RES MEDICA
Journal of the Royal Medical Society

The Pathology of Angina Pectoris

W. F. M. Fulton

Abstract

Mr. Chairman,

First let me express my deep appreciation of the honour which you have done me in inviting me to take part in this historic occasion. When speaking of the pathology of angina it is fitting not only to consider recent information but also to review some of the fundamental contributions of earlier workers.

In this respect my task is made lighter by the able presentation of historical aspects of angina by Miss Leach, and I should like to compliment her upon it.

Lauder Brunton and his contemporaries advanced many theories about the origin of cardiac pain. Brunton himself favoured weakness of the heart in the face of excessive load (Brunton, 1891). Nowadays few would question that the pain has its origin in the myocardium under conditions of ischaemia; and that this affects the heart when "the supply of energy and its expenditure do not balance each other" . In this statement of the modern concept I have borrowed the words of the Scottish anatomist Allan Burns, 1809.

PATHOPHYSIOLOGICAL SESSION

Chairman: Professor W. Melville Arnott *Olim Praeses*

THE PATHOLOGY OF ANGINA PECTORIS

W. F. M. Fulton, Glasgow

Department of Materia Medica and Therapentics, University of Glasgow

Mr. Chairman,

First let me express my deep appreciation of the honour which you have done me in inviting me to take part in this historic occasion. When speaking of the pathology of angina it is fitting not only to consider recent information but also to review some of the fundamental contributions of earlier workers.

In this respect my task is made lighter by the able presentation of historical aspects of angina by Miss Leach, and I should like to compliment her upon it.

Lauder Brunton and his contemporaries advanced many theories about the origin of cardiac pain. Brunton himself favoured weakness of the heart in the face of excessive load (Brunton, 1891). Nowadays few would question that the pain has its origin in the myocardium under conditions of ischaemia; and that this affects the heart when "the supply of energy and its expenditure do not balance each other". In this statement of the modern concept I have borrowed the words of the Scottish anatomist Allan Burns, 1809.

During the last century the evidence was relatively unsophisticated. Today, some simple truths are in danger of being submerged in a plethora of data, or of being displaced by the novelty of discrepant findings. Sometimes the discrepancies are more apparent than real. They are the product of discussion more critical than the data under consideration. Difficulties in distinguishing cause from effect abound in studies of coronary heart disease and atherosclerosis.

Let me therefore say categorically that when we are concerned, in the pathology of ischaemic heart disease, with detailed correlation of arterial and myocardial changes, or with reconstruction of clinico-pathological events, a satisfactory method of injecting and visualizing the coronary arteries is not merely an adjuvant to, but a requirement of, a comprehensive pathological examination of the heart.

In Fig. 1a (page 12) are shown two arteriograms prepared by radiography after the coronary arteries had been injected post-mortem with a contrast medium. Tissue shadow has been virtually eliminated by a special radiological technique (Fulton 1963a). On the left is an arteriogram of a normal heart. Note the richness of the blood supply to the heart wall; the smooth tapering outline of the major vessels on the surface of the heart; and the manner in which the calibre of a major vessel bears some relation to the arterial bed which it supplies.

On page 13 (Fig. 1b) is the heart of a patient who experienced angina for 10 years. On the surface of the heart the coronary arteries are the seat of widespread severe disease with great reduction in calibre and here and there complete occlusion. As a result there must have been severe restriction in the total volume of coronary blood flow. By contrast the channels available for distribution of blood to the heart wall are greatly increased. This increase in small vessel calibre has its main emphasis in the depths of the ischaemic muscle. I shall return to this point.

It is well recognized that obliterative disease of the coronary arteries is almost restricted to those portions which lie outside the heart muscle. Nevertheless, where conditions of blood flow are critical, details of fluid dynamics in the microcirculation of the heart wall also merit attention.

Implication of coronary disease in syncope anginosa is not new. We may look back to the observations of Senac, Morgagni, Jenner and Parry, even before the time of Allan Burns. During this era and well into the nineteenth century not surprisingly there was much preoccupation with "ossification" of the coronary arteries.

The illustration in Fig. 2 might well have been of the heart of John Hunter himself; for this patient likewise suffered from severe protracted angina. This radiograph was taken before

injection; the coronary arteries are outlined by calcification. Calcification is generally held to be a sequel not a cause in coronary disease. As Leary (1935) said, somewhat ambiguously: "calcification is merely of monumental character!"

At the end of last century Osler (1896) summarized the accumulated pathological evidence when he said that "in an immense proportion of all cases *angina pectoris vera is associated with disease of the coronary arteries* and of the myocardium." When a few years later Herrick published perhaps the first important clinico-pathological study of acute myocardial infarction, this condition came to be distinguished in life from angina pectoris without cardiac infarction.

