SYSTEMIC PATHOLOGY

SECOND EDITION

BY 38 AUTHORS

Edited by W. St C. Symmers

VOLUME 1

Systemic Pathology

SECOND EDITION

by THIRTY-EIGHT AUTHORS

VOLUME 1

Cardiovascular System
Respiratory System

CHURCHILL LIVINGSTONE
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Preface to the Second Edition

The first edition of *Systemic Pathology* was published by Longmans on the 31st December 1966, and went out of print four years later. The publishers had expected that the second edition would appear about four years after the first: it is deplorable that a succession of delays has more than doubled this interval. Fortunately, the cooperation of contributors has made it possible to ensure that the book is more up to date on publication than is usual for texts that are the joint work of many authors. Most of the contributors have had the vexatious necessity of reviewing their chapters at least twice during the preparation of the new edition: the publishers' appreciation and thanks, and mine, are due to all those who recognized the inevitability of the delays and generously helped to offset their effects, at the cost to themselves of much extra work and inconvenience.

There have been several changes in the panel of authors since 1966. Their other commitments made it necessary for two contributors to refuse the invitation to revise their chapters—Professor Robert H. Heptinstall, who wrote on the kidneys, and Dr J. H. Shore, who wrote on the gall bladder and bile ducts: it is a pleasure to acknowledge their work for the first edition and to thank them for their participation. Doctor B. S. Cardell has written the new chapter on the gall bladder and bile ducts in addition to revising his chapter on the pancreas; the new chapter on the kidneys is by Professor K. A. Porter, who joins the panel of contributors. Doctor Kristin Henry, who has written the chapter on the thymus, and Professor E. D. Williams, who has written the chapter on the parathyroid glands, have also joined the panel, taking over from contributors to the first edition who wanted to reduce the number of chapters that they are responsible for. Other contributors to the first edition asked that the revision of their chapters might be shared, or undertaken, by colleagues: among the latter are nine further new members of the panel—Dr K. G. A. Clark (diseases of blood), Professor I. M. P. Dawson (small intestine), Dr B. Fox (adrenal glands), Dr D. G. F. Harriman (skeletal muscle), Dr M. L. Lewis (diseases of blood), Professor J. A. Milne (skin), Dr Gwyn Morgan (eyes), Professor W. Thomas Smith (central nervous system) and Dr A. H. Wyllie (pituitary gland).

Sir Theo Crawford has revised the chapter on the heart that was written for the first edition by its editor, Professor George Payling Wright. This chapter stands in the new edition as a memorial to Professor Payling Wright's humanity and scholarship and to his unique stature as a pathologist. His death, in 1964,* deprived much of the book of the advantages that it should have gained from final revision under his editorship and in the light of his lifetime of experience of the practical application of the principles of pathology. Professor Payling Wright did not consider textbooks to be a medium appropriate for the publication of memorial eulogies: it is in deference to this view that no formal appreciation of his life and work is included here, and it is in accord with his belief that the use of eponyms in the title of textbooks is undesirable that this book appears with the simple name, *Systemic Pathology*, implicitly acknowledging that it is the contributors who have written it.

The text has been so extensively amended during the preparation of the new edition that the type has had to be completely reset. This has made it possible to produce the book in four volumes instead of two, with greater convenience for the reader. The contents of all four volumes are listed at the beginning of each volume.

The only major change in the presentation of the text is that the references are no longer printed as footnotes. Instead, they are numbered serially as they occur and are collected at the end of the chapter. As before, the names of periodicals are abbreviated in accordance with the practice of the World Medical Association in its publication, *World Medical Periodicals* (third edition, New York, 1961; supplement,

* Cameron, G. R., George Payling Wright: 4 April 1898–4 April 1964, *Journal of Pathology and Bacteriology*, 1966, 92, 613–630.

New York, 1968). The intention to give the title and inclusive pagination of all articles cited in the new edition had to be dropped because of the impossibility of meeting the cost of the professional bibliographical help that would have been necessary. This, like the change in the method of presenting the references, is one of several consequences of the increasing cost of production that have had to be taken into account in preparing this edition. If, as I believe, economies have not diminished the usefulness of *Systemic Pathology* on this occasion, this is in part thanks to substantial, outright and unconditional financial support from a pathologist who, anonymously, considers the book to deserve such help. The future for books of this type is uncertain, in view of the limited circulation that results from the high price at which they have to be marketed if the expenses involved are to be covered: it may be that the time is coming when they will be publishable only if they have independent, non-commercial, financial backing.

* * * * *

As a consequence of the reorganization of the publishers' medical interests, this edition appears over the imprint of Churchill Livingstone, the Medical Division of Longman Group Limited. It is an editor's privilege to acknowledge the help of the members of the staff of the publishing house who have worked most closely on a shared undertaking, although house policy may prevent him from thanking all of them by name. Miss E. M. Bramwell, the publishers' senior house editor assigned to *Systemic Pathology*, has been uncommonly helpful and constructive in preparing the edited chapters for the printers and in eliminating difficulties that could have arisen from the fact that our complementary work was carried out in cities four hundred miles apart.

