STUDIES ON THE MORBID ANATOMY

of

ACUTE RHEUMATIC DISEASE,

WITH SPECIAL REFERENCE TO FOETAL ENDOCARDITIS.

To which is appended a study of the technical methods used in this work.

A Thesis for the Degree of Doctor of Medicine

of the University of Glasgow

by Alan Chalmers Lendrum,

Bachelor of Medicine.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Perhaps it would have been well if Ballonius could have then discarded this word rheumatism, for he was not to foresee that it was to be used in these days for a disease which, when called acute, may occur without any polyarthritis and without even a rise of temperature.

F. J. Poynton

in

A Short History of Some Common Diseases, 1934, London.

Studies on the Morbid Anatomy of Acute Rheumatic Disease, with special reference to Foetal Endocarditis.

Statement.

In 1932 with the encouragement of Sir Robert Muir, a beginning was made in the study of the morbid anatomy of acute rheumatic disease. At that time the work of Pappenheimer (1926,1927), Von Glahn (1926), Clawson (1926,1929), Shaw (1929), Perry (1929), and of Klinge (1933), seemed to be completing the histological picture of rheumatic disease of the heart, but the appearance of a series of papers from the late Dr. Louis Gross and his fellow workers, based on a wide survey of acute cases further enlarged the conception of these morbid changes. It seemed highly important to discover if a similar widespread involvement of the heart could be found in the cases occurring in Scotland, and to give as full attention to the finer histology as was being done at the Mount Sinai Hospital. The first obstacle was the inadequacy of the current technical methods, and thus it was decided to explore the various histological processes. This was carried out concurrently with the examination of such/

such cases of acute rheumatic disease as occurred, and the modifications put into practice as soon as they were proved.

My observations on acute rheumatic disease in children encourage me to put forward the proposal that acute rheumatic disease shows characteristic histological changes in the heart. This is done briefly in that my observations on rheumatic cases, on other diseases, and on normal hearts go to confirm the publications of Gross et al. No statistical comparison is made since my series after eight years is still far short in number of the American series. It allows me, however, to understand and utilise their work, and justifies the summation of their experience, that of their predecessors, and my own, for two purposes significant in the present thesis; these are that the case of a woman to be described below is on histological grounds indisputably rheumatic, and that the changes in the heart of her undelivered foetus do not correspond to a known rheumatic lesion.

The intra-uterine transmission of acute rheumatic disease has been accepted in medical literature. The thesis now submitted is that critical examination of the earlier publications, that study of the pathological changes occurring in the foetal endocardium, and that/

that histological examination of a case in which conditions seemed at an optimum for the occurrence of this transmission all go to show that there is as yet no satisfactory justification for the accepted belief in the intra-uterine transmission of acute rheumatic disease.

General Purpose and Plan of the Work.

The primary purpose of this work is to study the question whether acute rheumatic disease can be transmitted from an infected mother to the foetus. If the published reports of this transmission be valid, the fact is of considerable importance for our understanding of the disease. Unfortunately most of these reports are far from recent, belonging to a period when knowledge of the disease was even less exact than it is to-day. Despite this they are quoted with acceptance in textbooks. By acute rheumatic disease is meant the acute febrile and toxic illness, variously called rheumatic fever, Bouillaud's disease, Gelenkrheumatismus, characterised in juvenile cases, where the diagnosis is generally most clear cut, by carditis with the possible addition of flitting arthritis, chorea or subcutaneous nodules. To this clinical definition it is as yet impossible to add any specific biochemical or bacteriological test. It will be assumed that in acute rheumatic disease we are dealing with one single disease, although it is worth recalling the query of Stockman (1920) whether there may not be different diseases classed together in ignorance as acute rheumatism because of close clinical resemblance; his instance of the enteric diseases seems very pertinent to-day in view of the attempts to treat/

treat rheumatic disease on serological lines (Eason and Thomson, 1934).

Firstly it is proposed to relate to the problem such facts of infectivity and virulence as are known for rheumatic disease. These are based, for want of anything more exact, on clinical observations but the accumulation of critical reports, dating largely from the early work of Poynton, is now large enough and of sufficient quality to justify a review of the problem in the light of these. Secondly the histological changes of acute rheumatic disease are described, and the proposal put forward that these are now of sufficient worth to be used as the ultimate criterion of diagnosis in this disease; it may be mentioned here that the work of the morbid anatomist on this disease is almost certainly as yet incomplete. On the basis of these modern criteria the reported cases of foetal rheumatism are critically reviewed.

This is followed by a study of the pathological changes, other than developmental abnormalities, occurring in the comparatively unexplored field of the foetal endocardium. The cases studied include normal material, cases of such well known abnormalities as the blood cyst of the foetal valve, and the myxoma of the foetal valve, and also cases in which an infective factor was present and in which it thus seemed probable there would be present the condition/

condition of so-called toxic endocarditis.

Next, on the basis of the described conception of the morbid anatomy of acute rheumatic disease, there are detailed the histological findings in a pregnant woman dying undelivered in the seventh month, of acute rheumatic disease. It is an essential part of the argument that the rheumatic nature of the mother's illness be fully established: the illustrations, to which the descriptions have been closely related, furnish, in my belief, as complete proof as is to-day possible that this is acute rheumatic disease. The endocarditis found in this foetus does not correspond to any of the known early manifestations of rheumatic disease, and it is therefore compared with the other lesions observed or reported as occurring in the foetal endocardium. Thus the various groups of observations, finally converge on the question under discussion the transmissibility of acute rheumatic disease; the conclusions drawn therefrom are put forward as establishing the thesis already stated.

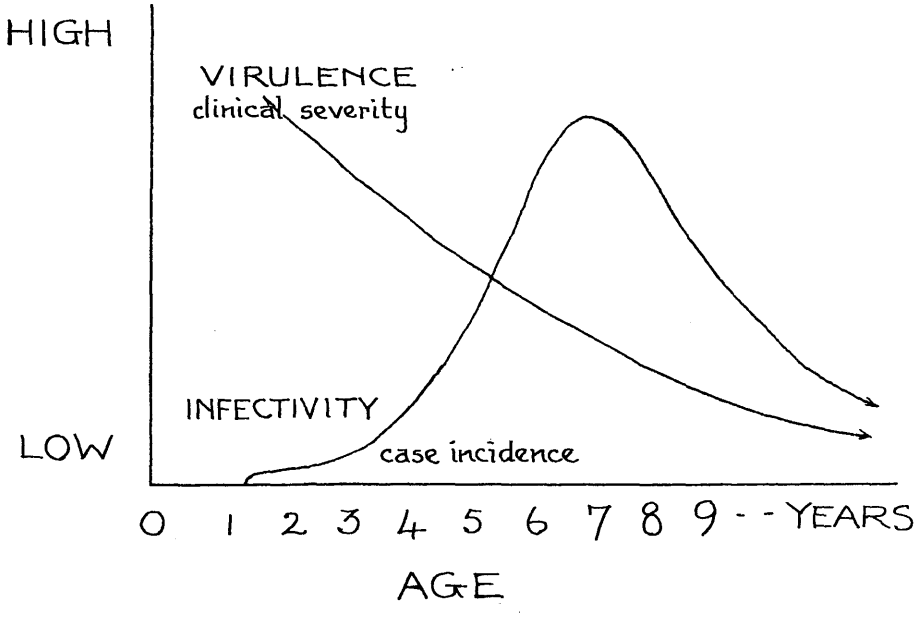
The technical researches on which so much of the histological investigation depends are detailed in an appendix; these are discussed on both practical and theoretical grounds, and suggestions are made for future advance along several lines.

The Infectivity and Virulence of Rheumatic Disease, and the Problem of the apparent Immunity of the Infant to Rheumatic Disease.

The study of the collected clinical data on acute rheumatic disease in childhood reveals that the different age groups show peculiarly different reactions. Apart from the reports to be discussed later, in which rheumatic disease has actually been diagnosed in the new born, no satisfactory proof has been found that rheumatic disease has ever been acquired or at least diagnosed during the first year of life. A few valid cases, proved on histological grounds, have been reported as starting in the second year of life, but the disease becomes common only after the age of three. The incidence then rises steadily and shows its main peak about the seventh year (Findlay 1931). In contrast with this curve of susceptibility is the relationship of the clinical severity to the age of the patient; here as is well known the disease has a higher morbidity and mortality the younger the child. Thus the infant appears to pass from a period of apparently absolute immunity to one in which there is a gradually increasing susceptibility to infection with at this first stage little or no resistance to the established disease; as childhood progresses the susceptibility becomes rapidly greater for/

some years, but resistance to the established disease is never again so low as in the earlier years.

SCHEMA OF RELATIONSHIPS OF AGE AT ONSET TO INFECTIVITY AND VIRULENCE



It will be recalled that the presumption was made above that the infecting agent is always the same; and therefore it is assumed that the odd lack of correlation between the infectivity and the virulence is due to differences in the host dependent on age. Thus if it be accepted that the infecting agent remains the same, we have for consideration in the study of a single disease, cases of foetal infection, then a complete absence of cases in the first year, a grow-/

growing number of cases in the following years characterised by a low resistance, and finally an increasing number of cases up to the age of seven accompanied, however, by a much improved resistance. If this extraordinary sequence be valid it would seem necessary to assume that the foetus absorbs something of the serological state of the mother which makes it susceptible to rheumatic infection, a something which is then lost at birth, and not present thereafter in the infant until the second or third year of life. This assumption is not altogether without parallel since Lippard and Wheeler (1936) have shown that the titre of antistreptofibrinolysin may be actually higher in the foetus than in the mother and that after birth this titre falls rapidly; while the work of Kobak and Pilot (1930) shows an extraordinary failure on the part of the newly born child to react with staphylococcal toxin, and Burky (1933) has found that newly born rabbits failed to show the usual skin reactions to staphylococcal toxin, and resisted without upset fully ten times the minimum lethal dose for the adult. Some caution, however, must be maintained in accepting, as we did above, the general belief that rheumatic disease does not occur in the first years of life. This belief is based merely on the absence of cases with the characteristic clinical picture, and on the /

the failure of the pathologist to see vegetations on the infant's heart. On the other hand, it is known, as will be discussed later, that clinically the disease in the young child may occasionally show a rapid cardiac failure unaccompanied by valvular murmurs, arthritis, or subcutaneous nodules, while the anatomical changes in the heart may be found only on microscopical examination. Thus in concluding this section on the biological behaviour of the disease, we must acknowledge a gap in our data, our ignorance as to the occurrence or otherwise of acute rheumatic disease in the first year of life. If the disease truly does not occur at this stage then the existence of cases of foetal rheumatism becomes extremely significant. Two obvious indications arise from this section, firstly, the need for microscopical examination of the heart, even if normal to the naked eye, of any infant dying of heart failure, and secondly, the necessity of a very critical investigation of the cases of foetal rheumatism.

The Morbid Anatomy of Acute Rheumatic Disease.

That there is a group of microscopical changes in the heart which taken as a whole is virtually specific for the acute stage of rheumatic disease is perhaps not yet adequately realised. The work of Chiari, Gross and Klinge in recent years has confirmed and enlarged the observations of Bulloch, Coombs, and Achoff, and despite the modern German tendency to consider the microscopical changes as characteristic merely of hyperergic inflammation, and not specifically of rheumatism, it is now reasonable to withhold the diagnosis of acute rheumatic disease from any case dying in the acute stage of a first attack which fails to show characteristic histological changes. The most complete and satisfactory studies of the micro-anatomy of the disease have come from Gross and his fellow workers. Their work covers a large number of cases and being well illustrated has been used as a standard of comparison during the present writer's study of fatal rheumatic disease as it occurs in Scotland. Although the number of cases studied in eight years in Glasgow is still short of that examined by Gross, it has already proved the general similarity of the disease as seen on different sides of the Atlantic, and in no way contradicts the diagnostic value of his criteria./

criteria. Certain aspects of the total conception of the changes in the heart seem to be slightly more obvious in my material but the division of the morbid changes into categories which I have essayed below, gives fully as much emphasis to these distinctions as they justify. The following description owes much to the publications of earlier writers but it contains nothing which I have not confirmed, and as far as possible mention is made by name of those who have in recent years drawn attention to special aspects.

There is no doubt that the histological changes are most marked in the heart and so far as is known they are most characteristic there. They are very striking in the not very common cases of death in the first attack; in young children a fatal recrudescence often gives a very comparable picture. The significance of the changes is so far from being understood that it is impossible to classify them in any rational way. A first group of changes may, however, be considered under the heading of acute generalised changes; these are oedema and cellular infiltration. The oedema is sometimes although rarely obvious to the naked eye; it tends to be most intense, as indeed are practically all the rheumatic changes, in the auriculo-ventricular region. The valves which are of course/

course closely related to this area show slight stiffening and thickening from the oedema of their substance. Microscopical study of the adjacent portion of the left ventricular myocardium reveals, especially at low magnification (x 30), a slight generalised broadening of the connective tissue stroma which is very characteristic and almost certainly due to an interstitial oedema. This change may well explain why rheumatic cardiac tissue is easier to cut on the microtome than is normal heart. The cellular infiltration, like the oedema, is also most evident in the auriculo-ventricular area, and especially in the region of the insertion of the posterior mitral cusp. This site can justifiably be considered the essential one in the histological investigation of any rheumatic case, especially if the section includes a portion of the endocardium of the left auricle. Von Glahn (1926) considers the cellular infiltrations in the left auricle to be quite as diagnostic of rheumatic disease as are MacCallum's auricular bands described below. The infiltrations are most intense at the junction of the auricular muscle and endocardium, and are composed mainly of indeterminate mononuclear cells generally of small size, with a few larger, somewhat degenerate forms, plasma cells, and a few tissue mast cells, neutrophils and eosinophils. The actual root of the mitral/

mitral valve and the papillary muscles of the left ventricle are also the occasional site of these indeterminate infiltrations.

The other changes are more focal, and the first of these can be considered as being dependent on the general type of upset described above. This is the formation of nets or spongeworks of fibrin in the oedematous tissues, a very striking feature in the auriculo-ventricular region related to the posterior mitral flap. This is almost certainly formed by precipitation from the oedema fluid, and is notable in that often there is no associated gathering of cells. At times the distribution of this fibrin suggests that it has been deposited on the lining of a lymphatic vessel. It is possible that a smaller more compact form of this change occurring in the myocardial stroma constitutes the reticular type of Aschoff body to be discussed below. It has been found that in the areas of inflammatory infiltration, special staining reveals very minute rod-like granules lying in the tissue spaces. With Gram's stain, Mallory's phosphotungstic acid haematoxylin, his trichromic method, and the author's phloxin-tartrazine method (1939) this fine dust gives the staining reaction of fibrin; this colour specificity and the focal distribution argue against its being a stain deposit or a precipitate produced by the fixative.

The remaining focal lesions can be roughly separated into two groups. The first of these includes the morbid changes related to the endothelium of the cavity of the heart, with valvular vegetation as the most obvious example; the other is of interstitial lesions of which the Aschoff body is the best known. The first group involves primarily the subendothelial tissue, and can well be considered as an intimal change; two main processes are seen here, connective tissue proliferation and subendothelial coagulation. The intimal proliferation, seen as outgrowths of the loose subendothelial tissues, is most obvious in two sites; one of these is the apex of the pocket of valves, the other is the left auricular wall. The valvular proliferation is seen as small projecting papillae of soft connective tissues; these occasionally show subendothelial coagulation in the tip (Fig.41). The proliferation of the intimal zone of the left auricle is apt to be overlooked unless the elastic tissue be specially stained. If this be done, the areas of proliferation are clearly seen as projecting cushions of soft cellular tissue lying on the cavity side of the elastica interna. The other subendothelial lesion, coagulation of a substance with, in its early stages, the staining reactions of fibrin, occurs apparently immediately under the endothelium. Where this/

this occurs in such sheltered sites as the crypts between the columnae carneae, it may be seen under a still intact endothelium (Fig.28). A more intense and more widespread example of the change is sometimes seen in the auricular wall just above the posterior mitral cusp, a site where reflux may add a localising mechanical factor; here the endothelium has apparently disappeared and there is a flat plaque of fibrin-like material forming the surface layer, with sometimes a superficial dusting of fibrin and platelets. Where the subendothelial upset is exacerbated by more definite mechanical stimuli as at the line of contact of the valves, the coagulated material tends to protrude above the general surface and gives the typical macroscopic appearance of early vegetation. Careful microscopic examination will, however, still show roots of the fibrin-like material extending downwards into the tissues and along under the endothelium, with exactly the same morphological and tinctorial appearances as in the purely subendothelial coagulations mentioned above. Rheumatic vegetation may be produced in sites other than the valves, as for example on that portion of the interventricular septum about 1/3 inch below the aortic valve. I have seen one acute case with typical vegetation at this site, and Professor Cappell has a slide of a somewhat similar lesion at practically the /

the same site. He suggests that a swollen chorda tendinea of the anterior mitral flap may provide the localising trauma. It is a striking fact that in the acute case there may be surprisingly little evidence of cellular reaction below these areas of coagulation.

The interstitial lesions are essentially lesions of the cardiac stroma, and in so far as they show any orderly distribution, tend to be in the perivascular tissues; a localisation that may mean a relationship to the lymphatics. An effort was made to confirm this suspicion by using on the heart of a child dead of acute rheumatic disease one of the recognised methods of demonstrating cardiac lymphatics, the injection of a suspension into the subepicardial tissue. "Hydrokollag" suspension was injected into the tissues of the epicardial wedge of the posterior left auriculo-ventricular region, a manoeuvre that demanded a surprisingly high initial pressure. Different areas then received injections at different pressures and the tissues were fixed and embedded by the method detailed in the appendix. Microscopically some of the injection material had obviously been forced into the muscular tissues and was seen, as had been done by Eberth and Belajeff (1866), closely applied to the true muscular substance. Elsewhere it appeared to be in vessels which were considered to be/

be lymphatic. Although the sections of the material thus treated contained numerous Aschoff bodies of fairly recent type there is no evidence of the injection material in the centre of these cellular aggregations; it is of course just possible that the lymphatic vessels were so disorganised and obstructed by the changes that none of the material could pass along them. Two forms of the early Aschoff body may be seen. In one there is firstly a very small tangle of eosinophilic fibrin-like material, around and in among which lie enlarged and later aberrant mononuclear cells. The fibrin-like material appears firstly as a coating on the fine collagenous strands of the area, which later become coated overall or are transformed into this fibrin-like material. This is the form which Gross and Ehrlich (1934 a & b) call the Reticular Type of Aschoff Body. It seems probable that there are true graduations between this form and the larger fibrin networks described above. The other early form is seen as a focal pale, almost granular swollen area of the connective tissue, much less eosinophilic and refractile than the network of the first type, around which are soon collected large mononuclear cells. During the development of this focus the cells become larger, the nuclei more aberrant and sometimes multiple. This is the form which Gross and Ehrlich call/

call "Coronal". A point which is perhaps worth emphasis is that the Aschoff body is a small focal granuloma, characterised by the presence of enlarged and altered cells of the connective tissue and adventitial series, not of muscular cells; a varying degree of myocardial degeneration may be revealed in the adjacent muscle by the use of special stains, notably Mallory's phosphotungstic acid-haematoxylin (Fig.50). The Aschoff bodies, submiliary nodules, occur most frequently in the stroma of the left ventricular myocardium in the region of the root of the posterior mitral flap. The Aschoff body itself undergoes developmental changes; these with their time relationships, are described by Gross and Ehrlich (1934 a & b). They are not discussed here, since despite their diagnostic significance they do not affect this study of the acute stage. Further comment on the cells forming the Aschoff body will be given with the description of the tissues of the rheumatic mother. Aschoff's recent statement (1939) may be noted here, "As a result of my experiences I can state emphatically that the rheumatic nodules which appear in the myocardium are specific to the Bouillaud-Gräff disease (rheumatic fever)."

The auricular lesion described by MacCallum (1924) is /

is more commonly seen in the left auricle, and is peculiarly diagnostic. This is basically the same lesion as the coronal type of Aschoff body described above, modified by the structure of the auricular endocardium. The earliest stage is seen as a collection of large mononuclear cells lying roughly in rows parallel to the endothelial surface. The lesion is best understood if sections are specially stained.

After treatment with permanganate and oxalic acid by Mallory's method, the section is rinsed very briefly in water and then stained by Weigert's solution for elastica. Thereafter it receives a brief (one third) staining with haemalum, is rinsed in spirit, and stained by the phloxin-formalin solution (Lendrum 1939) for about one hour. It is then differentiated with tartrazine as in the method quoted, rinsed in water to give a thin staining, dehydrated, cleared and mounted.

The early lesion shows the mononuclear cells lying in rows between the still apparently normal and undistorted sheets of endocardial elastica; sometimes there may be a row of ten to twenty cells lying in each cleft from outer to inner side of the "medial" coat of the endocardium. The appearances suggest very strongly that these cells are those of the part, and one can only presume that they are

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are the cells of the collagen sheets which originally lay in the clefts now occupied by the cells. In a more severe form of the lesion there is disruption of the elastic tissue; irregular nodules of collagen, stained yellow, are seen with surrounding cells which now show the aberrant, multinuclear and degenerate forms typical of The Aschoff bodies in the ventricle; small twigs of phloxinophil fibrin are present, sometimes apparently adhering to the fragments of the elastica. This more intense form is usually somewhat longitudinal, again lying parallel to the endothelium, and occupying the width of three or four of the clefts as seen in the less severe form. These auricular lesions are of frequent occurrence in acute cases, and form a striking and very characteristic change.

The final type of characteristic lesion is that involving the coronary arteries. These have not been found in the larger branches with the frequency described by some writers, but in the smaller branches, endothelial swelling and proliferation are common. Less commonly there is medial oedema, sometimes with the deposit of fibrin-like material, an appearance not far removed from polyarteritis nodosa, although there is distinctly less cellular infiltration. Small haemorrhages are far from rare in the acute case. The non-purulent pericarditis and some of/

of the muscular degeneration are possibly related to vascular upset. It has to be emphasized that this constellation of striking changes belongs to the acute stage of rheumatic disease, and is only found in the uncommon cases dying in a first attack, or occasionally in young children dying in a recrudescence.

CRITICAL REVIEW OF THE REPORTED CASES OF FOETAL RHEUMATISM.

When the investigators of a puzzling disease are so befogged that none can suggest the next step, it is a wise principle to re-assess the accepted facts, for if these be intrinsically false, or are but half truths they form no small part of the obscurity. Thus it would seem reasonable to review the reported cases of foetal rheumatism in the light of modern standards. This has apparently never been done. My own case, with a more complete examination than has been given to any in the past, by its very failure to provide any confirmation of the accepted belief adds a further demand for such a review.

Those who in the past have claimed to describe the intra-uterine transmission of acute rheumatic disease have generally based their interpretations on the clinical findings. Since then there has been a tendency to accept this transmission as proved. Loeser (1915) in an article on Foetal Endocarditis of non-rheumatic type says "Es sind wohl Fälle bekannt, wo Frauen während der Schwangerschaft an einem akuten Gelenkrheumatismus litten und die Föten derselben später einen Herzklappenfehler zeigten". (There are the well known cases of women who have suffered from acute rheumatic disease during pregnancy and of whom the /

the foetus has subsequently shown valvular damage). Swift in a Hektoen Lecture (1929) says of rheumatic fever, "It is rare in early infancy, and when it occurs at this age the mother is practically always suffering from the infection a suggestion at least that the child has inherited something - possibly a susceptibility - from her". St. Lawrence (1922) says, "Occasionally cases of congenital heart disease have been observed in which the mother had acute rheumatic fever during the period of that child's gestation". Like Swift he gives no references to the publications on these points. Maude Abbott in Osler's "Modern Medicine" (1927) says "Foetal endocarditis, which was believed by the earlier writers to play such an important part in the causation of cardiac anomalies, probably occupies a very minor role, being limited to those relatively few cases in which a rheumatic endocarditis is directly transmitted from the mother to her offspring".

In the literature, only one example has been found comparable to the writer's own case described below: v. Hansemann during a discussion (1909) described a woman who in the last month of pregnancy died of rheumatic disease with acute mitral endocarditis: the unborn child likewise showed a definite, although slight, endocarditis of the mitral. There is no mention of histological examination.

The remaining cases have been grouped; the first group contains four cases in which the mother had clinical acute rheumatic disease during the pregnancy, and where the child died within a few days of birth. Haig Ferguson's report (1893) is of a mother who had a severe attack of rheumatism in the early part of her pregnancy with continuation of a subacute condition. The well developed child was said to have been born with painful swollen joints; these later became tender and the general condition declined rapidly. Weakness and emaciation were extreme by the tenth day, when death occurred. The pericardial sac contained half an ounce of serous fluid in which flaky shreds were floating; the remainder of the heart seemed normal. The right knee was full of serous effusion. There is no mention of histological examination of the heart.

Strümpnell's case (1893) is mentioned rather briefly in his textbook. The mother at the time of delivery was suffering from a severe attack of acute articular rheumatism; the child died when a few days old and was found to have multiple purulent arthritis. There is no mention of the heart.

Abrahams (1896, Case I) reports a rather similar case in which the mother had acute rheumatism two weeks before delivery of a full time child. From birth the child /

child appeared ill; it was feverish and had red swollen, tender joints. By the twelfth day the temperature was 103.5°F., the heart's action tumultuous and irregular, and the left knee oedematous and purulent. On incision a thin pus escaped. The child failed rapidly and died about the twentieth day. There is no mention of post-mortem examination.

Poynton's case (1909) died on the second day; the mitral valve showed exuberant vegetations from which diplococci were obtained. There is no note of histological examination of the child's heart.

The second group is where a clinical cardiac abnormality has been noted in the newly born child of a rheumatic mother; this has been reported four times. Abrahams (1896) reports two cases (Nos. 2 & 3) in which a clinical diagnosis was made of cardiac damage in the infant. The first of these was a woman attacked in the ninth month of pregnancy by acute articular rheumatism, complicated by a large bed sore. She had high temperature and marked abnormality of the heart. Death occurred on the twenty-eighth day of illness, with a temperature of 109°F. Post-mortem examination showed acute endocarditis of aortic and mitral valves, purulent fluid in some of the joints, and a normal uterus. The child born on the twenty-fifth day of the mother's illness /

illness showed tenderness and stiffness of the knee joints within two hours of birth, a temperature ranging to 103.3°F. on the fifth day, and an irregular cardiac action with a distinct soft blowing mitral systolic murmur. Under salicylate therapy it made a complete recovery in six weeks, but died at six months of gastro-enteritis. His third case was a woman with an attack of subacute articular rheumatism in the seventh month, and of violent chorea in the middle of the ninth month. Labour came on within twenty-four hours, and on the expulsion of the placenta the chorea stopped abruptly. The child was noted as showing cyanosis on crying and as having an aortic insufficiency. There is no subsequent history of this family.

The case described by Kissane and Koons (1933) was the child of a mother suffering from acute rheumatic disease; it was born with red, swollen, painful joints, and showed cardiac murmurs when examined thirty minutes after birth. By six months there were no manifestations of active rheumatic disease. He continued to be dyspnoeic and when eight years old had his first onset of obvious cardiac failure. Death occurred at the age of ten; the heart showed changes typical of long standing, but not extinct, rheumatic disease. Aschoff bodies were seen in the thickened fibrous mitral valves.

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The last of this group where a clinical diagnosis of abnormal cardiac function was made immediately after birth, is the report by Glanzmann (1935). The mother had during pregnancy an endocarditis stated to be probably rheumatic in origin; the somewhat premature child showed both apical and mitral murmurs, and a marked enlargement of the heart to the left. This case is inadequately reported.

The third group is of those where the mother seemed to have rheumatic fever, and the newly born child showed clinical evidence of non-purulent arthritis but recovered on treatment. Pocock (1882) described an eighteen year old primipara, attacked by acute rheumatism in her eighth month of pregnancy; when seen, two days after the onset, she had multiple pains and a temperature of 106.5°F. The child was born the following day and showed fever and arthritis within twelve hours. Both patients were treated with salicylates. The child's temperature rose to 104°F. in the first day, but was normal by the eighth day and stayed so; no cardiac damage was detected. The mother was ill for five weeks and was left with definite valvular damage.

A rather similar picture is described by Schaefer (1886) This was a multipara of thirty-five years, attacked by acute rheumatism in the last days of pregnancy; she had multiple pains but the highest recorded temperature was here only/

only 102.9°F. The child was born on the fifth day of the illness and appeared to be normal until the third day of life, when a febrile flitting arthritis appeared; three days later the temperature reached 103.1°F. Salicylates disagreed with the child and could only be tolerated in small doses by the mother. In both, the illness lasted nearly two months but neither is recorded as showing any complicating or residual cardiac damage.