It did not take long for the issue to be clouded by confusion in nomenclature. Thus, in common parlance, "coronary thrombosis" came to be equated with myocardial infarction and "angina pectoris" with changes in the coronary arteries other than thrombosis. I suspect that these nosological distinctions still survive, and still encourage loose thinking in this subject. Again, when the unhappy term "acute coronary insufficiency" came to be reserved for those syndromes which lie between effort angina and myocardial infarction, an opportunity was created for confusion which would have delighted Lewis Carroll!

I do not decry the attempt to define the clinical illness in terms of its pathology, of course not, but merely emphasise that this disease cannot be so neatly compartmentalized. At different times an individual's illness may be correctly described under each of the three headings of myocardial infarction, angina pectoris and acute coronary
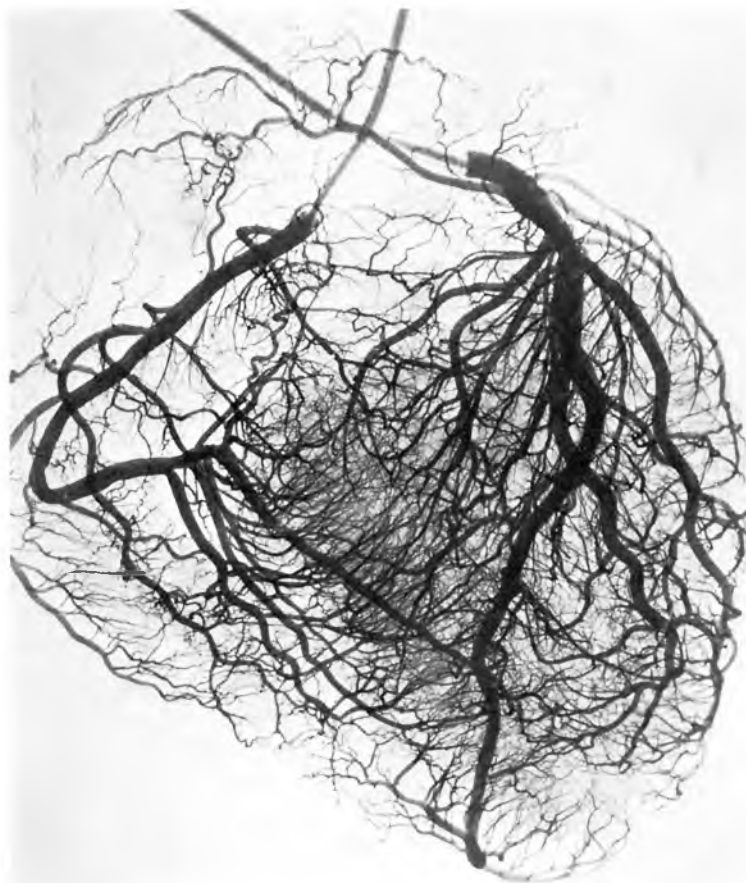

Figure 1A
The coronary circulation in health and advanced coronary artery disease (see text).
A. Arteriogram of a healthy coronary circulation. (× ⅔)

Figure 1A reproduced from the British Heart Journal, 1956, 18, 341 (by courtesy of the British Medical Association).

N.B. With the method of radiology employed tissue shadow has been virtually eliminated and all the density observed is due to contrast medium in injected vessels.

insufficiency, and there is no rule to the sequence of their manifestation. There is no surprise in this for the pathologist; for the ingredients of disease in the coronary arteries themselves are similar in each of the three settings.

Where angina is due primarily or solely to coronary artery disease, there is much evidence that obliterative changes in the coronary arteries are severe, perhaps even at the onset of symptoms. This is no new finding. When in 1889 Huchard cited the evidence of 145 autopsies on patients dying of angina pectoris, in every instance there was obliteration or stenosis of coronary arteries. If any should doubt the validity of these early observations they should read the now classic report by Zoll, Wessler and Blumgart (1951).

These workers in Boston (Massachusetts) reported on 905 unselected autopsies in which the hearts were submitted to arteriography. In this series there were 177 cases of angina of one month's duration or longer. In every instance obliterative changes in the coronary arteries were present, except where other causes such as valvular disease were severe. We may note particularly that in 20 out of 28 cases of angina, due to coronary artery disease alone, there was complete occlusion of one or more main stems. A lesser degree of coronary disease was sufficient to produce angina in the presence of hypertension but the picture was similar and occlusions were frequent.

Not surprisingly, old myocardial infarction was found among these cases. In some angina appeared before cardiac infarction, in others infarction preceded angina. Indeed, in about half the cases the onset of the anginal

Figure 1B
Arteriogram of the coronary circulation in a case of long-term angina pectoris based on advanced obliterative disease of the major coronary arteries. The anterior descending artery and right coronary artery were occluded and the left circumflex severely narrowed. Great increase is seen in the vascular pattern in the central left ventricular area. ($\times \frac{4}{5}$)

Figure 1B reproduced from the British Heart Journal, 1956, 18, 341 (by courtesy of the British Medical Association).

illness was heralded by cardiac infarction.