Many people, in many centres, have been involved in the preparation of this book. I cannot write personally about most of those whose technical, photographic, secretarial and other professional skills assisted the contributors, but I am sure that the latter would acknowledge the book's dependence on this help. It is a special pleasure to thank the senior members of the technical staff of the Department of Histopathology of Charing Cross Hospital and Medical School, London, for their interest—Mr F. D. Humberstone (Pathology Museum), Mr K. R. James (Hospital), Miss P. Naidoo (Medical School) and Mr H. Oakley (Mortuary). Their work is represented in many chapters, along with that of their colleagues in pathology departments of other hospitals and schools. Mr R. S. Barnett, in charge of the photographic laboratories of the Department of Histopathology at Charing Cross, has prepared many of the new illustrations, taking upon himself the responsibility of maintaining standards set in the first edition, to which his former chief, Miss P. M. Turnbull, head of the School's Department of Medical Illustration, contributed so notably. My thanks are also due to Miss S. M. Bennett, secretary of the Department of Histopathology of Charing Cross Hospital and Medical School, who not only produced much of the final typescript of the edited text—a classic exercise in decipherment—but also gave much other practical help in the preparation of the book.

In sum, as editor I owe much to many who have furthered *Systemic Pathology* by making it easier for me to work on it. They may not all be named, but I am glad to acknowledge their support. In particular, I would thank the histopathologists at Charing Cross, who have generously accepted, without remarking on it, the increase in their own work that resulted from my commitment to the book.

May the book prove useful, at least to the extent that what it has cost shall not be counted too great.

Northwood, Middlesex
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November 1975

William St Clair Symmers

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by the late G. PAYLING WRIGHT

Revised by T. CRAWFORD

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1: *The Heart**

by the late G. PAYLING WRIGHT

Revised by T. CRAWFORD

THE PERICARDIUM

The pericardial sac serves two functions in the physiology of the heart. First, its smooth mesothelium-covered inner surface facilitates the movements of the heart. Ordinarily, the visceral and parietal surfaces of the sac are separated by some 20 to 30 ml of limpid straw-coloured fluid—virtually a protein-free filtrate of plasma—the low viscosity of which renders it an excellent lubricant for the moving heart. Second, through its mechanically strong connective tissue matrix, the sac tends to preserve the myocardium from the injurious effects of any sudden excessive dilatation by preventing overfilling during diastole. That this latter function is probably of lesser importance seems to be shown by the fact that no cardiac disabilities manifest themselves in people who have the rare congenital abnormality of total absence of the pericardial sac.[1]

Abnormal Fluids in the Pericardial Sac

In consequence of the great resistance of the sac to any sudden stretching force, any abrupt increase of its fluid contents, such as may be brought about by a rapidly forming exudate or intrapericardial haemorrhage, may so severely restrict the diastolic filling of the heart that acute circulatory failure may soon follow. This condition is known as *cardiac tamponade*, and is met with most frequently in clinical work as a manifestation of haemopericardium—the result of rupture of a myocardial infarct or of an aneurysm of the aorta or the accompaniment of some serious injury to the heart or chest wall. The sudden entry of some 200 to 300 ml of blood under high pressure into an intact pericardial sac will cause death almost at once. Should the haemorrhage follow some injury to the thorax—especially if ribs are fractured—the accompanying laceration of the wall of the sac may allow the escape of some of this blood into the pleural cavity or the mediastinal tissues. The relief afforded by this leakage may prolong the period before the heart becomes irremediably embarrassed and thus may allow time for effective surgical measures. Should the patient survive, the residual blood in the sac coagulates and in time undergoes organization, with partial or complete obliteration of the pericardial cavity.

Although the pericardial sac yields little to a sudden stretching force, it distends gradually when the tension is applied continuously over periods of weeks or months. In slowly developing cardiac and renal failure—in which venous pressure may be raised or plasma protein concentration lowered—fluid often accumulates gradually in all the main serous cavities; in such cases, as much as 500 ml or more may collect slowly in the pericardial sac without serious hindrance to the diastolic filling of the atria. An excessive pericardial transudate of this kind, whatever its volume, is known as a *hydropericardium*. Eventually, however, the limit may be reached beyond which the sac can expand no further; after this stage has been attained, the pressure within it begins to build up and when it reaches about 10 mmHg the incoming veins suffer compression, the return of blood to the heart is impaired and cardiac output falls in consequence. The effects of progressive cardiac tamponade in raising venous pressure and lowering systemic arterial pressure were shown very clearly by Cohnheim when he introduced gradually increasing amounts of oil into the pericardial sacs of dogs.[2] Clinically, in man, an improvement in the circulation follows almost at once when hydropericardium is relieved by paracentesis.[3] As with transudates in general, the fluid that collects in hydropericardium

* Congenital diseases of the heart are the subject of Chapter 2 (page 73).

is clear and pale yellow and contains very little protein. Its presence does not injure the mesothelial lining of the sac and its removal is not followed by pericardial adhesions such as commonly follow the absorption or paracentesis of an inflammatory exudate.