Guthrie (1888) reports the onset of vague abdominal upset and febrile polyarthritis in an eighteen year old primipara three days after delivery of a healthy child. On the tenth day the child started a febrile flitting arthritis. Both were treated with salicylates; the mother obtained rapid relief and was soon convalescent, but the child was upset and apparently not benefiting. Under alkaline therapy it improved quickly and was not revisited after the eleventh day of its illness. No mention is made of the cardiac condition in either.

The last group is included for the sake of comparison and consists of some cases where the mother showed severe rheumatic fever during pregnancy, but where the child gave no evidence of a comparable disease. Brochin (1876), who makes no mention of illness in the child, emphasizes the severity and persistence of the disease when occurring in pregnancy. Squire (1886) describes a severe case with a/

a marked amelioration of the arthritic pains immediately after delivery. No permanent heart damage was noted, and the child apart from ophthalmitis was apparently healthy. Langwill's case (1900) was a severe but not fatal rheumatic hyperpyrexia in the fourth month of pregnancy. No cardiac damage was noted in the mother. The child was born at the seventh month, and careful examination failed to reveal any affection of the joints, endocardium or pericardium. It died suddenly overnight but autopsy was not permitted. Hefferman (1922) reports the rapid onset in a twenty-five year old primipara, of flitting arthritis, fever, and myocardial failure following a soaking to the skin two days before; the clinical story is almost identical with the present writer's own case. As her condition was obviously deteriorating, labour was induced four weeks after the onset; after delivery there was a rapid change for the better although the salicylic and antiseptic therapy had not been changed. The eight and a half month child is noted as being perfectly healthy.

Critical Comment on Published Cases.

The unique case described by v. Hansemann suggests very strongly, in virtue of the absolute rarity of macroscopic foetal endocarditis, that the cause of the changes was active in both mother and foetus: unfortunately there is no histological confirmation of the rheumatic nature of the disease in either.

Of the first group as described in the review, Haig Ferguson's case is no less acceptable than v. Hansemann's since the normal appearance of the valves is, in the infant at least, still compatible with a diagnosis of rheumatic carditis. Thus in a case reported by Rothman and Leonard (1928), a child of five died of a rapid myocardial failure with no other clinical evidence of rheumatic disease than vague and transient pains in the knees and wrists; at post-mortem examination there was no obvious pericarditis, the mitral valve appeared merely a little thickened, and showed only one small point of hyaline vegetation, yet microscopically there was abundant evidence of carditis in the numerous myocardial Aschoff bodies. Likewise McIntosh and Wood (1935) reporting one of their known rheumatic cases dead of pneumonia at the age of three state that there was no evidence to the naked eye of vegetation although/

although microscopically the myocardium showed large numbers of Aschoff bodies. And Swift (1925) describes two cases dying of acute rheumatic disease, in which although no vegetations were visible to the naked eye yet the microscopic examination showed typical histological changes with evidences of very early verruca formation.

In the cases described by Strümpnell and by Abrahams, the finding of purulent arthritis in the infant suggests that the mother's illness was possibly not true rheumatic disease but rather a low-grade pyogenic infection. The similarity of viridans streptococcal infection to acute rheumatic disease is discussed below in the comment on the cases of Guthrie and of Schaefer.

Poynton's case may be one of the rare and not generally accepted cases of ulcerative rheumatic endocarditis; until this type of case receives further confirmation it is more reasonable to consider his case as one of bacterial endocarditis. Of these first cases it can be said that v. Hansemann's and Haig Ferguson's are possible cases of transmission but the others by their own data can suggest diseases other than rheumatic. In the absence of supporting histological evidence, none at least are proof of congenital rheumatism.

The second group is of those reports where the child of a rheumatic mother showed cardiac abnormality immediately/

immediately after birth. In Abrahams' case (his second case) the mother almost certainly had rheumatic disease, although this was not confirmed histologically. The argument that the child's upset was due to rheumatism is based on the clinical association of pyrexia, arthritis, and cardiac abnormality. In view of the large bed sore which complicated the mother's illness the question has also to be considered whether the abnormalities in the infant could indeed be septic in origin. A presumptive diagnosis remains acceptable only in the continued absence of equally valid possibilities, and later work has shown that a pyogenic infection in the mother can be the explanation of the appearance in the child of one or more of the triad, fever, arthritis and cardiac abnormality. From the cases collected by Geiger (1926) and by Farber and Hubbard (1933) it seems certain that pyogenic infection in the mother is a cause of endomyocarditis in the foetus, and as will be discussed below, it is known as a cause of febrile arthritis in the infant.

The other infant reported by Abrahams showed aortic incompetence and cyanosis on effort, a clinical picture which coupled with an entire absence of subsequent history does not of itself justify a diagnosis of rheumatic disease, despite the apparent rheumatic nature of the mother's /

mother's illness.

The history described by Kissane and Koons certainly suggests that the child was born with rheumatic disease but if so, it would seem that the transmitted infection was surprisingly mild as the child lived to the age of ten. Another difficulty in accepting this case as one of proved inherited rheumatic disease lies in the fact that the mother had a further and fatal attack of acute rheumatic disease two years after the birth, and from the investigations of Paul and Salinger (1931, see especially the family described by them, 4 - Ds) it is apparently possible for a young child to be infected from the mother without showing any characteristic clinical upset at the time, and yet later show obvious cardiac damage. Glanzmann does not mention arthritis in his case and it seems too briefly reported to be more than suggestive.

The third group is of the three cases where the child showed arthritis but recovered on treatment. These cases suffer from premature publication since milder degrees of the cardiac damage which would later tend to confirm the diagnosis may be easily missed; Guthrie does not even mention the infant's heart.

The studies of Poynton (1908) and of McIntosh and Wood (1935), which are better supported by extended clinical/

clinical observation and microscopic evidence than the cases under discussion, show how high is the incidence of cardiac damage in the young child suffering from rheumatic disease. Of the twenty-four cases reported by McIntosh and Wood as starting before three years of age, twenty-three showed cardiac involvement and eleven died; while in Poynton's series of fifty-two cases starting before five, there was cardiac involvement in forty-three, eight died, and five others had a hopeless prognosis. Twelve of his cases started before three and of these, five showed definite cardiac disease before three, five others were noted later, and only two escaped (both were cases of chorea). There is no mention of an immediate death rate in this group and four at least, lived to be six years of age. There is thus considerable difference in the fatality rate of the two series, but the incidence of definite cardiac damage is fairly comparable, and on summing the cases it is found that of thirty-six children infected by rheumatic disease before the age of three, thirty-three showed significant cardiac involvement. From these figures it seems unjustifiable to report arthritis in an infant as rheumatic unless there be at least the confirmatory evidence of cardiac damage. A further reason for doubting the cases of the third group as proof of transmission, lies in the difficulty of making

making a complete clinical diagnosis in cases of infantile arthritis. The mother described by Pocock went on to show valvular disease which seems an acceptable corroboration that she really had rheumatic disease, but none of the three infants gives stronger evidence of the rheumatic nature of the disease than a clinical arthritis. This in itself is uncertain ground and Senator (1877) goes so far as to say, "we occasionally come across instances, especially in the older authors of 'acute articular rheumatism' occurring in infants just after birth, or still at the breast; the majority of these records are probably to be attributed to errors of diagnosis, pyaemia or syphilitic diseases of the bone or joints having been mistaken for rheumarthritis". Denzer (1924) although he considers the view to be too extreme, quotes Friedjung as saying, "cases of rheumatic arthritis published as occurring in infancy in association with endocarditis.....are always dependent on gonorrhoea, syphilis or pyaemia, not on rheumatism". While Miller (1899) in a review of the cases published as acute articular rheumatism in infants, quotes Marfan as doubting the accuracy of the earlier reports, on the grounds of confusion with scurvy, the pyogenic arthritides of sucklings, or "the recently recognized gonorrhoeal infection". Hellmann (1926) has shown how cryptic this last infection may be in the newly born by/

by reporting a case of purulent gonococcal arthritis in an infant of three weeks in whom careful search failed to reveal gonococcal inflammation or organisms in nose, mouth, conjunctiva, urethra or rectum. It is worth recalling Barlow's (1883) significant statement, "For there are in children many affections of joints, and of structures round joints, which do not suppurate, and yet are not rheumatic." Thus even if it be expedient to treat these cases as possibly rheumatic, it is surely not justifiable to publish them as such merely on the basis of a clinical arthritis.

A further criticism of these reports can be based on their peculiar clinical similarity to that described by Richdorf and Griffith (1926). This was a primipara of eighteen, with an upper respiratory infection four weeks before the birth of her child. A fortnight later she had headache, chill and nightsweats, and five days before delivery, began a flitting polyarthritis with fever ranging to 102.8°F. The temperature settled ten days after delivery, and she was discharged ten days later with only slight pain in the affected joints. The heart had shown merely a soft apical systolic murmur. The child seemed normal till the sixth day when it also began to have a flitting arthritis with fever; on the thirteenth day there was fluctuation in the right knee joint and culture from the/

the stringy mucoid fluid gave streptococcus viridans in pure culture. Culture of the mother's blood, taken on the same day, showed an identical organism. The infant was discharged on the fifty-sixth day in good condition apart from slight flexion of the knee; its heart was normal throughout. Although the authors in their subtitle call the mother's illness acute rheumatic fever, they make no effort in their paper to show why her illness should not be accepted as a streptococcal infection. The facts they present seem to indicate this diagnosis.

In comparison with this case Schaefer's and Guthrie's cases both show an apparently comparable flitting arthritis in the mother, occurring within a few days of parturition. Also in all three cases the child appeared normal for the first day or two, and then showed a flitting arthritis; in none is there any mention of cardiac disease.

The similarity of these three reports might be used as an argument that acute rheumatism is a mild form of viridans streptococcal infection, but it seems more reasonable to believe that the two reported as rheumatic were not really so, but merely mild streptococcal infections, as the third appears proved to be. Whatever be the explanation of these three cases which have been thus grouped on their clinical similarity, they constitute an interesting sidelight on low/

low-grade streptococcal infection. It is perhaps of some significance that Rothschild and Thalhimer (1914) noted the occurrence of arthritis in half of 42 rabbits receiving intravenous injection of streptococcus viridans, and that the arthritis was typically evanescent; only one went to pus formation.

There are some points of value to be drawn from the next group, those in which the mother's illness was severe but the child showed no abnormality. Firstly it should be realised that acute rheumatic disease occurring in pregnancy can be peculiarly severe and rapid, with serious effect on the myocardium even though the patient be in an age group considered comparatively safe in this respect. Secondly it would seem from the reports of Squire, Abrahams (third case), and Heffernan that delivery, whether spontaneous or induced, was to the benefit of the mother. Thirdly the child in the cases of Squire, Langwill, and Heffernan failed to reveal any evidence of disease in heart or joints, despite the marked severity of the mother's infection.

Thus, of the cases reported as intra-uterine rheumatic infection, none has been adequately examined and most could be otherwise explained. In the past, arthritis was considered the prime diagnostic pillar until it was realised that rheumatic disease in younger patients merely licks the/

the joints while biting the heart (Lasegue), and further study actually showed that arthritis in infants was more commonly due to diseases other than rheumatic. The focus of interest was next centred on endocarditis and pericarditis but again it came to be realised that in infants the cause of these conditions was more often some other disease (White 1926, Geiger 1926). Cardiac failure was then considered more characteristic of rheumatic disease in infants than murmurs or friction (McIntosh and Wood, 1935), and since this could proceed so quickly and so secretly it was a short step to demanding the confirmation of post-mortem examination. There, although the frankly ulcerative type of endocarditis was easily recognised, at the other end of the scale cases were seen with pericarditis, (said to be rheumatic, White 1926, page 543), but no vegetations, while still others showed no naked eye evidence of rheumatic disease and were unmasked only on microscopic examination (Swift, 1925, Cases 1 and 4, McIntosh and Wood, 1935, Case 2).

The present position is thus, that in infants the diagnosis of rheumatic disease demands microscopic examination of the heart, as therefore does death of an infant from unknown cause. Failing this, it seems that an appreciable number of rheumatic cases in infants will be completely missed, and it is just possible that this may be the whole /

whole explanation of the generally recorded rarity in infancy. There still remains the theoretical possibility, to be mentioned again below, that acute rheumatic disease, if it be lethal in infancy may yet fail to elicit the characteristic histological response in the stroma of the heart, either through serological differences in the host, or indeed through lack of time. The youngest child in which typical Aschoff bodies have been reported, so far as can be ascertained, is one of sixteen and a half months reported by White (1926, Case II). Fischer (1934) in his report on a child of thirteen months, although making no mention in the text of myocardial Aschoff bodies, illustrates a cellular lesion in a papillary muscle which appears to be a characteristic rheumatic submiliary nodule. Thus in a study of the cases of reported foetal rheumatism and incidentally of acute rheumatic disease in infancy, two important facts stand out. One is that no histological confirmation has been found, in the literature, of rheumatic disease acquired in the first months of life, a state of affairs, as mentioned earlier, that demands the attention of the morbid anatomist. The other fact is that no cases of intra-uterine rheumatic infection have been completely established.

Other Lesions of the Foetal Endocardium.

Since as will be shown later, a distinct although not characteristically rheumatic lesion has been found in the valves of an unborn child (Foetus I) from a woman dead of acute rheumatic disease, it is important to find if this be an example of a known foetal lesion and has occurred in association with rheumatic disease merely through coincidence. Foetal endocarditis, so called, has been reported not infrequently, the term covering a group of cases ranging from fibrous thickening of the mural endocardium unaccompanied by valvular changes, to sclerosis and other deformity of the valvular orifices. In a number the foetal disease has been related by the describer to some infection in the mother during the later part of pregnancy (Farber and Hubbard 1933, Abraham 1937, Püschel 1938). The cases reported as foetal endocarditis form a relatively homogeneous group, the majority being really forms of endomyocarditis (Bartak 1935); this is something quite different from any of the known lesions in the heart of the adult. Another distinguishing feature is the frequency of calcification in the fibrotic area (Jacobsthal 1900; Mönckeberg 1907; Suwalischin 1908; Farber and Hubbard 1933, case I; Stohr 1934; Abraham 1937), and in this relation it is of interest that Dr. J.S. Faulds of Carlisle showed, at the July meeting of the Pathological/

Pathological Society 1938, a case of chronic endomyocarditis with calcification in the child of a rheumatic mother. Steinbiss (1923) in a study of congenital rhabdomyoma of the heart has shown that these tumour-like abnormalities are frequently the site of retrogressive changes (vacuolation, calcification) and a replacement fibrosis. It is just possible that some of the cases of foetal endomyocarditis with calcification, and possibly some of the earlier of the other reported cases of calcification in the hearts of infants (Fischer 1911; Farber and Hubbard 1933 case 2 and additional case; Donat 1939; Diamond 1932; Abbott 1927) may have belonged to the rhabdomyoma group since the associated abnormalities which characterise this condition could well be missed if the attention were unduly focussed on the heart. Other conditions which, as Ariel (1930) and Bartak (1935) point out, may have led to erroneous description as Foetal Endocarditis are the haematomata of the foetal valve, (Levinson and Learner 1932, Harper and Dow 1936) and the proliferative condition called myxoma of the foetal valve, an abnormality occasionally seen also in the adult heart. Through the kindness of Dr. H.L. Sheehan of the Royal Maternity Hospital, Glasgow, I have been able to examine thoroughly two cases with haematomata. With careful histological technique there seems no reason why this condition/

condition should be confounded with any other. In the examination of an infant's heart (Infant I to be described below), small examples of haematomata were found microscopically although not noticed with the naked eye; in the serial sections on both sides of one of these blood cysts phagocytes containing blood pigment were seen in the tissues of the valve. Thus if the valve had not been examined serially it would have been difficult to explain these phagocytes. Two points arise from this finding, one that the frequency of haematomata is not justifiably measured on naked eye observation, the other that one must accept with caution the suggestion that haemosiderin pigment in the foetal valve is confirmatory of an earlier inflammation as Willer and Beck (1932) and Abraham (1937) tend to do.

The condition of myxoma of the valve (Review by Jaleski, 1934) has in the past, as Bartak (1935) noted, been reported as a foetal endocarditis, probably because there sometimes is an associated fibrous thickening of the ventricular endocardium. Dr. Sheehan kindly gave me an infant's heart with this change in the tricuspid valve, but with no evidence of mural endocardial fibrosis, while Professor J.S. Young and Dr. Lumsden of Aberdeen were good enough to give me the heart of a three day old infant in which the pulmonic valve showed a very irregular thickening of this type and in which the/

the endocardium of the adjacent ventricle was distinctly fibrosed. Microscopical examination of the affected valves showed a condition which can best be described as the presence of an excessive amount of the loose reticulo-cellular tissue that normally forms the spongy layer of a valve, unaccompanied by any evidence of excessive fibrosis or other sign of previous inflammation. The thickened area of endocardium over the muscle in the Aberdeen case is seen as a distinct fibrous layer, sharply demarcated from the underlying muscle, presenting a perfectly quiescent appearance with no evidence of previous inflammation. It is possible that this thickening is to be explained by an upset of the normal currents and hydrostatic pressures brought about by this overgrowth of the valve; some of the German writers have described the change as "funktionell-Elastische Wandendokardfibrose" (Straus 1930). Bearing on this, a case recently seen at postmortem (Western Infirmary A4469) is somewhat suggestive; this was a woman of thirty-nine with a history of dyspnoea on exertion since the age of five. The postmortem examination which was performed by Professor Shaw Dunn showed no evidence of rheumatic disease but there was a patent interventricular foramen and on the anterior wall of the right ventricle, one cm. below the pulmonic valve, a distinct patch of fibrosis of the endocardium with/

with tiny vegetations on its central part. There seemed little doubt that this patch was where the blood coming through the foramen impinged on the ventricular endocardium. Professor Shaw Dunn kindly allowed me to examine this area histologically. It shows a thick layer of dense connective tissue, sharply demarcated from the underlying muscle, with on its surface scattered thin plaques of fibrin. This fibrous layer is very comparable to, although much grosser than the layer in the foetal case; it also resembles the type of endocardial fibrosis described in some of the cases of so-called foetal endocarditis (Stiassny 1901, Ruge 1905, Kockel 1908, Fischer 1911, Loeser 1915, von Zalka 1924, Lahm 1928, Straus 1930, Bellet and Gouley 1932, and Stohr 1934). These findings go to confirm the view of Bartak (1935) that cases of this type even when the ventricular endocardium is fibrosed can be considered as due primarily to abnormalities of growth rather than to foetal inflammation. The two cases of myxoma examined conform adequately with the condition described in the past as myxoma, and thus allow one to state that this type of upset of the foetal endocardium in no way resembles the changes seen in foetus I.

Perhaps the most striking fact arising from a survey of the literature in this subject of non-rheumatic foetal endomyocarditis is that in the 26 cases collected from the/

the literature where the age of the child precludes the possibility of postnatal infection and in which the tissues have been examined microscopically (Jacobsthal 1900; Stiassny 1901; Ruge 1905; Mönckeberg 1907; Kockel 1908; Suwalischin 1908; Nagel 1908; Ganeff 1910; Loeser 1915; Ipsen 1912 and 1915; Von Zalka 1924; Lahm 1927; Straus 1930; Ariel 1930; Dissmann 1932; Bellet and Gouley 1932; Willer and Beck 1932; Farber and Hubbard 1933, cases 1 and 4; Stohr 1934; Bartak 1935, cases 1 and 2; Abraham 1937; Püschel 1938), only two cases showed acute inflammatory changes. Von Zalka describes fresh endocarditic deposit on a congenitally deformed heart of a two day old child. Geneff is the only one to describe an acute inflammatory lesion in a foetal heart not the seat of growth deformity. This was reported in a thesis which is unfortunately not available to me; Loeser, however, quotes Ganeff as saying that the endocardium shows "stellenweise noch Herde frischen Entzündung". It would appear that later German writers have ignored or refused to accept Ganeff's statement, as Ribbert in 1924, Ariel in 1930 and Willer and Beck 1932 all state that a fresh endocarditis in the foetus or newborn child has never been reported, and Ariel agrees with Ribbert that all the cases reported have been of a burnt out process. From the descriptions given of the microscopic changes in foetal endomyocarditis, it is difficult to envisage the se-/

sequence of previous changes, since the process appears to be something quite different from any known to occur in postnatal life; some of the cases might be the foetal analogue of acute interstitial myocarditis (so-called Fiedler's myocarditis, Taussig and Oppenheimer 1936) but others are obviously something quite different. On general principles and the evidence available there seems no reason for suggesting that the lesion found in Foetus I is the early stage of the condition described as foetal endomyocarditis

The somewhat indeterminate type of endocarditis first described by Libman and Sacks, and since then been shown to occur in association with certain bizarre groups of clinical manifestations has not been described in the infant. A case of this type in an adult has been examined, resembling closely the subgroup described by Baehr et al (1935) in which vascular lesions in the viscera, and endocarditis are associated with lupus erythematosus. Although this case has not yet been fully studied, it can be stated that the tiny valvular lesions, not seen by the naked eye, are suggestive of the rheumatic type of lesion but in no way resemble the lesions seen in Foetus I.

The only known condition to which the lesion in Foetus I appears to bear any resemblance is the toxic endocarditis first described by Baldassari (1909). This change has been/

been further studied by Czirer (1913); his material consisted of the apparently normal semilunar and mitral valves from 27 cases of young people dead of infective disease. On microscopical examination, 21 of these showed marked upset, and of his 9 cases aged 2 or under, all showed valvular abnormality. The changes are of two main types, one an oedema associated with both irregularity of the elastica and hyaline changes in the stroma, the other a cellular infiltration and proliferation. The former of these changes is difficult to assess as will be understood by any who have studied the differing reaction of cardiac valves to the usual fixing fluids and technical methods. The infiltrative and proliferative abnormality, which he records in 6 out of the 9 cases aged 2 or under, should be capable of fairly just estimation. He mentions plasma cells among the infiltrating lymphocytes but no polymorphs. It is unfortunate that his illustrations do not confirm or even support his descriptions. De Vecchi (1931) studied the valves in children and infants dying of infective disease, and of the 23 cases up to the age of 20 months only 2 failed to show microscopic lesions; of the 6 cases up to 4 months, one is not detailed but the remaining 5 showed valvular changes, noted as very grave in 4. He says "Rather exceptionally, there was present a scanty number of /

of polymorphonuclear leucocytes; these occurred only in very severe and relatively advanced cases. Early thrombotic phenomena overlying the valvular lesions were rarely demonstrable". His illustrations are suggestive in part but poor. Capelli (1933) studied 62 foetal hearts and believes that he has found microscopic changes in the valves of proliferative and degenerative type; these he relates to what he describes as toxic or toxinic factors. His illustrations are not informative.

The descriptions given by de Vecchi for his more severe cases seem rather similar to those found in Foetus I but in view of the inadequate illustrations and the lack of control observations in the papers of those describing toxic endocarditis, it seemed desirable to ascertain if with the technique used here a similar lesion could be found for comparison with their descriptions and with the changes found in Foetus I. For this purpose one foetal heart and two infantile hearts were fixed in formol-sublimate with after-hardening in saturated aqueous sublimate, dehydrated by graded butyl alcohol and embedded by Peterfi's method modified by the addition of tricresylphosphate as plasticizer to the celloidin (the standard technique as described in the appendix). The hearts were cut into blocks more or less on the basis of the method suggested by Gross et al./

al. (1930); virtually the whole valvular apparatus and the larger proportion of the myocardium was prepared for histological examination by serial section. After examining the first 926 slides, the myocardial areas were examined in alternate sections but the valvular tissues were studied throughout; a total of 1,884 slides was thus examined. Foetus II was of just over 5 months age and was obtained by abdominal hysterotomy from a woman suffering from chronic rheumatic disease of the heart with subacute bacterial endocarditis, later confirmed at post-mortem. Infant I died at 19 days, toxic and dehydrated, with coliform infection of the middle ears. Infant II died at 21 days, after some days of enteritis; paracentesis of the ear drum was performed the day before death. At post mortem, pus and streptococci were found in both middle ears. In none of these cases, Foetus II, Infant I or Infant II was there any naked eye evidence of abnormality in the heart.

The microscopical examination of these cases revealed three points of interest. In foetus II, removed from a woman with subacute bacterial endocarditis, two small lymphatic glands were found in the auriculo-ventricular wedge of the epicardium; these were apparently undergoing atrophy. Patek (1939) quotes Mouchet as finding "small lymph nodes embedded in the epicardium overlying the interventricular /

interventricular sulci. He found these small lymph nodes quite readily in the dog and horse but was unable to locate any in human hearts." It is therefore of particular interest that in this human foetus the two tiny glands found should have been composed of cells obviously in a state of regression.

In Infant I an area of unusual cellularity was seen in a part of the aortic valve fairly near its insertion (figure 62); many of these cells were of the lattice type, described more fully below. In the study of these foetal and infantile cases such cells were infrequently seen and it is tempting to suggest that this accumulation must have some pathological significance but Ehrlich and Lapan (1939) state that the embryonic valve cushion contains large numbers of these cells and that large numbers are present in the valves throughout embryonal development. My own observations do not confirm this later statement but in view of it there is some hesitation in accepting the collection illustrated as being pathological. It is perhaps worth noting that none of the writers on toxic endocarditis makes any mention of these cells.

The third point of interest was the finding of a change that seems definitely pathological. In the tricuspid valve of infant II a small focus is seen (figure 63), fairly well/

well defined and composed of rather indeterminate mononuclear cells with round or slightly lobed nuclei. There is the suggestion of a central space beginning to appear, while the presence of a few small pyknotic distorted nuclei and nuclear fragments rather confirms an early necrotic lesion in the subendothelial tissue. This tiny focus appears to answer to the description given by the writers quoted above for toxic endocarditis, but in view of the high frequency with which the continental writers encountered clear evidence of toxic endocarditic, it is rather surprising that in a study of nearly two thousand sections only this one abnormality should have been found. It may be argued that I have failed to note the really early changes but it is doubtful if a less defined focus than this could be appreciated as such. Notinfrequently during this part of the study, an appearance has been seen at the surface of valves that has been interpreted as tangential cutting of the endothelial layer; this may perhaps have been the basis of the endothelial proliferation described by these writers. Whether or not there be such a thing as toxic endocarditis the lesion here illustrated, and there seems little doubt that this appearance is not the product of artefact, shows changes to which the published accounts of toxic endocarditis could be applied; it is however a much more focal/

focal and better defined change than is shown in any illustration in the literature on this subject. It is perhaps worthy of note that in over a thousand sections of myocardium from these three cases, no abnormality was noted. To summarize this section it may be said that of the reported and observed lesions in the foetal endocardium the only one to which the changes in foetus I have any resemblance is the condition of so-called toxic endocarditis.

A CASE OF FATAL ACUTE RHEUMATIC DISEASE DURING PREGNANCY.

The last case to be described is that of a young woman who died undelivered in the seventh month of her first pregnancy of a very acute rheumatic pancarditis. As this appears to be a case of a type not hitherto reported on a basis of histological examination, and as it bears very directly on the problem of foetal rheumatism it is proposed to submit a series of illustrations that may stand as evidence that the mother's disease was truly rheumatic.

Clinical History:

Mrs. Mary M., age 20 was admitted to Seafield Hospital, Ayr under the care of Dr. W.I.C. Morris,(Obstetrician to Ayr County Council) with the complaint of joint pains and general weakness. She was then about the seventh month of her first pregnancy. Her health prior to the present illness had been good and there was no history of serious illness in the past.

Three weeks before admission she had been badly soaked and chilled by rain at a funeral. Next day the knees and ankles were painful and later the joints of the arms. She went to bed and continued to suffer at intervals from the same pains. After a week there was slight mental confusion/

confusion. By the third week, the joint pains had gone but there was now insomnia with very marked lethargy. On admission she was noted as being anaemic and somewhat emaciated, with slight breathlessness and slight mental confusion. No definite joint involvement was found but the heart appeared dilated and there were soft continuous murmurs in the aortic and mitral areas. During the week in hospital there was mild pyrexia with a tachycardia varying around 130. The mental confusion grew progressively more severe and the physical condition steadily deteriorated. Transient joint pains and swelling were noted two days before death. Some six hours before death there was acute respiratory distress with blood stained expectoration.

Abstract of Findings at Post Mortem Examination - 13 hours after death.

No obvious peripheral oedema and no subcutaneous nodules were found. The pericardium showed a thickened oedematous parietal layer and contained three or four ounces of slightly turbid fluid. The heart showed on its epicardial surface a finely granular exudate. The aortic valve had a row of tiny vegetations on one of its cusps. A similar row was seen along the line of closure of both the mitral and tricuspid valves. The pulmonic valve looked normal. The myocardium appeared pale in colour and definitely soft to/

to the touch; no focal lesions were seen nor any evidence to suggest a previous rheumatic carditis. The coronary arteries seemed normal. The lungs were heavier than normal and showed a peculiar pink colour with a solid but rather translucent appearance. They were slightly irregular to the touch but no definite areas of infarction were found. The liver and spleen both showed slight congestion. The kidneys had an unusual patchy pallor in the medullary portions. The stomach and intestines, pancreas, adrenals, uterus and ovaries showed nothing of note. The head was not opened.