When the findings were viewed from the other aspect, to see how many cases with complete coronary artery occlusion *post mortem* had suffered from angina in life, it was found that only just over half had experienced this symptom; and where the coronary arteries were merely narrowed, not completely occluded, only 5 per cent had experienced angina.

Perhaps these post-mortem findings may not truly reflect the situation during life? The development of selective cineärteriography of the coronary arteries of man, as a clinical investigational procedure, has thrown light upon this question. I look forward to hearing what Dr. Friesinger and Dr. Gorlin have to say about this. I refer here to a recent report by Mason Sones and his colleagues from Cleveland, Ohio (1966), which concerns one thousand patients submitted to this procedure. They confirmed, in life, that arterial obstruction in anginal patients was almost always severe; occlusion was usually total or almost total in one or more major coronary vessels.

If then the nature and severity of the underlying condition in the coronary arteries is similar in the several syndromes of ischaemic heart disease, how is it that in some instances the myocardium suffers massive necrosis and in others the damage is trivial and possibly even absent?

I have given some attention to the phenomena which may determine the extent and distribution of myocardial damage following coronary artery occlusion. Among many possible determinants, the factor which appeared to stand out was the extent of the collateral blood flow through intercoronary anastomoses, available at the time of occlusion (Fulton, 1964a).

In my opinion coronary artery anastomoses are normal structures (Fulton, 1963b). In health they remain small because they are required to carry only a tiny measure of blood flow. However, occlusion of a coronary artery in life alters this by introducing abnormal pressure gradients; and blood is made to flow through arterial communications between the coronary branches. As the collaterial blood flow increases in volume the vessels which carry it enlarge.

The existence of arterial anastomoses can be demonstrated. I mention two reliable methods:

(1) *Perfusion* from one arterial territory to another using a medium which does not

Figure 2
Radiograph of a heart with long-term angina showing calcification of the major coronary arteries.

Reproduced from Fulton, W., Coronary Arteries, 1965. By courtesy of Charles C. Thomas, publisher, Springfield, Illinois .

penetrate the capillary bed. For illustrative purposes, in a normal heart a large branch of the left circumflex coronary artery was ligated before injection of the contrast medium. In a short time the territory distal to the ligature was perfectly filled in retrograde fashion through normal interarterial communications (Fig. 3). (2) *Stereoarteriography:* The structure and distribution of anastomoses can be studied directly when arteriograms of adequate quality are examined stereoscopically at magnification × 5.

Let me show you three typical examples which illustrate the complex inter-relationship of coronary occlusion, myocardial damage and anastomotic development.

I shall deal with the first example very briefly (Figs. 4 and 5). This is the heart of an elderly woman whose coronary arteries were healthy apart from a short stretch of the anterior descending artery. The pattern of anastomoses in this case showed only a slight increase over that found in normal hearts (Fig. 4). When complete occlusion took place as the result of coronary thrombosis the outcome was massive infarction of the anterior wall of the left ventricle and the interventricular septum. A very large part of the territory of the affected artery was involved in acute necrosis (Fig. 5). There was no previous history of angina.

In this second case the situation is more complex because the first clinical episode of coronary artery occlusion was survived. This occlusion involved the anterior descending artery. Enlarged anastomoses carried blood flow from the right coronary artery across the interventricular septum to feed the territory of the descending branch of the left – until the right coronary artery itself was occluded (Fig. 6). The sequence of events may be described along with the diagram (Fig. 7). Two years before death cardiac pain occurred, without prior warning, and lasted for about 1 hour. On reconstruction it was evident that this event was represented by thrombotic occlusion of the anterior descending artery and patchy infarction (now fibrotic) in its territory. When the attack of pain eased off the patient, who was a farmer, returned to his work and was never laid off. He continued to suffer from effort angina though with diminishing severity. When right coronary artery occlusion overtook him its effects were both disastrous – and interesting. Not only did it cause necrosis in its own territory but it provoked damage in the territory of its neighbour, the anterior descending artery, of greater severity than had taken place at the time of its own occlusion. This is the phenomenon of pararegional infarction (infarction at a distance). This case points the lesson that enlargment of anastomoses can mitigate the effects of coronary

Figure 3
Arteriogram of upper left ventricular wall of a normal heart. A major branch of the left circumflex coronary artery was severed between two ligatures before injection of the contrast medium, which did not penetrate the capillary bed. In the space of 20 seconds retrograde filling of the arterial tree beyond the ligatures took place through arterial anastomoses which communicated with other branches; and the pathways followed could be traced when examined steroscopically. ($\times \frac{3}{2}$ approx.)

