemical estimations of hexosamine, hydroxyproline, and tyrosine in auricular appendages

RESULTS ON THE BASIS OF GM. PER 100 GM. TISSUE NITROGEN

| Specimen No. | Hexosamine | Hydroxy-proline N | Tyrosine N | Ratio Hexosamine / OH-proline N | Histological Findings |
|---|---|---|---|---|---|
| 1 | 4.65 | 1.24 | 0.95 | 3.75 | +++ |
| 2 | 6.7 | 1.7 | 1.24 | 3.95 | ++ |
| 3 | 6.3 | 1.57 | - | 4.0 | ++ |
| 5 | 7.17 | 1.76 | - | 4.1 | + |
| 8 | 4.2 | 1.39 | 0.89 | 3.0 | ++ |
| 9 | 5.5 | 1.42 | 0.90 | 3.9 | ++ |
| 10 | 6.06 | 1.05 | 0.74 | 5.8 | +++ |
| 11 | 5.0 | 1.33 | 0.99 | 3.75 | + |
| 13 | 7.3 | 1.49 | 1.33 | 4.9 | +++ |
| 14 | 7.15 | 2.03 | 1.35 | 3.5 | + |
| 4 | 4.63 | 1.33 | 1.15 | 3.5 | - |
| 6 | 8.87 | 1.89 | - | 4.7 | - * |
| 7 | 6.1 | 1.54 | - | 3.95 | - * |
| 12 | 7.1 | 2.0 | 0.92 | 3.55 | - |
| 15 | 3.37 | 1.57 | 1.01 | 2.15 | - |

* Specimens showing organising thrombus

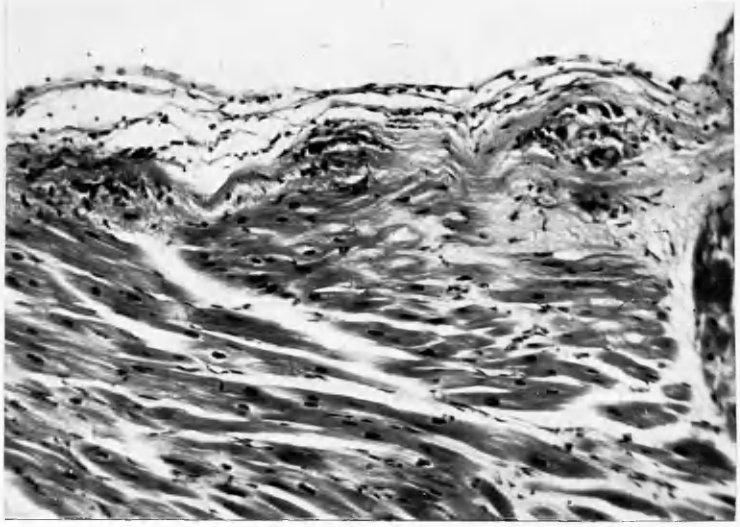


Fig. 113. Note the collagen fibres passing through the lesions.

(C.2913/56) H. and E. X 150.

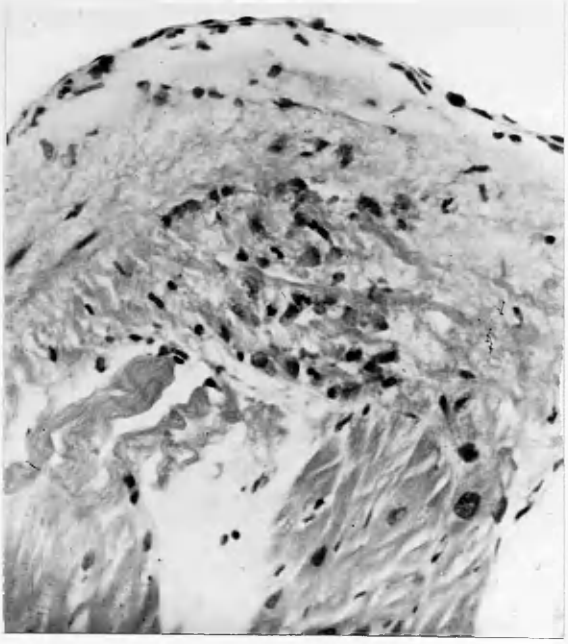
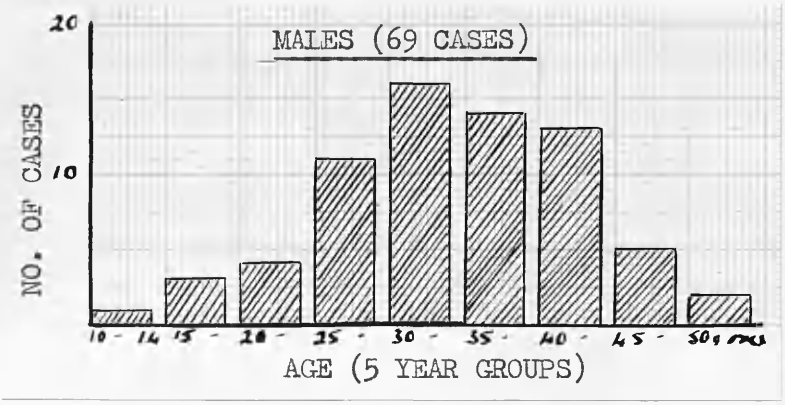
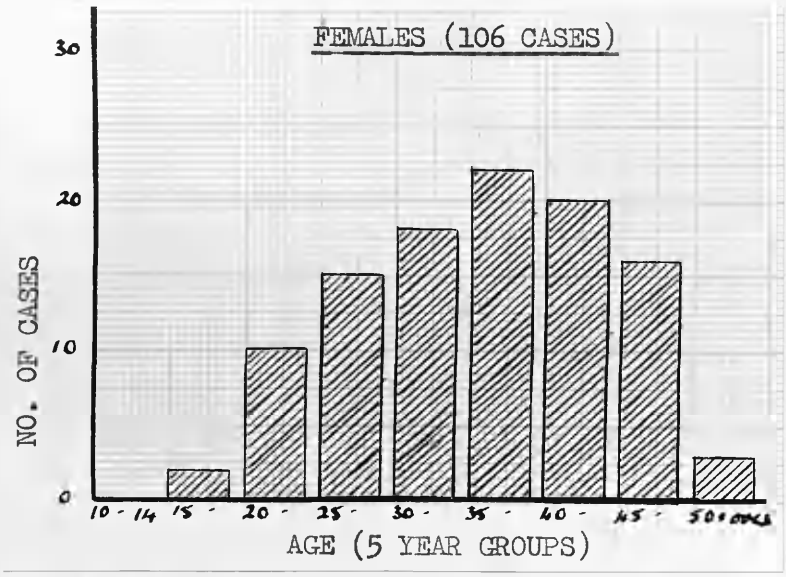


Fig. 114. Collagen fibres passing through a lesion.

(C.73/56) H. and V.G. X 250.

Fig. 115. Age distribution of patients in the valvotomy series.