Blood-Stained Effusions

Blood-stained pericardial effusions (as distinct from frank pericardial haemorrhage) are strongly suggestive of invasion of the pericardium by a malignant tumour. A useful diagnostic guide may be obtained by examination for the presence of tumour cells in fluid removed by paracentesis but it is necessary to warn that skilled interpretation is needed to avoid confusion between tumour cells and desquamated mesothelium.

Further causes of blood-stained effusion include leukaemia and other blood diseases associated with a haemorrhagic tendency. A small blood-stained effusion may be found in association with myocardial infarction.

Pericardial 'Milk Spots'

Opaque fibrous thickenings of the visceral pericardium, 1 to 3 cm in diameter, are frequently found on the anterior surface of the ventricles, oftener on the right than on the left side. They are commonly referred to as 'milk spots' and were formerly termed the 'soldier's patch' in the belief that they resulted from mechanical trauma by knapsack-straps. The notion that trauma is the causative factor is almost certainly erroneous, but nothing better has replaced it. The patches are of no clinical significance but it is to be noted that they are more numerous on hypertrophied hearts and on those with valvular disease than on hearts of normal size.[4]

Acute Pericarditis

Aetiology

Acute inflammation of the pericardial sac, which may be fibrinous, serofibrinous or purulent in character, may result from a wide variety of causes, some infective, others toxic or allergic.

Bacterial infections of the pericardium, notably those due to pneumococci, streptococci and staphylococci, have become less common since the introduction of antibiotics.[5] Such pyogenic organisms, however, may enter and infect the sac through perforating wounds of the chest wall. Occasionally, too, they may extend into it from some infection of the pleura or peritoneum, or from some infected neoplasm in the thorax, such as a carcinoma of the oesophagus or bronchus. In cases of pyaemia, the sac may be infected either by the escape of pus from a superficial abscess in the myocardium or directly from the blood stream. Although suppurative pericarditis is thus an occasional complication of acute bacterial endocarditis,[6] it usually follows some purulent lesion in other parts of the body: notable among these are carbuncles and acute osteomyelitis, and thrombosis of the cavernous or lateral sinus in cases of facial sepsis or otitis media.

In recent years, various forms of pericarditis have been described of which the pathogenesis is still in question. Sometimes, pericarditis develops acutely, with precordial pain and a local friction rub. This form may run a prolonged course, often with periods of exacerbation and remission.[7] In many cases, the serum titre against some strain of Coxsackie B virus has been found to rise during the course of the disease, and there thus seems a likelihood that this may be the responsible organism.[8] During an outbreak of Coxsackie virus meningitis in Melbourne an increased incidence of 'idiopathic' pericarditis was noted: Coxsackie virus type B5 was isolated from 2 of 14 cases studied, and other cases showed serological evidence of a similar infection.[9] In other cases, acute pericarditis of a relapsing kind has been associated with cardiac infarction, and the suggestion has been made that the inflammation may be part of a local reaction to cardiac muscle proteins that have escaped from the necrotic fibres.[10]

Acute pericarditis has also long been recognized as a frequent accompaniment of acute rheumatic carditis. Two variants of this form may be distinguished—one with and one without an effusion of fluid into the sac; the former has much the worse prognosis.[11] A sterile, apparently toxic, form of pericarditis also develops commonly as a terminal complication in acute and chronic renal failure with uraemia.[12]

The term 'malignant pericarditis' is sometimes used to describe the condition when the pericardial sac is involved by tumour: it is better avoided, however, as the lesion is essentially non-inflammatory and is characterized by a blood-stained effusion (see above).

Morphological Changes

In acute serofibrinous pericarditis, especially that associated with acute rheumatism or the early

stages of bacterial infection, the lining of the sac, especially over the posterior surface of the atria, presents the features typical of inflammation of a serous membrane.[13] The smaller blood vessels in the subserosa of both the visceral and parietal surfaces are much dilated, and this hyperaemia gives them a dusky redness. The early erythema is often obscured by a rough, tawny, overlying film of fibrinous exudate—the 'bread and butter' appearance described by Laënnec, or 'cor villosum' of other writers (Fig. 1.1). In the early stages of