Figure 4
First case: Arteriogram of heart with acute myocardial infarction and no previous history of angina. Note complete occlusion of the anterior descending artery. The coronary arteries are otherwise unobstructed. Anastomotic changes are slight.
Reproduced from the British Heart Journal, 1964, 26, 1 (by courtesy of the British Medical Association).
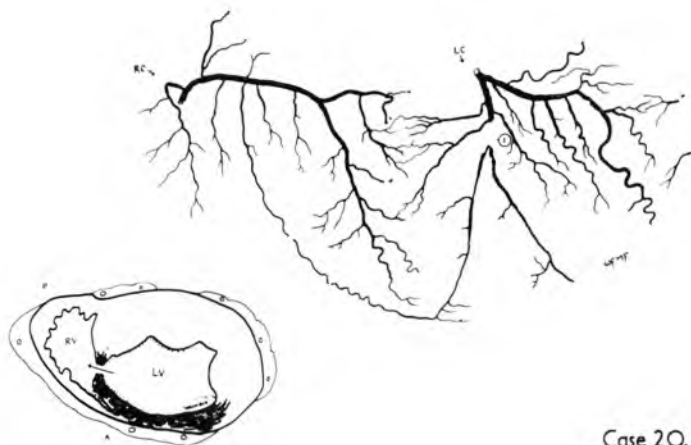

Case 20.

Figure 5
First case: Diagram of coronary circulation and myocardial damage. Solid black indicates acute myocardial necrosis.
Reproduced from Fulton, W., Coronary Arteries, 1965. (By courtesy of Charles C. Thomas, publisher, Springfield, Illinois).
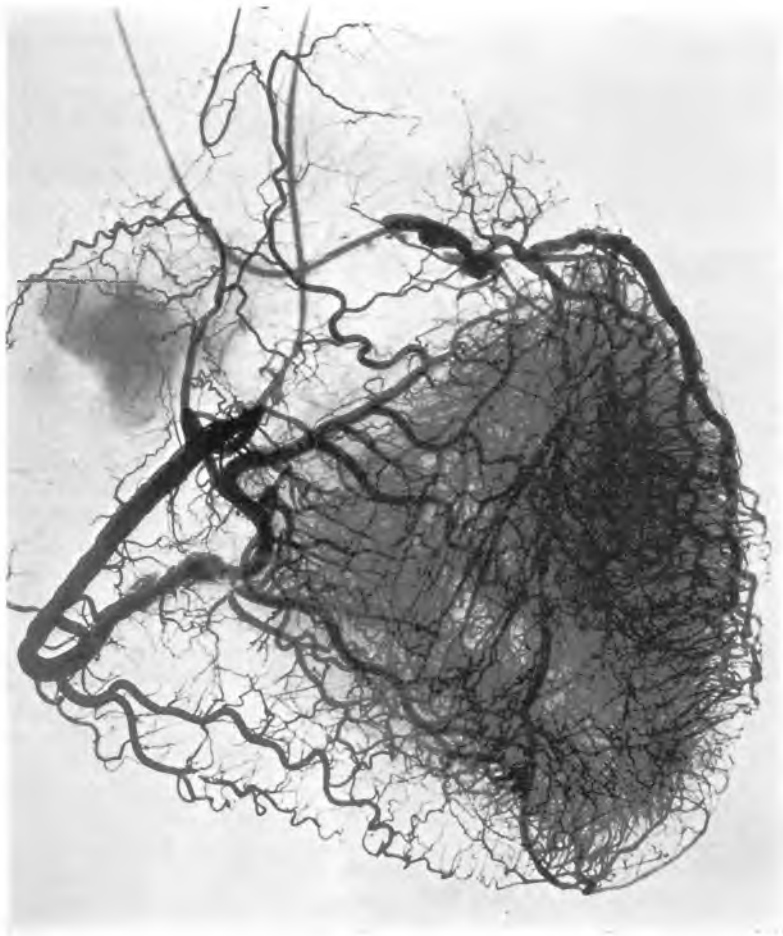
Figure 6
Second case: Arteriogram of heart with two episodes of coronary artery occlusion, two year history. Note old complete occlusion of anterior descending artery and recent complete occlusion of distal right coronary artery; and increased vascularity in portions of the left ventricle. Anastomotic communications were largely deeply placed. A communication is seen between mediastinal and atrial arteries. ($\times \frac{3}{4}$) Reproduced from Fulton, W., Coronary Arteries, 1965. (By courtesy of Charles C. Thomas, publisher, Springfield, Illinois).
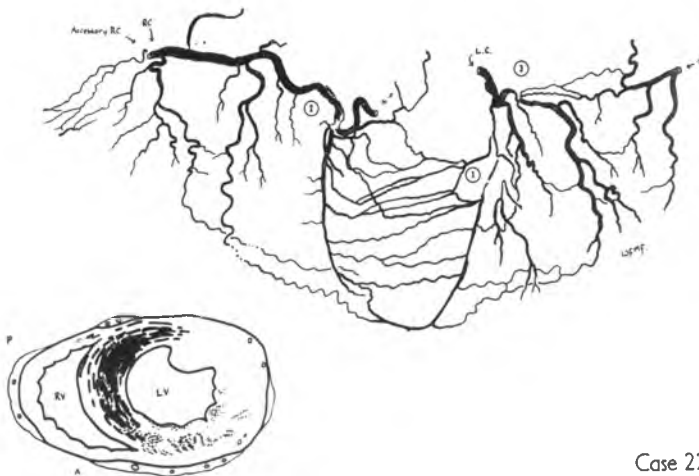

Case 22.

