

# RES MEDICA

Journal of the Royal Medical Society



## Contents

WELCOME	3
<b>HISTORICAL SESSION</b>	
OPENING ADDRESS	5
LAUDER BRUNTON	7
HISTORY OF ANGINA	9
<b>PATHOPHYSIOLOGICAL SESSION</b>	
THE PATHOLOGY OF ANGINA	11
EXPERIMENTAL STUDIES ON THE MYOCARDIAL COLLATERAL CIRCULATION	25
FIRST DISCUSSION	27
CORONARY BLOOD FLOW AND MYOCARDIAL METABOLISM IN ANGINA PECTORIS	30
CARDIAC FUNCTION IN PATIENTS WITH ANGINA	32
SECOND DISCUSSION	37
<b>THERAPEUTIC SESSION</b>	
THE MODERN EPIDEMIC	41
IS ANGINA PREVENTABLE?	43
THIRD DISCUSSION	49
CHEST PAIN, EXERCISE ELECTROCARDIOGRAPHY AND CORONARY ARTERIOGRAPHY (CORRELATIVE STUDIES IN ANGINA PECTORIS)	51
PROGNOSIS OF ANGINA PECTORIS	54
PANEL DISCUSSION	60
SUMMING UP	64

Copyright Royal Medical Society. All rights reserved. The copyright is retained by the author and the Royal Medical Society, except where explicitly otherwise stated. Scans have been produced by the Digital Imaging Unit at Edinburgh University Library. Res Medica is supported by the University of Edinburgh's Journal Hosting Service: <http://journals.ed.ac.uk>

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, April 1967, Special Issue – Lauder Brunton Centenary Symposium on Angina Pectoris

doi: [10.2218/resmedica.v5i3-4.473](https://doi.org/10.2218/resmedica.v5i3-4.473)

# **RES MEDICA**

**THE JOURNAL OF  
THE ROYAL MEDICAL SOCIETY**

**SPECIAL ISSUE**

**LAUDER BRUNTON  
CENTENARY SYMPOSIUM ON  
ANGINA PECTORIS**

**APRIL 1967**

Published by Geigy (U.K.) Limited,  
Pharmaceuticals Division, Macclesfield, on  
behalf of the Royal Medical Society.  
Printed in England.

# Contents

	<i>Page</i>		<i>Page</i>
Welcome	3	Is Angina Preventable?	43
Dr. M. H. Kaufman		Dr. M. F. Oliver	
		Department of Cardiology	
		Royal Infirmary, Edinburgh	
<b>Historical Session</b>			
Opening Address	5	Third Discussion	49
Dr. R. B. L. Ewart <i>Olim Praeses</i>		Chairman: Sir John McMichael, F.R.S.	
Lauder Brunton	7	<i>Olim Scriba</i>	
R. D. Hunter		Director, British Postgraduate	
History of Angina	9	Medical Federation, London	
Miss Alison Leach		Chest Pain, Exercise Electrocardiography	51
<b>Pathophysiological Session</b>		and Coronary Arteriography	
The Pathology of Angina	11	(Correlative Studies in Angina Pectoris)	
Dr. W. F. M. Fulton		G. C. Friesinger	
Department of Materia Medica and		Associate Professor of Medicine	
Therapeutics		Johns Hopkins Hospital, Baltimore, U.S.A.	
University of Glasgow		Prognosis of Angina Pectoris	54
Experimental Studies on the Myocardial	25	C. F. Borchgrevink	
Collateral Circulation		Ullevål Hospital, Oslo	
Dr. J. Russell Rees		Panel Discussion	60
Cardiac Department		Chairman: Dr. D. G. Julian	
Westminster Hospital, London		Department of Cardiology	
First Discussion	27	Royal Infirmary, Edinburgh	
Chairman: Professor Melville Arnott <i>Olim</i>		Summing Up	64
<i>Praeses</i>		Sir John McMichael, F.R.S.	
Department of Medicine			
University of Birmingham			
Coronary Blood Flow and Myocardial	30		
Metabolism in Angina Pectoris			
Dr. Richard Gorlin			
Director, Cardiovascular Laboratory,			
Peter Bent Brigham Hospital,			
Boston, U.S.A.			
Cardiac Function in Patients with Angina	32		
Ottar Müller			
Ullevål Hospital, Oslo			
Second Discussion	37		
Chairman: Professor Melville Arnott			
<b>Therapeutic Session</b>			
The Modern Epidemic	41		
Professor J. N. Morris			
Director M.R.C. Social Medicine			
Research Unit			
London Hospital			



# WELCOME

At the Lauder Brunton Centenary symposium on "Angina Pectoris" held on 21st-22nd April 1967 in the Hall of the Royal College of Surgeons, Edinburgh, by the Royal Medical Society, the chairmen were: Sir John McMichael, Professor W. Melville Arnott, Dr. D. G. Julian and Dr. R. B. L. Ewart.

Senior President (Dr. M. H. Kaufman): It is my pleasurable duty to open the Lauder Brunton Centenary symposium and on behalf of the Society to welcome the speakers and our other guests. Without more ado, I call upon Dr. Robin Lockhart Ewart, past Senior President of the Society, Lauder Brunton Medalist of this year and who graduated with distinction and honours in medicine, to chair the first session this afternoon.