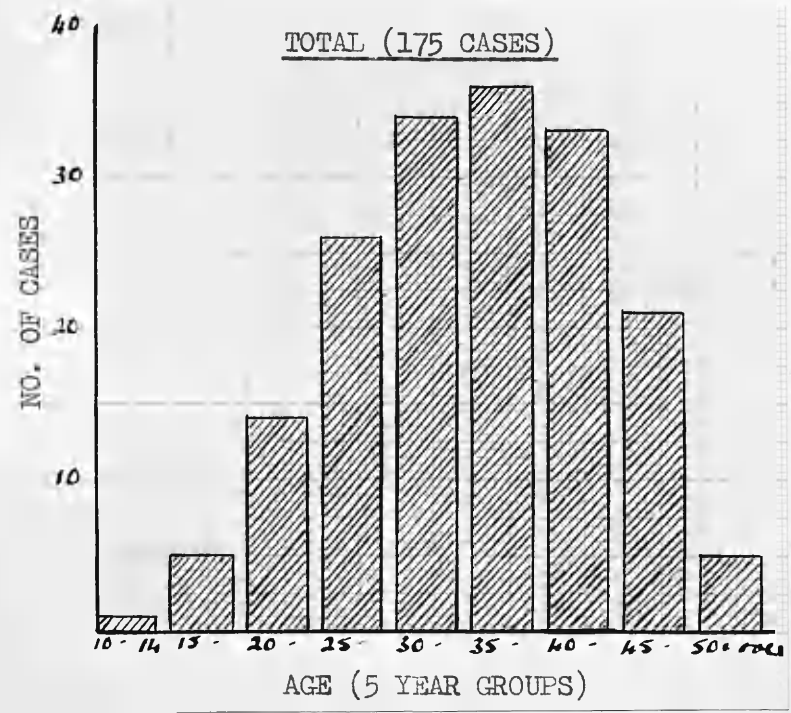
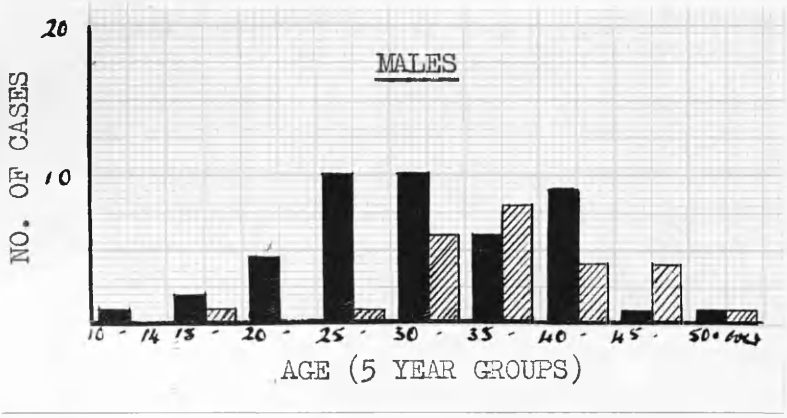
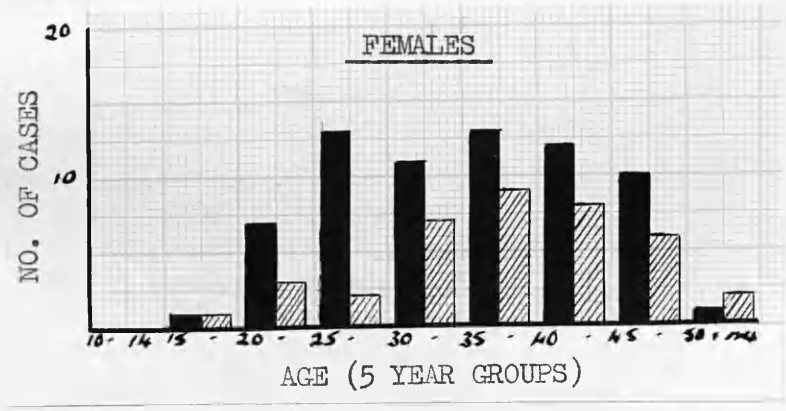



Fig. 116. Distribution of patients in the valvotomy series with respect to age and the presence or absence of active rheumatic lesions.



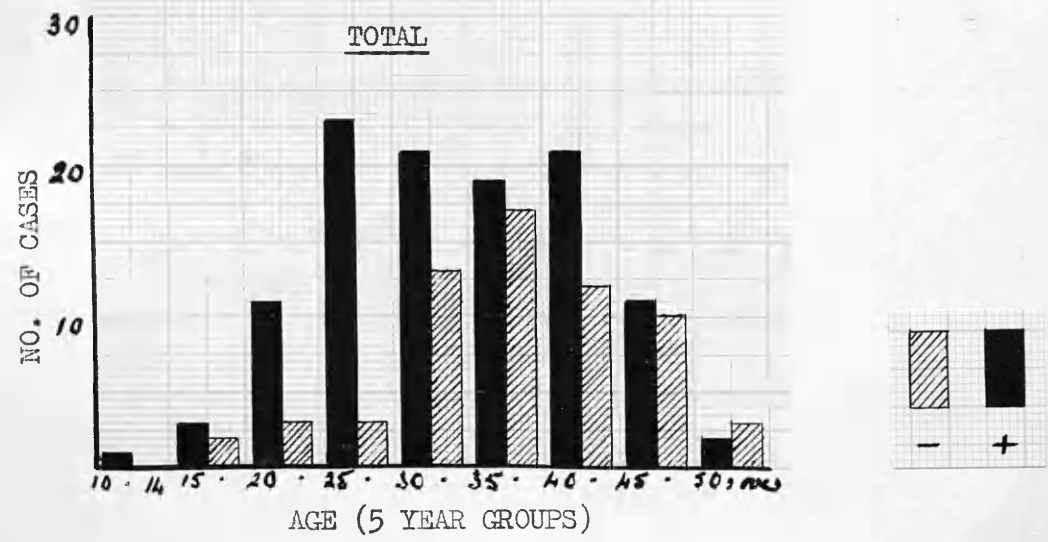



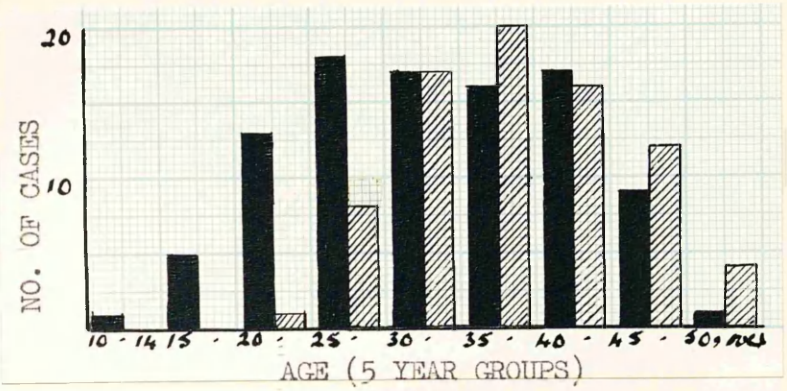
Fig. 117. Clinical data analysed with respect to the presence or absence of active rheumatic lesions in the left auricular appendage. Valvulotomy series.

| CLINICAL FINDINGS | No. of Cases | + | - |
|---|---|---|---|
| Sinus rhythm | 97 | 86 | 11 * |
| Auricular fibrillation | 78 | 26 | 52 * |
| Raised E.S.R. | 23 | 12 | 11 |
| W.B.C. above 10,000 | 14 | 9 | 5 |
| C.C.F. before operation | 34 | 20 | 14 |
| History of C.C.F. at some time prior to operation | 17 | 9 | 8 |
| Mitral and aortic disease | 32 | 20 | 12 |
| Mainly regurgitation at operation | 27 | 16 | 11 |
| Calcification of valve | 50 | 31 | 19 |
| Total no. of cases: | 175 | 112 | 63 |

* For sinus rhythm and auricular fibrillation $\chi^2 = 57$ $P < .01$

For other clinical findings no conventional level of statistical significance was found.