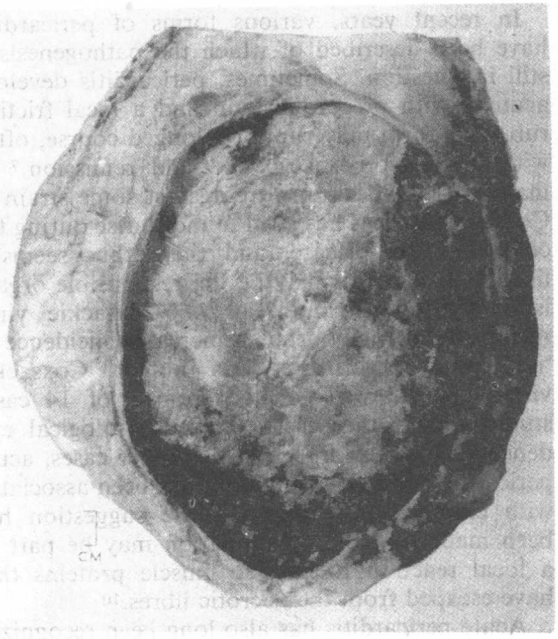


Fig. 1.1.§ Acute fibrinous pericarditis. The pericardial sac has been opened by cutting a window in its parietal aspect, exposing the thick, rough layer of fibrinous exudate on the visceral surface, and the stringy, fibrinous connexions between the apposed surfaces.

the inflammation this fibrin layer can usually be peeled away to expose the still glistening but injected red serosa beneath. If the inflammatory reaction has been present for several days, however, organization will have begun, so that the fibrinous exudate adheres much more firmly to the subserosa on which it lies. If it is detached forcibly, the surface of the heart can be seen to have lost its smooth, shiny appearance, and this change is reflected histologically in the loss of its mesothelium (Fig. 1.2).

When acute pericarditis is of recent origin, little

§ See *Acknowledgements*, page 71.

Fig. 1.2. Acute fibrinous pericarditis. The section is of the superficial zone of the visceral layer of the pericardium. The mesothelium has disappeared, and the pericardial surface is covered by a thick layer of fibrin in which there are only very scanty leucocytes. Vascular granulation tissue has begun to appear deep to the fibrin; dilated capillaries are conspicuous. *Haematoxylin–eosin.* × 140.

or no excess of fluid is found on opening the sac: this is the 'dry' form, in which friction rubs are usually audible clinically over the precordium. In cases of longer duration, much yellowish fluid, rendered turbid by many suspended shreds of fibrin, may be present. The protein content of such fluids, like that of all inflammatory exudates, is much raised—often to 4 or 5 per cent—and the many leucocytes add further to the turbidity. Should the inflammation subside, the gradual absorption of the excess of fluid which separated the visceral and parietal walls of the sac allows the two rough, fibrin-covered surfaces to come again into contact. Over the apposed areas, particularly when they lie near the base of the heart where the excursion of the chamber walls is small, the two surfaces may then become adherent to one another. Organization, which proceeds simul-

taneously from both surfaces (Fig. 1.3), finally completely replaces the exudate, adhesions forming that lead in time to partial or complete obliteration

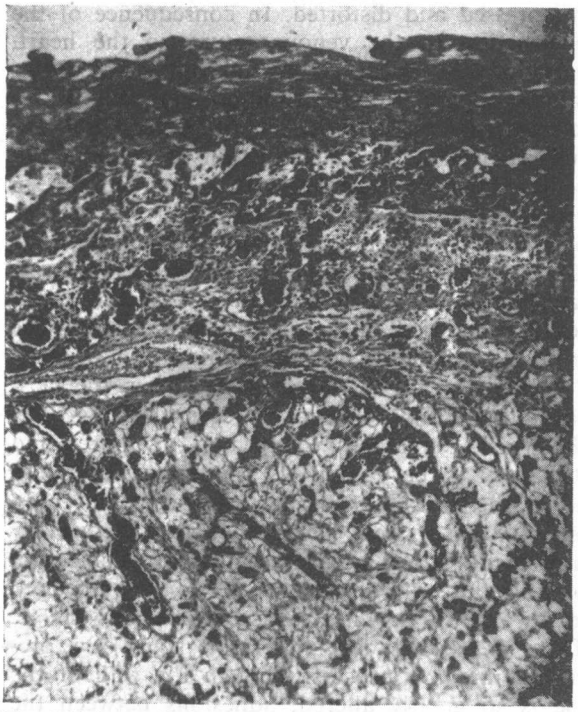


Fig. 1.3. Acute fibrinous pericarditis. The condition is at a stage later than that shown in Fig. 1.2. There is a well-formed zone of vascular fibrous tissue between the inflamed epicardial adipose tissue and the fibrinous exudate on the surface. Vascular dilatation is a prominent feature (the red blood cells appear black in the photograph). *Haematoxylin–eosin.* × 50.

of the cavity of the pericardium. Adhesions in this sac, however, never acquire the sclerotic character of those that form as a result of inflammation in the other serous cavities, for the constant movement of the heart tends to stretch them and so preserve their flexibility.