The foetal lungs had multiple fresh subpleural haemorrhages. The heart appeared normal. The other foetal viscera were not examined. Nothing was seen to suggest a pyogenic infection in either, and a provisional diagnosis was made of acute rheumatic disease of four weeks' duration, with pancarditis and progressive cardiac insufficiency.

Description and Discussion on the Morbid Anatomy.

In describing the histological changes in the maternal heart an effort has been made to show photomicrographs of truly diagnostic lesions, capable of standing as evidence. These are given in some detail because the case provides a wealth of characteristic material, because the lesions in practically every category are among the most striking and well defined that have been seen in any publication or in any of my own cases, and because in the past many of these microscopic changes have not been adequately illustrated. 110 blocks were examined from the heart alone, many of these by multiple sections and by different staining methods but nothing was found that contradicts the general conception already stated of the morbid anatomy of acute rheumatic disease. Certain changes are present that have not been emphasized by previous writers on this subject; since these are something quite different from banal inflammation and since they do not correspond to anything observed elsewhere in the general routine of a pathologist's work they are taken to be rheumatic and to be salient in this case merely because of its extreme severity. Some of the sections have been photographed through rather unusual combinations of colour filters to emphasize the distribution of special elements; accompanying an example of each of these less/

less common screenings there is a coloured sketch as key to the photograph in monochrome. The colour sketches were made with waterproof inks on duplicate prints and the silver image thereafter removed by iodine and sodium thiosulphate.

The verbal descriptions of the morbid anatomy are for the most part given with direct reference to the photo-micrographs since it is considered that the function of the latter is to make good the inadequacies of the verbal report. In conjunction they cover the significant findings in the cardiac tissue of the mother and are presented as a detailed proof that her fatal illness was in truth acute rheumatic disease.

The first figure (1) is a low power view (x 70) of the myocardium of the left ventricle near the insertion of the posterior mitral flap. It shows the localisation of the Aschoff bodies in the cardiac stroma, which itself is some-what oedematous and immediately obvious as it never is in the normal heart. There are twenty seven of the character-istic bodies in the field, an evidence of the extreme sever-ity of the infection.

Figure 2, at a higher power, shows a group of Aschoff bodies of the early coronal type, each formed of a central collagenous core and a circlet of large somewhat basophilic cells. Figure 3 is of another group of these lesions lying/

lying in the ventricular stroma.

Figure 4 shows a single coronal body situated as always in the stroma; there is a centre of faintly fibrillar, virtually amorphous poorly stained material with a surround of large cells and a few lymphocytes. The colour sketch of this field (fig.5) shows the rather dull staining with eosin that is typical of the coronal Aschoff body. Whereas fibrin and the well fixed erythrocyte take a more brilliant red staining with eosin than does even muscle, this material stains to the same flat pink as collagen. The use of other staining methods confirms this physicochemical similiarity with collagen. Thus with van Gieson's method, the material takes the acid magenta (fuchsin) as pointed out by Geipel (1906); with Mallory's trichromic method or its modifications (Masson's, or Lendrum and McFarlane 1940) this material shows a strong avidity for the soluble blue (aniline blue), light green, or fast green F.C.F.; with phosphotungstic acid haematoxylin it takes the same reddish brown colour as does collagen; and with the writer's phloxin tartrazine method it shows no more affinity for the red dyes than does any loosely textured collagen. Very dense collagen has a tendency in the differential staining methods to retain some of the more acid dye; with the Mallory trichromic methods, as is well/

well known, there is sometimes difficulty in replacing the red dye by the blue or green in tendon or the hyaline collagen of old scars. Similarly the phloxin element may be extracted very slowly by the tartrazine from such dense connective tissue. The substance in the centre of the coronal Aschoff body shows no such affinity for the more acid dyes and there is thus no difficulty in demonstrating that there is no fibrin at all in this type of lesion. Some writers have taken the descriptions given by Klinge of the fibrinoid deposition seen in early stages of the rheumatic lesion and rather uncritically stated that the early lesion of acute rheumatic disease is the focal appearance of this material. There seems no doubt that the coronal type of Aschoff body is an early lesion and that it is one in which there has not been an earlier deposition of fibrin, a presumption strengthened by the observation that the fibrin deposits occurring in the rheumatic heart are by no means rapidly removed. This last statement will be amplified below in discussing Klinge's conception.

Fig. 6 shows a lesion that can be best described as a longitudinal type of coronal Aschoff body. The site of this is again the stroma of the left ventricular myocardium adjacent to the insertion of the posterior mitral flap, and it again conforms to the general description of a central/

central core of faintly fibrillar poorly staining material surrounded by large rather basophil cells. The only other published illustration that has been found of such a large elongated form is in the first paper to show photo-micrographs of rheumatic myocarditis, that of Geipel (1906); although I have examined some five times as many cases as he quotes, this long type of lesion has been seen only once. A tendency in recent years, in the discussion of the Aschoff body has been to suggest that each lesion is a site of sensitisation produced by the death there of a streptococcus during an earlier phase of the disease. Some such explanation however reckless it may seem, is possibly less speculative than the recent suggestion that the host develops antibodies to his own collagen following a hapten-linkage between an invading streptococcus and the collagen it damages to give a new complex antigen, strepto-collagen; some hypothesis is certainly needed to explain the marked focal distribution and form of these early Aschoff bodies. To return to the lesion under discussion it is difficult to imagine any noxious agent acting <u>focally</u>, in the punctate way that we presume cocci to do, and yet eliciting damage along a whole segment of stroma as seen in this longitudinal Aschoff body. The auricular changes to be described below are somewhat comparable to this lesion but on a much lesser /

lesser scale.

In the coronal type of Aschoff body, the morbid anatomical appearances point to a primary, not very severe, generally focal damage of collagen, with no evidence in the early stages of any of the vascular or cytological phenomena that characterise inflammation. The cells of this lesion are of a type that so far as is known have no exact counterpart in any other disease. They resemble in a faint way the appearances seen at the damaged ends of skeletal muscle, which may explain the now less commonly made statement that they are of muscular origin. The closest similarity is seen in the large sometimes multinucleated cells of the subcutaneous nodules of acute rheumatic disease and of rheumatoid arthritis. Cells apparently identical with the large cells of the subcutaneous nodules are a major constituent of some of the so-called myelomata of tendon sheath; in these tumours (be they granulomata or neoplasms) the more fully formed multinucleated cells are quite different from those of the cardiac lesions, the essential difference being apparently the absence of necrosis in the cells of the myeloma. From a study of these four sites it seems not unreasonable to suggest that the large cells in all cases are connective tissue cells in which the normal relation of the cell to its collagen fibre has been upset /

upset and that the noxious influence goes on, in the case of the Aschoff body, to produce further damage to the cell. Coombs (1924, page 50) says, "these large cells develop from vascular endothelium, and some of them probably represent sprouts of new capillaries," a speculation that receives no support from my observations.

The cytoplasm of these cells is slightly basophilic and in the earlier years of the century much emphasis was laid on their red staining with Unna-Pappenheim's stain. To achieve the correct tinctorial reactions with this method, fixation should be with alcohol or zinc chloride (Unna 1913), neither of which is satisfactory for cardiac tissue. A comparable staining method is that suggested by Hitchcock and Ehrich (1930), using malachite green and acridine red on tissues fixed in Zenker's fluid. This method was shown (Kerr and Lendrum 1936) to be applicable to tissues otherwise fixed, if preceded by a treatment of the section with one per cent acetic acid. An example of the results obtained is shown in fig. 36 where the granuloma cells are seen to take the red stain. There is however nothing particularly diagnostic about this reaction; it merely makes more evident those cells with the less acidophile cytoplasm. Thus, plasma cells, young fibroblasts, haemocytoblasts and malignant cells all show shades of red /

red in their cytoplasm while the granules, of eosinophil polymorphs, of Paneth cells, and of enterochromaffine cells, and the Russell bodies of plasma cells take a brilliant green. It is not a method with which it is easy to produce an even differentiation and in well fixed material, properly stained by haemalum and eosin there is really no difficulty in recognising these cells from their situation and morphology. Thus far I have failed to show the presence of intracellular inclusions in any of the forms assumed by these cells. The further development of the lesion shows changes in the cells; some become shrunken and pyknotic, others are enlarged and show aberrant or multiple nuclei (fig.7), while the formal arrangement of the coronal stage of a central collagenous core surrounded by cells is now replaced by an irregular collection of the altered granuloma cells. This is the stage described by Gross as mosaic. Among these cells in this later phase there appear tiny twigs of fibrin, a fact apparently not noted by Gross. The lesion later goes on to become a fibrous nodule but these stages do not belong to the acute phase of rheumatic disease and will not be discussed here.

Another type of granuloma occurs in the rheumatic heart, one that does not yet seem to have received recognition. This is one that is largely built up from a type of cardiac /

cardiac cell that itself is scarcely known by most histologists. Figure 8 is a high power view of such a cellular aggregation from the loose endocardial layer of the right ventricle. This lesion is thought to be a further stage in time, or a more severe form of a subacute coronal Achoff body. There is now no evidence of a central core of altered collagen and among the cells there are a few tiny twigs of fibrin. The giant cells present are different from those of the coronal and mosaic Aschoff bodies already illustrated; a new element has come into the picture. In the general view of this lesion the most striking fact is the presence of cells with a peculiar lanceolate nucleus, characterised by a firm longitudinal bar of chromatin with thin transverse ribs running to the well marked nuclear membrane. The lanceolate cells might be called "Lattice cells"; it is at least a better term than "myocytes", their first name (Anitschkow 1913), since Ichteimann (1934) in his study of scar formation in the heart following coronary occlusion, has shown that they have no derivative relationship with muscle. Gross and Ehrlich (1934 a & b) have, without reference to the work of Anitschkow, called them "fibrocytoid" cells, but this term seems to suggest a closer relationship with the fibrocyte than we know to exist. Ehrlich and Lapan (1939) in the first contribution in English on these cells as such, have suggested the term/

term "myocardial reticulocyte", but this is not altogether satisfactory in that a very similar appearance has been seen elsewhere than in the myocardial stroma, as will be discussed below.

Among the lattice cells in the lesion illustrated are multinucleated forms that seem to arise from the lattice cells; it is noteworthy that identical multinucleated forms are illustrated by Anitschkow, and also mentioned by Ichteimann ("Doppelkerne und Kernabschnürungen") as occurring among the lanceolate cells toward the periphery of his experimental necrotic areas. The appearances in the present case, and in my other acute rheumatic material, seem clearly to indicate an origin for the multinucleated types from the lattice cells (fig.9). The arrangement of the chromatin in the large cells tends to retain the general arrangement of a central aggregated mass of chromatin with thin connections to the distinct peripheral chromatin layer, an appearance which differs from that seen in the large cells of the coronal Aschoff body. Thus one is forced to the conclusion that two types of multinucleated cell may be seen in the rheumatic heart. The earlier to appear, that of the coronal Aschoff body, is related to an area of altered collagen and there presents what is probably an appearance specific to this disease; it has in the main /

main an appearance of degeneration and may be explained on the Hansen-Haggquist theory (Johansson 1937) as being the result of aggregation of the damaged nucles of connective tissue subsequent to degenerative changes in the related collagenous exoplasm. This other type is the result of an abnormal proliferation of lattice cells, a fact that hitherto does not seem to have been appreciated in relation to rheumatic disease.

These lattice cells have been found in small numbers in the stroma of the normal foetal juvenile and adult human heart, and in the normal adult guinea-pig's heart. Ehrlich and Lapan in a recent paper describe their presence in the hearts of a long series of normal vertebrate animals. These cells show a definite increase in relation to the cardiac granulomata of rheumatic cases when the disease has lasted a month or more before death. They also occur in parts of the heart far removed from the myocardium; Wätjen (1921) noted this nuclear appearance, apparently in its simple mononuclear form, in relation to rheumatic granuloma in the epicardial tissue around the pulmonary artery. Gross and Ehrlich pointed out that these cells, called by them fibrocytoid, are very rare in relation to the earliest Aschoff bodies, a finding with which the present writer agrees, and one which tallies with the observations of/

of Ichteimann on the different stages of ischaemic necrosis in the heart. The latter's suggestion that these cells as seen in the cardiac stroma represent a stage in the development of the cardiac histiocytes, seems reasonable and is confirmed by the findings of later workers. The use of the writer's phloxin tartrazine stain has not only revealed the somewhat surprising number of mast cells present in rheumatic lesions but also allowed a study of the nucleus of these cells; when eosin-methylene blue is used the darkly stained granules completely hide the nucleus. It is of course well known that haemalum and eosin staining fails to make these cells evident. In a few of the mast cells the chromatin shows a central bar formation reminiscent of the lattice cell, but the nuclear shape is less elongated and the parallel ribs are not seen. On this subject of the lattice cell, it only remains to make some comments on the paper of Ehrlich and Lapan. They used formalin as their only fixative fluid; my tissues were fixed also by formol-sublimate, Zenker's fluid, or by "Susa", and all showed an exactly comparable nuclear formation. The majority of my rheumatic material has been fixed by sublimate containing fluids and this may explain why in contrast to that of Ehrlich and Lapan it has shown the distinct presence in many of the lattice cells of one or two round acidophil /

acidophil intranuclear bodies, probably nucleoli (Fig.10, which is, however, not rheumatic material). Ehrlich and Lapan note the finding of this type of nucleus in a bronchial epithelial cell and on rare occasions of a suggestively similar form in other tissues. In my own observations this nuclear form has been seen in only three sites other than in the cardiac connective tissue. The lining cells of the epicardium have shown this appearance in several rheumatic cases, sometimes in all the cells over a considerable sheet; groups of these epicardial cells showing the typical longitudinal chromatin bar have also been seen in the human foetus. The same appearance has also been noted in the swollen endothelium of capillaries in regions of rheumatic inflammation in the heart, although not in the vessels of the subcutaneous lesions. The third site, and the only purely extracardiac one, in which these cells have been seen was the subepithelial connective tissue of a rabbit's tongue; here the cells were in small number but were apparently identical with those seen in the heart.

Fig.11 shows for purposes of comparison with the Aschoff bodies a focus of myocarditis found in the heart of a rabbit; this was discovered during the examination for control purposes of hearts from presumed normal animals. No obvious lesion was noted in the other viscera of this animal when/

when the heart was fixed for examination.

Fig. 12 shows the insertion of the posterior mitral flap at x 13. The thickened valve with its vegetation may be noted but firstly before leaving the study of the granuloma cells, attention must be directed to the auricular lesions. In this photograph two cellular collections can be seen in the thickened auricular endocardium. Fig. 13 is a section of the left auricular endocardium, taken parallel to and about 1 cm. above the insertion of the posterior mitral flap; it shows four cellular collections of the typical type. Fig. 14 is again left auricle at a slightly higher power and the tendency for the cells to be arranged in rows is clearly seen. Fig. 15 shows a development of the auricular lesion that occurs in many acute cases, the appearance of a band of material giving the same staining reaction as does the core of the coronal Aschoff bodies described above, with gathered against it cells that are similar to those of the coronal Aschoff body. This linear type of Aschoff body was first brought to notice by MacCallum (1924) but there has been apparently some uncertainty since then as to the constitution of this lesion. Von Glahn (1926) said that fibrin could not be demonstrated in the homogeneous material about which the Aschoff cells are gathered; whereas Klinge (1933) describes the bandlike/

bandlike material as fibrinoid (his.fig.10, page 47), a material which he elsewhere (p.34) states gives the staining reactions, although somewhat irregularly, of fibrin. In the earlier stage of this lesion I have found that the band gives the staining reaction of collagen, red with van Gieson (as von Glahn noted), blue with Mallory's trichromic method, brown with phosphotungstic haematoxylin, yellow with phloxin tartrazine. Later stages, however, show changes which seem comparable to the development of the coronal Aschoff body; the granuloma cells become larger and more aberrant (fig.16) a few lymphocytes and even polymorphs appear and there is now deposit of fibrin among the granuloma cells. Although these findings differ from the descriptions given by MacCallum, von Glahn, and Klinge, they are based on clear cut tinctorial and morphological differences and hold good for cases other than the present. Toward the deeper part of the endocardium in fig.15 there is one of the more common focal collections of cells, similar to those already shown. This type of aggregation is most frequently seen in the deeper part of the endocardium; while the band lesions are usually in the more superficial zone. The structural difference between the two may well be due to the different texture of their milieu. The next figures (17 & 18) show at a higher power the relation of these cells to the elastica in an early stage of one of these foci; Shortly thereafter/

thereafter the cells become more irregular, the elastica becomes broken up and an irregular juxtaposition is seen of granuloma cells, masses of collagen, distorted ends of elastica, and fine fibrin twigs. The morphology of these lesions is best understood if the sections be stained by Weigert's method for elastica followed by the phloxin tartrazine method. The next figure (19) is from the auricle of a rheumatic child, stained by this procedure and not only gives a fair representation of the cellular changes in the endocardium but also shows the oedematous thickening of the subendocardial layers with a deposit of fibrin on and just under the surface. This figure from my other material is included since a comparable illustration has not been seen in the literature. Gross (1935,b) notes that none of his cases showed necrosis of the superficial layers of sufficient intensity to warrant the form "verrucous change". One of my other juvenile cases showed a thicker and more irregular deposit of fibrin at the surface than the one illustrated here (fig.19).

A lymphocytic and plasma cell inflitration of the region between the endocardium and the auricular muscle is an almost constant finding in acute rheumatic cases.

Hadfield and Garrod (1938) state that the "morbid changes in the wall of the left auricle, described by MacCallum are frequently present in long standing cases of/

of rheumatic carditis". That they are present in 44 per cent of acute cases was shown by the papers of Thayer (1925) von Glahn (1926) and Kugel and Epstein (1928), but Clawson (1929) later went so far as to say that microscopic evidence of infection in the auricle is found almost constantly. In my own material of nine cases under twelve years of age, for which I am indebted to Professor Blacklock and Dr.Montgomery, three died in the first attack, five in a first recurrence, and one aged 11 with early evidences of the chronic fibrotic type of change; in this last case the auricular changes although marked were obviously resolving but the other eight all showed extreme acute inflammation of the auricle. Over the age of twelve, there were seven cases of acute recurrence showing Aschoff bodies in the ventricular myocardium; of these, six showed definite auricular lesions while the seventh which was not very fully examined showed a small focus of granuloma cells. Thus in sixteen cases of active rheumatic myocarditis, fifteen showed distinct and characteristic changes in the left auricle.

Fig.20 of the myocardium of the left ventricle near the posterior mitral insertion, shows toward the left a typical coronal Aschoff body and at the right an example of the other early interstitial lesion of acute rheumatic disease, the form described by Gross as the reticular Aschoff body. This is seen as a tangle of material, giving/

giving the staining reaction of fibrin; in the meshes are small cells with darkly stained nuclei. The appearances suggest that this deposit has occurred in relation to a vascular lumen, possibly lymphatic. Fig.22 shows in more detail one of these reticular Aschoff bodies at the junction of the auricular muscle and the epicardial tissue. Again there is the suggestion of a vascular lumen in which lie mononuclear cells. The cells enmeshed in the fibrin show some of the characteristics of granuloma cells. A mast cell is seen in the upper part of the figure. This epicardial zone of the left auricle is the main site of the reticular bodies, and in other cases I have failed to find them elsewhere in the heart; in this region they frequently assume larger forms with a diffuse arrangement that seems to argue against any close relationship to a vessel. Fig.24 shows such a lesion from this area with the characteristic semblance of the collagen fibres' of the part becoming transformed into fibrin-like material as they run into the lesion. Fig.25 is a similar lesion and shows, middle right, an area of swollen collagen with a thin layer of fibrin deposited on its sides. This is shown at a higher power in Fig.26; although this is a rather gross example it allows, as does not the usual minute form, photographic demonstration of the process. Figures 28 and 29 are studies of the/

the reticular change from one of my other cases, occurring here as a complication of a mosaic coronal Aschoff body. The section was stained by the picro-Mallory method and so shows collagen as blue and fibrin as red. Figure 28, taken through an orange screen shows up the collagen black and everything else in light tones; figure 29 with blue screening shows the fuchsinophil elements, the muscle, the nuclei, and fibrin as black. Even at this magnification the left hand network reveals the coating of collagen fibres by material giving the fibrin reaction. In figure 30 this relationship of fibrin to collagen is shown at a higher power. It seems likely that a similar process is present in the acute subcutaneous rheumatic nodule (figure 31) but thus far no convincing proof has been seen; it is possible, however, that the deposition of fibrin in the nodule is more comparable to the process described below of perivascular precipitation.

In any discussion of the Aschoff body, the data to be gathered from the literature have to be critically examined since many of the earlier papers were based on scanty material, several are not supported by illustrations, while the fuller appreciation of the developmental stages of the focus is of fairly recent date. The old controversy on the origin and constitution of the Aschoff body is doubtless/

doubtless to be explained by the myogenic theory's supporters' having based their arguments on study of cases past the first acute stage. If attention be confined to the acute case the difficulties are resolved and no doubt can persist as to the truth of Romberg's description (1894) of an interstitial myocarditis, or Geipel's statement (1906) that, "Ihr Sitz ist ausschliesslich das intermuskuläre Bindegewebe..." Doubtless less ambiguity about the rheumatic lesion would have arisen if more attention had been given to Geipel's paper. In it he gives what I believe to be the first photomicrograph of a rheumatic lesion, an excellent illustration of a coronal Aschoff body; he also describes another form containing fibres that gave the fibrin reaction, almost certainly a reticular body. The existence of the two primary types of Aschoff body, however, was not properly realised until 1934 when Gross published his papers on the Aschoff body. With his view I entirely agree. Klinge (1933) recognises both types but considers the reticular form, called by him the "Frühinfiltrat," to be the one and only primary lesion and that the coronal form, granuloma in his term, is a development of the reticular form. My own material reveals no appearance that could be interpreted as a developmental stage between the reticular and the coronal form; rather it confirms the/

the view of Gross that both are primary foci of independent origin. A further argument against this transition will be propounded below in a more suitable place. Aschoff (1939) influenced perhaps by his own early description of the focal lesion as a granulomatous nodule, attempts to disprove Klinge's view of the earliest changes; he says "Despite the cellular overgrowth which has caused the formation of the nodules, there is no trace of a fibrinoid degeneration of the ground substance. I therefore think that I have brought sufficient evidence to refute the ideas expressed in the systematic drawings made by Klinge". Further on, he says, "It is in no way essential that the formation of the richly cellular nodules should be preceded by fibrinoid degeneration of the ground substance." On the other hand, Aschoff has apparently failed to recognise the reticular form; for example, in his textbook (1936) he mentions only the granulomatous form. MacCallum likewise in his textbook gives no evidence of having distinguished the two forms; in the third edition (1924) he shows two drawings one of which is probably a coronal type, the other probably reticular, but these are replaced in the fifth edition (1932) by a single photomicrograph of the late fibrillar stage of an Aschoff body.

Coombs (1910) appreciated the fact that a fibrin/

fibrin containing lesion was characteristic of the disease and states, "The pericardial and endocardial nodules have more room; in these there is often a central area consisting of nothing but fibrin, surrounded by a zone of cells either mingling with the fibrin at its margin or marking it off from the surrounding tissues." This corresponds with my own finding that the reticular Aschoff body is more common in the epicardial tissues and in some cases is found only there. Gross, although aware of the descriptions given by Coombs, states (1934, p.476), "Finally concerning the properties of all types of Aschoff bodies found in the heart, it may be said that, contrary to what has been stated in the literature, these lesions rarely, if ever, show a fibrin constituent." Further on (p.480) he says in discussing the reticular Aschoff body, "This swollen reticulum frequently takes on the tinctorial properties of fibrin. In their configuration, however, the fibres can easily be distinguished from fibrin. Furthermore, it can readily be determined that these 'fibrinoid' fibres are continuous with collagen fibres in the vicinity, where they show the characteristic staining for collagen." In answer to this, it is certain that in some of the mosaic stage Aschoff bodies, developed from coronal forms in which there is no fibrin, there appear twigs and branches of a material that not only gives the/

the colour reaction of fibrin but also is morphologically fibrin; the lesion from which figure 8 was taken contains such twigs. Morbid anatomy can go no further than this, and the onus of proof would seem to be on those who deny that this material is fibrin, merely because it occurs in a rheumatic lesion. In his description of the reticular Aschoff body, Gross appears to fall under the spell of Neumann's (1896) word "fibrinoid", popularised recently by Klinge. In my material, study of the periphery of reticular Aschoff bodies has shown that a substance, reacting to dyes in every way as does fibrin, is deposited on the surface of collagen fibres. If such a fibre be traced inwards toward the centre of the lesion, it is seen to change from a collagenous fibre coated by fibrin to a swollen hyaline fibre coloured throughout with the colour characteristic of fibrin. It is not possible to say whether the fibres are coated overall with fibrin or whether the collagen fibre is so altered that it soaks up fibrin but one or other of these ways of interpreting the changes seems on the grounds of my observations to be better justified than the fibrinoid hypothesis. It is surely too much in our present state of ignorance to insist that a substance giving the staining reaction of fibrin be called something else if it fails to show the morphology of the /

the fibrin net seen in inflammatory exudates; must we then describe as fibrinoid the substance in the walls of the afferent arterioles of malignant hypertension, in the walls of the vessels of a torsed viscus, in the wall of an artery the seat of polyarteritis, or for that matter the material that coats the pericardial surfaces in so-called fibrinous pericarditis, or that forming the hyaline droplets of renal tubular cells?

This substance or appearance called fibrinoid is very far from defined even in the work of those who use the word. Klinge in his monograph applies the term to the homogeneous band of the auricular lesion, and in describing the lesions illustrated in his figures 5 and 6, obvious early coronal Aschoff bodies, he says (page 44), "die Zellen bilden einen Wall rosettenartig um einen fibrinoiden Mittelpunkt"; yet my material proves quite conclusively that the central core in both these lesions in their early stages consistently gives the staining reaction of collagen. On the other hand, the appearance described and illustrated by Klinge as the Frühinfiltrat (his figure 52) is apparently morphologically identical with the forms recognised in this work as early reticular Aschoff bodies, formations as said above that show a distinct and striking network of fibres giving the reaction of fibrin. It is difficult to /

to see what justification there is for Klinge's use of the term fibrinoid for the core of the coronal form as well as for the tangle of fibrils of the reticular form, since various staining methods give such strikingly different reactions with the two substances.

Earlier in this section it was stated that no lesions have been seen in acute cases that could by any means be interpreted as transitional stages between the reticular and the coronal forms, and that the complete absence of fibrin reaction in the small coronal forms is a further argument against Klinge's view that the coronal is a development of the reticular form (Frühinfiltrat), since fibrin in the rheumatic heart is peculiarly resistant. This persistence of fibrin is proved by the appearances in subacute cases; for example in epicardial tissue, already the seat of diffuse fibrosis, the fibrin of reticular Aschoff bodies may be seen to be still perfectly distinct with little or no signs of lysis or organisation; similarly in the valves, the fibrin mass of the vegetation may show practically no organisation at a time when the myocardial nodules have all gone on to become fibrous scars. Clawson et al.(1926), in discussing this material, in the valves which they call hyaline, say "The peripheral hyaline layer becomes more homogeneous and glassy and remains in this /

this condition indefinitely. It is not absorbed and does not become organized. Hyalin in the deeper parts of vegetation or in the body of the leaflet may likewise persist indefinitely...".

Thus to sum up the findings in the interstitial tissue of the heart in this case and my own views on the lesions described, it may be said that there are present typical coronal Aschoff bodies in considerable numbers in the interstitial tissue of the ventricular myocardium, that there are reticular Aschoff bodies, the other type of acute primary lesion, not only in the auriculo-ventricular wedge and the periauricular part of the epicardium but also in the interstitial tissue of the myocardium, and that there are the typical auricular manifestations of acute rheumatic disease. The illustrations of these lesions are believed to prove that the changes which I am accepting as diagnostic are of exactly the same type as the changes illustrated by Geipel, Coombs, von Glahn, Shaw, Chiari, Klinge, and Gross, and that I am not misrepresenting these writers. Such opinions as I have expressed are based not only on a comparison of the present case with their published illustrations and descriptions, but also on the basis of my own observations in sixteen other cases showing active lesions.