Figure 7
Second case: Diagram of coronary circulation and myocardial damage. Solid black indicates recent necrosis and stippling fibrosis of about 2 years duration.
Reproduced from the British Heart Journal, 1964, 26, 1 (by courtesy of the British Medical Association).

17

artery occlusion, both at the time and later; but only so long as the foster artery remains itself unobstructed.

Anastomoses in the interventricular septum are of special importance. In Fig. 8 is the upper part of a normal septum showing small communicating channels which link the anterior and posterior descending arteries. These channels can enlarge in disease. In Fig. 9 are shown on the same scale the anastomoses of the ischaemic heart I have just described as they cross the interventricular septum. Their calibre, and thereby their capacity for transmitting blood flow, is greatly increased.

The case I have just described probably exemplifies a common situation in which coronary

Figure 8
Arteriogram of upper interventricular septum in a normal heart. Small cliabre communications link the anterior descending (on right) and the posterior descending (on left) coronary arteries. ($\times \frac{5}{4}$)
Reproduced from the Scottish Medical Journal, 1963, 8, 420 **(by kind permission of the publishers).**

Figure 9
Arteriogram of upper interventricular septum in the second case. Great enlargement of anastomotic vessels has taken place, cf. normal in figure 8. ($\times \frac{5}{4}$)

artery occlusion leads to a small deep-seated patchy infarct; this is survived and the patient goes on to experience effort angina.

Now we turn to the heart of a patient who had suffered from severe intractable angina for many years during which there was only very little ischaemic myocardial damage. We can observe severe affection of all main stems with numerous areas of severe narrowing or complete obliteration (Fig. 10). Round the apex you can trace a large superficial communication.

In my investigation I have been impressed also with the deep anastomotic communications which have been largely overlooked in former studies. You can observe a great increase in the density of the small vessel pattern in the central area of the left ventricle. The appearances indeed are due to a network of vessels lying in the deepest layers of the left ventricular wall. This can be better seen in section (Fig. 11). Here you see the vessels in the inner third of the left ventricle greatly dilated to form a system of wide-bore intercommunicating channels. These are derived from the enlargement of normal structures (Fulton, 1956). In the section through a normal heart at the same scale (Fig. 12) you can see the normal pattern and realize how far the circulation of the heart with long term angina had departed from it.

We may ask what influence had the adaptive changes of the small vessels upon the distribution of myocardial damage? In the diagram (Fig. 13) you see that, despite widespread obliterative coronary artery disease, massive regional infarction had not occurred. Instead, numerous small areas of earlier damage, now represented by fibrosis, were restricted to the inner zone of the left ventricle. Terminally there were also numerous fresh foci of necrosis likewise in deep zonal distribution.

The coronary arteries bore evidence of numerous episodes of thrombotic occlusion in the past. There was however no recent arterial change to account for the recent myocardial damage. This terminal state exemplifies acute coronary insufficiency – so called – in which some additional factor altered the precarious balance of impoverished coronary supply and myocardial need. It is popular notion that angina and acute coronary insufficiency result from occlusions which are incomplete or affect only relatively small branches. It is hard to find satisfactory

evidence to support this, or to know how frequently it may be true.

The three examples I have presented were deliberately chosen to illustrate the opposite point of view. They showed how the extent of coronary artery disease and the extent of myocardial damage can be inversely related to each other. This paradoxical situation was determined by the extent of anastomotic development.

I turn now, therefore, to consider briefly factors which govern the enlargement of anastomoses. I look forward to what Dr. Russell Rees has to communicate on this topic. I wish however briefly to observe that anastomoses appear to enlarge in response to increased volume of blood flow through them. In this process the main determinant is the pressure gradient created by coronary artery occlusion (Fulton 1964b). For this stimulus to be strong, the evidence of human pathology as well as of work on experimental animals indicates that stenosis of the artery in question must be severe, so that the cross-section of the arterial lumen is reduced to the order of *one tenth or less of its original area* (Blumgart *et al.* 1950; Sewell, 1961). It is understandable that where the stimulus is less than maximal a very long time may be required for anastomotic enlargement; and my own findings have borne this out (Fulton, 1964c).

It is often said that the existence of lesser degrees of coronary artery disease prepares the heart against the effects of coronary artery occlusion. Nearly thirty years ago Schlesinger drew attention to the importance in this context of the rate of evolution of the atherosclerotic disease. Where the disease proceeds slowly there is greater opportunity for small vessel adaptation to keep pace. But let it be clearly understood that there is no evidence whatsoever that any purpose underlies the process of anastomotic enlargement; or that the response ever exceeds the stimulus which has existed up to that time. We are dealing with a pathological sequel, not a forerunner: it never anticipates the next exigency.