Suppurative Pericarditis

When the pericarditis is caused by such pyogenic bacteria as the staphylococcus, the streptococcus or the pneumococcus, the initial serofibrinous exudate soon assumes a frankly purulent character. Leucocytes, particularly neutrophils, emigrate in large numbers from the hyperaemic vessels in the inflamed serosa and the fluid gradually becomes more viscous and correspondingly more difficult to remove by paracentesis. Purulent pericarditis, with its clinical features of general intoxication, swinging fever and high leucocytosis, has a serious prognosis, for the inflammatory reaction beginning in the serosa may extend into the underlying muscle and give rise to a superficial myocarditis. Moreover, even in patients who are recovering, resolution of the inflammation may be delayed through the survival of bacteria in pockets of exudate. If the infection is overcome and the exudate eventually undergoes organization, constrictive pericarditis is likely to result (see below).

Chronic Pericarditis

The nomenclature of chronic pericardial diseases has long been confused, partly through uncertainty as to their aetiology and partly through the use by different authors of the same term for conditions that differ significantly in character and pathogenesis.[14] The following main varieties can be distinguished:

(a) adherent pericardium
(b) mediastinopericarditis
(c) tuberculous pericarditis
(d) constrictive pericarditis (Pick's disease).

Adherent Pericardium

In this not uncommon condition, which succeeds an earlier episode of serofibrinous inflammation, the cavity of the sac may be partially or wholly obliterated through the organization of the original exudate. The resulting adhesions vary widely in character: sometimes they merely connect the two layers of the pericardium with one or more tenuous fibrous bands ('synechiae cordis'); oftener, they fill much or all of the space between the visceral and parietal layers with a fine and rather lax connective tissue. In cases of this kind, the sac wall is neither thickened nor firmly attached to nearby rigid structures, and so the adhesions, even when they enclose the heart, hardly impede its contractions and its musculature shows no hypertrophy. The condition gives rise to no symptoms and is often first recognized at necropsy.

Mediastinopericarditis

When the original inflammation has involved the connective tissues of the mediastinum as well as the serosal lining of the pericardial sac, the succeeding fibrosis often unites all these structures firmly together. Consequently, each contraction of the ventricles pulls on the now adherent chest wall, and this is seen clinically as a systolic retraction of the sternum and lower ribs. This additional and

wasteful mechanical effort adds materially to the work of the heart, and in time results in myocardial hypertrophy and, eventually, cardiac failure. Since this uncommon form of pericarditis is generally of rheumatic origin, other chronic cardiac lesions, particularly in the valves, may also contribute to enlargement of the heart.[15]

Tuberculous Pericarditis

Tuberculosis of the pericardium is the most frequent form of tuberculosis of the heart.[16] In most cases, the sac is invaded by bacilli that have traversed lymphatic channels between infected mediastinal lymph nodes and the base of the heart: the pericardial infection is almost invariably the sequel to some preceding tuberculous disease of the lungs or pleura.[17]

When seen in its early, active phase, tuberculous pericarditis shows the changes typical of serofibrinous inflammation, though should fluid be present the exudate is usually more copious and likelier to be bloodstained in tuberculosis than in other infections. If the visceral and parietal layers of the pericardium are separated, the remains of the serosal surface of each are seen to be covered with thick fibrin, often mingled with caseous material; when this is removed, small grey or yellow tubercles are disclosed. On microscopical examination, this lining granulation tissue is distinctive in that it contains many tubercles;[18] their presence, together with areas of caseation, is strongly suggestive of tuberculosis, though occasionally a similar histological reaction can be found in other conditions, for example, in blastomycosis. Acid-fast bacilli can sometimes be detected in sections, but proof of the tuberculous nature of the infection depends upon the results of the inoculation of the exudate into guinea-pigs or of its culture upon suitable culture media.

It is now believed that in some patients a tuberculous pericarditis, after following a chronic course, can heal through the absorption of much of the exudate and the organization of the residual, partly caseous lesions. If this takes place, the fibrous tissue formed in the much thickened and adherent sac wall can gradually contract and give rise to the condition known as 'constrictive pericarditis' (see below).