The next type of lesion to be described is one that /

that can be aptly described as subendothelial precipitation of fibrin; this is a manifestation of the disease that appears to have received practically no comment in the past. Figure 32 shows one of the little crypts between the columnae carneae of the posterior wall of the left ventricle, a site that can reasonably be considered as sheltered; the question thus arises why this subendothelial precipitation should be localised in this secluded cove. It is of course possible that a minute lesion in the endothelium may have allowed the seeping in of fibrin but a study of the composite picture suggests that some noxious influence is in the tissues, eliciting both the fibrin deposit and the cellular changes described below. The primary change appears to be the precipitation of fibrin in the tissues immediately under the endothelium, on a much grosser scale than that seen in the early stage of the reticular Aschoff body; this greater intensity may explain why it has not been possible to identify the deposit of fibrin on pre-existing collagen fibres. In the meshes of the ramifying fibrin the local cells show changes that bring them into line with the granuloma cells of the coronal Aschoff body and the auricular lesions, and in the further development of the lesion these cells increase and show both multinucleated and frankly degenerated forms (figure 34). Figure 36, like the two /

two preceding it, shows subendothelial precipitation in relation to a vein in the ventricular wall; it is stained by the malachite green, acridine red method (Kerr and Lendrum 1936) already mentioned, and shows the typical appearance of the granuloma cells when this method works satisfactorily. The form assumed by subendothelial precipitation appears to be dependent in part on the structure of the involved tissue and figure 37 shows the more stratified disposition of the fibrin deposited in the apex of the pocket of the mitral valve; in this situation the arrangement of the fibrin clearly recalls the reticular Aschoff body. If these various forms can be considered together, as seems justifiable on morphological grounds, then it may be suggested that the noxious agent producing the focus of damage comes by the blood stream but is active on collagen rather than endothelium; if the site of change be near a source of supply of fibrinogen, large both in terms of quantity and replacement (time factor) then the amount of precipitation will be comparatively great and the resultant picture will be that described here, whereas if the site be far from such ample supply as exists in the blood in the cardiac cavity and venous sinuses, then the fibrin precipitation is slight and shows the fine and more easily analysed deposition of the reticular Aschoff body.

From these forms of fibrin precipitation it is a short step to the changes in the valves that for so long dominated all thought on the pathology of this disease. These differ from the other forms of subendothelial precipitation in that they are macroscopically obvious in almost all cases, in their very common situation on what we consider to be the line of contact, and in the more intense local changes brought about doubtless by the same mechanical effects that determined the site. Figure 39 shows the contact surface of the tricuspid valve at a part where no abnormality was visible to the naked eye. The darkly stained fibrin is seen not only as a surface layer, as is similarly shown in figure 37 of the mitral apex and figure 19 of the auricular endocardium, but also ramifying down into the tissues; deeper in the valve are scattered little knots of fibrin comparable to those seen in areas of intense rheumatic inflammation, such as occur at the root of the mitral or at the junction of auricular muscle and endocardium. Although the valve is œdematous and apparently more cellular than normal, the portion illustrated is considered to be still an early stage of vegetation formation in that there is a striking lack of cellular response around this fibrin.

Figure 40 of the mitral valve shows how deep in the/

the valve substance fibrin may be deposited, both in relation to the surface lesion and also at a considerable distance from any superficial abrasion. In the meshes at the periphery of these valvular precipitations large cells later appear as described above, which come to show all the characteristics of the granuloma cells. The cellular reaction varies in different valves and even at places in the same valve; thus in the tricuspid of this case (figure 42) there is an early appearance of the proliferative reaction, producing a little fibrin capped verruca, with but little immigration of wandering cells, while in the mitral (figure 44) there is a considerable infiltration of cells, lymphocytes, polymorphs and fibroblasts, many of which seem to be undergoing necrosis.

In the figures there is manifest a distinction in the structure of the fibrin mass which is usually not discernible after ordinary eosin staining. The deep roots of fibrin in the tissue of the valve show a strong affinity for the specific stains, an affinity that is partially lost in the central part of the mass, but is seen again at the surface in a thin sharply defined layer staining with vigour and precision. It is suggested that the distinct superficial layer is fibrin deposited from the passing blood, and that the less specifically stained material is the /

the fibrin originally deposited in the subendothelial tissue and now, in virtue of its age, beginning to lose as fibrin can its characteristic staining except on the deeper aspect where new fibrin is being added.

The proliferative reaction of subendothelial tissue is shown in figure 45, occurring in the wall of a vein in the left ventricle; two mosaic Aschoff bodies are also present in the field. Apart from the proliferative cushions on the endocardium of the left auricle (figure 46) the most characteristic type of intimal proliferative lesion is, as was shown by Gross, the formation of little papillae in the apex of valves. Figure 47 shows a group of these papillae at the root of the pulmonic valve with deposition of fibrin in their substance. That the fibrin in this site is not necessarily the eliciting cause of the proliferation is suggested firstly by the fact that Gross makes no mention of fibrin deposition in the papillae observed by him, and secondly by my own experience in that this present case is the only one of my series showing precipitate in the papillae. The lesion provides yet another example of fibrin deposition under a more or less intact endothelium, clearly similar to the group of figures shown as subendothelial precipitation, and one to be considered along with them in their relationship to the formation of

of vegetation.

Swift (1924), in describing vegetation says, "on microscopic examination these verrucae are seen to be made up of coagulated elements derived from the circulating blood, in other words, small globular thrombi deposited on the valvular endocardium at a place where the lining endothelium has disappeared." Hadfield and Garrod (1938) say, "Microscopically they are platelet thrombi, free from bacteria, immediately overlying a subendocardial area rich in the characteristic rheumatic nodules.... This breach of surface, the superficial destruction of endothelium, occurs along the closure line, and along this line the platelet thrombi are deposited which, when they have reached a certain size, appear as visible vegetations." Against this old but persistent view certain queries may well be raised. Is there any proved example in general or experimental pathology of the formation of a mass of "platelet thrombus" in sites other than recesses or blind ends (Rowntree and Shionoya, 1927)? Why should the thrombus on a cardiac infarct, a site of flow, or that in the auricular appendage, a site of stagnation, be structurally so very different from rheumatic vegetation? Why does the vegetation that occurs in the apex of a valve (figure 48) stay small, instead of enlarging not merely until it reaches visibility but till it fills up all the cavity of the/

the valve? If it were really composed of platelets would they not elicit the formation of red thrombus? Why should the rheumatic vegetation fail to increase in size beyond the well known tiny nodules, whereas the vegetation of infective endocarditis does not seem to have its size limited by any hydrostatic factors?

Clawson et al. (1926) were apparently the first to put forward a view similar to the one which my observations demand; they say "Dense hyalin material is found constantly on the surface of fresh vegetations, some small vegetations consist chiefly of hyalin. It may also be found deep within the substance of the leaflet apart from vegetations. It seems to be chiefly a coagulated exudate and not a product of tissue disintegration. When the hyaline breaks through the endothelium, platelets may accumulate upon it. A platelet thrombus cannot be distinguished from this hyaline material except by its position." There seems no doubt that the substance they call hyalin is what I have described throughout as fibrin. The only point on which I would disagree is in his last sentence; as mentioned already the use of stains other than eosin, for example phosphotungstic haematoxylin, picro-Mallory, or phloxin tartrazine, shows a thin sharply defined layer on the surface of the main mass of vegetation which is almost certainly/

certainly the superficial coating that they postulate. Klinge (1933) on valvular endocarditis accepts Koniger's view that the material of the vegetation is formed in-with the valve, in the subendothelial tissue. He believes this to be a fibrinoid degeneration of the connective tissue, the reaction he considers general for rheumatic disease; to this he adds "Allein die Quellung Kann aber auch ganz aus sich zur Wärzchenbildung führen". Gross (1936,c) like Coombs (1924) believes that the vegetation is formed by a coagulative necrosis of the proliferated cells and of exudate, and that the deposition of platelets or fibrin plays very little part in their formation. Poynton and Schlesinger (1937) give Poynton's and Paine's early theory on vegetations, that these "are mainly necrotic areas of the valve substance, akin to the necrotic tissue in subcutaneous nodules and pericarditis. Certainly a thrombus would be unlikely to have such a firm attachment as the verrucose lesions constituting a simple rheumatic endocarditis." Elsewhere they state (p.31) "...valvular vegetations owe their formation to a subendothelial inflammatory process and not to a primary destruction of the endothelium. This means that the infection reaches the valves through the coronary circulation and not from the blood in the cavities of the heart." It is questionable if there is real justi-/

justification for this last statement. The much debated problem of the vascularisation of cardiac valves is too large to be discussed here but it now seems fairly certain that at the level of the line of closure there are normally no blood vessels. The tissue doubtless has a low metabolic rate but its continued existence is proof that adequate nutriment is being received. This may be either from the capillary loops at the base of the valve or from the blood in the cavity; since there is no greater development of the basal capillary loops in the valves on the right side of the heart, it must be assumed that the valves depend for their nutrition almost entirely on diffusion of the nutritive solutes from these loops with their oxygenated coronary blood rather than on diffusion from the blood in the cavities. For if the cavity blood maintained the greater part of the nutritive supply, then on the right side the capillary loops would be called on for oxygen supply to a much greater extent than on the left side where the cavity blood is itself oxygenated. Thus it is reasonable to say that any solute in the blood, normal or abnormal, physiological or toxic, that is of a molecular size to penetrate endothelium can be dispersed throughout the substance of the valve from the basal capillaries; it is not reasonable to deny the possibility of similar diffusion from the cavity/

cavity blood. On the basis of these presumptions it is possible to imagine acute rheumatic inflammation occurring not only at the base of a valve and showing there the characteristics of this inflammation as seen in any other fairly loose connective tissue in the heart, but also at a distal or superficial part of the flap and showing there the characteristics of acute rheumatic inflammation as seen in subendothelial tissue elsewhere in the heart. Such indeed are the observed facts. Examination of acute rheumatic cases not infrequently reveals an acute valvulitis with cellular infiltration, oedema, Aschoff body formation, and even the early deposit of tiny twigs of fibrin on the deep collagen fibres, all still confined to the proximal part of the valve, while at the line of contact there is a solid mass of fibrin erupting through the endothelium with a slight to moderate cellular proliferation or infiltration in relation to its roots. Between the two areas of change the valvular tissue may seem virtually normal. Putting this in another way, we can say that the reaction of the tissue to the noxious agent is obvious in the proximal part of the valve where it is general, and again at a distal part where it is focal. One hypothesis to fit these facts is that the spread of the noxious agent to this distant focus may quite well occur in the substance of the valve,/

(Turn two pages to page 93 →

is well shown in figure 50 where the normal muscle stained by phosphotungstic haematoxylin is dark, and the fibres nearest the Aschoff body show loss of their normal staining. Whether or not there is a toxic influence emanating from the subendothelial precipitations of fibrin, Clawson's view mentioned above, the data given by Gross and Ehrlich (1934 a & b) on the incidence of vegetation at different stages of the disease, and my own findings all suggest that there is some inhibition of the usual processes of lysis and organisation. The apparent contradiction between this fact of morbid anatomy and the known fibrinolytic activity of the streptococcus does not appear to have been mentioned by the supporters of this organism as the causal agent. So far as my observations go this subendothelial fibrin is confined to the heart, either in the tissue adjoining the cavities or in relation to a vein; admittedly no other organ has received quite such intensive study.

Thus to sum up the findings in the endothelial and subendothelial tissues of the heart in this case, and my own views on the lesions described it may be said that there are present foci of damage in the subendothelial tissues which in virtue of their close relationship to a large supply of blood are characterised by a comparatively massive precipitation of fibrin, that the extent of this precipitation

(Turn two pages to p. 95→

valve, travelling toward the distal portions ahead of the tissues' reaction, and producing a separate focus in the distal part through an intensification of its necrotic effects brought about locally by the trauma of closure. This certainly would be nearer to fitting the facts than the view at present in fashion that vegetation occurs where the surface of an oedematous inflamed valve has been abraded. The other possible interpretation and the one which my observations tend to favour is that the formation of vegetation is the same process of subendothelial precipitation as described above for other sites, and that its frequency at the line of contact is explained on the usual mechanical grounds. The absolute explanation of its localisation remains a mystery. There is, however, still one significant fact about these precipitations, and that is the combination of the cellular changes and the persistence of the deposit. It would seem that there must be some local toxic effect, in that the surrounding cells take on the characteristics of granuloma cells, degeneration of these cells occurs, and there is curiously little evidence of organisation of this fibrin at later stages. It is obvious from the appearances in muscular tissue near the early type of myocardial Aschoff body that this rheumatic lesion at least, is a centre of toxic radiation; this is/

(← Turn back one, to page 94.)

precipitation is, in the early stages, obviously out of all proportion to any visible damage of the endothelium, that the focus thus made visible is a site of toxin formation just as we must presume the myocardial Aschoff body to be, and that where mechanical effects intensify the damage, as at the line of valvular contact, there is a greater degree of the change and the production of those frequently projecting little masses called vegetations.

Pulmonary changes in acute rheumatic disease have of recent years become the subject of much argument. Some have stated that there are characteristic interstitial lesions, but Coburn (1931), Klinge (1933), and Masson (1937) have failed, as I have, to confirm this. On the other hand a very striking change is commonly present in the lung of cases dying in an active stage of the disease. The lung has a solid red somewhat translucent appearance in which can be seen the septal tissue as grey wet looking bands; the change has aptly been called splenization. On microscopical examination under low power (figure 51) there is seen an intense somewhat irregularly distributed congestion, sometimes with considerable haemorrhage into the alveoli, an alveolar exudate occasionally fibrinous, and a distinct oedematous swelling of the septae. In some parts an odd appearance is produced by the contrast between/

between alveoli filled with exudate and the empty alveolar ducts; the contrast is intensified by a peculiar membrane lining the duct and resting on the spurs of the alveoli (figure 52). This so-called "hyalin membrane" is best demonstrated by the use of the picro-Mallory method (figures 53-54). It takes generally a somewhat different shade of red from that seen in fresh fibrin and has a more homogeneous appearance apart from the cells lying in its midst. Masson believes that this substance is the product of partial lysis of the type of fibrin plug shown in figures 55 and 56, with subsequent plastering of the sticky material around the periphery of the duct by the action of the moving air. Occasionally these true fibrin plugs become organised (figure 57); this according to Masson is more likely to happen in the less mobile central parts of the lung. I have not seen sufficient evidence of organisation to allow comment on this view. Masson, although admitting that a similar picture may be seen after inhalation of Ypérite (= sulfure d'éthyle dichloré, Petite Larousse 1940), and in the newborn after inhalation of amniotic liquor, still considers that the changes described above are specific for rheumatic disease. On the other hand Farber and Wilson (1932) point out, partly from their own experience, that the hyalin membrane may be formed in influenzal, streptococcal/

streptococcal, plague, and vernix (inhalation of amniotic fluid) pneumonia, in death from poison gas, in cases of poliomyelitis after unsuccessful treatment in an artificial respirator, and in cases of cardiac failure where there has been congestion of the lung with increasing dyspnoea; they succeeded in producing a similar formation by injecting a partially decomposed fibrino-purulent fluid into the tracheas of dead animals that were then subjected to artificial respiration. As long ago as 1917, Shaw Dunn and McNee demonstrated the hyalin membrane in the lung of cases of Trench nephritis, and I am indebted to Professor Shaw Dunn for the opportunity of testing the reaction of this membrane with the picro-Mallory stain; in this material the appearances are exactly comparable to those in the rheumatic lung except that the congestion is not quite so intense and there are rather more polymorphs in the alveolar exudate. Professor Shaw Dunn also was good enough to allow me to examine lung from a poisonous gas casualty (probably phosgene); this showed fairly gross oedema and some fibrin threads scattered throughout but there was no definite formation of hyaline membrane.

Brannan and Goodpasture (1924) in a study of the hyaline membrane in non-rheumatic cases, state that with phosphotungstic haematoxylin the membrane does not take the blue stain characteristic of fibrin but a brownish colour. Masson/

Masson says that in the rheumatic lung also the membrane takes the brown stain, while with the trichrome method it takes a purplish colour between that of fibrin and collagen. In the lung of the present case the membrane shows as mentioned above, generally a purplish red colour with the picro-Mallory method, but in parts the membrane is more fibrillar and takes more distinctly the fibrin staining; with phosphotungstic haematoxylin a considerable proportion of the membranes in this material shows the blue staining and fibrillar form of fibrin. It seems therefore that the structure described as the hyalin membrane is formed of a coagulable exudate containing varying amounts of fibrin and that if this be not too solid and the patient live long enough, it will be distributed in the manner described. The degree of congestion seen in these acute rheumatic lungs is probably explanation enough for an exudate-containing coagulable material. The remaining question is whether an acute diminution of cardiac output is sufficient cause for this pulmonary congestion or whether there is some local change as Coburn suggests (1931, p.43); "The frequency of epistaxis, purpura, haematuria, haemorrhagic pulmonary solidification during the activity of the rheumatic process strongly suggests physiological changes resulting in increased permeability of capillaries and smaller blood/

blood vessels." Thus although it does not seem justifiable to accept Masson's statement that this is a specific change, it is an observed fact that this change is commonly seen in cases dying of active rheumatic disease; in the present case the changes are seen in a florid degree, explanation enough for the respiratory distress present shortly before death, while their occurrence here is a further confirmation of the rheumatic nature of the mother's disease. There is nothing in the morbid anatomy of the mother to suggest that she had suffered from an earlier attack of rheumatic disease.

The findings in the foetal heart are strikingly different from those in the maternal heart. Apart from haemorrhages the only lesions seen are in the valves; they are illustrated in figures 58 to 61. The first of these shows the posterior mitral cusp with a cellularity toward the contact surface which is distinctly greater than anything seen normally; many of these cells have somewhat vesicular muclei with slight lobulation. Figure 59 shows a more intense cellular infiltration with a fair proportion of polymorphs; the appearances are indeed almost those of a septic inflammation but despite this there is no sign of any vegetation formation. Figures 60 and 61 are of a more focal type of lesion; the latter is from the tricuspid and shows not only mononuclear and polymorphonuclear cells but/

but also quite definite evidence of nuclear remains and necrotic debris. No organisms have been demonstrated in these valves. The five blocks of the foetal heart were examined by serial section; apart from the changes in the valves, no lesion of endothelial or subendothelial tissue was found. The myocardium, as did also the pulmonary tissue, showed merely engorgement and haemorrhages.

Thus in the mother we have not only changes which I believe can be accepted as rheumatic but a group of these changes that signify an extraordinarily severe onslaught of the disease. Whereas in the foetal heart the only changes seen fail to correspond with any known manifestation of rheumatic disease.

COMMENT ON THE RHEUMATIC CASE.

In the tissues of the mother's heart there is evidence which on present day knowledge must be considered as proof that her infection was rheumatic. Further, the character of the changes points to a peculiarly acute and severe form of the infection, resembling in many ways the fulminating rheumatic pancarditis occasionally seen in children. Despite this extreme severity, however, the changes found in the foetal heart can in no way be accepted as characteristic of rheumatic disease. This dissimilarity of histological appearance in the two hearts may mean firstly that the rheumatic infection even at such a degree of virulence is incapable of crossing the placental barrier. It is of interest therefore to note the types of infection known to produce intrauterine disease. Alpers and Patten (1936) in their review of this subject have shown that the foetus can be infected by coccaceae (to which may be added a case of gonococcal transmission reported by Hellmann (1926) and one of scarlet fever described by Liddell and Tangye (1916), by spirillaceae, bacteriaceae, bacillaceae and mycobacteriaceae. They also accept transmission of smallpox, measles, malaria, and syphilis, to which may be added the cases of encephalitozoic infection recently reported by Wolf and/

and Cowen (1938). Thus intrauterine disease has been reported as due to representatives of the three main groups of infective agents, the schizomycetes, the viruses, and the protozoa. It is not justifiable however, to assume that the infective agent of rheumatic disease does not belong to any of these groups.

The second question raised is whether the foetal heart can be a less suitable nidus for the rheumatic infection than is the heart of the child. In answer to this it can be stated quite definitely that, down to infancy at least, the younger the child the more likely is rheumatic disease to involve the heart. Also it is known that so far as pyogenic infection is concerned, the foetal heart and pericardium are not immune (Berblinger 1921, Cruickshank 1930, Farber and Hubbard 1933, Bartak 1935, Feldmann 1937).

A third problem arising from the dissimilarity of the two hearts, is whether foetal tissue fails to react to the rheumatic infection in the characteristic morphological way. Wohlwill and Beck (1930) have shown that the reaction of the fixed cells of the tissues is the first defence mechanism seen in the foetus, whereas a polymorphonuclear response to infection is not produced before the sixth month. So far as is known, the tissue reactions of the foetus in its later months are remarkably similar to those seen in extrauterine/

extrauterine life; this applies not only to the naked eye appearances of pneumonia, tubercle formation, and characteristic skin rashes but also to the histological findings of purulent inflammation, reparative fibrosis, and tuberculous follicles (Whitman and Greene 1922, Tingle 1926, Palmer 1928, Cruickshank 1930, Alpers and Patten 1936). A further aspect of this question of reaction is the underlying serological state; some have considered that an abnormality in this, a state of so-called hyperergy, is the explanation of the unusual tissue changes seen in rheumatic disease. That the typical morphological changes of an allergic disease such as tuberculosis can indeed be formed in the foetus has been shown by Whitman and Greene (1922).

The transmission of serological activities to the human foetus, as tested in vitro, has been studied by Ratner et al. (1927) and Felsen et al. (1937). They accept the passage of antibodies for diphtherial and scarlatinal toxins, for tetanus, poliomyelitis, and measles, while the latter authors have shown an apparently quite unobstructed transference of antibodies, bacteriolysins, against the streptococcus viridans. In contrast to this unobstructed passage, Wiener and Silverman (1940) show that the titre of certain antibodies in the foetal serum is only one eighth of that in the maternal serum, but Lippard and Wheeler (1936) in their/

their studies on betahaemolytic streptococcal infection report the presence in the foetal serum not only of anti-haemolysin in titre fully equal to that of the mother, but also of antifibrinolysin at a concentration actually higher than in the mother's serum. Thus from what is known of the serological state of the foetus, there seems no obvious reason why the foetus should react in so very different a way from the mother. No very definite conclusions can be derived, however, from the data, and the only hypothesis suggested is that the damage in the mother's heart, in all its severity, was the result of interaction of a simple infection, possibly streptococcal with tissues which had been prepared or sensitised in the past, that as it were the Dragon's teeth had been sown in the mother's heart before the foetus was conceived.

Thus to summarise the above, the failure to prove intra-uterine infection by the agent of rheumatic disease gives us no immediate clue to its nature since cases of foetal in-fection have been shown to be caused by examples of the three main types of infective agents, schizomycetes, viruses and protozoa. The possibility that the heart of the foetus would not be the best site for diagnostic exam-ination is improbable in view both of the high incidence of cardiac damage in younger children suffering from acute/

acute rheumatic disease, and also the known susceptibility of the foetal heart to pyogenic infection. The distant possibility still remains, however, that the reaction of the tissues to rheumatic infection are different in later foetal life from those seen in postnatal life, even though this has been shown not to be so in other diseases. The study of the serological state of the foetus suggests no obvious reason why the foetus should fail to behave in a manner similar to the mother.

It remains to assess the actual changes in the foetal valves. The lesions themselves do not have the appearances as seen in the early stages of rheumatic inflammation of the child's cardiac valves; in this case the infiltrations are in a distal portion of the valve whereas in the rheumatic valve they are obviously most intense at the root of the valve, and spread distally from there. The cellular infiltration in this case is not only confined to a distal part of the valve but is more intense there than has been seen in any rheumatic case. Despite the extreme degree of valvulitis there is not the slightest suggestion of vegetation formation. It can thus be stated that the histological picture in the valves is neither characteristic nor even suggestive of rheumatic disease, while the complete absence of morbid change in the auricles, in the auriculo-

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auriculo-ventricular region, or in the myocardial stroma emphasises the dissimilarity.

The only known lesion of the foetal valve to which the present case could be likened is the so-called toxic endocarditis. After an intensive search for examples of this lesion, one small focus was found (figure 63); this apparently comforms to the descriptions given for toxic endocarditis but it is a much more definite lesion than any of those illustrated in the publications on this subject. It is, however, a very slight abnormality in comparison with the changes found in the present case. Thus the present case shows a degree of valvulitis greatly in excess of any of the illustrated forms of toxic endocarditis; some of the verbal descriptions, however, of the more severe cases of toxic endocarditis would fit the picture and so it seems impossible to do otherwise than accept this as toxic endocarditis. It certainly bears no resemblance to any other abnormality thus far described in the valves of the foetal heart.

CONCLUSION.

The work detailed above began with a study of the morbid anatomy of acute rheumatic disease. Out of it arose the need for research into technical methods; this was maintained concurrently and has not only provided results of general value both for present use and for future study, but has also allowed the observation and illustration of certain changes not previously described in the rheumatic heart.

My studies on acute rheumatic disease have been compared and correlated with those published by other investigators; on these bases there has been built up a composite histological picture which is thought to be characteristic of the disease. On this the present thesis is founded.

The thesis put forward, in opposition to the accepted belief, is that the transmission of acute rheumatic disease to the foetus cannot be accepted as proved. Critical examination of the published clinical data on rheumatic disease in general, makes this transmission seem improbable, while a review of the published cases of foetal rheumatism shows that in none is the diagnosis adequately established. The present case of possible transmission, the first to receive microscopical study of the tissues, has revealed the/

the absence of any characteristically rheumatic lesion in the foetal heart. Definite changes, however, are present in the foetal valves, and in conjunction with the various clinical and anatomical abnormalities in the reported cases of foetal rheumatism, they must be taken to mean that the foetus can be affected in some way or other, even though the result is not the complex, recognised clinically or histologically as acute rheumatic disease. On the grounds detailed above it is only possible to say that the manifestations observed in the foetus are those of a reaction to toxin and not those of acute rheumatic disease.

Thus an observational study of the morbid anatomy of acute rheumatic disease, based on an improved technical procedure, and a study of the pathological changes occurring in the foetal and infantile endocardium have together been focussed on the question of the intra-uterine transmission of acute rheumatic disease. The conclusion drawn from this is that no confirmation has been found for the accepted belief that acute rheumatic disease may be transmitted to the foetus.

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APPENDIX
ON THE TECHINCAL ASPECTS OF THE HISTOLOGICAL STUDY OF THE HEART

The continued addition, over the last fifty years, of newly found observations on the morbid anatomy of acute Rheumatic Disease may be explained by a change in the disease itself, but the possibility exists that gradual improvement in histological technique has played a large part in revealing the changes noted by the later workers. With this possibility in mind an attempt was made to re-assess critically the accepted technical methods. In the study of the rheumatic heart it was considered necessary not only to examine the finest changes under the high power but also the distribution of the changes, and so the need arose for thin and precise sections from blocks of considerable size; the commonly used routine methods failed to fulfil these demands with this rather difficult tissue, and so controlled tests were made of various suggested fixatives and methods of impregnation. The results of this work and the modifications introduced are detailed below; these have proved not only satisfactory in the study of the rheumatic heart, but also of general histological value, and as such have been adopted by colleagues for their own work.

Langeron (1934, p.322) states, "la fixation est la pierre angulaire, le fondement de toute bonne histologie" and though, as will be shown later, it is no more than the first step, it is the basic essential of good histology. It is virtually impossible to give a compendious definition of good histology, for the standard of any single worker is inevitably based on his training, and if he be accustomed to and satisfied with the results of a highly acid fixative then lysed blood and rather empty nuclei will seem no loss to him. Tennyson's phrase, "We needs must love the highest when we see it" (Guinevere), is not always true of the morbid anatomist's reaction to a section, but even though every histological section is no more than a consummation of artefacts, seen in a glass darkly, there does exist a certain standard of excellence. And on this, in part aesthetic and otherwise utilitarian basis, fixatives can be relatively judged. Certain absolute demands can be formulated for general histology, and a fixative solution should fall short of producing these, only when it provides some specific action not otherwise procurable, as for example with Flemming's solution. A fixative must have such penetrating power that its inhibition of enzymatic action in the tissues will occur rapidly and so far as possible contemporaneously throughout the tissue. In its/

its interaction with the tissue it must form the same fixation compound throughout the mass and to a uniform degree, not producing a different degree at the periphery or in the depths. It must preserve certain generally recognised elements in the tissues, and those with diagnostic significance. There should be, either as an effect of the primary solution or through the action of a secondary fixative a stabilising coagulating effect that will prevent immediate maceration or swelling, distortion or retraction, or the later production of these changes by the dehydrating and clearing solutions. To prevent ambiguity in photomicrographs it should not produce irremovable deposits or refractory behaviour to the standard staining methods. For the pathologist, the cardinal virtues of good fixation and good after treatment are the easy visual separation of the various elements in the mounted section, and the possibility of an easier rather than a more difficult diagnosis.