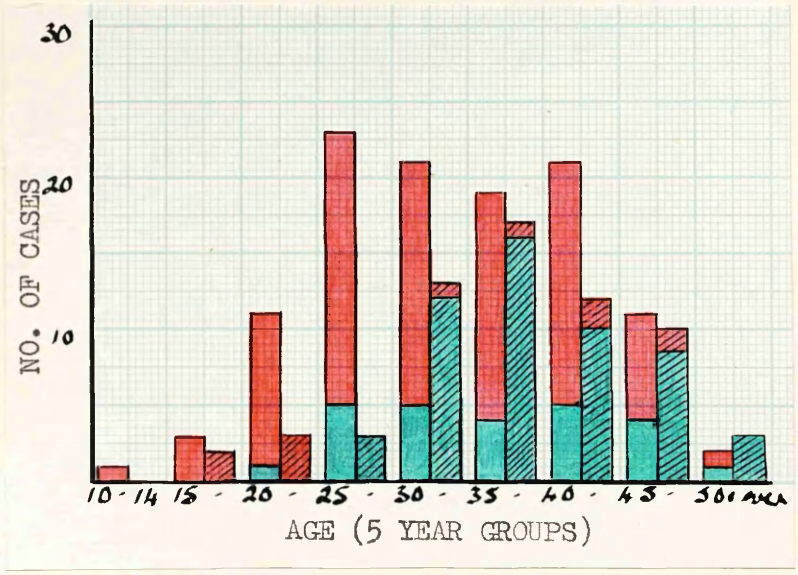
Fig. 118. Distribution of cases in valvotomy series with respect to age and cardiac rhythm.




Sinus rhythm

Auricular fibrillation

Fig. 119. Distribution of cases in valvotomy series with respect to age, cardiac rhythm, and the presence or absence of active lesions.




Sinus Rhythm +

Auricular Fibrillation +

Sinus Rhythm -

Auricular Fibrillation -

Fig. 120. The relationship of the presence or absence of active lesions to the interval between first acute attack of rheumatic fever and time of operation.

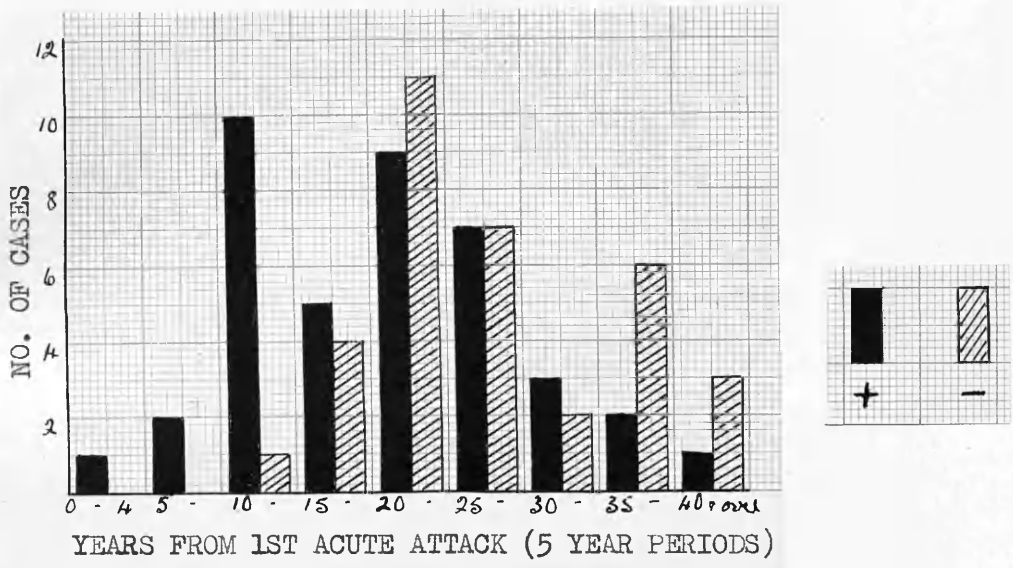



Fig. 121. The relationship of cardiac rhythm to the time interval between first acute attack of rheumatic fever and date of operation.

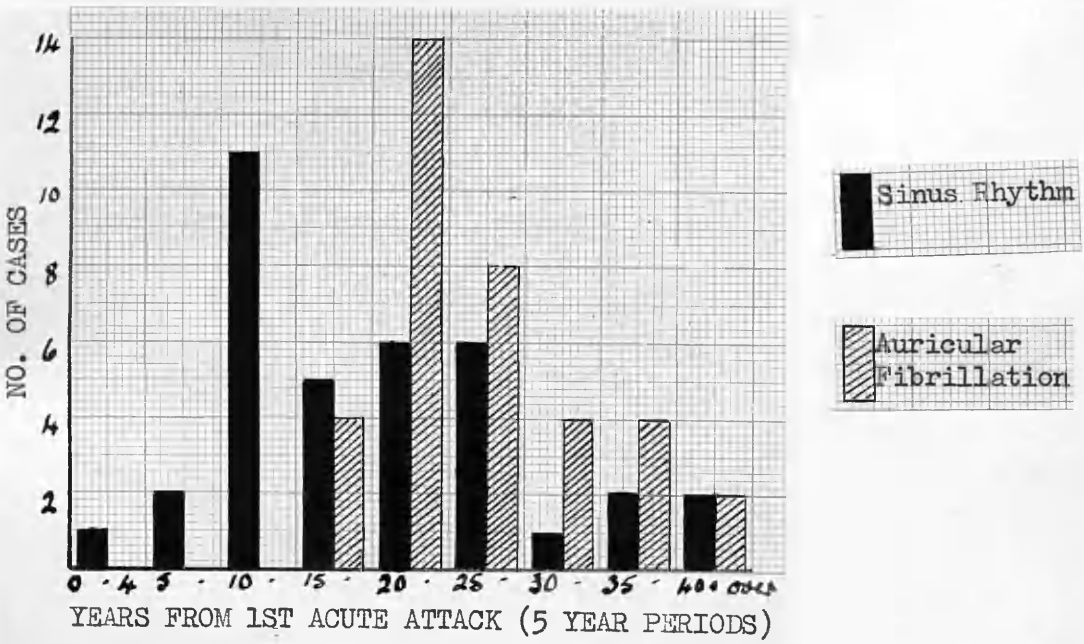


Fig. 122. The relationship of the time between first acute attack and date of operation, the presence or absence of active lesions, and the cardiac rhythm.