On the other hand the continued enlargement of anastomoses after coronary occlusion is an important mechanism in the mitigation of anginal symptoms.

Time does not permit discussion of the atherosclerotic lesion itself, or of the many controversies that centre on the nature and significance of the arterial changes and their pathogenesis. My own

Figure 10
Third case: Arteriogram of a heart with a 10-year history of angina, without regional infarction. ($\times \frac{4}{5}$) Note widespread obliterative disease of main coronary arteries and extensive increase in vascular density in the left ventricular area. A large superficial communication links the anterior descending and the left circumflex coronary arteries at the apex. Reproduced from the Scottish Medical Journal, 1963, 8, 420 (by kind permission of the publishers).

Figure 11
Third case: Arteriogram of 1 cm. thick section through the left ventricle.
The inner ⅓ of the left ventricular wall is occupied by a network of wide-bore intercommunicating vessels derived from the subendocardial arterial plexus. ($\times$ ⅔)
Reproduced from the British Heart Journal, 1964, 26, 1 (by courtesy of the British Medical Association).
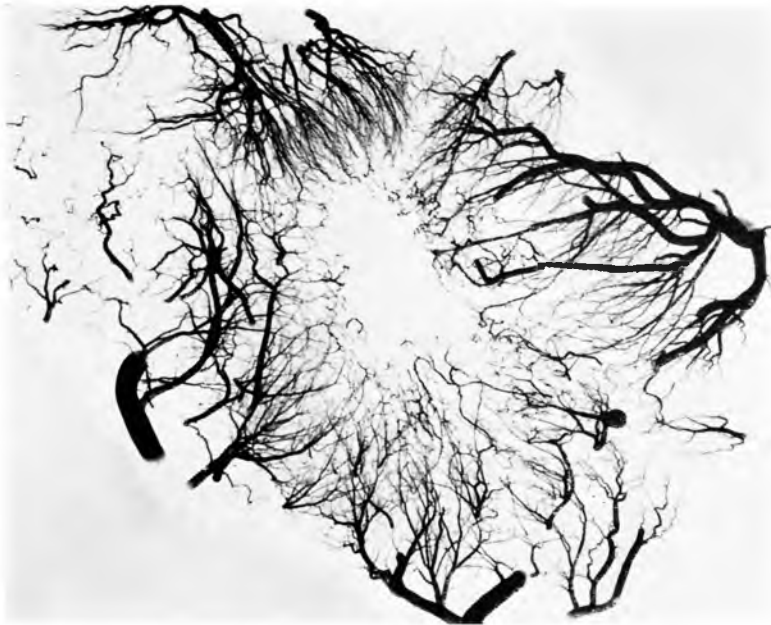
Figure 12
Normal: Arteriogram of
1 cm thick section through a
normal heart showing the
normal pattern of myo-
cardial blood supply
and the dimensions of
normal subendocardial
anastomotic vessels, for
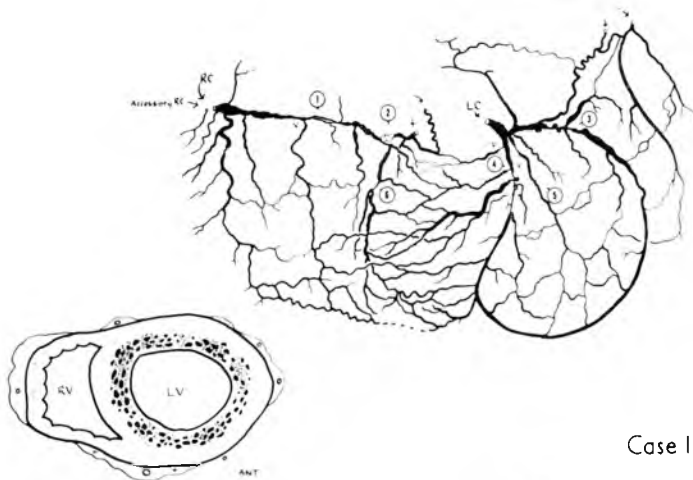comparison with Figure 11.