Judged by these standards, the commonly used solutions of formalin in water or saline, neutral or acid, are poor fixatives. They penetrate slowly as has been shown by Underhill (1932) although it is perhaps worthy of note that a block of liver some 2 cm. square, after 72 hours fixation in formol saline (10 per cent of commercial formaldehyde) still showed a small area in the centre with a distinct/

distinct pink colour in marked contrast to the grey shade of the remainder, an area which although presumed to have escaped fixation was on examination of the final section indistinguishable from the tissues at the edge of the block. Before dehydration this tissue received treatment for 24 hours with saturated sublimate (saturated aqueous solution of mercuric chloride) which may well have stabilised the tissue, but the significant point is that despite the colour appearances there was no obvious evidence that the central area had undergone more autolysis than the periphery. Formol solution continues to penetrate (Underhill), a faculty which is of course not possessed by all fixatives, but this may not catch up on autolysis in larger pieces of tissue or where the consistency is dense. As a fixative it fails to harden the tissue quickly enough to allow easy trimming of large blocks, whereas if the desired block be cut at the beginning there is a high probability of its undergoing twisting in the fixative, especially if two types of tissue such as muscle and connective tissue are present, a twisting that is certain to be aggravated during dehydration. Tissues fixed in formalin show a high final coefficient of shrinkage (Underhill). The process of dehydration has to be very gradual and slow after formol fixation. Finally, in post mortem material or in tissues the site of haemorrhage/

haemorrhage, there is a strong liability to the formation of an intractable deposit in relation to the blood. By itself formalin solution is a bad fixative for post-mortem material.

The sublimate-bichromate group of fixatives have a small but valuable place in this work. Zenker's solution is too acid for human post-mortem material. Zenker-formol a more slowly acting mixture seems to produce an intensified form of the formalin deposit in relation to blood. Zenker solution without acid or formalin has excellent properties in the fixation of small portions of soft cellular or open tissues but unless the material is fairly fresh it tends to increase the lysis of red cells. The bichromate element of the mixture penetrates slowly and the long fixation needed for large portions of tissue produces an overchroming of the surface which vitiates staining. The bichromate is reputed to continue its action on the tissue even after embedding in paraffin, but I have not yet experienced this reported difficulty in staining such tissue. None of these mixtures is therefore a good fixative for large or tough portions of post-mortem material.

Bouin's solution is much too acid for human post-mortem material, even if the content of acetic acid is much reduced, in that blood is lysed and the connective tissue /

tissue assumes a swollen gelatinous form. Tarkham (1931) has shown that picric acid by itself produces swelling and dissociation of ligament and tendon; while Underhill proved it to be a slow penetrator. The modifications suggested by Allen (McClung & Allen, 1937, p.561) which contain urea as a reputed aid to penetration, were tried but found to be little more penetrant than the simple picroformol solutions. They are good fixatives for the cellular tissues of fresh surgical material. Hollande's solution (Langeron, 1934, p.345), a picroformol mixture containing copper acetate, with diminished or no acetic acid is an excellent fixative for fairly fresh post-mortem material, but for the present purpose its penetration was too slow and there was still some liability to distortion during dehydration. Thus none of the picroformol type of solutions was considered satisfactory for the study of the human heart.

The Susa fixative of Heidenhain (Romeis, 1932, p.91) which is a formol-sublimate solution containing acetic and trichloracetic acids, has the advantage of making tissues rather more plastic than any other fixative but its action, even when the acetic acid is omitted, of lysing the blood and of making the connective tissue swollen, made it seem undesirable as a fixative for post-mortem material.

Saturated aqueous mercuric chloride, corrosive /

corrosive sublimate, despite its high coagulant activity, is a rapid penetrator but it causes distortion of the tissue during fixation and produces a block which is difficult to cut; further, unless the tissue is very fresh, the blood is usually lysed.

The ideal fixative for post-mortem material is formol-sublimate, 90 c.c. of saturated aqueous corrosive sublimate with 10 c.c. of commercial formalin, a stable mixture that seems to combine the coagulant virtue of the corrosive with the more kindly action of the formalin. The coagulation of tissue is more rapid and less destructive with this than with any other known fixative and so it becomes possible to trim and select blocks from larger portions after some four or five hours fixation. The degree of fixation already achieved means that the faces thus chosen will remain more or less undistorted during further fixation. The main disadvantages of this solution are that in post-mortem material it produces a very obvious deposit in relation to the blood, and if the case be at all old it exacerbates the lysis of the blood. Acidifying the mixture leads to less deposit but much more complete lysis; an attempt to strike a medium by partial neutralisation of the acid (5 per cent, acetic acid) with potassium hydroxide, was occasionally successful but in some cases it produced painfully evident/

evident and quite irremovable deposit. The final technique was the use of formol-sublimate for four to six hours followed by three or four days in saturated aqueous sublimate. If the material is long dead then an hour or so in 5 per cent, aqueous formalin fixes the blood with minimal lysis; this is followed by formol-sublimate to give a coagulating effect, so that the blocks may be trimmed three or four hours later; after a short further spell (half an hour appears ample) in the formol-sublimate the tissue is transferred to saturated aqueous sublimate. If the tissue is removed from the formalin-containing fixative within six hours there will very rarely be any evidence of formalin deposit in the blood. This secondary use of saturated sublimate does not seem to have the undue hardening effect seen when it is used as a primary fixative. The tissue is left in the sublimate for three or four days at least, and can be left there for a month with no obvious deterioration. Thus the technique of fixing a heart is in summary; opening of chambers in the usual way for examination, with avoidance of water or rough sponging; fixation, in formol-sublimate if fairly fresh, or 5 per cent formalin if old with transfer after an hour to formol sublimate; the semilunar valves are loosely packed with cotton wool soaked in fixative: various cuts are made to/

to aid penetration, ones which will, despite the bulging that ensues, not prevent the later selection of desired portions; blocks are cut after 5 to 6 hours, (these may be thick and are then bisected the next day, undercutting to reveal the better fixed face) and returned to the fixative for half to one hour: tissues are finally transferred to saturated aqueous sublimate. At the very least the blocks suggested by Gross et al (1930) should always be taken; since they include all the significant areas for examination of the rheumatic heart. It is possible that this empirically discovered sequence of fixation fulfils Langeron's demand, "que la mort des cellules doit être immédiate et que leur coagulation doit être médiate", (p.322) as far as is compatible with the need of being able to trim within a few hours the faces which are to be ultimately examined.

It was hoped that saturated sublimate might be the answer to the pathologist's search for a solution in which tissues could be left indefinitely, but it was found that one year's immersion produced a deterioration in the ultimate definition and staining comparable to that seen in tissues stored in 30 per cent. glycerin or 60 per cent alcohol, both of which appear preferable to 10 per cent formalin. The shorter time of immersion, up to three or /

or four weeks, however has a beneficial effect in improving the ultimate staining and in consolidating the tissue without any distinct hardening. This consolidating or stabilising effect is difficult to define, but its advantages are quite distinct; the result may be described as the formation of a firm but plastic coagulum which with a minimum of shrinkage, distortion or swelling continues to fill the space originally filled by the cytoplasmic colloids. The "ferment" on which the oxydase reaction depends is destroyed by corrosive sublimate (Shaw Dunn 1911). In the earlier stages all the tissues were treated with iodine in alcohol during dehydration but for the last two years this has been omitted without any clear evidence of damage to the razors. In fact during the last four years an increasing percentage of the routine surgical tissues has been fixed in formol-sublimate and no attempt has been made to remove the mercury during dehydration. Despite the many warnings of the earlier histologists on the danger of sublimate crystals, our finding has been that the general standard of the cutting has improved rather than deteriorated; this applies not only to the tough specimens such as skin lesions but also to such delicate tissue as uterine curettings which are received directly into formol-sublimate.

The Further Outlook on Fixation of Tissues with Special Reference to the Pathologist's Work.

Of the many modified or new fixative solutions suggested in the literature of the last 40 years, the majority have come from those working with the tissues of animals other than man. The increase in number of these solutions is probably due to a growing realisation among comparative anatomists that the tissues of different species demand different techniques, and it is interesting that this distinction is now applied to the very staining methods (Scott 1940). The pathologist is of all the histologists the most concerned with human tissues but in the stress of routine work and burdened by the necessity of a diagnosis he is all too apt to accept a universal validity for fixatives hallowed by time and occasional successes in the past. It is obvious that this attitude of mind has vested in it the seeds of decay but there exists a present trouble, serious enough, and that is the failure to reach the same standard of success as did our elders with formalin fixation. It would appear on olfactory grounds that the chemical constitution of comparatively expensive formalin solutions is still not uniform, and some writers (Russell, 1939) emphasize the histological importance of using some particular brand.

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A comparative study of the formalins produced by British Drug Houses, by Schering, and by a local manufacturer failed to reveal any difference in histological merit; none had apparently the virtue possessed by formalin as a fixative 30 years ago. It is believed that the procedures given above constitute the best schema for the fixation of post-mortem tissues but much remains to be investigated before the pathologist can say that opportunities are not being wasted. The method as suggested is expensive in that the salts of mercury are dear, and it is possible that secondary fixation could be as well if not better done by other metallic salts. Lead chloride advocated by Mallory (1936) as a mordant for myelin in peripheral nerves following formalin fixation shows itself to have many of the virtues of mercuric chloride judged by stabilisation of tissue, ease of cutting, and by the disposition and precision of the colours on haemalum and eosin staining. Zinc chloride, the fixative suggested by Unna (1913) for the study of plasma cells has been found to be an execrable primary fixative, very much worse than mercuric chloride, and at a concentration of 4 per cent has clearly less merit than the mercuric salt as a secondary fixative. The salts of copper, as present in Hollande's fixative, have excellent mordanting properties, shown by the brilliance of staining/

staining in tissues fixed primarily or secondarily in this solution; they do not, however, have the same stabilising effect as mercuric chloride or lead chloride. It is possible that the stabilising value of these metallic salts is directly related to their weight; (the specific gravity of mercury is 13.6, of lead 11.35, of copper 8.95, of zinc 6.92); the mordanting value seems if anything to run in the opposite direction. Investigation of the heavy metals as primary fixatives is not yet complete and some idea of the magnitude of the task can be seen in the work of Schiller (1930), a strong advocate of Uranium; to this has still to be added their use as secondary fixatives.

A further line of research for the pathologist is the problem of the temperature of fixation. McClung and Allen (1937,p.564) point out the very different type of action shown by Flemming's fluid when used at 37°C. and at 0°C., and advise its use at 0°C. whereas they state that the picroformol solutions should be used at 35 to 40°C. In an attempt to make large undistorted sections of breast tissue, the whole breast as received from the surgeon was immersed in a bowl of formalin or formol-sublimate and placed in a refrigerator (minus 15°C.) for six hours; it was then removed, sliced, put back into the fixative and left at room temperature. This manoeuvre was carried out/

out on breasts with obvious carcinoma from which apparently involved glands were available for ordinary histological examination; the tumour in the breast in these cases showed a very bizarre appearance, somewhat reminiscent of mucoid carcinoma. A controlled experiment was then made by bisecting a breast through a scirrhous carcinoma present in its substance, fixing one half as detailed above and taking portions from the other half for the usual method of examination. This confirmed the suspicion that at least this method of cold fixation is useless for the pathologist. Heat as a fixative and coagulant has generally been used for the sake of speed but in certain tissues it appears to have a specific value. Seminoma of testis is a tissue which is extraordinarily difficult to fix well but of the various methods tried quite the best result ever achieved followed fixation for 10 minutes in water just off the boil, followed by transfer to 95 per cent. alcohol.

Apart from experimental work on animals, the pathologist seldom deals with absolutely fresh tissues; this is believed indeed to have some advantages. The passage of one or two hours between surgical removal and fixation may mean the loss of certain intracellular formations, but in the absence of bile or organisms little else is lost and it seems to give a block which fixes more evenly and which cuts better. /

better. If muscular tissue is present, it is of advantage to postpone fixation until the excitability of the muscle fibres has disappeared. The problems of the immediate fixation of fresh animal tissue are not confined to the pathologist and have therefore not been the subject to special study. There are still sufficient difficulties facing the pathologist, not the least of which is to find the ideal compromise that will give tissues without obvious autolysis. Regulations and human sensibilities mean that delay often intervenes between death and the performance of the post-mortem examination, and certain tissues show a hopeless degree of autolysis within a few minutes as has been shown by Rosenberg (1940) to happen in the duodenum of the turkey, and presumably likewise in man. The pathology of the gastric mucosa of man was in part unknown until the method was adopted of running formalin into the stomach immediately after death (Magnus 1937) and the difficulty of cutting freshly fixed muscle avoided by the ingenious expedient of loosening strips of mucosa for study. In an attempt to dissociate the enzyme-killing and anti-putrefactive action of a fixative from its coagulating effect, some experiments were made by introducing some 10 c.c. of saturated sodium fluoride by needle into the abdomen of guinea-pigs, killed one hour before by bleeding. The bodies/

bodies were left lying at room temperature; after 24 hours, portions of stomach, small and large intestine, liver, spleen and kidney were fixed from one fluoride and one untreated animal, and similarly at 48 and 96 hours. Tissues from the control animal fixed one hour after death were better preserved than those from any of the experimental animals. There appeared to be little value in the use of the fluoride but what was most striking in this experiment was the absence of any increased autolytic or putrefactive change in the untreated animal dead for 96 hours. The guinea-pig would thus appear to be unsatisfactory for such an experiment. It has not been concluded that the value of fluorides or other substances with antiferment activity has been fully explored and their use in aiding the pathologist is something for the future. Such methods as these, as likewise the current methods of so-called embalming in which a formalin-glycerin-phenol solution is run into the vessels, diminish or completely destroy the possibility of bacteriological investigation by cultural methods at post-mortem.

On the after treatment of the fixed tissue:

The method of dehydration of tissues has a considerable effect on the ease of cutting and on the ultimate image, as is suggested by the multiplicity of methods in the literature. It is old knowledge that tissue fixed in formalin needs very slow dehydration but not so fully realised that the prolonged action of absolute ethyl alcohol can produce an irreversible hardening; as Johansen (1935) puts it, not only is the water replaced but the water absorbing capacity of the tissue is destroyed. It may indeed be suggested that absolute ethyl alcohol produces a form of denaturing, a removal as it were of the bound water of the cells, and that some of the recent more kindly dehydrants, such as butyl alcohol, stop short of this intimate dehydration. During the early stages of the work before the possible use of butyl alcohol had been appreciated, an investigation was made of the use of phenol during dehydration. This method, (Lendrum, 1935), has a definite value and has now been in routine use for some years in the dehydration of tough surgical tissues; the general plan is to allow the tissues during dehydration to lie overnight in 95 per cent. alcohol containing 6 per cent of phenol. They are put next day into absolute spirit (methylated ethyl alcohol approximately 75 degrees over proof) for seven hours with one change, and

and thence in the usual way to alcohol and chloroform. Longer times in the absolute spirit give a distinctly poorer result and it is presumed that the phenol linked to the tissues can be released by the alcohol on longer contact. Two possible explanations of the benefit may be suggested: one is that the presence of the phenol exercises a true plasticizing effect on the colloids of the tissues, a possibility that has not yet been adequately explored but one that opens up interesting lines for the histologist since the organic chemist has in recent years found many substances with plasticizing effect. Another explanation is that the phenol slows up the attack of the absolute alcohol on the bound water of the tissues. As a clearing agent, chloroform was thought to be less hardening than xylol or benzol. Ralph (1938) found chloroform to be the best clearing agent after ethyl alcohol dehydration.

In the hope of avoiding the use of absolute ethyl alcohol, many substances have been proposed in recent years, most of these being miscible at one end with 95 per cent. or lower percentages of ethyl alcohol, and at the other end with the paraffin solvents. Examples of these are anilin (Painter, 1924) miscible with 50 per cent alcohol, and cinnamic aldehyde (McClung and Allen, 1937, p.257) miscible with 95 per cent. Both of these were tried on human /

human material and found to offer no great advantage, certainly not one commensurate with the unpleasantness of these substances. Since the combined celloidin-paraffin method of Peterfi is advocated by Romeis (1932, p.107) it was given careful study; in this method tissue is transferred from 95 per cent. alcohol to methyl benzoate, a fluid which not only tolerates a percentage of water but is also a solvent for nitrocellulose. The results obtained by the use of this method were better than those with the phenol-alcohol-chloroform method. Certain tissues, however, seemed rather more difficult to cut than with the control method; this was especially marked after fixation in solutions containing picric acid. The trouble appeared to lie in an unexplained occasional hardening or cornification of the celloidin. The method had definite merits but further investigation was postponed by the discovery of some contributions on the use of butyl alcohol.

N-butyl alcohol (butanol), $CH_3 . CH_2 . CH_2 . CH_2OH$, is a water clear liquid with a slightly butyric but not intolerable odour; it dissolves only one twelfth its weight of water but being freely miscible with ethyl alcohol it allows the preparation of a series of solutions such that tissues can be brought gradually to absolute butanol without undergoing the denaturing action of absolute ethyl alcohol. From/

From butanol tissue can be transferred directly to paraffin, although it is of advantage to use an intermediate step of butanol and paraffin. Unlike xylol, butanol is lighter than paraffin. The replacement of butanol by paraffin is a slow process and even small delicate tissues should be allowed to remain in the oven for four or five days. The larger and denser tissues of the writer's main study, the heart, need ten to fourteen days for impregnation. It was found that a prolonged stay in the oven fails to produce any obvious damage in the tissues; a piece of spleen from butanol, after three months in paraffin at 54°C. was found to cut easily and to show no cracks in the stained section. Stiles (1934) notes that with his insect material long periods of infiltration with hot paraffin at 58°C. did not harden the tissues, and suggests that it is not hot paraffin that causes the serious hardening of tissue during infiltration as Walls (1932) has surmised, but rather hot paraffin following certain types of dehydration and clearing. In this respect it is interesting that Tarkhan (1931) has shown that tissues dehydrated by ethyl alcohol and cleared by xylol, continue to shrink in medicinal paraffin (B.P.) at room temperature. The original publication on butanol is apparently that of Mlle. Labraud (1921) whose series is given in the table below; she mixed equal parts of butanol/

butanol and 95 per cent alcohol, and made dilutions with water to give a series fairly comparable to the usual ethyl alcohol series. The amounts given in her paper have been changed for purposes of comparison, to show amounts of absolute ethyl alcohol, butanol and water in 100 c.c. quantities. After this the publications of special interest to a pathologist were those of Stiles (1934) and Lang (1937); the former's series is apparently of quite empirical nature. Lang's suggested dilutions are based on the theoretical possible one-phase mixtures of the three liquids with an attempt to keep the ethyl alcohol content as low as possible; this, although seemingly desirable on theoretical grounds, may not be wise when there is much routine use of the bottles, because of the danger of exceeding the water tolerance of the butyl-ethyl mixture and thus forming a two-phase system.

	Water	70	40	20	5	-	-
Labraud	Ethanol	15	29	39	47.5	-	-
	Butanol	15	31	41	47.5	100	100

	Water	49.5	22.5	4.5	-	-	-	-
Stiles	Ethanol	40.5	52.5	40.5	25	-	-	-
	Butyl	10	25	55	75	100	100	100

	Water	95	89	82	70	57	43	30	18	9	3	-
Lang	Ethanol	5	11	16	23	28	30	30	27	21	12	-
	Butanol	-	-	2	7	15	27	40	55	70	85	100

Stiles's simple method of preparing his dilutions is given in his paper and quoted in Muir and Ritchie's Manual of Bacteriology (1937). Mlle. Labraud's dilutions were not tried as they were only discovered recently, but a thorough trial has been made of Stiles's gradation and of the one of Lang's gradations especially commended by him. It was found that with human tissue, both fresh and post-mortem, that the method suggested by Stiles gave the better results; presumably the ethyl alcohol has virtues that are overshadowed in the usual methods. This method of dehydration has now been in constant use since 1934. It has several outstanding advantages and so far only two obvious drawbacks. It is unfortunately a slow method and sometimes with the tougher tissues there is a peculiar dryness in the tissue even when apparently fully embedded; this failing may possibly be due to overrapid dehydration and impregnation, but this was not fully investigated at the time because of a further improvement that was then made in the technique, and will be described below. Some of the/

the earlier workers who failed to get good results with butanol almost certainly allowed too short a time for impregnation with paraffin. The histological advantages of the method are obvious in the stained section; if impregnation has been completed the tissue cuts better than after Peterfi's methyl benzoate celloidin-paraffin method, and it had been already found that, with the exception of tissues fixed in solutions containing picric acid, the Peterfi procedure was preferable to the standard ethyl alcohol-chloroform series. The improvement in tissue treated by butanol was seen after all the standard fixatives, particularly after fixation in formol saline or Kaiserling. These fixatives as already pointed out have not been found satisfactory in the study of cardiac tissue but during an investigation on the Paneth cell reported elsewhere (Kerr and Lendrum, 1936) it was found that they preserved the granules of this cell better than fixatives containing corrosive sublimate. It became obvious at this time that not only did the butanol method give better histological preservation but it also improved the staining qualities of the tissue thus fixed. Stiles also in his material found that the Peterfi method was better than the standard but not as good as the butanol method. The schedule advocated by Lang gave tissue which cut as well as that treated by Stiles's method but there was a /

a slight swelling and lack of definition in the final picture, similar to that seen in tissues, prepared by the two Dioxan techniques tested (McWhorter and Weir, 1936, and Mossman, 1937); for this reason these techniques were soon dropped and Stiles's method made the routine. Perhaps the outstanding advantage of the butanol method is the fact that tissue can be left without harm in any of the dilutions; the general routine followed has been to move the tissues once a day but an extra twenty-four hours apparently does no harm, and it is probably of benefit to leave tough tissue for some days in the last butyl bottle. Stiles found that sections from aphids stored in this reagent for one year before embedding were perfectly satisfactory.

At this stage in the work it was decided to reinvestigate the possibilities of Peterfi's principle of double embedding, for it had been realised that impregnation with thin nitrocellulose gave a support to delicate tissues which was of histological advantage and added something which the butanol technique did not give. The obvious drawback to the double embedding method was the hardening or cornification of the nitrocellulose, a change which under other circumstances had been the origin of much research in the cellulose and later the synthetic plastic industries. There it had been found that a film of nitrocellulose, for example/

example cellulose paint, tended on drying to become brittle and so break at corners; the addition of castor oil to these synthetic paints was tried and found to impart a plasticity to the film. This, however, was but a temporary improvement and after a time the castor oil, which belongs to the non-solvent group of plasticizers, tended to come out of the paint, a fact that was only too obvious on the motor cars in the early nineteen twenties. Since then a number of substances has been found showing both considerable stability and a distinct plasticizing effect on nitrocellulose film. The utility of these substances has been further increased through the realisation that many are also capable of exerting a plasticizing effect on synthetic plastics. This latter action has been utilised in histological technique by the incorporation of one of these plasticizers, tricresyl phosphate, in a xylol solution of a glass clear plastic, a polymerised styrene, to replace Canada balsam (Kirkpatrick and Lendrum, 1939). The use of this same substance, tricresylphosphate, was tried in the standard Peterfi method. Normally in this method after the tissue has lain for some time in the methyl benzoate-nitrocellulose solution, it is transferred to chloroform or benzol in which the nitrocellulose is insoluble; the tissue with its impregnation of nitrocellulose thus precipitated is

is then transferred to paraffin for its second impregnation. Tricresylphosphate is soluble in chloroform, and theoretically it should be leached out from the nitrocellulose when the tissue is transferred to chloroform, but in practice this loss is apparently not complete in that the block has a plasticity which is not present if the tricresylphosphate is omitted from the technique. Thus it is presumed that the improved consistency of the block is due to a plasticizing effect brought about by the tricresylphosphate and not completely removed by six to sixteen hours' immersion in chloroform. It is of interest that this modification allows the use of tissues fixed in picric acid solutions; it would appear that the picric acid had, in the original method, intensified cornification of the nitrocellulose. Almost all plasticizers are soluble in the fluids which are both nitrocellulose precipitants and paraffin solvents, such as benzol, toluol, xylol, chloroform, and heptane, but through the courtesy of Dr. Gourlay of Imperial Chemical Industries it became possible to try out a plasticizer (I.C.I. number 120 - 501) relatively insoluble in heptane. This was used in place of tricresylphosphate and in comparable amount along with the nitrocellulose in methyl benzoate; from this solution the tissue was transferred to heptane and thence to paraffin. The end results were, however, inferior/

inferior to those by the tricresylphosphate and chloroform method. The form of nitrocellulose used in this work was in the earlier stages the purified pyroxylin marketed by Schering as Celloidin, and later the equally satisfactory pyroxylin, Necoloidine, made by Imperial Chemical Industries.

As the addition of a plasticizer to Peterfi's method appeared to have prevented cornification of the nitrocellulose, it was next decided to combine butanol dehydration with double embedding. After saturation with butanol, the tissue was left for 24 hours in equal parts of butanol and methyl benzoate, and then for the same time in pure methyl benzoate. Thence it was transferred to methyl benzoate containing 2 per cent. of nitrocellulose and 1.5 per cent. of tricresylphosphate; there the tissue was left for 7 to 14 days. It was found advantageous to use these long times rather than the brief immersions advocated by Peterfi. To fix the celloidin both chloroform and benzol have been tried; although Romeis prefers the latter, chloroform seems to me to be the better. The tissue is left in the oven for eight to twenty-four, or even thirty-six hours, depending on the size and consistence. Romeis states that heat has a crumbling effect on the nitrocellulose but this danger is apparently avoided or at least much reduced by the action of the plasticizer.

This now rather lengthy although highly flexible method gave clearly better results than any other method yet tested and it remained to be seen if any short cuts were possible which would retain the advantages gained. As a working hypothesis it was accepted that the success of the method rested on three hitherto unrelated principles, the use of butanol with the avoidance of absolute ethyl alcohol, the combination of this excellent type of dehydration with the double embedding method of Peterfi, and the use of a plasticizing substance in association with the nitrocellulose.

With the full method, outlined above, as standard, experiments were next performed to test the use of tertiary butyl alcohol, $(CH_3)_3 \cdot COH$, (trimethyl carbinol), as advocated by Johansen (1935). The series were exactly comparable except that tertiary butyl alcohol was used in the experimental set and n-butyl alcohol in the control. The results shows no obvious gain from the use of the tertiary alcohol; its odour is unpleasant. Isobutyl alcohol, $(CH_3)_2CH \cdot CH_2OH$, also has an unpleasant odour, and is said to cause headaches on inhalation (Baird, 1936); it was not tried.

Methylal, $CH_2(OCH_3)_2$ was tried according to the method suggested by Dufrenoy (1935) but as it showed no advantage/

advantage over the standard, its uses were not further investigated.

The next attempt was to shorten the method by so modifying n-butyl alcohol that it would become a solvent for nitrocellulose. No known nitrocellulose is soluble in n-butyl alcohol, but the addition of small quantities (10 to 20 per cent.) of ketones such as acetone, or alkyl acetic esters such as butyl acetate allows the solution of 3 per cent of nitrocellulose. Tissues were brought to butanol in the usual way, and thence to butanol containing 20 per cent. of butyl acetate, and then to this mixture containing 3 per cent. of nitrocellulose and 2 per cent. of tricresyl phosphate. Here they were left for the same time as the control tissues were in the methyl benzoate solution of plasticized nitrocellulose, and then both sets were fixed in chloroform and embedded in paraffin. Several series were again compared and again the standard method proved the better.

The next substance that seemed to justify investigation was ethylene glycol monoethyl ether, $\begin{matrix} CH_2 - OH \\ CH_2 - O - C_2H_5 \end{matrix}$ (Cellosolve), a substance which, presumably in virtue of the presence of both an ether and an alcohol group, is a nitrocellulose solvent and is miscible with water. Its valuable use as a solvent for aniline dyes has been reported

reported elsewhere (Lendrum, 1939). In the treatment of tissues it was used both as a substitute for methyl benzoate in the standard method, and also in a series without butyl alcohol. In this latter scheme, tissues were transferred from 50 per cent ethyl alcohol to equal parts of 50 per cent ethyl alcohol and cellosolve and thence through three stages of pure cellosolve to cellosolve containing 4 per cent nitrocellulose with 3 per cent tricresylphosphate. Fixation of the nitrocellulose was done by chloroform and followed by paraffin impregnation. This schedule was rather more rapid than the standard, but the results were not so good, although they proved better than the original Peterfi method. The use of cellosolve in place of methyl benzoate in the standard method gives results which if inferior to the standard are but very slightly so. For over a year now tissues have been put through both series, and from examination of a large number of tissues the impression has been gained that the methyl benzoate method is slightly better.

The Further Outlook on After-Treatment of Fixed Tissues.

Ample room still exists for the application of modern discoveries in organic chemistry to the still highly important technique of histology. The more immediate lines of investigation seem to me to include the wider use of the/

the newer solvent mixtures, starting with such simple mixtures as the butyl-acetone mixtures suggested by Lang, and going from them to solutions of plasticized nitrocellulose in butyl-acetone. Many alkyl esters such as methyl salicylate, butyl lactate, or ethyl lactate, this last much cheaper than methyl benzoate, are not only solvents for nitrocellulose but have some power of plasticizing the mass. Preliminary experiments with ethyl lactate have proved disappointing. Acetate cellulose, readily available in many hospitals from discarded "safety" X-ray film, may be worthy of trial in place of nitrocellulose. It is for example soluble in dioxan but difficulty has been experienced in finding a fluid which will precipitate the cellulose from this solution (Mossman, 1937). The addition of 10 per cent of acetone to dioxan, as to butanol, gives a mixture capable of dissolving nitrocellulose.