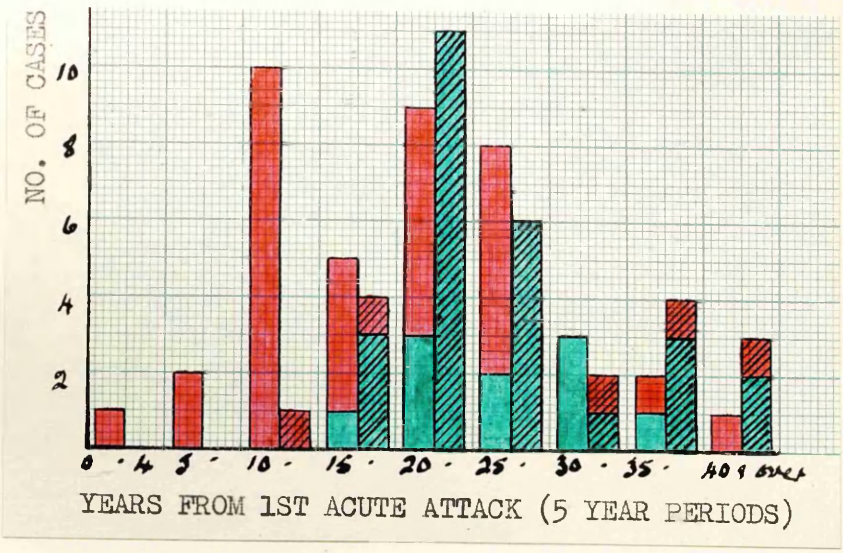
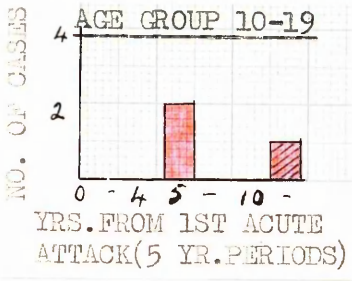
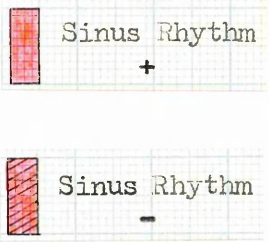


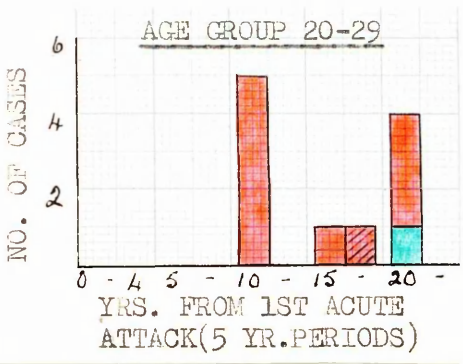
Fig. 123. The relationship of the time interval from first acute attack to date of operation with respect to the presence or absence of active lesions and the cardiac rhythm. The patients have been separated into 10 yr. age groups.

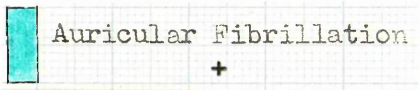


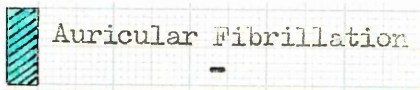



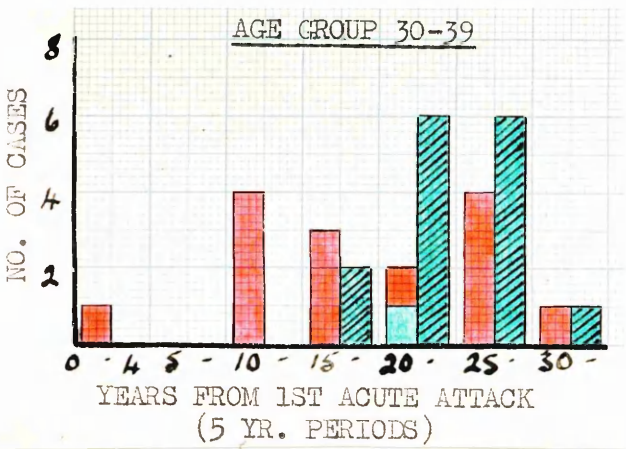






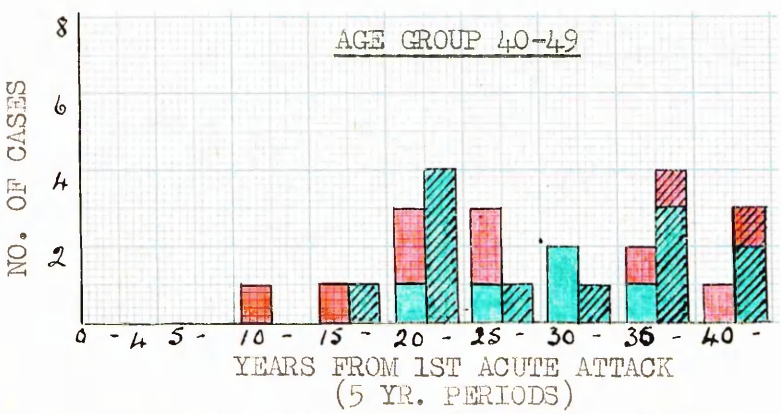



Fig. 124. Distribution of valvotomy cases with respect to the duration of symptoms and cardiac rhythm.

Fig. 125. Distribution of cases with respect to the duration of symptoms, cardiac rhythm and the presence or absence of active lesions.