Case 17

Figure 13
Third case: Diagram of the
coronary circulation and
myocardial damage. Solid
black indicates acute focal
necrosis and stippling
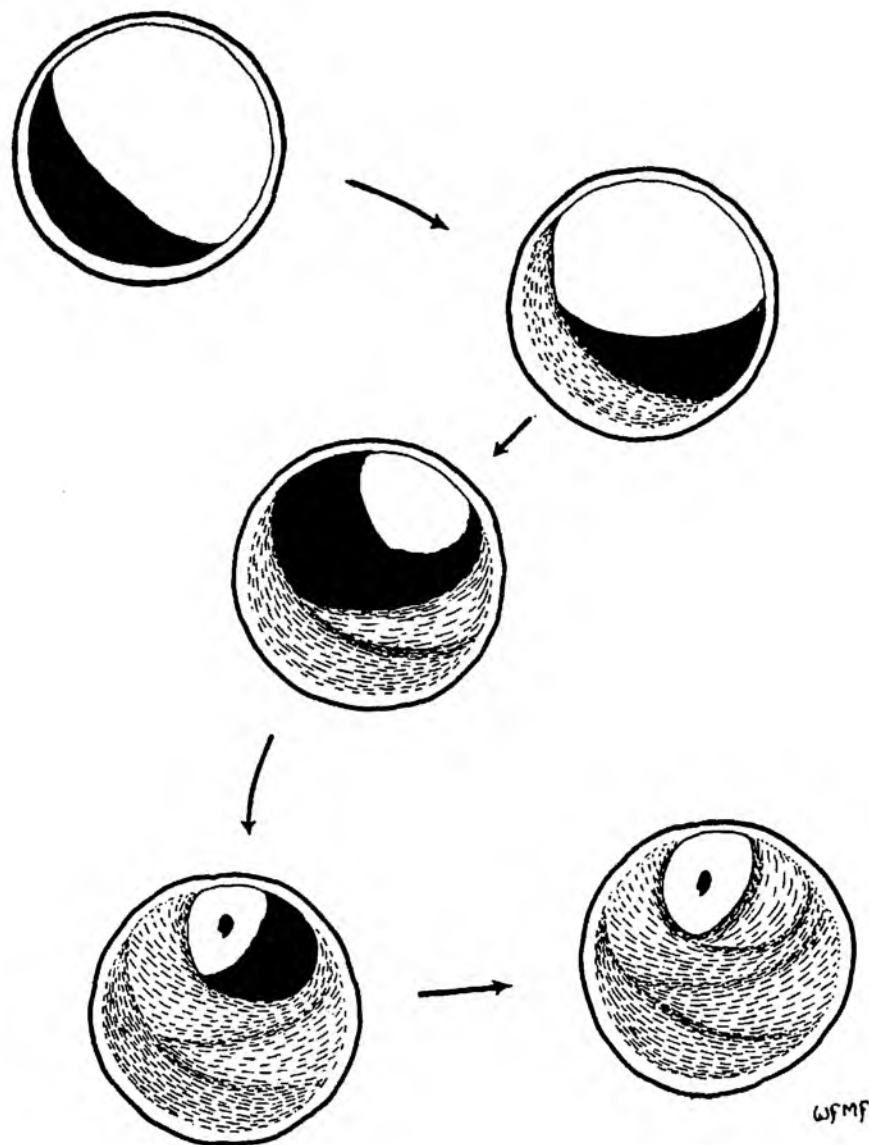old-standing replacement
fibrosis.

Figure 14
Diagram of the thrombogenic origin of atheroscler-
otic narrowing of a coronary artery.

Reproduced from Fulton, W., Coronary Arteries.
1965. (By courtesy of Charles C. Thomas, publisher,
Springfield, Illinois.

observations (Fulton 1965) have led me to conclude that those stages of the disease which cause ischaemic symptoms or myocardial damage are represented by lesions which have their origins in thrombus. With the passage of time layers of thrombus become incorporated in the arterial wall to form atherosclerotic plaques (Fig. 14). Successive episodes of thrombosis occur at widely separated intervals. Sometimes the episodes may be defined in symptoms and in morphological changes in the coronary arteries and myocardium.

In the section (Fig. 15) through a diseased coronary artery, we may note the manner in which the atherosclerotic tissue has been formed in laters. This in turn would have been the fate of the layer of thrombus which has formed upon its surface.

So far I have considered angina as an expression of coronary artery disease. There are of course many other factors extrinsic to the major coronary arteries which may impede blood flow within the heart wall, impair the quality of the blood delivered, or increase the requirements of the myocardium. The presence of any of these factors may provoke angina at a lesser degree of coronary artery obstruction. Moreover, if sufficiently severe, each of these several factors may cause coronary insufficiency even in the presence of normal coronary arteries. This is of particular note in aortic valvular diesese; and recently attention has been drawn to its occurrence in obstructive cardiomyopathy. In these conditions probably the most important factors are connected with the problems of coronary perfusion pecular to the deeper layers of the heart wall.

Mr. Chairman,

I have tried to show that cardiac ischaemia depends on insufficiency of coronary inflow in relation to myocardial needs; and that the extent of structural damage – and thereby the distinction between cardiac infarction and simple angina – depend as much on the distribution of blood through collaterals in the heart wall as upon the extent of obstruction to the arteries on its surface.