Constrictive Pericarditis (Pick's Disease)

It has been known for more than a century that in certain forms of chronic pericarditis in young and middle-aged adults, the sac wall may be much thickened and may press not only on the heart, limiting diastolic expansion, but also on the main veins, which, as they approach the atria, become compressed and distorted. In consequence of the obstruction to the venous return to the heart, many of the clinical features of congestive cardiac failure appear.[19] This condition, now known as 'constrictive pericarditis', is often amenable to surgical treatment. The resection of much or all of the thickened sac leads to a marked fall in venous pressure, and to a return of the cardiac output toward a more normal value as a result of the greater stroke volume of the ventricles, now freed from the enveloping fibrous sheath; as a result, most or all of the clinical features that arose from the circulatory congestion disappear.[20]

When seen at operation or necropsy, the pericardium in this condition is seen to be grossly thickened—sometimes to 10 mm or more—and its cavity to be completely obliterated by dense adhesions.[21] It is as though the heart had been enclosed in a strait-jacket that restricted every movement. Sometimes, large areas of calcification or collections of cholesterol crystals are embedded in the dense, hyaline, avascular fibrous tissue. There are seldom any discernible signs of a preceding infective process. Though the wall of the sac is so greatly altered, adhesions between the pericardium and the adjacent mediastinal structures are rarely present. In this important respect, and in the associated absence of myocardial hypertrophy, constrictive pericarditis differs from mediastinopericarditis.

Occasionally, as a result of compression of the inferior vena cava by the coarse fibrous tissue, a syndrome known as '*polyserositis*' (Concato's disease) develops in which fluid gradually collects in the pleural and peritoneal cavities. The liver and spleen become enlarged, and their surfaces, and often the serosal covering of the underside of the diaphragm, may be patchily or uniformly thickened by an opaque, white mass of hyaline fibrous tissue. This material, which may form a layer several millimetres in thickness, is covered by mesothelium; it is debatable whether it represents a reactive subserosal fibrosis, with hyaline changes in the collagenous tissue and its matrix, or whether it is the end-result of the deposition of fibrin from the peritoneal effusion and its eventual organization on the serosal surface.

Although the aetiology of constrictive pericarditis is still in some respects obscure, there are cogent reasons for believing that in many cases the

condition is tuberculous in origin.[22] This view rests on three pieces of evidence: (i) known cases of tuberculous pericarditis when followed clinically can in time progress into the constrictive form; (ii) the occasional finding of histological appearances suggestive of tuberculosis in portions of the sac wall; and (iii) the occasional recovery of tubercle bacilli by animal inoculation. In a minority of cases, the dense fibrous tissue may be the remains of an old suppurative pericarditis that has healed. Rarely, the condition is the outcome of pericardial involvement in the course of systemic lupus erythematosus (see below).

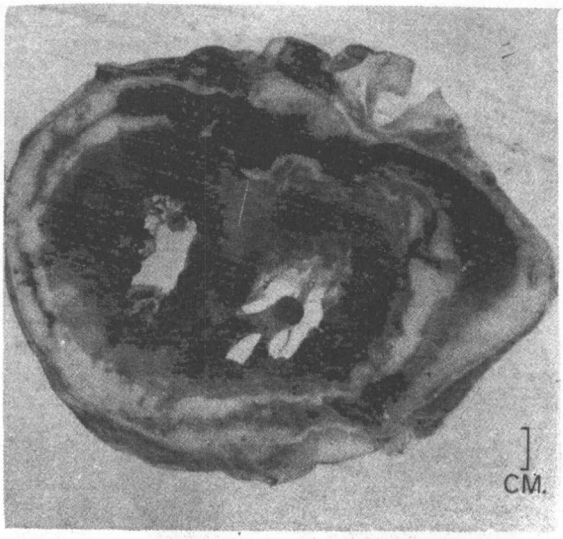


Fig. 1.4.§ Carcinomatous invasion of the pericardium. The two layers of the pericardium are covered by a thick, irregular growth of cancerous tissue. The layers of tumour on the visceral and parietal surfaces are in part separated by haemorrhagic exudate. The primary tumour was a bronchial carcinoma.

Pericarditis in the 'Collagen Diseases'

The occurrence of pericarditis in association with *rheumatoid arthritis* was described by Charcot,[23] and, in the juvenile form of the disease, by Still.[24] Wilkinson[25] observed this complication in four among 197 patients. Usually the layers of the pericardium are markedly thickened and adhesions are present. Microscopy shows degenerate collagen and non-specific chronic inflammatory changes. Occasionally vasculitis and fibrinoid necrosis are seen. Progression to constrictive pericarditis has been observed[26] and beneficial results from pericardiectomy have been reported.[27]

The pericardium is usually abnormal in *disseminated lupus erythematosus*. A study[28] of 27 cases coming to necropsy showed pericardial involvement in 20. In most the sac was obliterated by adhesions but some showed effusion or fresh deposits of fibrin. Microscopy showed fibrinoid areas and numerous haematoxyphile bodies amongst the degenerate collagen and chronic inflammatory tissue. Progression to constrictive pericarditis has been observed.[29]

Scleroderma of the progressive systemic type (systemic sclerosis) is not infrequently accompanied by pericardial effusion, the fluid being rich in protein but having a low cell content. [30, 31]