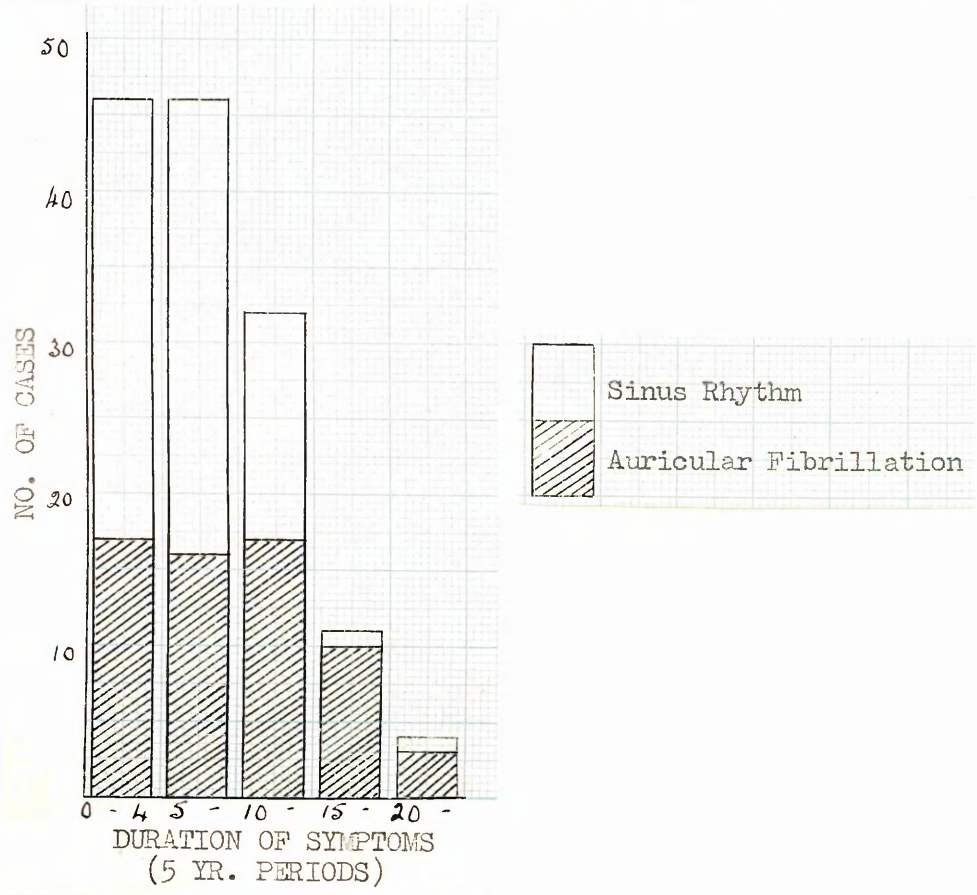



Fig. 124

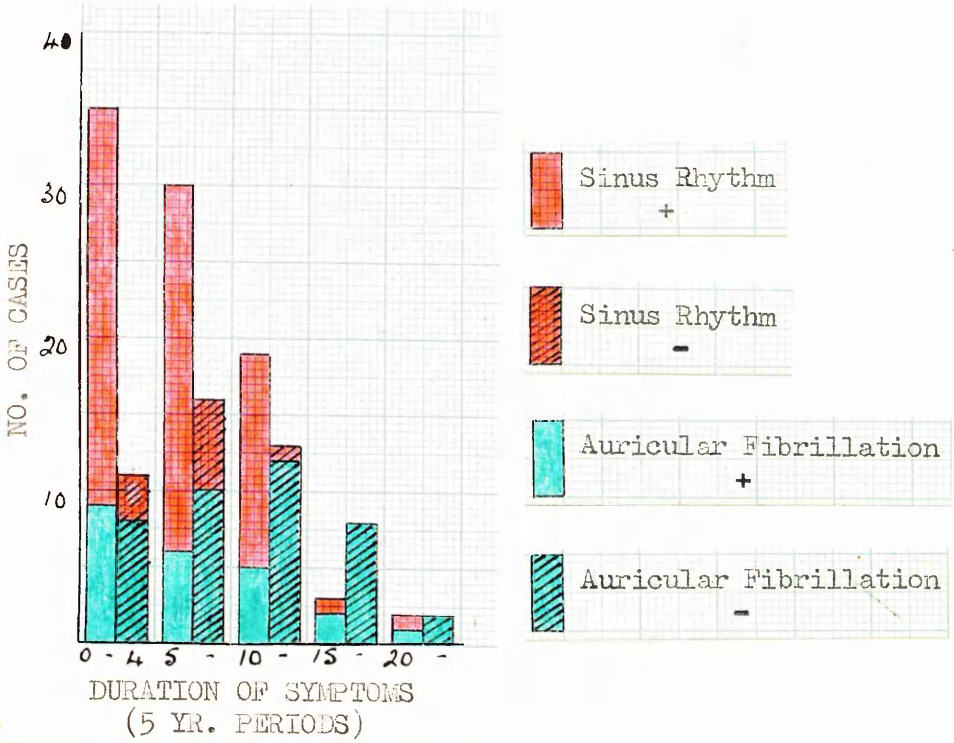
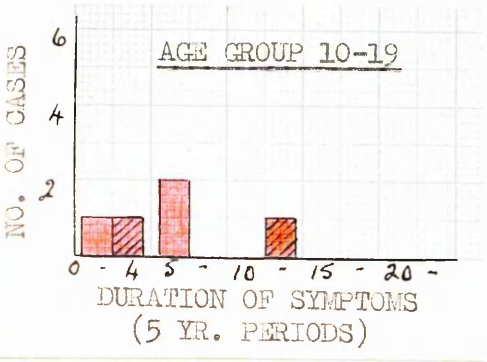
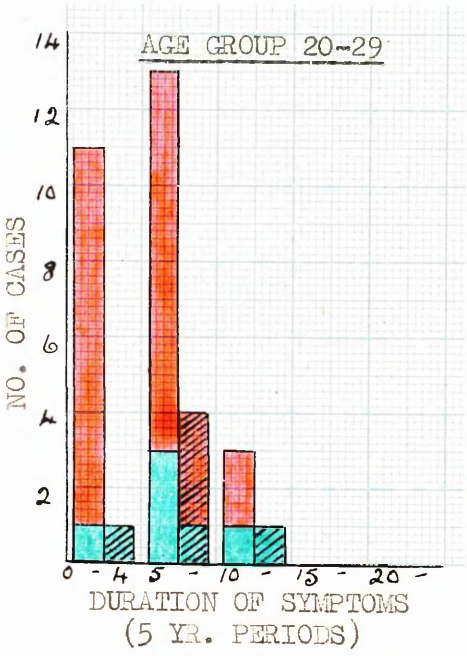
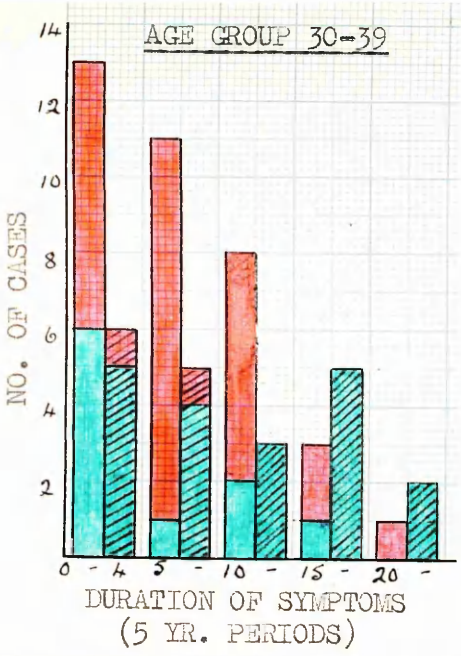


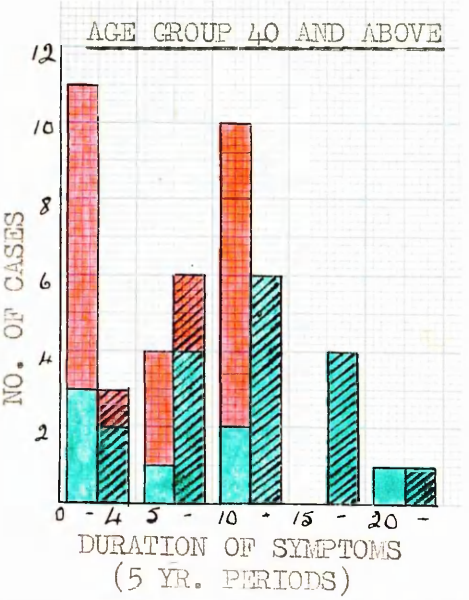

Fig. 125

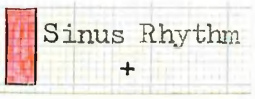
Fig. 126. Distribution of cases with respect to the duration of symptoms, cardiac rhythm, and the presence or absence of active lesions. The cases have been separated into 10 yr. age groups.