I conclude with three drawings in contemporary style. It is with regret that I acknowledge that they were not drawn by me but came from the pen of that man of genius, Lauder Brunton, whom we commemorate today.
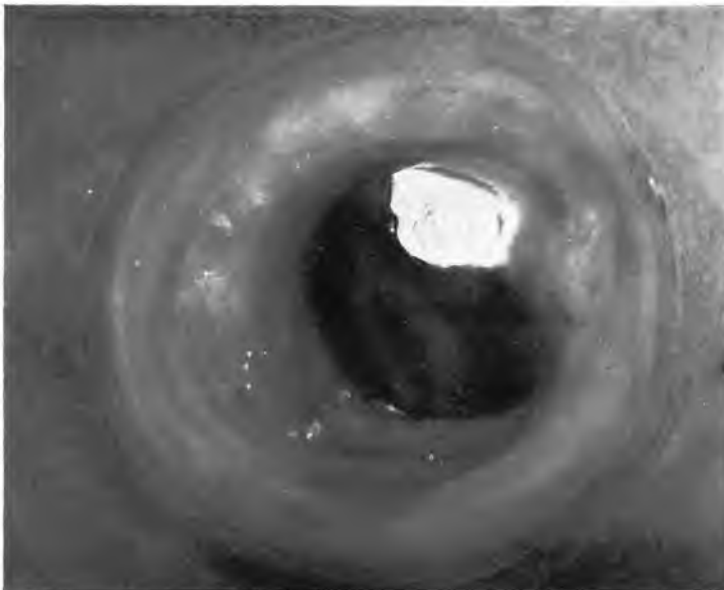

Figure 15
**Section through a coronary artery:
photograph of cut surface, incident
light. White contrast medium
outlines the remaining lumen
which has been encroached upon by
layered thrombus. The underlying
crescentic layers of atherosclerotic
disease show appearances
consistent with their earlier origin
in thrombus. (× 15)**

REFERENCES

Blumgart, H. L., Zoll, P. M., Freedberg, A. S. and Gilligan, D.R. (1950). "The experimental production of intercoronary anastomoses and their functional significance." Circulation, *1*, 10.

Brunton, T. L. (1891). "On cardiac pain and angina pectoris." Practitioner, *47*, 241.

Burns, Allan (1809). *"Observations on some of the more frequent and important diseases of the heart."* Edinburgh, Muirhead.

Fulton, W. F. M. (1956). "Chronic generalized myocardial ischaemia with advanced coronary artery disease." Br. Heart J. *18*, 341.

Fulton, W. F. M. (1963a). "Immersion radiography of injected specimens." Br. J. Radiol. *36*, 685.

Fulton, W. F. M. (1963b). "Arterial anastomoses in the coronary circulation. I. Anatomical features in normal and diseased hearts demonstrated by stereoarteriography." Scot. med. J. *8*, 420.

Fulton, W. F. M. (1964a). "Anastomotic enlargement and ischaemic myocardial damage." Br. Heart J. *26*, 1.

Fulton. W. F. M. (1964b). "The dynamic factor in enlargement of coronary arterial anastomoses and paradoxical changes in the subendocardial plexus." Br. Heart J. *26*, 39.

Fulton, W. F. M. (1964c). "The time factor in the enlargement of anastomoses in coronary artery disease." Scot. med. J. *9*, 18.

Fulton, W. F. M. (1965). *"The coronary arteries. Arteriography, microanatomy and pathogenesis of obliterative coronary artery disease."* Springfield, Thomas.

Herrick, J. F. (1912). "Clinical features of sudden obstruction of the coronary arteries." J. Am. med. Ass. *59*, 2015.

Huchard (1889). *"Traite clinique des maladies du coeur et des vaisseaux."* Paris (cited Osler, 1896).

Jenner, E. (1778). Letter to Heberden. (*Life of Edward Jenner*, by John Barron, London, 1838).

Leary, T. (1935). "Coronary spasm as a possible factor in producing sudden death." Am. Heart J. *10*, 338.

Morgagni, J. B. (1761). *"De sedibus et causis morborum per anatomen indagatis libri quinque."* Trans. Alexander, B., London, Millar and Cadell, 1769.

Osler, W. (1896). Lectures on angina pectoris and allied states. N. Y. med. J. *64*,

Parry, C. H. (1799). *"An enquiry into the symptoms and causes of the syncope anginosa commonly called angina pectoris."* Bath, Cruttwell.

Proudfit, W. L., Shirey, E. K., and Sones, F. Mason (1966). "Selective ciné coronary arteriography. Correlation with clinical findings in 1000 patients." Circulation, *33*, 901.

Schlesinger, M. J. (1938). "An injection plus dissection study of coronary artery occlusions and anastomoses." Am. Heart J. *15*, 528.

Sénac, J. B. de (1749). *"Traité de la structure du coeure, de son action et de ses maladies."* Paris, Jacques Vincent.

Sewell, W. H. (1961). "Physiologic and technical requirements for experimental strong stimulation of coronary collateral arteries." Circulation, *24*, 1036.

Zoll, P. M., Wessler, S. and Blumgart, H. L. (1951). "Angina Pectoris. A clinical and pathologic correlation." Am. J. Med. *11*, 331.