Another line of investigation now under study in America is the use for embedding of the new water-tolerant waxes, the so-called soap waxes (Lebowich 1936, Moritz 1939); so far these do not appear to be serious rivals to paraffin inclusion. It is an observed fact that after the ethyl alcohol technique tissues stain more precisely than after dioxan dehydration; this may be related to the reducing action which Zirkle (1930) believes ethyl alcohol to/

to exercise on tissues. In relation to this it is possible that some of the newer dehydrating and embedding techniques may be rejected because of weak and uncertain staining. It should be realised, however, that staining methods might be modified to suit the different methods of embedding through the use of solvents other than water or ethyl alcohol; it has been found for example when tested on histological sections from paraffin, that several yellow dyes tartrazine, tartrazine N.S., primrose and fast yellow, of little value in aqueous or alcoholic solution show lively tinctorial activity when dissolved in cellosolve (Lendrum, 1939) almost as if they had acquired a new auxochromic linkage. Such changes might well be necessary if research produces a satisfactory embedding mass based on aqueous solution. On the other hand another possible method of staining, derived from a thus far little used principle, is the use of solutions of the free acid or base of a dye in a solvent such as xylol (McLean, 1934, Krajian, 1938). That this works with acid dyes has been fully confirmed, and a jar of xylol-eosin has proved, over the last three years, a useful adjunct to the stains on the work bench. Its main use has been to restore the cytoplasmic colouring in sections overtreated by the blue dye in the eosin-methylene blue method. The use of basic dyes in similar solution has proved much/

much less successful.

A further source of possible technical improvement may lie in the newer synthetic plastics. By the use of the appropriate degree of plasticizing it may be possible to produce a cold embedding material comparable to pyroxylin, having the same supporting function and lack of distortion, and at the same time possessing the advantages of paraffin, ability to be cut on the convenient rocking or rotary microtome and to give sections of extreme thinness.

For the histologist there lies open a wide region of new and untried materials, and for the morbid anatomist it is still true that an improvement in technique may well be the prelude to new and unexpected discoveries.

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STUDIES ON THE MORBID ANATOMY

of

ACUTE RHEUMATIC DISEASE

with

SPECIAL REFERENCE TO FOETAL ENDOCARDITIS

VOLUME II.

ILLUSTRATIONS.

The illustrations are mainly from the tissues of the rheumatic mother and the foetus. These are all designated A.C.C. (Ayr County Council) followed by two numbers; the first number is that of the block of tissue; the second is of the section from that block. The nomenclature of the various blocks as given below, follows that of Gross et al. (1930) but the terms used are explanatory enough. The illustrations are described and discussed in the chapter on the Morbid Anatomy of the mother and foetus. The remaining illustrations of rheumatic changes are from my other material and are included for the purpose of comparison with the Ayr case, and to elucidate the verbal descriptions; only such lesions from this material are shown as seem to me to be truly rheumatic and yet have not been satisfactorily illustrated in the literature. They are thus complementary to the illustrations of Gross, Klinge, and others. Against the comprehensive array of their material as available in their publications, and the additions from my other material shown here, the illustrations of the rheumatic mother and foetus must be judged.

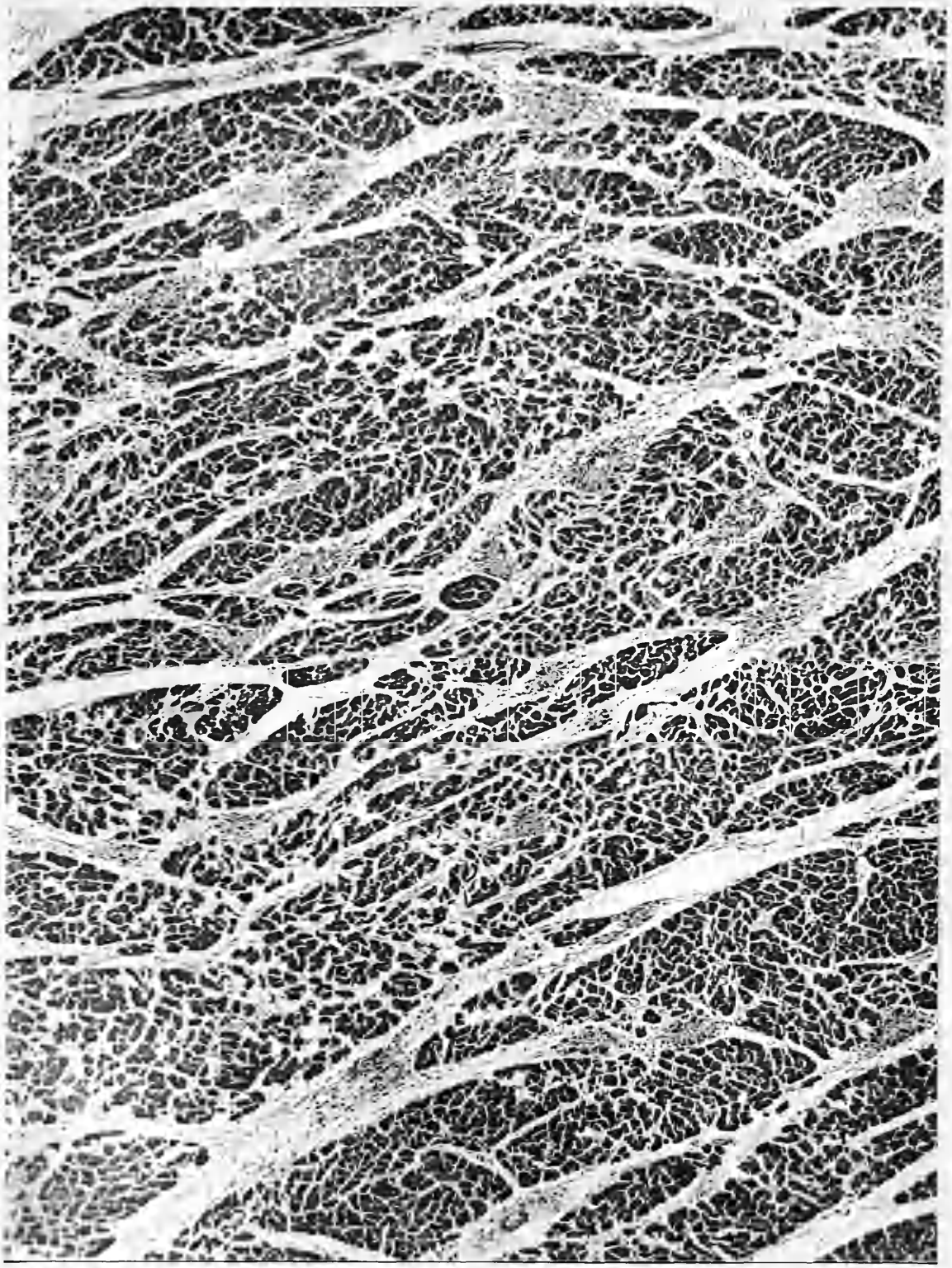

Figure 1. ACC. 20/3. Posterior mitral block. H.& E. c70.
This shows the widespread nature of the changes in the stroma of the left ventricle close to the insertion of the posterior mitral flap. 27 Aschoff bodies are present on the field.

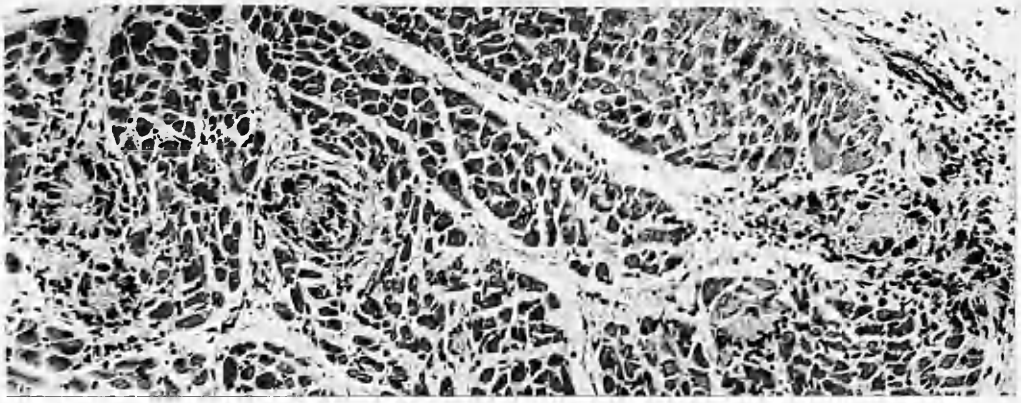

Figure 2. ACC. 1/1. Posterior mitral block, H.& E. c140. This shows a group of typical coronal Aschoff bodies in the ventricular myocardium.

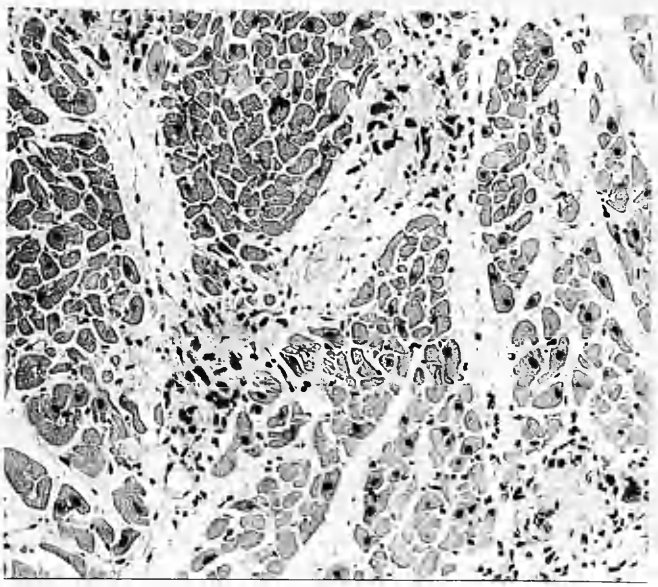

Figure 3. ACC. 95/3. Posterior mitral block. H.& E. c145. A further group of typical coronal Aschoff bodies in the ventricular myocardium.

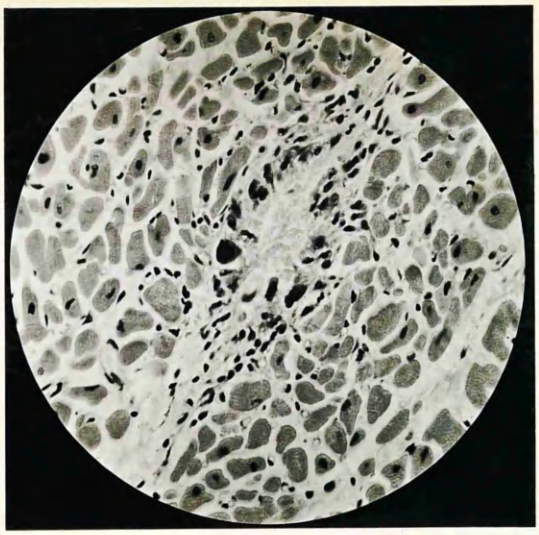

Figure 4. ACC.2/1. Posterior left ventricle block, H.& E. c250. This shows the structure of the early coronal Aschoff body.

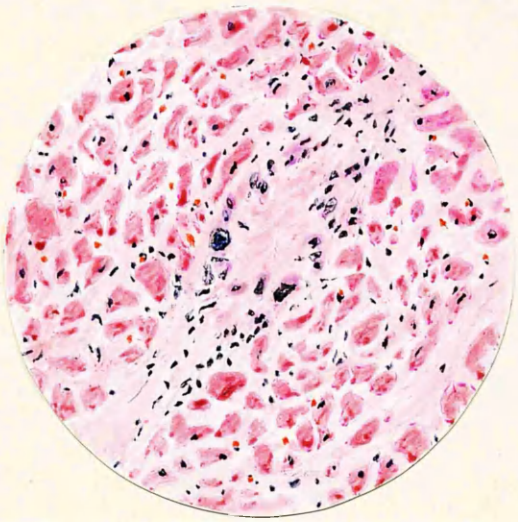

Figure 5. Colour sketch of figure 4, data as given, observed by white light.

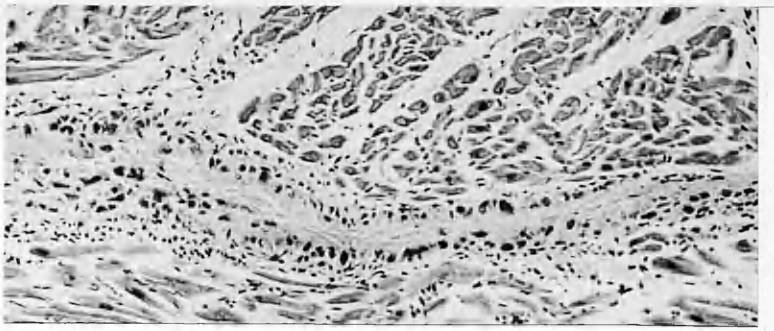

Figure 6. ACC. 20/2. Posterior mitral block. H.& E. c130. This is a longitudinal form of the coronal Aschoff body from the ventricular myocardium.

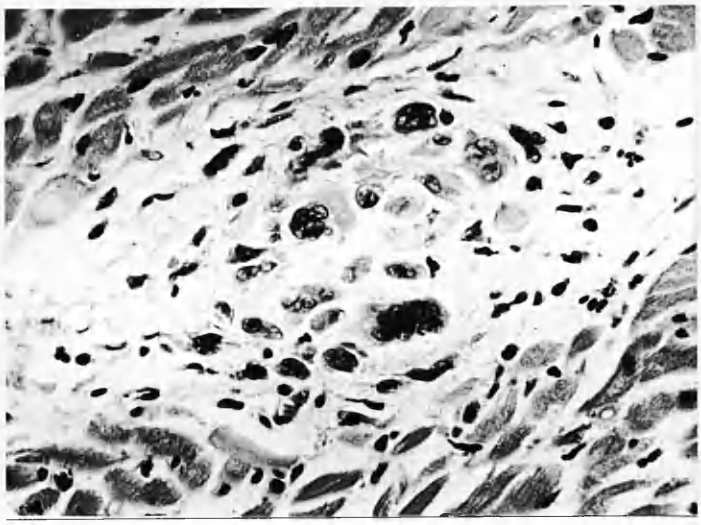

Figure 7. ACC. 37/1. Posterior left ventricle block, H.& E. c390. This shows the development of the coronal Aschoff body, the stage called mosaic by Gross.

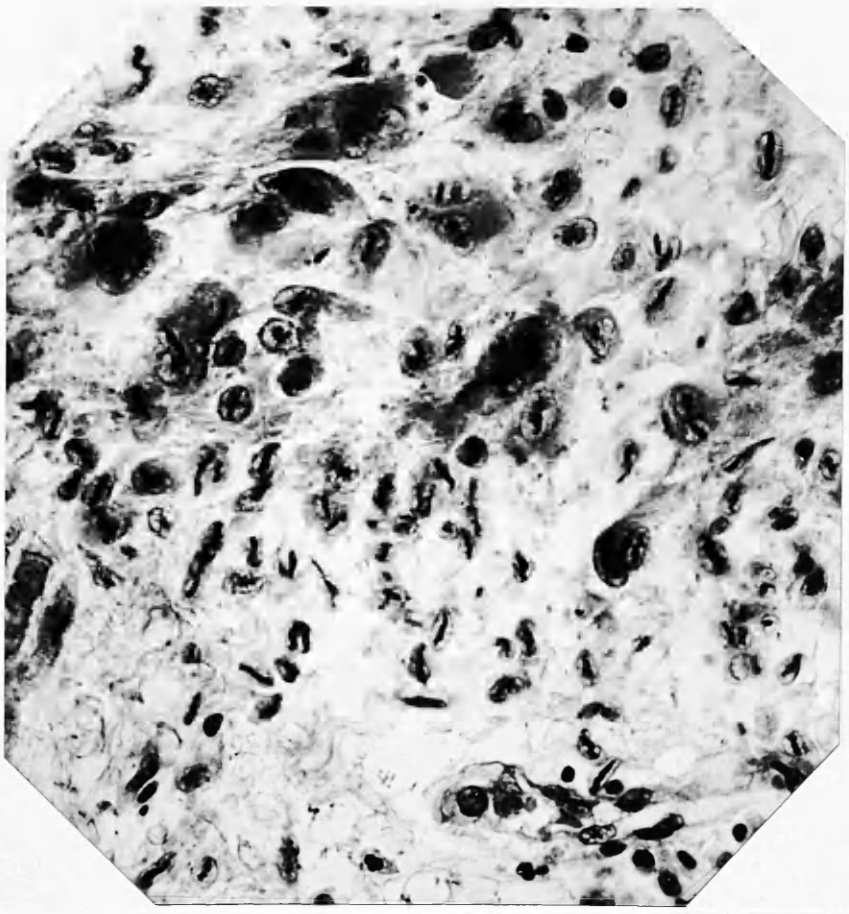

Figure 8. ACC.63/2. Right ventricle block. Celestin blue, haemalum, and phloxin followed by differentiation in phosphomolybdic acid. c520. This shows a granuloma with lattice cells and giant forms derived from these.

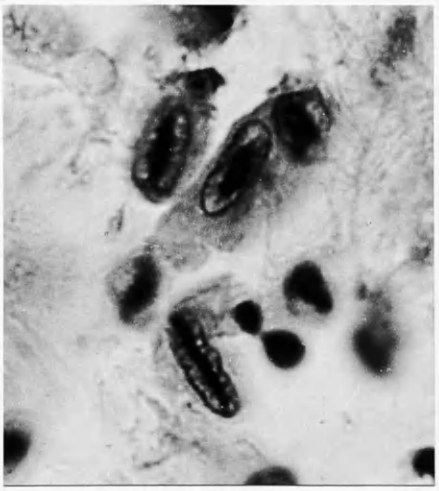

Figure 9. Royal Hospital Sick Children, case 3588. Left ventricle block, H.& E. c1350. This shows below a typical lattice cell, with above multinucleated forms.

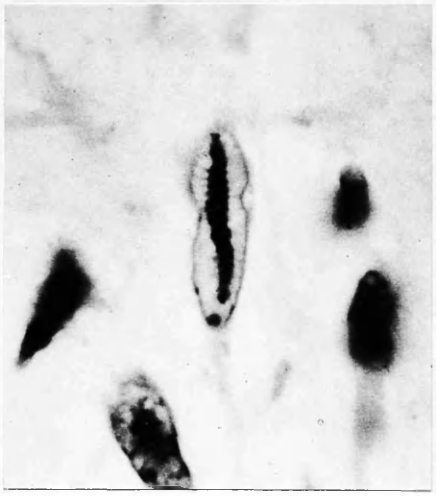

Figure 10. Infant II. Posterior mitral flap, H.& E. c1875. In this lattice cell can be seen the fine threads of chromatin running from the central bar to the distinct nuclear membrane. Also visible is a nucleolus, strongly eosinophilic in the section.

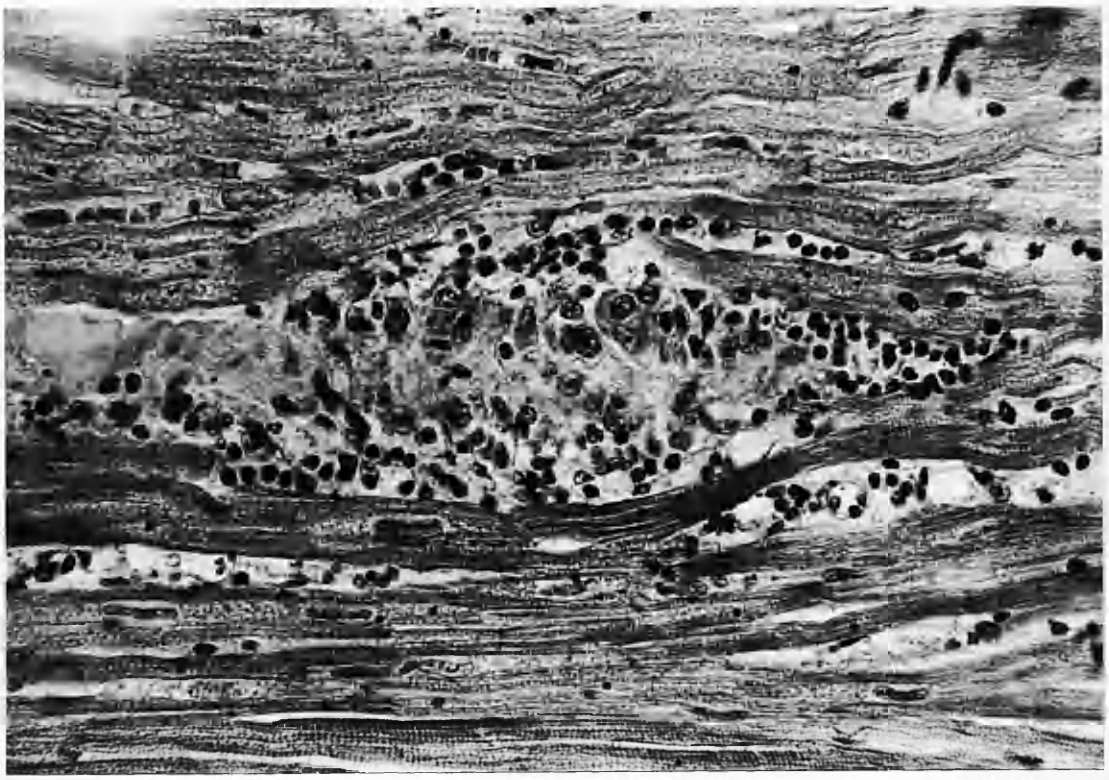

Figure 11. Rabbit, left ventricle. H.& E. c365. This shows a focus of myocarditis found in the examination of an untreated, presumed healthy animal.

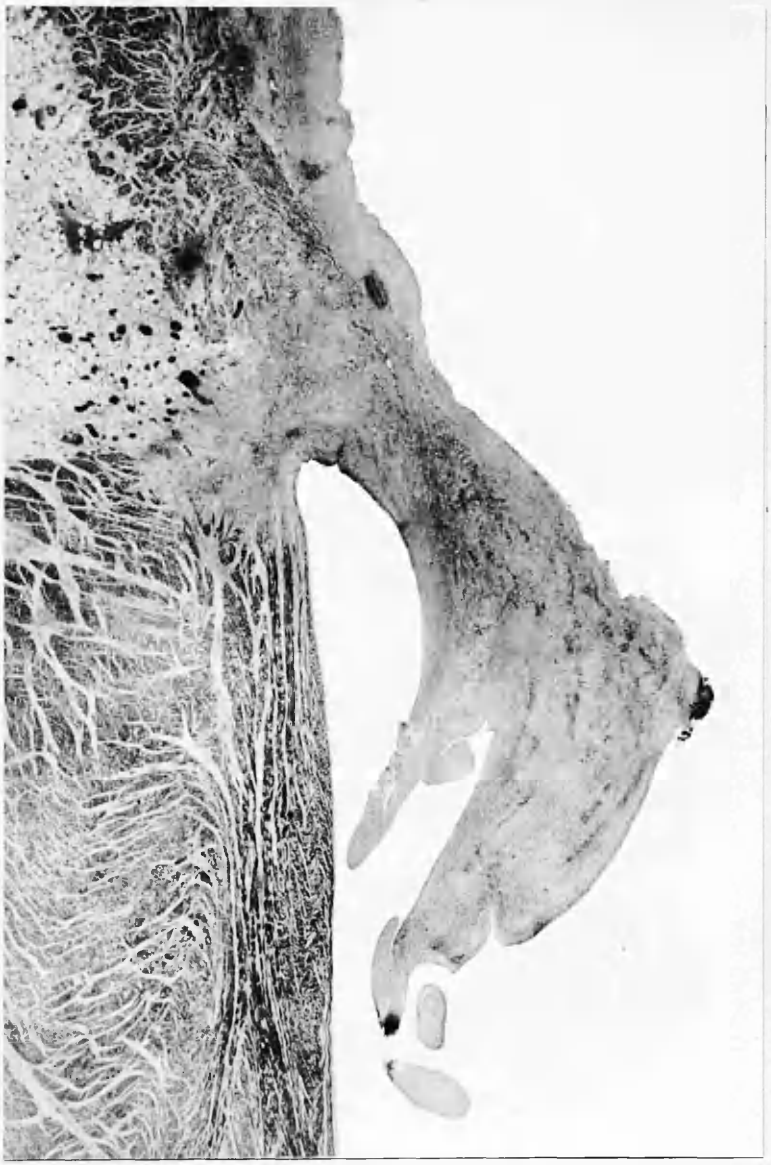

Figure 12. ACC. 95/3. Posterior mitral block. H.& E. c13. This general view shows two cellular foci in the swollen auricular endocardium. Valvular thickening and two areas of vegetation are seen, also congestion of the auriculoventricular region.

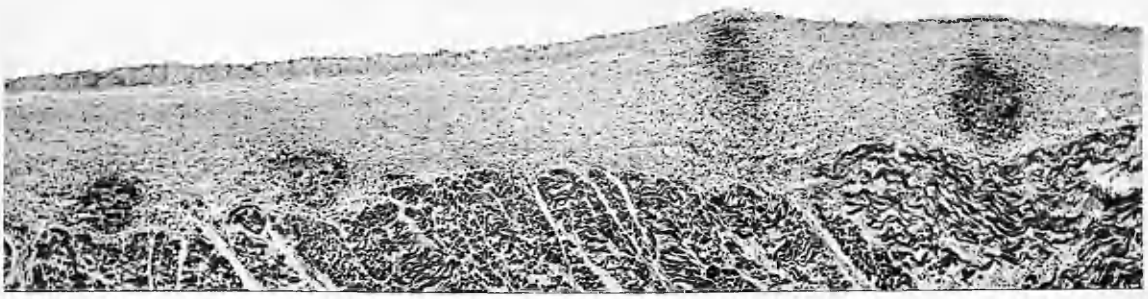

Figure 13. ACC. 62/1. Right auricular block. H.& E. c50. Four focal lesions are present in the swollen endocardium.

Figure 14. ACC. 98/1. Left auricular block. H.& E. c95. Two lesions are present, showing the cells arranged in rows;

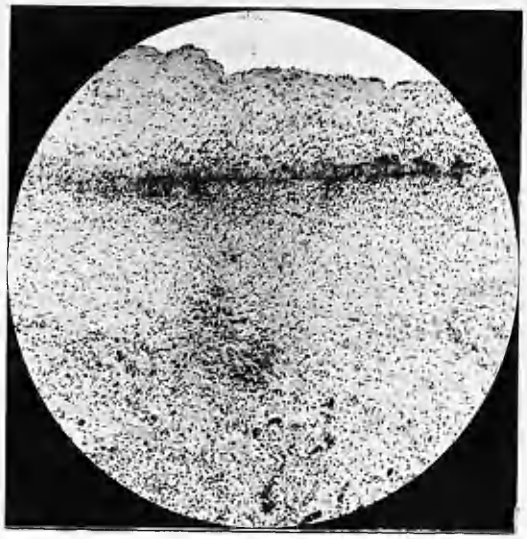

Figure 15. ACC.1/1. Posterior mitral block. H.& E. c65. This shows the more intense band-like formation of collagen change described by MacCallum.

Figure 16. Royal Hospital Sick Children, case 3827. Left auricular block; H.& E. c145. This is the typical band lesion of the auricle, showing a band of altered collagen with apposition of granuloma cells.

Figure 17. ACC. 15/4. Left auricular block. Orcein, celestin blue, haemalum and tartrazine. c360. This shows the relation of the granuloma cells to the elastic tissue of the auricular endocardium.

Figure 18. Colour sketch of the field shown in figure 17, data as given, observed by white light.