# **HISTORICAL SESSION**

Opening Address by the Chairman  
Dr. R. B. L. Ewart

Senior President, may I thank you for your kind introduction, and may I also extend my thanks to the Presidents and members of the Royal Medical Society for giving me the honour to chair this first session of the symposium. It is now my very pleasant duty to introduce our first speaker – Mr. Robin Hunter, who is a notable member of the Royal Medical Society. Mr. Hunter recently interrupted his medical studies to pursue a course leading to his graduation – with first class honours – in Pharmacology and amongst his distinctions he is Lauder Brunton Memorial prize winner and medalist of 1966. It is therefore particularly apposite that he has chosen “Lauder Brunton” as his subject for this symposium.



# LAUDER BRUNTON

**Mr. R. D. Hunter**

A mere glance at this, the chronological details of the career of Thomas Lauder Brunton would suffice to convince even the most uninformed that this symposium bears honour to one whose contribution to medicine and her allied sciences is of a degree which cannot adequately be assessed a full century later. When one considers that by the age of 30 he had gained the Gold Medal Doctorate in Medicine, a Doctorate in Science and had been elected to a fellowship of the Royal Society, it becomes obvious that his secret of success must have been present from the very beginning of his career. I make no apology therefore for not attempting a full biographical view of his distinguished career but merely illuminating some details of his early years in Edinburgh, when those firm foundations were being made.

Brunton came to Edinburgh in the autumn of 1863, and at that time began his association with our Society. Some feature of his character must have attracted the attention of the members of that day as he was immediately appointed to the Finance Committee. On reading the "Fines" book, his sponsor may have had second thoughts when he read of the fines that Brunton incurred for non-attendance at early meetings. Professor Sir James Y. Simpson, the discoverer of chloroform and at that time a distinguished Professor of Midwifery in the University, was also a member of the Society and it is perhaps interesting to note that Simpson's death, 6 years later, was preceded by 3 years of suffering with Angina Pectoris, and one wonders if he had tried Lauder Brunton's remedy. To have been a member of the Society which numbered among its small active membership a man of Sir James's distinction cannot have failed to influence young Lauder Brunton. Aside from his ordinary medical studies and his active participation in the affairs of our Society, Lauder Brunton also managed to carry out some personal work on two drugs; that this was of a high

quality can be judged by their mention as the official reason for his election to the Royal Society at the age of 30. The first of these, Mercury was the subject of his dissertation to the Society in 1865. This is a logical analysis of the known facts on this drug which descended from the panacea of empirical therapeutics to absolute disrepute in many medical centres. The other drug is the subject of his book on Digitalis with some observations on the urine, which appeared in 1868. The inter-relationship between this work and the Society can be judged from some of his own records; he was living to a strict daily food intake and studying the effect of digitalis on volume: urea, chloride and phosphate concentration of 24-hour urine samples. His first attempt to keep to the regime ended after 6 days; at the Royal Medical Society dinner he consumed one glass of champagne, threequarters of a glass of claret, a cup of coffee and 150 cc.s of water, greatly exceeding his limits. A second experiment, however, lasted 80 days following which he earned a Gold Medal for his thesis. Following his success in his final examination and a month after his election to Senior Presidency of the Society, Brunton was appointed Resident Physician to the University Clinical Wards of the Royal Infirmary at Edinburgh for a period of 6 months. It was while he was attached to these wards, that he made the observation which stimulates our present gathering. His early experiments with digitalis had included a number in which he had studied the effects of the drug on arterial pressure in animals, and he records the great and essential aid afforded to him by a Dr. Gamgee, who worked with him in the same laboratory and was also a member of the Royal Medical Society. After observing the effects which Gamgee obtained in a similar series of experiments, but with a different drug - amylnitrite, Lauder Brunton took his experimental finding and applied it in a clinical situation; the pathophysiology, he reasoned could be reversed by the

pharmacological action of the drug. His famous paper "On the Use of Nitrite of Amyl in Angina Pectoris", which was published in *The Lancet*, July 27th, 1867, accords his success. The progression from experimental observation to clinical application was a logical but immense step at that time when pharmacology was still very much in its infancy. Lauder Brunton's contributions were not all made in his early years. I take as an example, not his establishment of the first pharmacological laboratory in the old pantry of St. Bartholomew's Museum or his authorship of many books and papers, which includes the first physiologically-based textbook on Pharmacology and Therapeutics, but a small article, "Preliminary Notes on the Possibility of Treating Mitral Stenosis by Surgical Methods", which appeared in *The Lancet* of 1902, two years before his retirement, and which demonstrates the continuation of his rational scientific approach to his patients' problems. In this article he described not only his idea of the value of splitting the stenosed valve, but he went on to mention his experiments on the technique and the type of instruments involved, before offering the idea to his colleagues. This approach drew the rather caustic comments of the leader writer in the next issue of *Lancet*. We gather that he had proceeded no further than the table of the dead-house in making his investigations. Brunton's defence of his article includes the quotation: "Art is long, but time is fleeting". The Art of Mitral Valvulotomy is here today, but following this article in the *Lancet* over 20 years elapsed before the further experiments of Cutler and Levine led to the first successful operation in 1924. The importance of this as an example lies in the fact that not only did Brunton suggest valvulotomy as a therapeutic procedure, but he took time to perform some preliminary experiments to convince himself of the feasibility of his procedure. Lauder Brunton was a man whose mind lay not in the laboratory or in the ward, but half-way between the two. We do well to pay tribute to one whose contribution to scientific medicine must stand as an inspiration to all those who now work or hope to work in that ever expanding field.