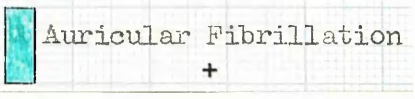


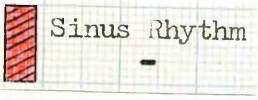



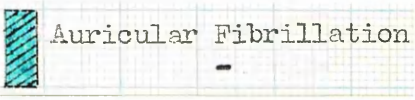
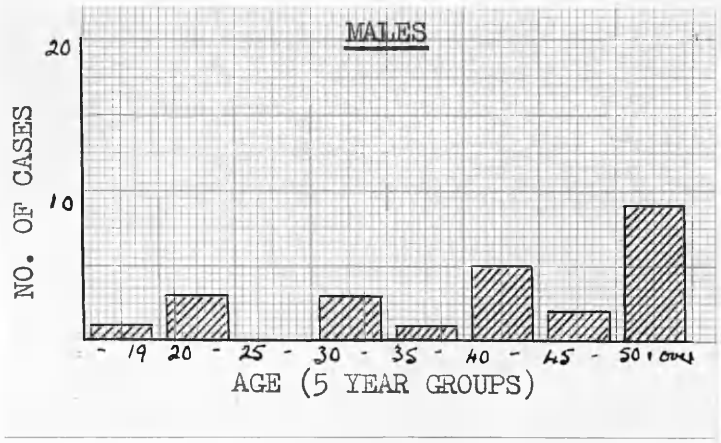
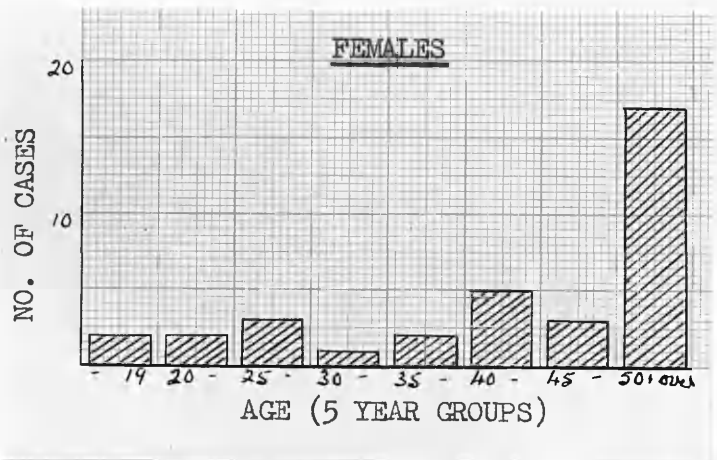



Fig. 127. Age distribution of patients in autopsy series B.



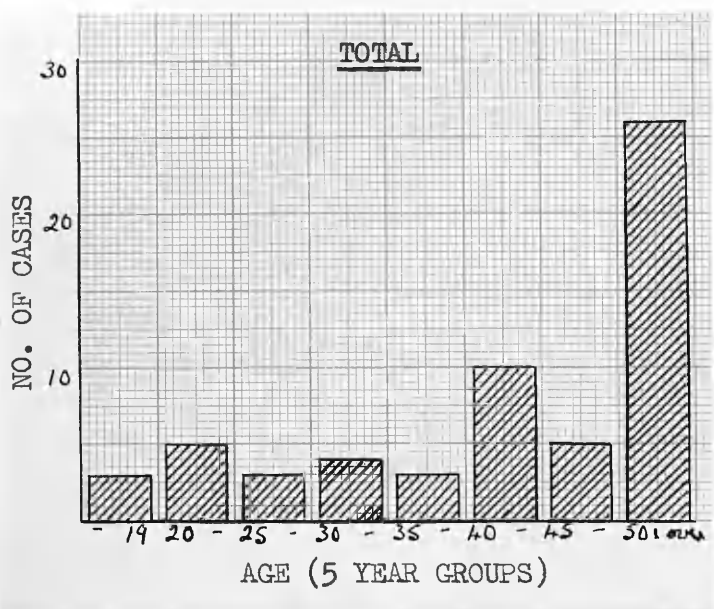
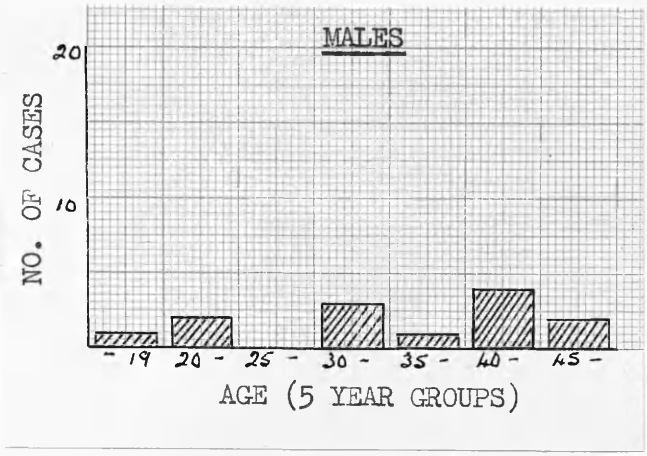
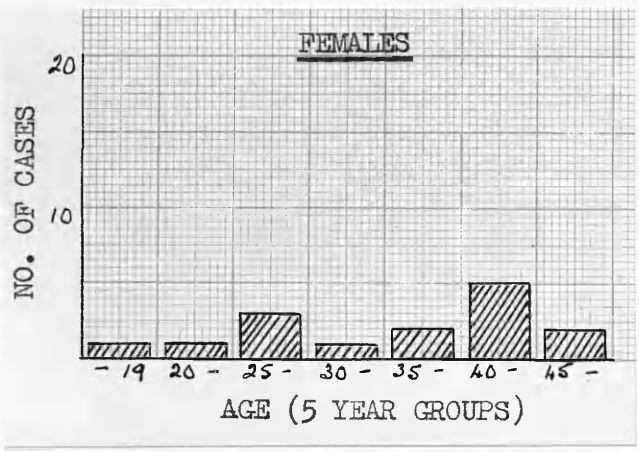



Fig. 128. Age distribution of patients in autopsy series B. used for comparison with valvotomy series.