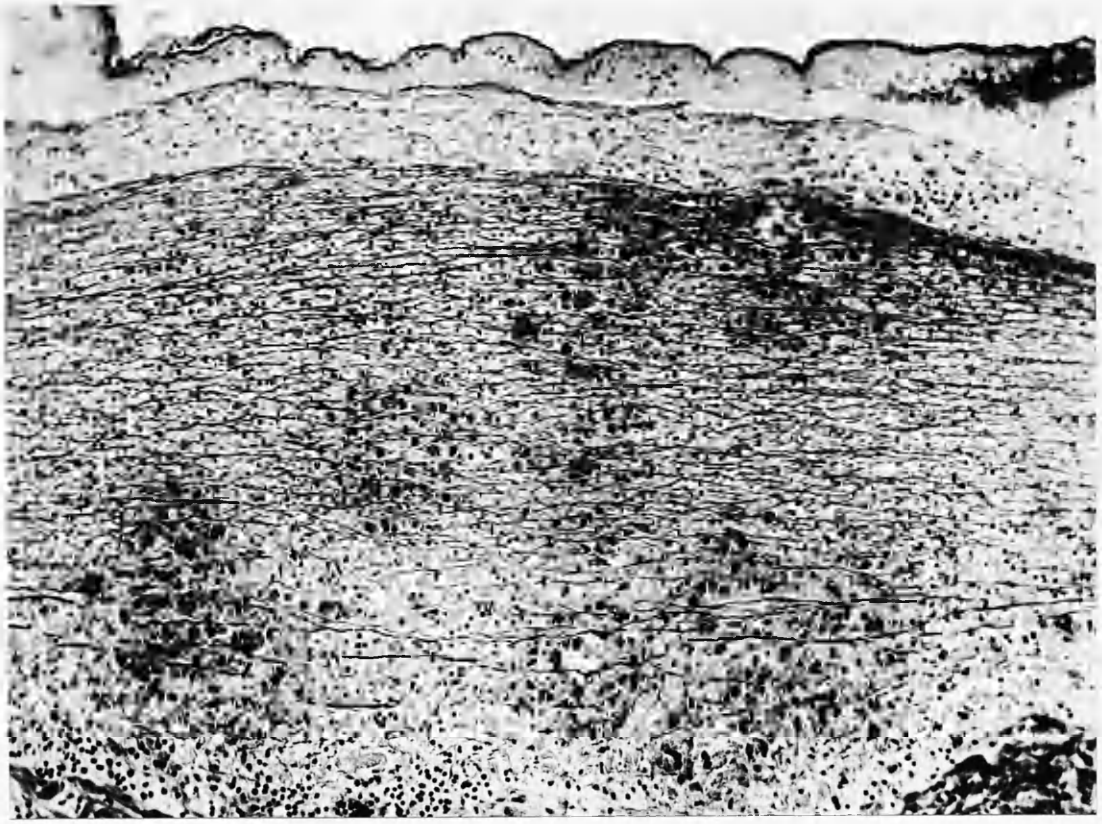

Figure 19. Royal Hospital Sick Children, case 4164. Posterior mitral block. Weigert's elastica, haemalum, phloxin and tartrazine. c155. In the main coat of the endocardium the granuloma cells are seen lying in rows between the elastic laminae. Above, the subendothelial layers are seen to be swollen and have a layer of phloxinophil fibrin both on the surface and partly in the subjacent tissue.

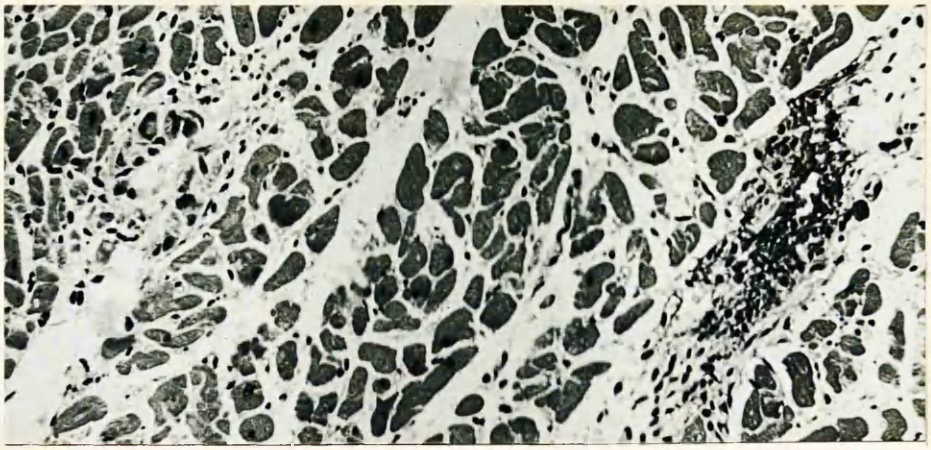

Figure 20. ACC. 20/8. Posterior mitral block. H.& E. c220. This shows one coronal and one reticular Aschoff body. The fibrin shows black in virtue of the blue green screening used.

Figure 21. Colour sketch of field shown in figure 20: since being photographed the section has been restained with phloxin and tartrazine, and from this the sketch was made. Note absence of fibrin (phloxinophil) in the coronal nodule. The reticular body may be related to a lymphatic. Observed by white light.

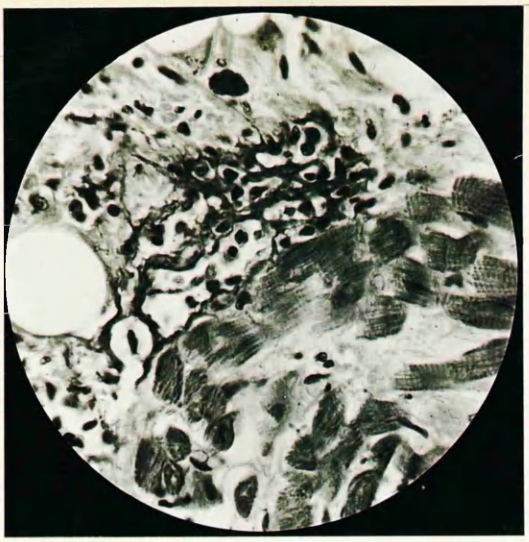

Figure 22. ACC. 15/2. Left auricular block. Haemalum, phloxin and tartrazine. c375. Blue green screen. This is an early stage of fibrin deposition; again the central space may be a lymphatic. A mast cell is seen above.

Figure 23. Colour sketch of field shown in figure 22, data as given, observed by white light.

Figure 24. ACC.20/9. Posterior mitral block. H.& E. c270. Blue green screen. This shows in the general view of a large reticular Aschoff body from the auricular endocardium, how the darkly stained fibrin takes support on the collagen fibres of the part. The cells are mainly small and many are pyknotic.

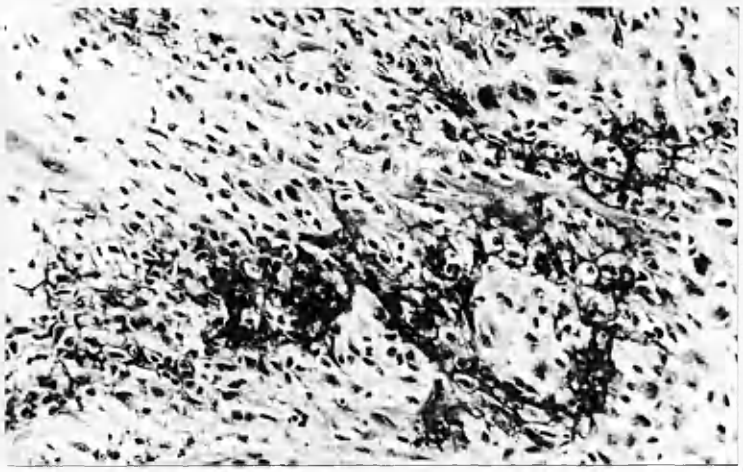

Figure 25. ACC. 15/2. Left auricular block. Haemalum, phloxin and tartrazine. c240. Blue green screen. The general relation of fibrin (dark) to the stroma is again seen: the next figure is from the upper right hand area.

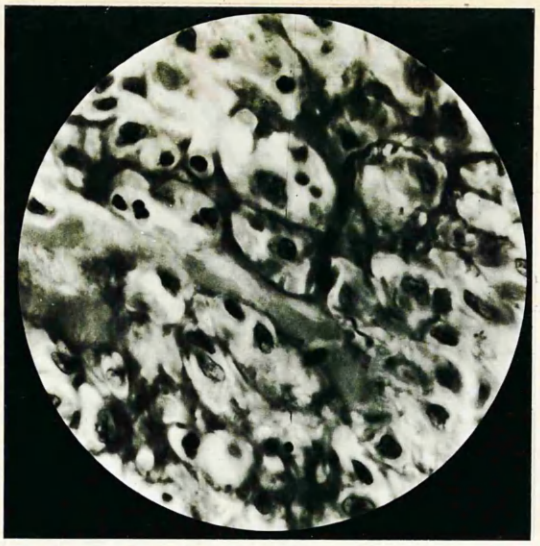

Figure 26. ACC. 15/2. As above, c600. This is an area from the previous figure of a fairly early reticular Aschoff body; it shows fibrin adhering to the surface of what appears to be a swollen collagenous band.

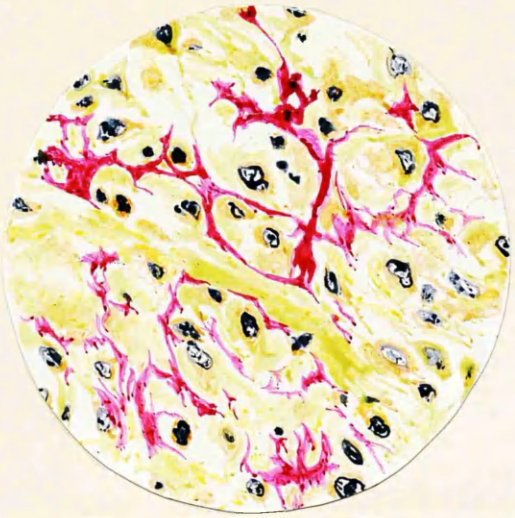

Figure 27. Colour sketch of field shown in figure 26, data as given, observed by white light.

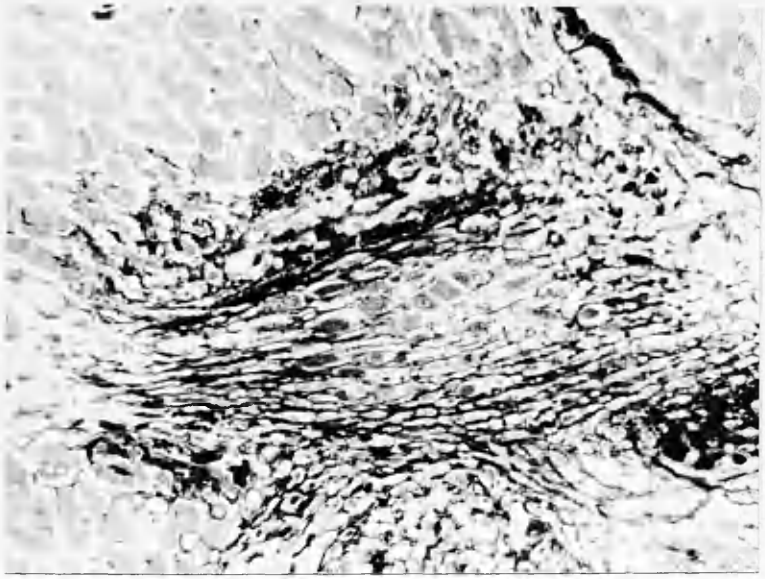

Figure 28. Royal Hospital Sick Children, case 4155. Left ventricle block. Picro-Mallory staining method. c200. Orange screen. This shows up as black the blue stained collagen of the area.

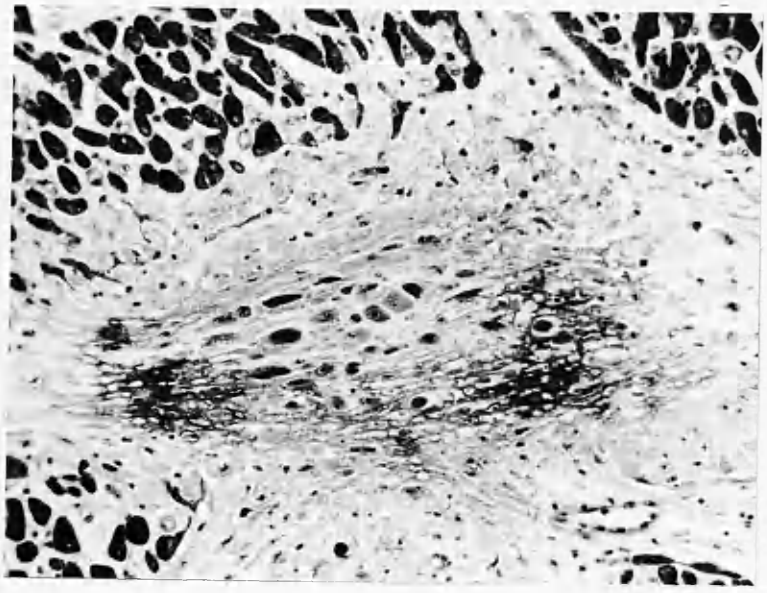

Figure 29. Same data as for figure 28, but taken through a blue screen. The red staining elements now show up darkly. The disposition of the fibrin in the two networks should be correlated with the previous illustration.

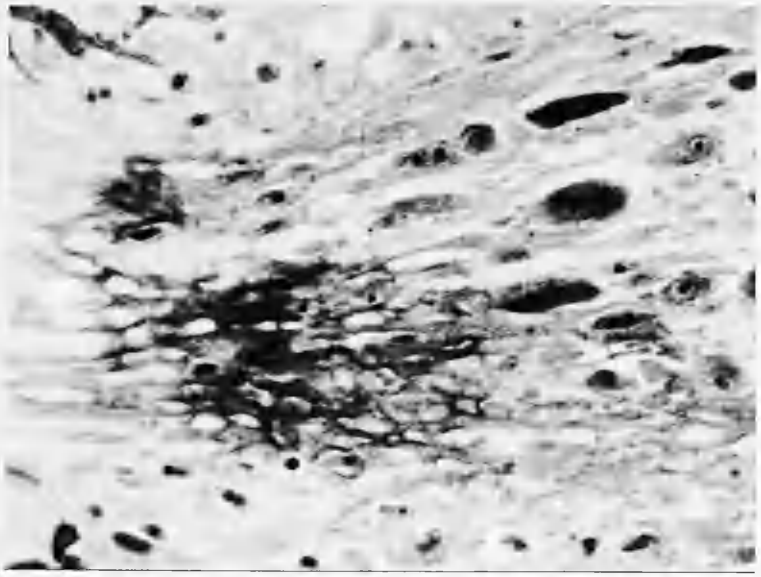

Figure 30. Enlargement(c500) of the left fibrinous network from fig.29. This shows the deposition of fibrin on the collagen fibre.

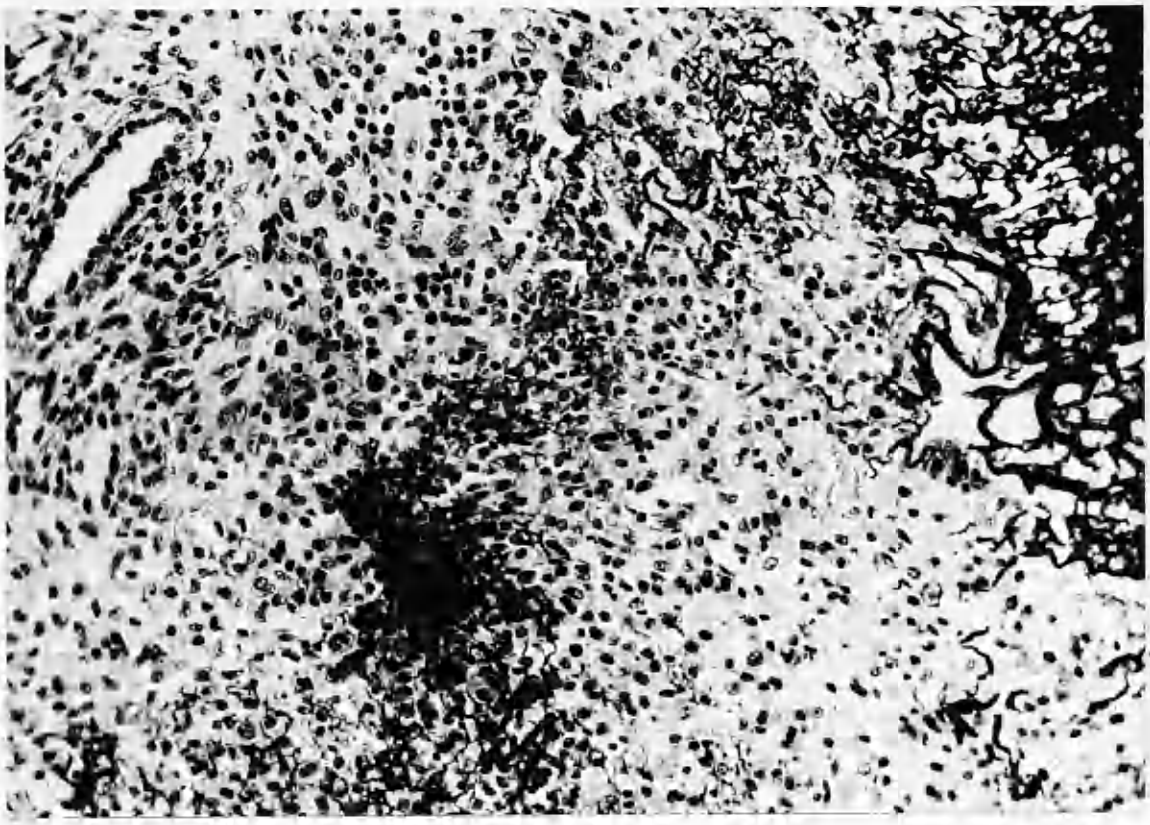

Figure 31. Royal Hospital Sick Children, case from Dr.Graham's ward. Subcutaneous rheumatic nodule. Haemalum, phloxin and tartrazine. c230. Blue green screen. The fibrin shows up black. The endothelium of the blood vessel should be noted.

Figure 32. ACC. 142/1. Left ventricular block. H.& E. c390. Blue green screen. This shows the precipitation of fibrin in the subendothelial tissue of a crypt of the left ventricular wall, with associated granuloma cells.

Figure 33. Colour sketch of field shown in figure 32, since being photographed the section has been restained with phloxin and tartrazine, and from this the sketch was made. Observed by white light.

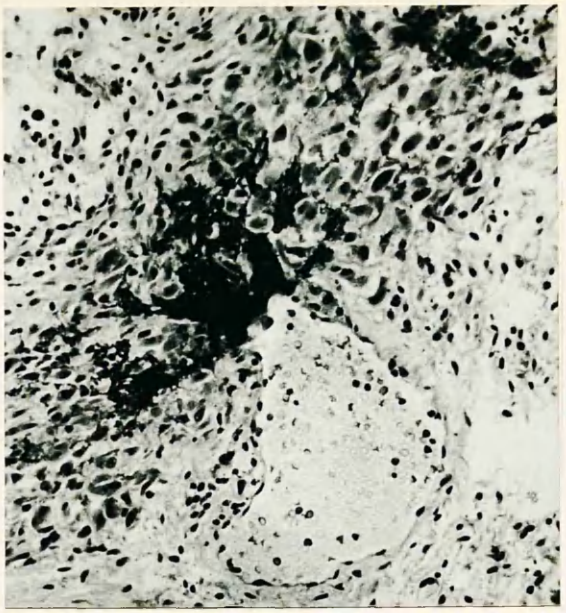

Figure 34. ACC. 16/7. Left auricular block. Haemalum, phloxin and tartrazine. c190. Blue green screen. This shows fibrin deposition alongside a vein, comparable to the subendocardial deposition of figs. 32 and 33. Granuloma cells are present in greater number.

Figure 35. Colour sketch of field shown in figure 34, data as given, observed by white light.

Figure 36. ACC. 113/7. Left ventricular block. Malachite green and acridine red. Roughly 400. Projection drawing showing fibrin, emerald green, in relation to a vein. The granuloma cells show the typical red staining. Observed by white light.

Figure 37. ACC. 20/10. Posterior mitral block. Weigert's elastica, haemalum, phloxin and tartrazine. c300. Blue green screen. This shows the fibrin, dark, deposited in the tissues at the apex of the pouch of the posterior mitral flap. In this lesion the granuloma cells are as yet scanty.

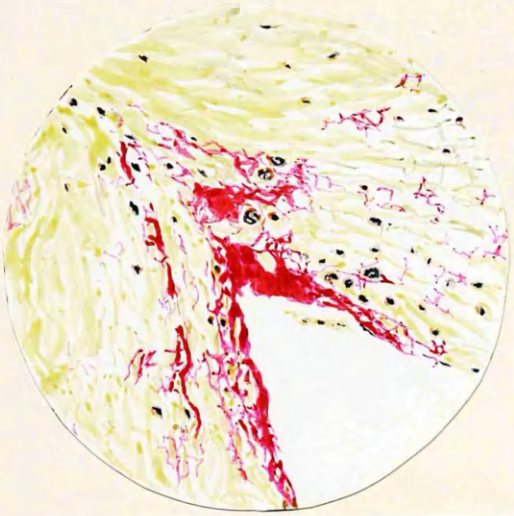

Figure 38. Colour sketch of field shown in figure 39, data as given, observed by white light.

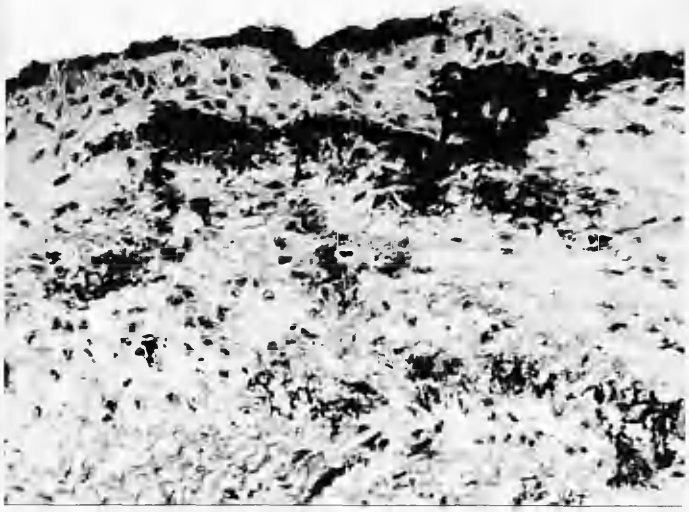

Figure 39. ACC.46/1.
Tricuspid valve block.
Phosphotungstic haematoxylin.
c160. The screening shows up the fibrin as black. It is deposited both at the surface and in the tissue of the somewhat oedematous but not unduly cellular valve.

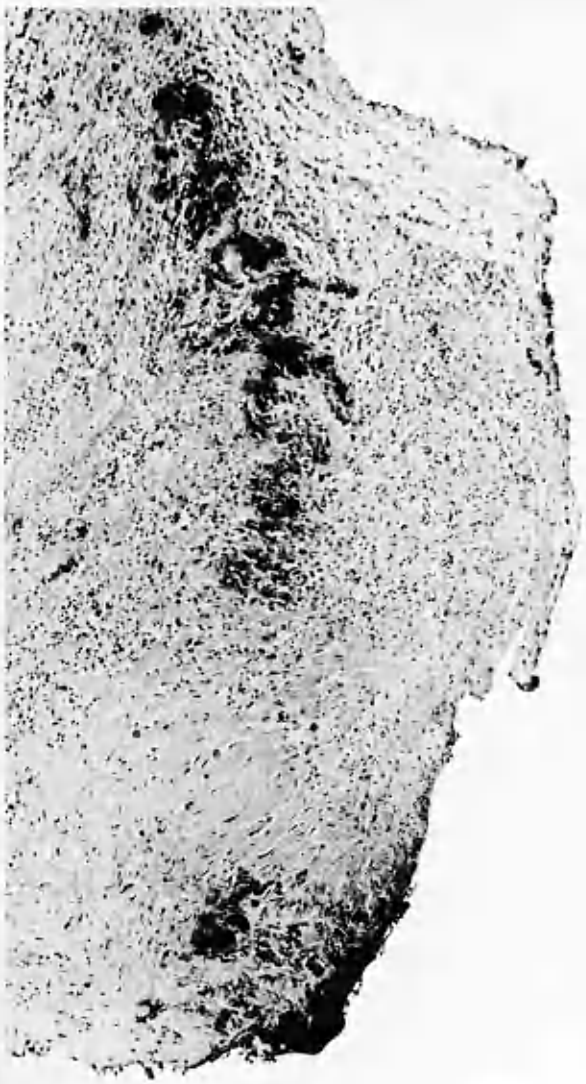

Figure 40. ACC.95/6.
Posterior mitral block.
Weigert's elastica, haemalum, phloxine and tartrazine.
c95. Blue green screen.
There is little or no elastica in this area, but in virtue of the screening, the phloxinophil fibrin is shown up black.
There is considerable deposit in the valvular tissue, with early apposition of granuloma cells, just discernible in the outer meshes of the deposits.

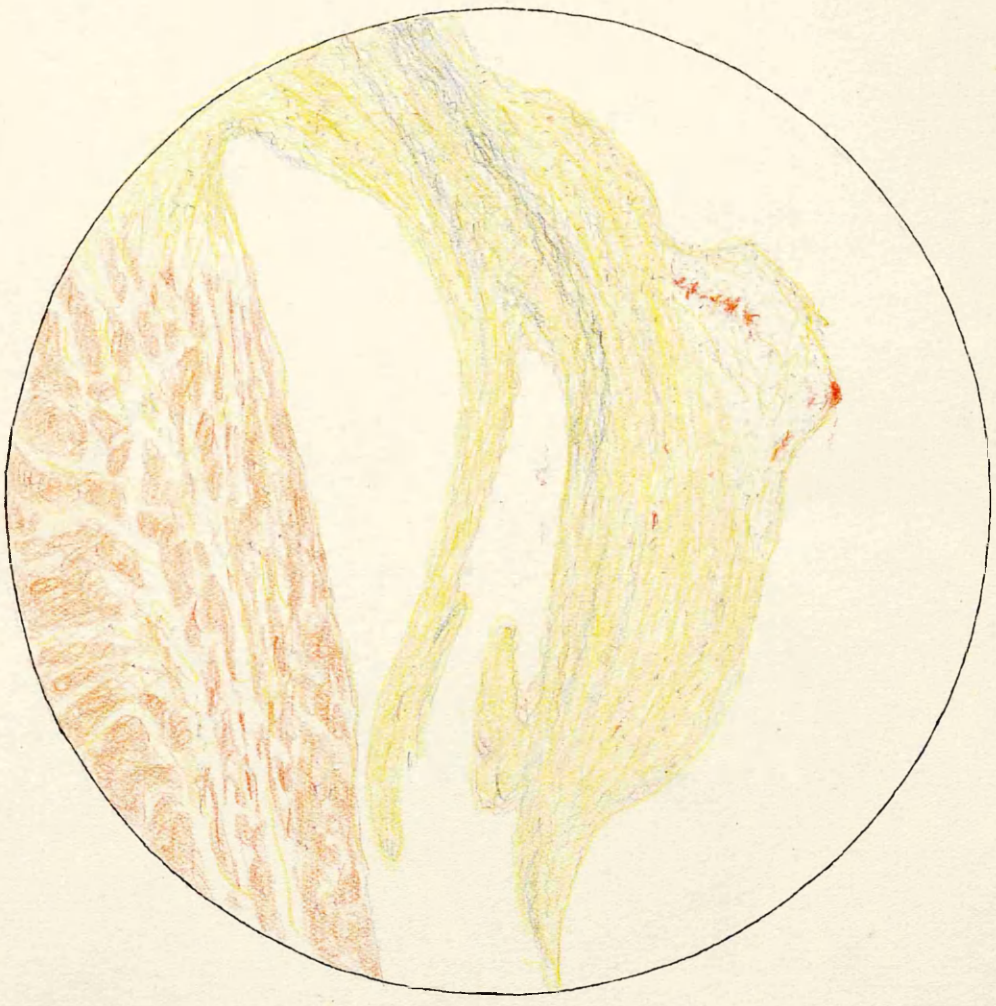

Figure 41. Colour sketch of the section from which figure 40 was photographed.

Figure 42. ACC. 48/1. Tricuspid valve block. Phosphotungstic haematoxylin. c125. This slide illustrates the differential staining observed almost constantly in the fibrin of rheumatic vegetation. Although the material is uniformly eosinophilic, this stain as do others shows the characteristic fibrin reaction at the surface and in the deep roots, with loss thereof in the centre of the main mass. Verruca formation is probably due to local proliferation.

Figure 43. Colour sketch of field shown in figure 42, data as given, observed by yellow light.

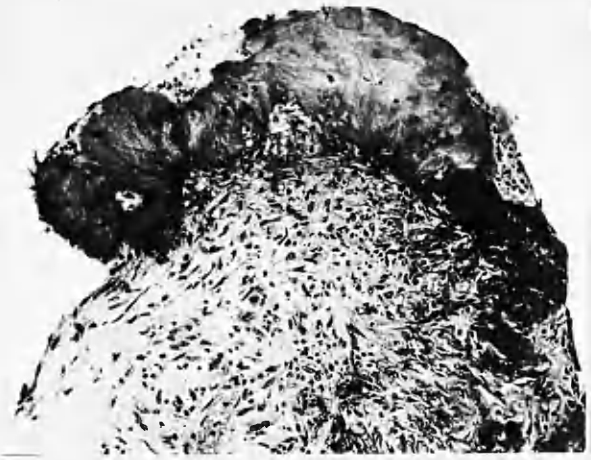

Figure 44. ACC. 20/4. Posterior mitral block. Haemalum and eosin-phloxin. **c125.** Blue green screen. This shows the vegetation on the line of contact of the posterior mitral flap. The section was fully differentiated in spirit to show up the more phloxinophil fibrin; this in virtue of the screening is seen as the darker material, mainly on the under side of the vegetation, running into the substance of the valve.