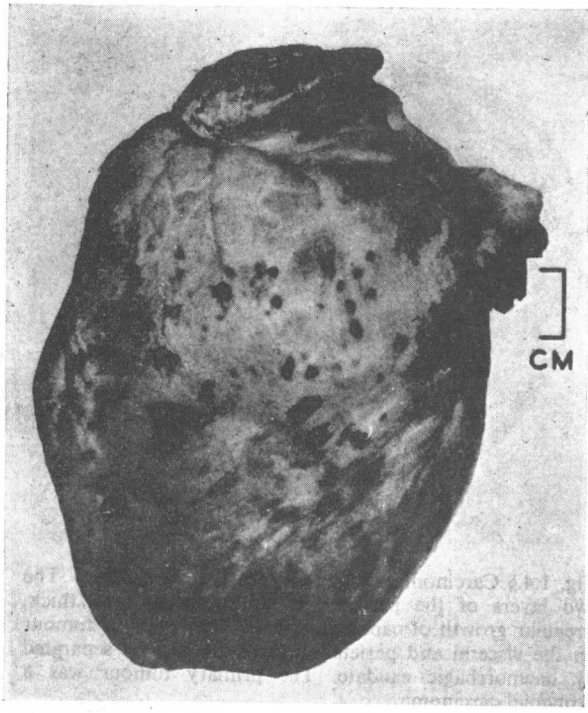
Other Forms of Chronic Pericarditis

Among the rarer forms of chronic pericarditis, with thickening of the wall of the sac by granulation tissue, are actinomycosis[32] and amoebiasis.[33] The actinomyces usually invades the pericardium from the lungs or pleural cavity; it gives rise at first to a copious effusion and later, if the patient survives, to extensive obliteration of the sac—in both forms the action of the heart is seriously embarrassed. Amoebiasis of the pericardium almost invariably follows from the extension of an abscess of the liver through the diaphragm; the condition is generally fatal unless chemotherapy is accompanied by surgical drainage.

Neoplasms of the Pericardium[34]

Primary neoplasms of the pericardium[35] are rare and when they occur may present considerable difficulty in diagnosis to both the clinician and the pathologist. Among benign tumours, lipomas, myomas and fibromas are most frequently recorded. The least rare malignant tumours are fibrosarcoma and mesothelioma: in recent years the latter diagnosis has been made with increasing frequency and the probability is that many tumours formerly regarded as fibrosarcomas would today be categorized as mesotheliomas.

Primary *mesothelioma* may involve the pericardium diffusely or as one or more localized nodules.[36] In the diffuse type the heart may be sheathed in greyish-white rather slimy tumour tissue, a centimetre or more in thickness, and there may be a loculated blood-stained effusion. Microscopically, the tumours may be predominantly of



spindle-cell type, or mainly 'epithelial' in appearance. A review of 25 cases showed 14 spindle-cell tumours, 6 of 'epithelial' type and 5 of mixed type.[37] About half the tumours metastasize to the lymph nodes, pleura or lungs: when this occurs it is difficult to be certain of the primary site.[38] There is as yet no evidence that primary pericardial mesotheliomas, as distinct from pleural and peritoneal tumours, are particularly associated with exposure to asbestos (see page 407).

Invasion of the pericardium is a relatively common feature of the late stages of *carcinoma* of the bronchus (Fig. 1.4), oesophagus, breast and stomach. It occurs also with *thymoma*.

In *leukaemia*, the pericardium, like the other serous sacs, may show numerous petechial haemorrhages (Fig. 1.5).

Fig. 1.5.§ Petechial haemorrhages and ecchymoses in the visceral layer of the pericardium of a boy, aged 12 years, who died of monocytic leukaemia.

THE HEART

ISCHAEMIC HEART DISEASE

The term 'ischaemic heart disease' is now applied to those conditions in which the nutrition of the heart is impaired as a result of some abnormality of its coronary arteries. Rarely, the abnormality is congenital, as when these arteries arise from the pulmonary artery instead of from the aorta, but in the vast majority of cases it is acquired and takes the form of atherosclerosis in their main trunks. The effect of such arterial obstruction on the myocardium can readily be appreciated: the milder forms result in some reduction in the capacity of the heart to meet the circulatory stresses of exercise; severer obstruction leads to local necrosis of myocardial fibres (myocardiolysis) and their replacement by scar tissue (replacement fibrosis) and often eventually, especially when complicated by thrombosis, to gross infarction.[39]

In the past, obstructive lesions in the main coronary arteries had long been recognized as occasional post-mortem findings, sometimes associated with sudden death after angina pectoris—as in the case of the great surgeon-pathologist John Hunter. It was only after the first world war, however, that the clinical syndrome of coronary arterial occlusion became sufficiently defined for the disease to be diagnosed with confidence. Formerly, many cases of ischaemic heart disease were unrecognized either clinically or at necropsy, and as a consequence it is only in recent years that mortality statistics have disclosed its prevalence.[40] In the Registrar General's *Statistical Review of England and Wales for the Year 1973* rather more than a quarter of all deaths were attributed to 'ischaemic heart disease'. Most of those who died from this cause were men of 45 years or over, but in recent times the incidence of this type of heart disease among women and younger men has shown a significant and disturbing rise. Coronary disease is particularly prevalent among professional men: it was named in more than a third of 500 obituaries of American physicians who died in 1969 in which the cause of death was stated. On the whole, as Morris and his colleagues have pointed out, it tends to be less common among the physically more active men of the labouring classes.[41, 42]