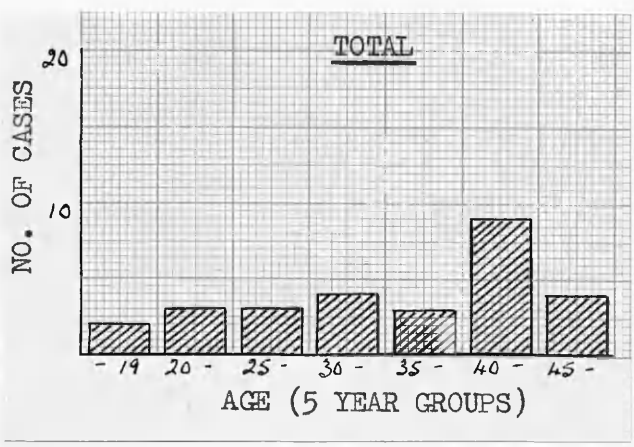



Fig. 129 Analysis of clinical data of cases in autopsy series B. comparable in age and valvular lesions to the valvotomy series

| CLINICAL FINDINGS | No of Cases | + | - |
|---|---|---|---|
| Sinus rhythm | 6 | 3 | 3 |
| Auricular fibrillation | 22 | 4 | 18 |
| Raised E.S.R. | 5 | 1 | 4 |
| W.B.C. above 10,000 | 5 | 2 | 3 |
| C.C.F. on last admission | 26 | 7 | 19 |
| History of previous attacks of C.C.F. | 21 | 4 | 17 |
| Post-mortem findings | | | |
| Mitral and aortic disease | 14 | 4 | 10 |
| Calcification of valve | 12 | 2 | 10 |
| Total no. of cases: | 28 | 7 | 21 |

Fig.130 Table showing incidence of active rheumatic lesions in left auricular appendages of mitral valvulotomy cases of other published series

| | No. of cases | No. with active lesions |
|---|---|---|
| PINNIGER (1951) | 15 | 10 |
| KUSCHNER ET AL (1952) | 11 | 4 |
| CATTO ET AL (1952) | 25 | 15 |
| SABISTON and FOLLIS (1952) | 43 | 32 |
| BIÖRCK ET AL (1952) | 18 | 8 |
| WAALER (1952) | 12 | 3 |
| JANTON ET AL (1952) | 78 | 14 |
| ENTICKNAP (1953) | 71 | 29 |
| DECKER ET AL (1953) | 183 | 83 |
| McKEOWN (1953) | 53 | 24 |
| THOMAS ET AL (1953) | 40 | 22 |
| DENST ET AL (1954) | 75 | 21 (i) |
| LUSE ET AL (1954) | 77 | 32 |
| MANCHESTER ET AL (1955) | 35 | 13 (ii) |
| TEDESCHI ET AL (1955) | 400 | 8 (iii) |
| CLARK and ANDERSON (1955) | 78 | 39 |
| CHIARI (1955) | 53 | 27 |
| ELSTER ET AL (1955) | 20 | 7 |
| GIL ET AL (1955) | 60 | 36 (iv) |

(i) Another 21 cases showed chronic non-specific myocarditis

(ii) Another 9 cases showed chronic non-specific myocarditis

(iii) Another 67 cases showed senescent Aschoff bodies

(iv) Another 9 cases showed healing lesions

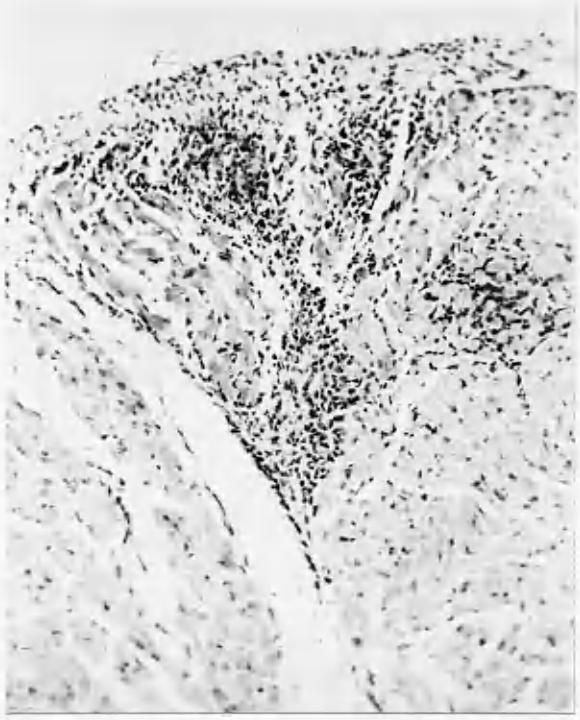


Fig. 131. Wedge-shaped lesion in the heart. Lymphocytes, polymorphs, larger monuclear cells and necrotic muscle are present.

Group I rabbit. H. and E. X 125.

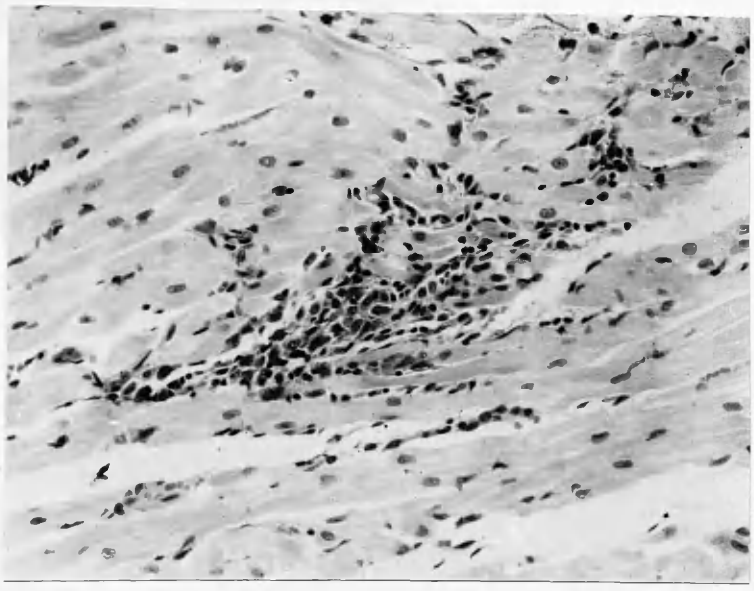


Fig. 132. Lesion in the myocardium consisting of groups of cells resembling lymphocytes.

Group II rabbit. H. and E. X 250.