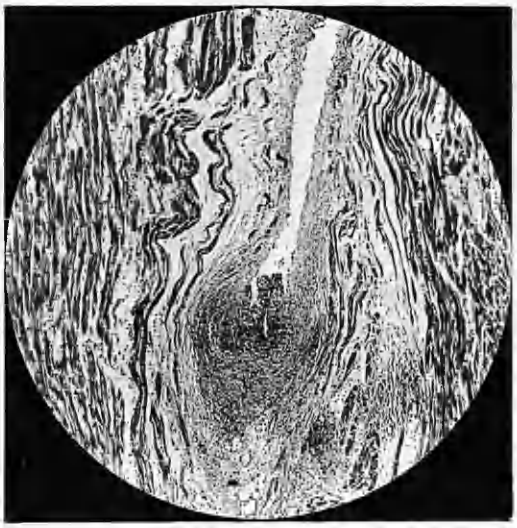

Figure 45. ACC. 49/1. Left coronary artery block. H.& E. **c40.** This shows a vein in the myocardium with a cellular lesion; related to this are two small papillae of proliferated intimal tissue. Also in the field are two Aschoff bodies.

Figure 46. Royal Hospital Sick Children, case 3827. Left auricular block. Verhoeff's elastica method. c65. This shows the internal elastic lamina of the auricular endocardium as a well defined line; internal to this are seen the intimal cushions of soft proliferated tissue.

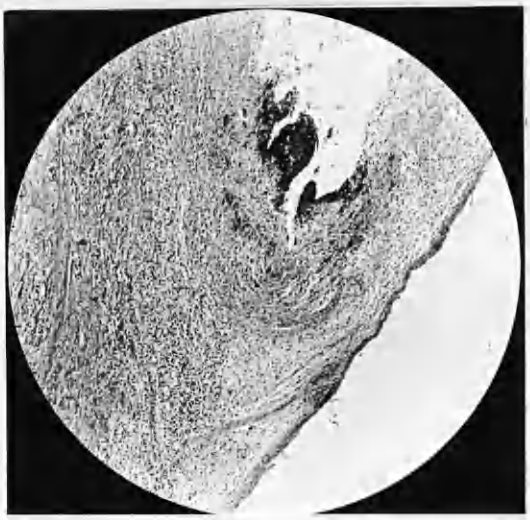

Figure 47. ACC. 55/1. Pulmonary artery block. H.& E. **c45.** Blue green screen. In the apex of the pocket of the pulmonic valve there are small papillae, showing in their substance the deposit of fibrin.

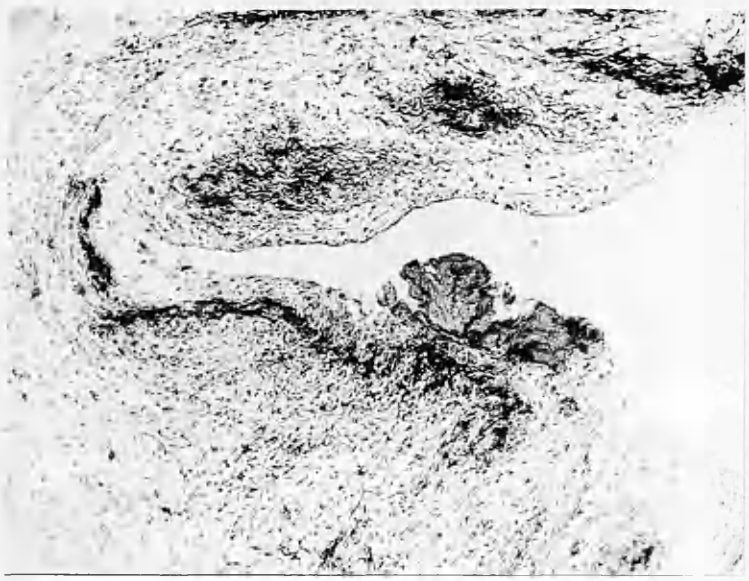

Figure 48. Royal Hospital Sick Children, case 3588. Aortic and mitral block. Phosphotungstic haematoxylin. **c130.** This shows aortic valve. The vegetation, seen sprouting from the oedematous cellular valve tissue in which there is obvious fibrin deposit (black), is not on a contact surface but in the pocket of the valve. For relationship see next figure.

Figure 49. Low power sketch of the section from which figure 48 was photographed. It shows the posterior aortic cusp; from the region of its insertion the dense fibroelastic tissue runs down to form the anterior flap of the mitral.

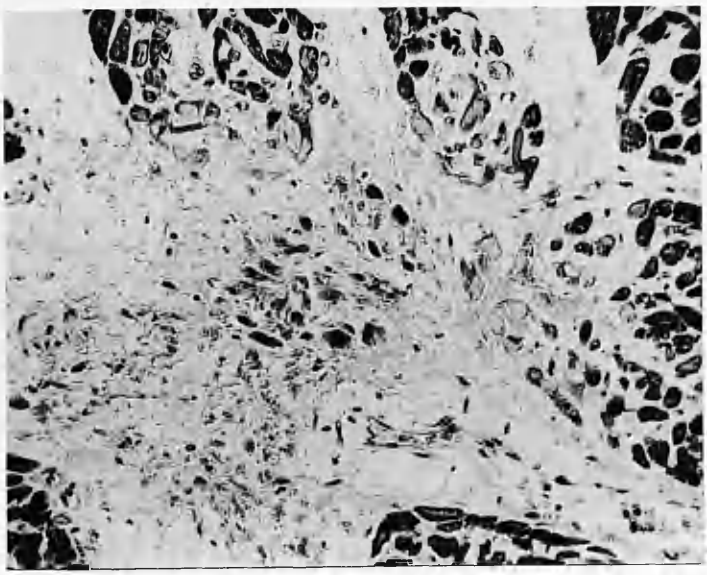

Figure 50. Royal Hospital Sick Children, case 3827. Left ventricular block. Phosphotungstic haematoxylin. c350. This method of staining reveals the alteration in the muscular cells lying nearest the Aschoff body. There is no evidence yet that fibrous scarring is taking place; the appearances suggest, rather, a toxic emanation from the central focus.

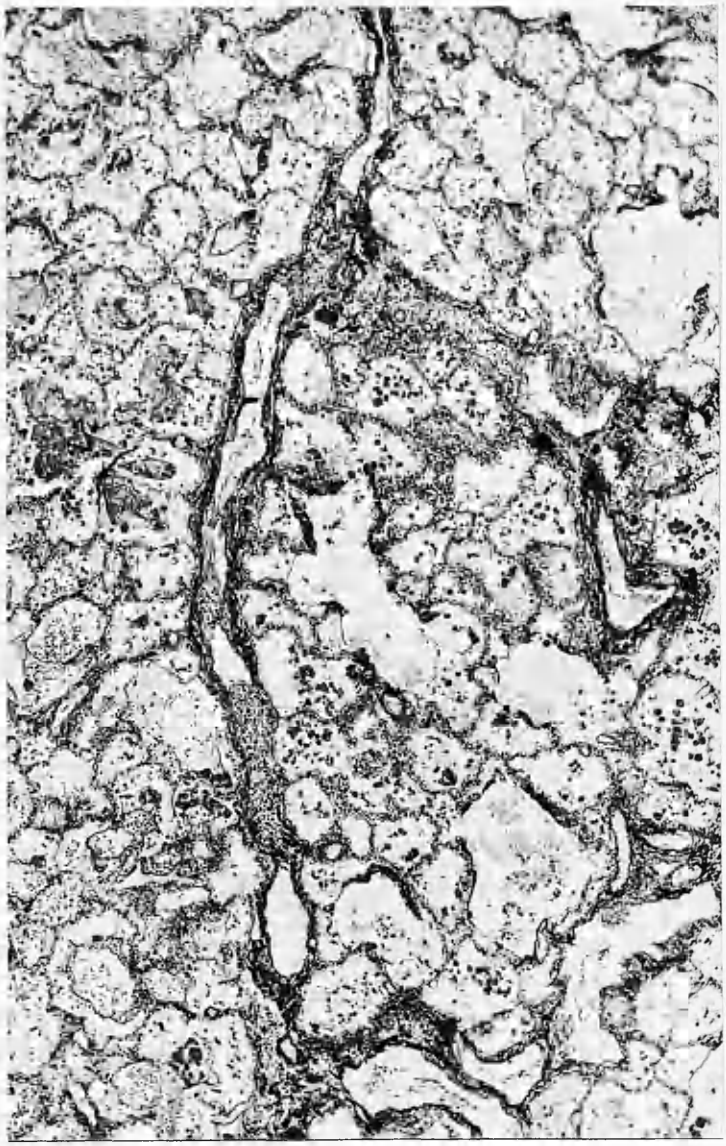

Figure 51. ACC. 25/2. Lung. Picro-Mallory method. c70. Green screen. The septum running vertically in the photograph shows a cellular oedema, and a series of distended vessels, several of which are lymphatics. Also visible at this power are the varicose capillaries, and the alveolar content of cells, exudate and occasionally fibrin.

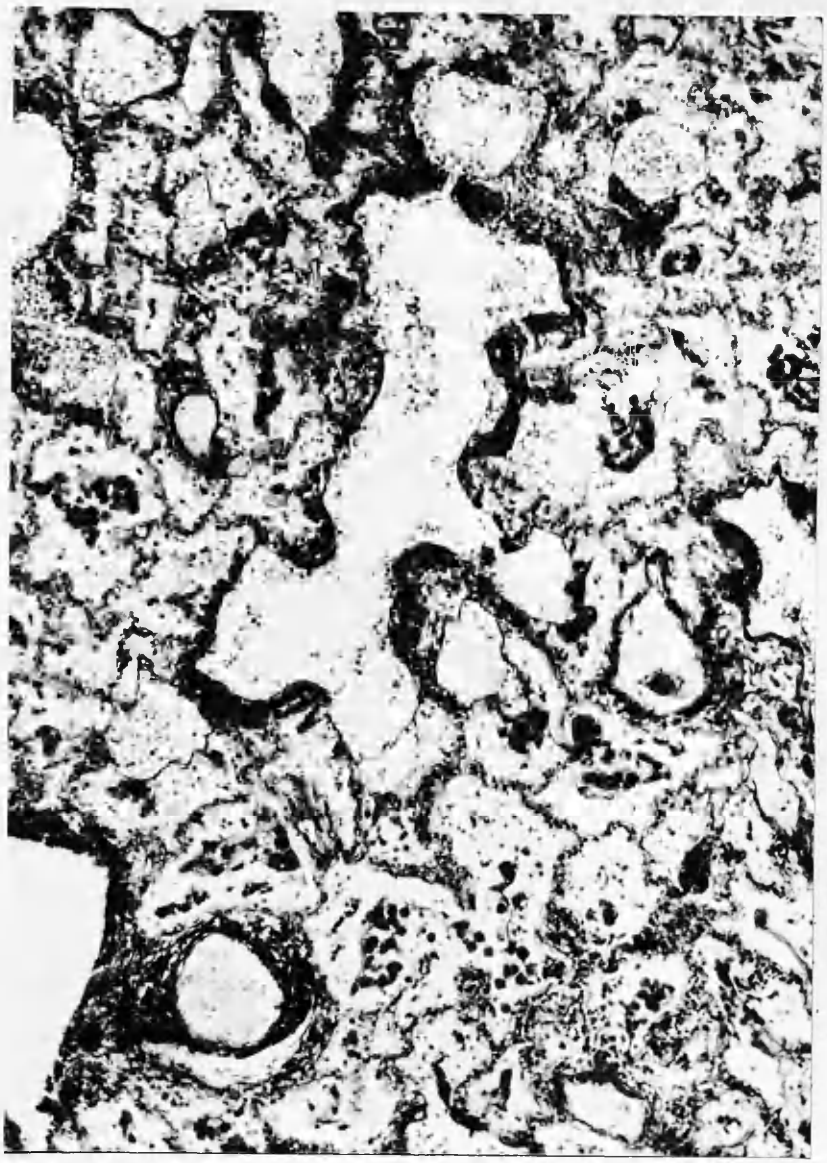

Figure 52. ACC. 31/2. Lung. Picro-Mallory. c190. Blue green screen. This is typical of many areas in the lung and shows centrally and bottom left a terminal duct characterised by its lack of exudate in comparison with the alveoli, and by its lining of fuchsinophil material (black) which appears to occlude some of the alveoli (so-called "hyaline membrane"). This material does not give quite the same red by this method as does fibrin.

Figure 53. ACC. 25/1. Lung. Picro-Mallory. c245. Blue green screen. This shows the way in which the fuchsinophil material is plastered across the mouths of the alveoli.

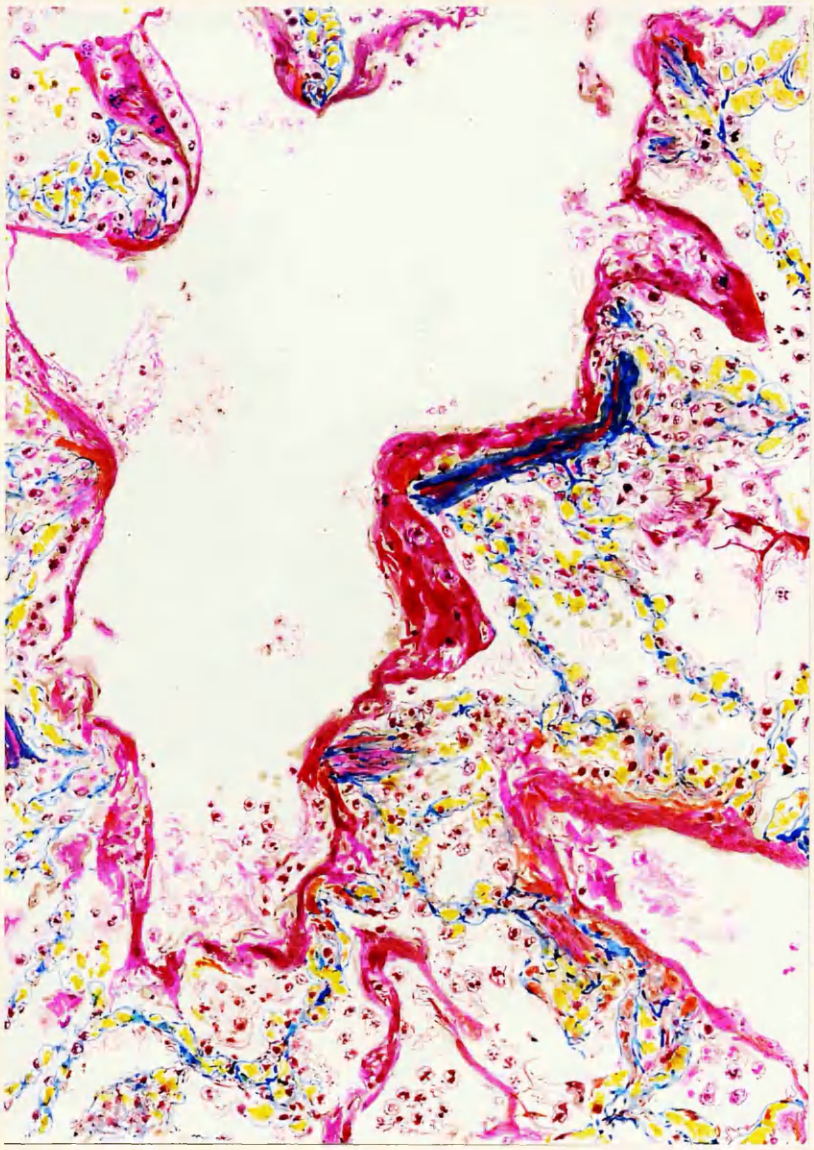

Figure 54. Colour sketch of figure 53, data as given. Observed by yellow light. The colour differentiation of the various elements is well shown by this stain and is not intentionally exaggerated in this sketch. The colour of the hyaline membrane is toward cerise.

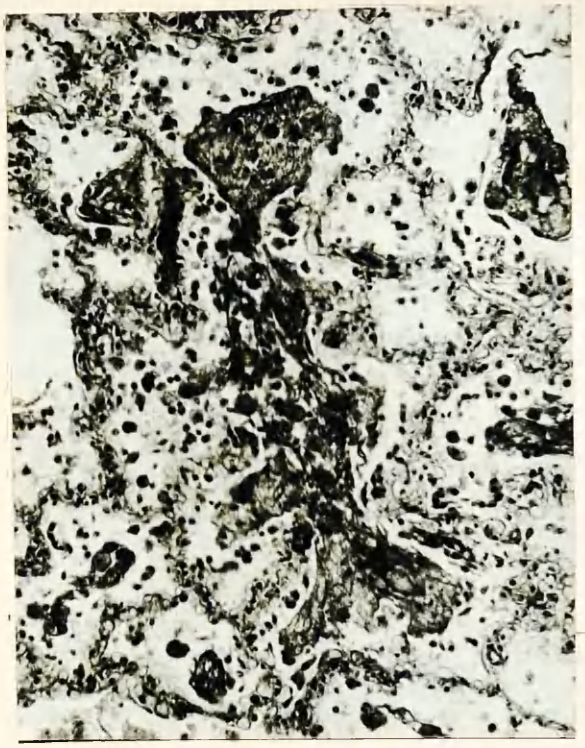

Figure 55. ACC. 32/2. Lung. Picro-Mallory. **cl45.** Blue green screen. This plug of material is more obviously composed of fibrin than the "hyaline membrane" illustrated in the previous figures, in that it is formed of fine threads and gives the rather more vermilion colour characteristic of fibrin. Masson believes that central softening of this mass leads to the formation of the hyaline membrane.

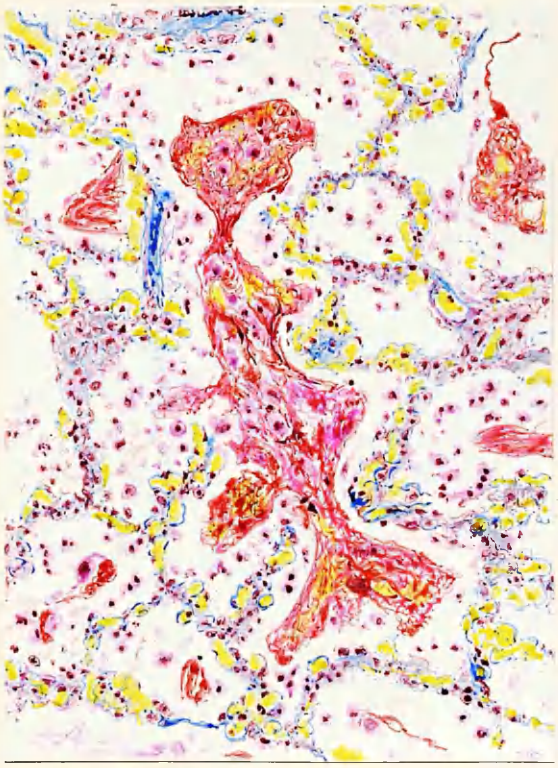

Figure 56. ACC. 32/2. Lung. Colour sketch of the field shown in figure 55, data as given. Observed by yellow light.

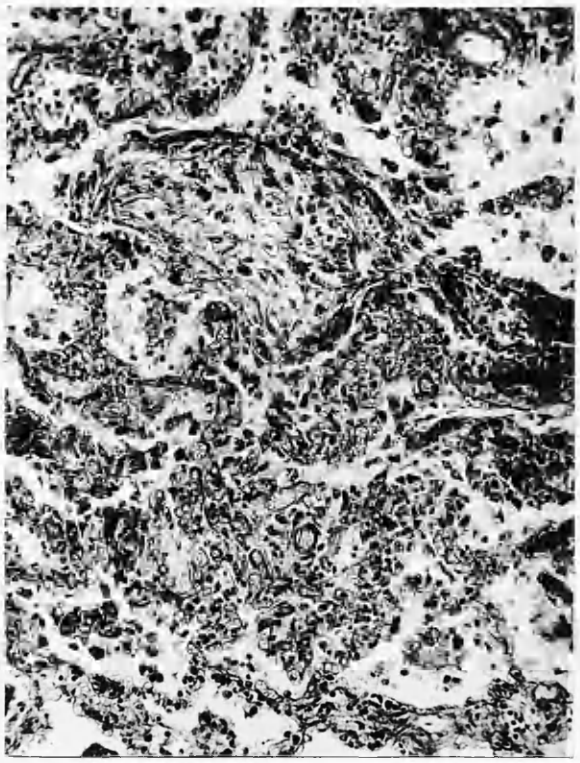

Figure 57. ACC. 31/2. Lung. Picro-Mallory. Blue green screen. c145. This shows in the upper half of the print, well advanced organisation of alveolar exudate; there is no evidence of fibrin in the mass. The general intense engorgement is well seen in the lower half.

Figure 58. ACC. 89/1. Foetal mitral valve, posterior flap. H.& E. c275. This shows an abnormal cellularity of the auricular aspect of the valve, with no sign of an endothelial lesion.

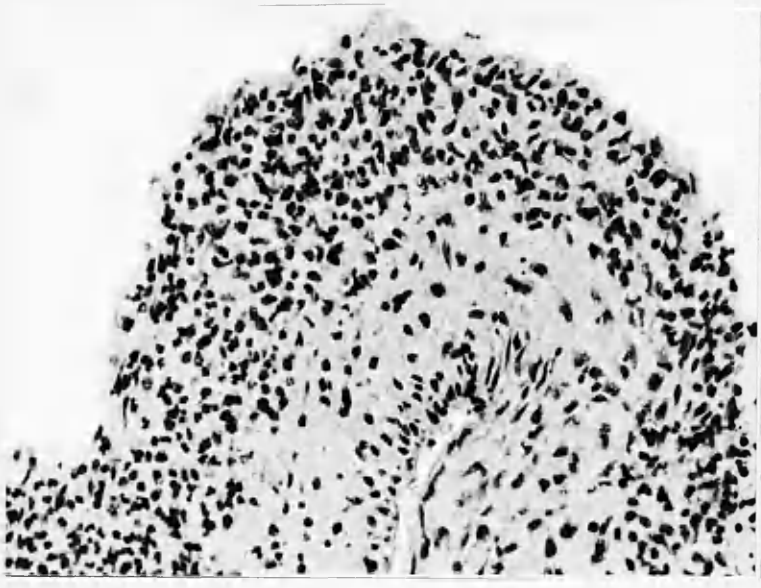

Figure 59. ACC. 89/46. Foetal mitral valve, posterior flap. H.& E. c320. This shows a sharply flexed portion of the mitral valve about the level of the line of closure. The contact surface of the valve is uppermost. The infiltration is here intense and contains many polymorphs; despite this almost purulent aggregation there is no suggestion of vegetation.

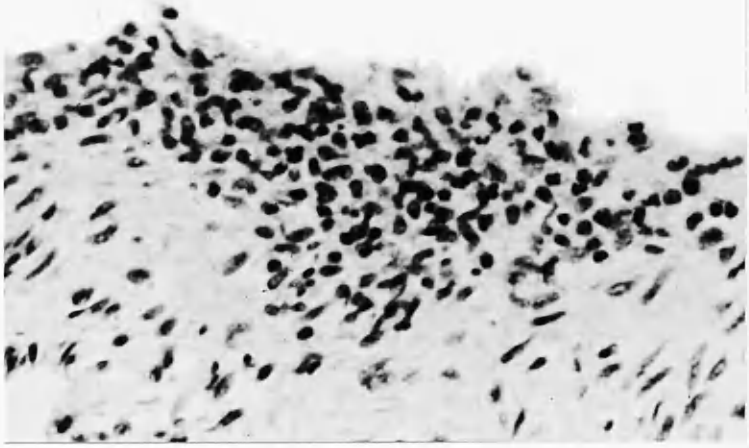

Figure 60. ACC. 89/29. Foetal mitral valve, posterior flap. H.& E. c480. This shows a somewhat more focal infiltration, again from the contact surface of the mitral about the region of the line of closure.

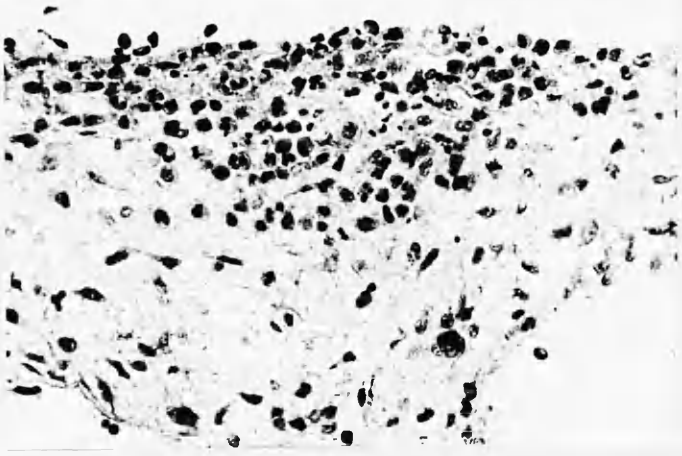

Figure 61. ACC. 93/4. Foetal tricuspid valve. Eosin and methylene blue. c370. This focal lesion shows the same type of cells with convoluted vesicular nuclei as compose the cellular zone of figure 58, and a proportion of the cells in figures 59 and 60; as in these latter two, there are also polymorphs and somewhat more definite evidence of necrosis, in the presence of pyknotic nuclear fragments and fine eosinophilic granular debris lying between the cells.

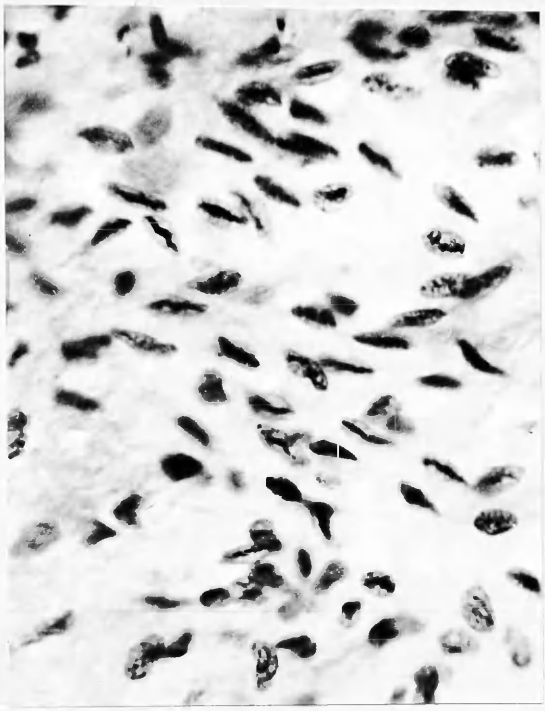

Figure 62. Infant I. Aortic valve. H.& E. c700. This shows an area of cellularity in the valve, containing numerous lattice cells.

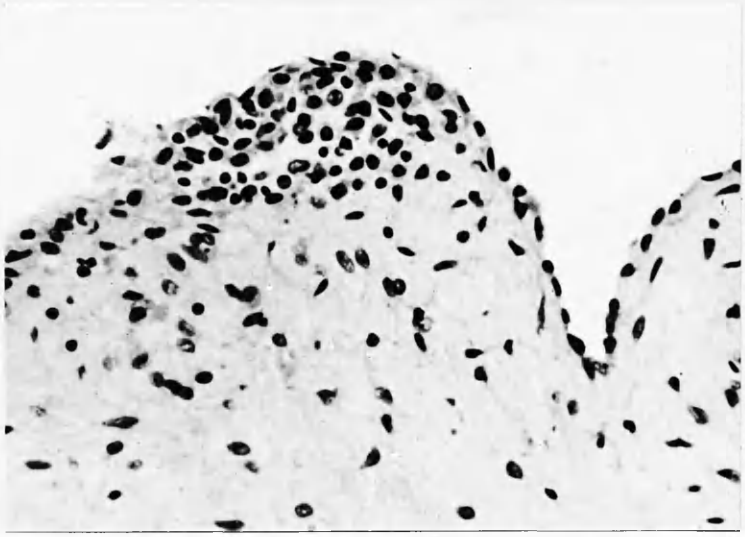

Figure 63. Infant II. Tricuspid valve. H.& E. c325. This focus in the subendothelial tissue is composed mainly of mononuclear cells. Some nuclear debris is present, indicative of a necrotic process -- toxic endocarditis.