The Anatomy of the Main Coronary Arteries

Our knowledge of the distribution of the two main coronary arteries and of their wide variations from person to person has become better appreciated through the use of coronary angiography in both the living individual and the necropsy specimen.[43–46] The technique of first injecting a lead-agar preparation into the arteries and then opening the organ before it is radiographed has made it possible to identify all the coronary branches with a calibre of a millimetre or more (Fig. 1.6). Such studies have shown that about one-third of all hearts

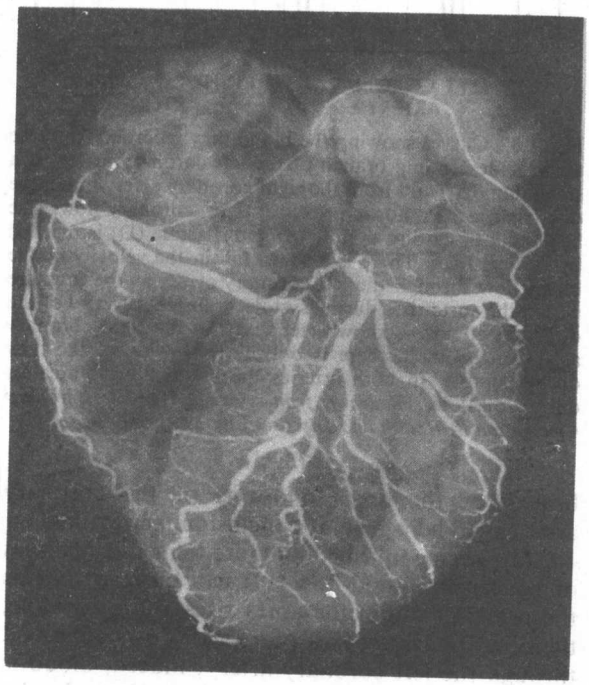


Fig. 1.6.§ Post-mortem coronary angiograph in the case of a man, aged 25 years, who had been killed in a road accident. The arteries are free from significant atheroma.

possess left and right main arteries of about the same size—the right coronary artery then supplies almost the whole right ventricle and the posterior part of the left ventricle and of the interventricular septum, while the left coronary artery is distributed to most of the left ventricle and the anterior part of the septum. In the other two-thirds, however, one of the main arteries, usually the right one, is larger—often considerably so—and supplies proportionately more of the cardiac muscle. It should be noted that the effects of atherosclerosis tend to be more serious in hearts with a preponderating left coronary artery.

During early life the anastomoses between the terminal branches of the two coronary arteries, although numerous, are very small, so that in the event of an obstruction to one of the main trunks neither can take over the function of the other. They are 'end arteries' in Cohnheim's sense of that term. The size and number of these anastomoses have been estimated in various ways, most of which depend on the examination either of histological material or of radiographs of injected hearts. The method that has probably provided the best estimate of their calibre, however, is that employing the perfusion of the coronary arteries with suspensions of glass or wax spherules and the subsequent determination of the size of the largest spherules capable of passing from one main artery to the other.[47] Even this method probably underestimates the effective size of these small precapillary anastomotic channels during life. Though differing in detail, all the methods that have been employed for determining the size and number of these anastomotic vessels agree in indicating that both increase with advancing years (Fig. 1.7). In young people they are few and small, but in the older they may become large enough to contribute materially to maintaining the blood supply to a portion of myocardium rendered ischaemic by an obstruction of the major artery by which it is ordinarily supplied.[48]

Injection studies have further shown that small arteries round the ostia of the aorta and pulmonary arteries and of the systemic and pulmonary veins form tortuous anastomoses with the two coronary arteries.[49] Although their contribution to the myocardial circulation is normally insignificant, even these small pre-existent vessels can, if the need arises, gradually undergo very considerable enlargement and provide a functionally important collateral circulation for the heart.

The major coronary arteries in their course in the epicardium are often partially or wholly embedded in its adipose tissue. At frequent intervals they give off branches which pass more or less perpendicularly into the underlying myocardium; their calibre becomes smaller and their walls thinner as they approach the lining of the ventricles.[50–52] It is these finer ramifications of the arterial tree that are compressed or even obliterated by the contraction of surrounding cardiac muscle fibres during systole.

The Physiology of the Coronary Circulation

The investigation of the coronary circulation provides problems of peculiar technical difficulty, yet