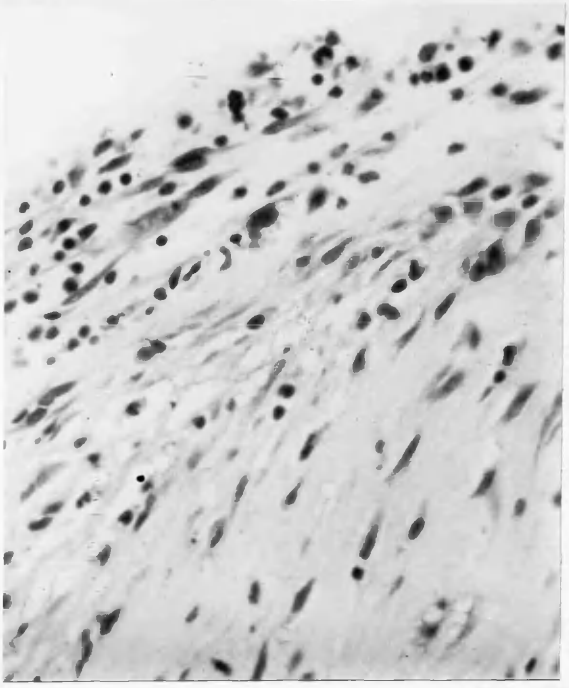


Fig. 133. Lesion in mitral cusp showing lymphocytes and large cells elongated in the long axis of the cusp.

Group II rabbit. H. and E. X 450.

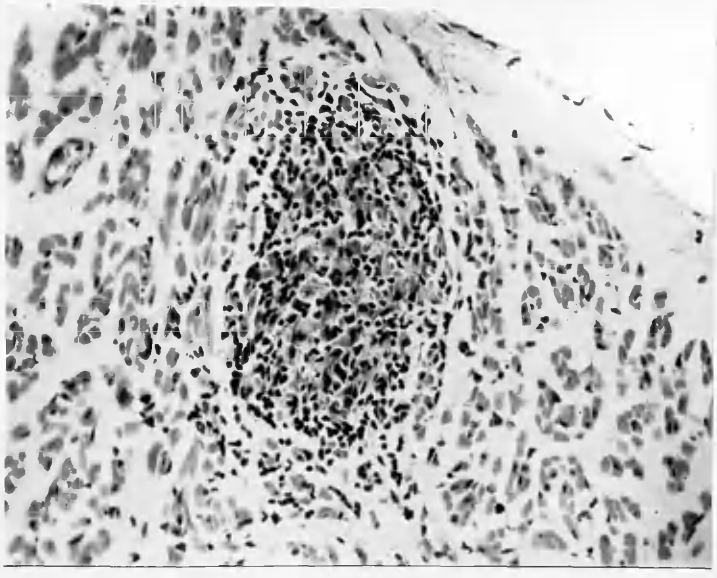


Fig. 134. Lesion in myocardium of left auricular appendage consisting of lymphocytes and altered muscle fibres.

Group III rabbit. H. and E. X 250.

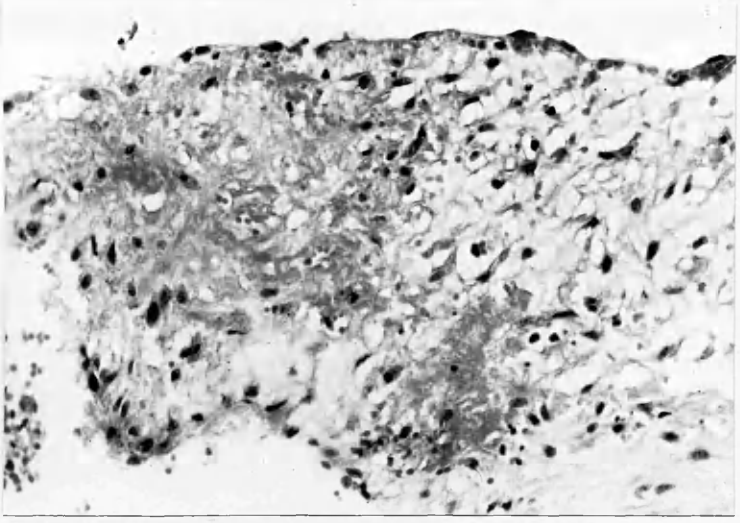


Fig. 135. Cusp of tricuspid valve showing granular eosinophilic material and oedema of the cusp.

Group IV rabbit. H. and E. X 250.

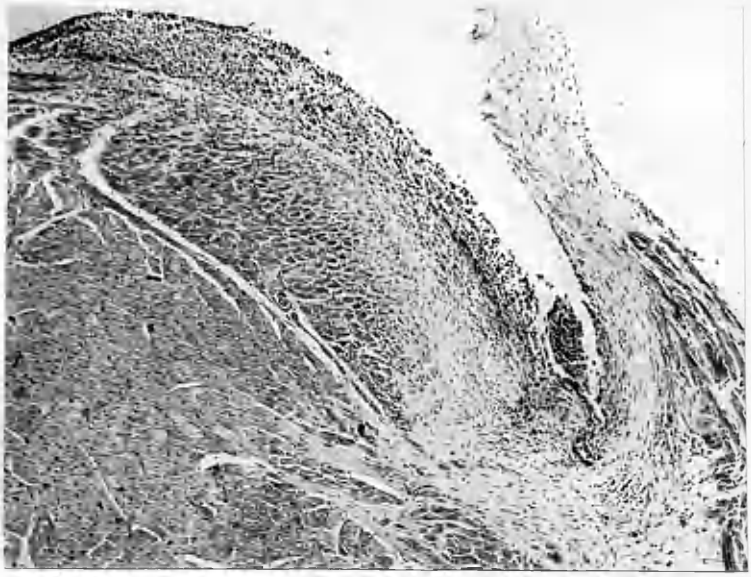


Fig. 136. Lesion of endocardium showing cellular infiltrate of large mononuclear cells which are closely packed together.

Group IV rabbit. H. and E. X 100.

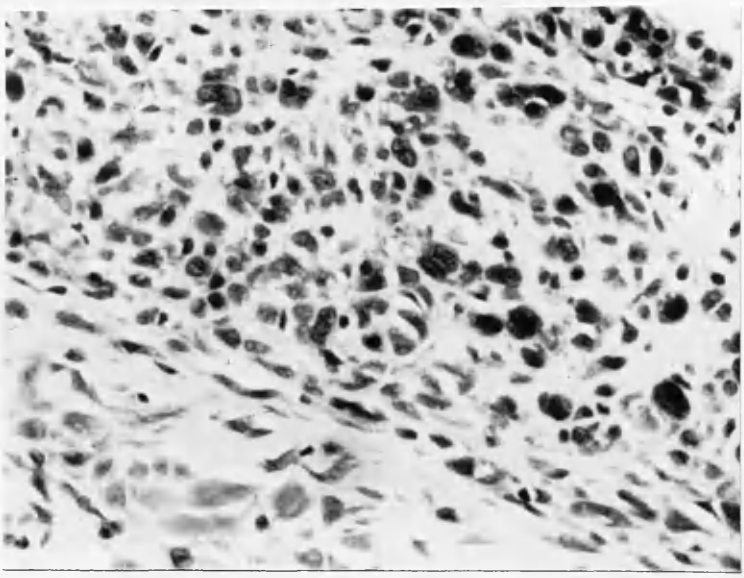


Fig. 137. Same lesion as in Fig. 136 at a higher magnification. Some of the larger mononuclear cells have a recognisable owl-eye type of nucleus.

H. and E. X 450.