# HISTORY OF ANGINA

**Miss A. Leach**

Ladies and gentlemen, Angina Pectoris was first brought to the notice of the medical profession by William Heberden in 1772, although references to pain in the breast and arm in relation to disease affecting the heart and occurring on exercise are found in ancient Egyptian and Roman literature, and more particularly in the 17th and early 18th centuries. It was not until 1768, however, when Heberden read his paper entitled, "Some Account of the Disorder of the Breast", before the Royal College of Physicians in London, that the condition was given the name of "Angina Pectoris". Heberden's observations were based on a study of twenty cases and by the time he had incorporated the description in his book, "Commentaries on the History and Cure of Diseases", this number had grown to one hundred of which three were women, one was a boy twelve years old, and the rest were men of fifty years of age or over. In one or two of the patients mentioned original pain lasted for some hours; in one case the first attack continuing all night. Some died suddenly but these were more probably cases of myocardial infarction; in fact he mentioned that if the disease goes on to its height, the patients suddenly fall down and perish almost immediately. Heberden had no clear concept of the true nature of the syndrome; which he suggested may be a strong cramp or an ulcer or possibly both. "What the particular mischief is, is not easy to guess and I have had no opportunity of knowing with certainty; the opinion of its being a convulsion of the part affected will readily present itself to anyone who considers the sudden manner of its coming on and going off, the long intervals of perfect ease and the influence which the passionate affections of the mind have over it. The pulse is sometimes not disturbed by this pain and consequently the heart is not affected by it."

In 1772 Heberden received a letter from Dr. Wall in Worcester concerning a 66 year old patient with angina pectoris on whom he had per-

formed an autopsy and found that the semilunar valve of the aorta was found to be perfectly ossified. Wall wrote, "The preternatural induration of the parts to the circulation to the heart may be the predisponent, if not the efficient cause of the disorder". It is remarkable that the first case of angina pectoris in which any abnormality had been found in the heart was due to calcific aortic stenosis. Edward Jenner was responsible for the first suggestion that there was a probable association of disease of the coronary arteries with angina pectoris. In 1776 he wrote to Heberden describing two hearts which he had examined from patients who had died with a condition. He described the coronary arteries in these words: "a kind of fleshy tube formed within the vessels with a considerable quantity of ossific material dispersed irregularly through it."

John Hunter, the great anatomist and physician who suffered from angina first mentioned the effect of emotions in promoting an original attack, and for many years, declared that his life was in the hands of any rascal who chose to annoy and tease him. Indeed Hunter suddenly collapsed after a dispute with a colleague at St. George's Hospital, and among other things marked atheroma was found at post-mortem.

In 1698 Shirak found that after the coronary arteries of a dog's heart were tied, the heart stopped beating very soon, thus proving that they are essential for normal heart function. In 1809 Allan Burns, a lecturer in anatomy in Glasgow, propounded the theory that myocardial ischaemia was the cause of angina pectoris, he likened the impairment of the heart's function when the coronary arteries are diseased to the inability of a limb to continue vigorous action if a ligature is placed tightly at its base. He predicted the importance of an adequate blood supply for normal cardiac function and concluded that ossified coronary arteries impaired the blood supply to the myocardium. His theory was supported by

Hodgson in 1815 who stressed the importance of a collateral circulation when the major arteries are atherosclerotic. Other theories included that of spasm of the heart put forward by Heberden and also held by Laneck and Cauldron. Lauder Brunton ascribes angina to spasms of the vessels of the hearts, others thought that the condition was due to irritation of the nervous elements of the cardiac plexus. Sir Wm. Osler mentioned the irritable heart of smokers in his book on angina pectoris and suggested that the condition in some is readily relieved by stopping the use of the "weed". The vasomotor hypothesis was put forward by Knoknagal in 1867, who suggested that the symptoms of angina were not due to primary disease of the heart but to secondary factors comprising generalized arterial spasm. In spite of the attention drawn to the condition throughout the 19th century, it is interesting to note that Osler saw only 40 cases in his entire clinical experience; indeed Sir James Mackenzie recorded in 1923 that in his early experience as a general physician and later as a cardiologist, only 380 patients consulted him with regard to angina pectoris. It is only later in this century that angina has been commonly diagnosed, though the condition must have existed from the earliest age, or at least been "coeval with the introduction of luxury and refinement" to quote an earlier member of this Society. Among the descriptions of angina pectoris there was some confusion with myocardial infarction. Coronary thrombosis was first diagnosed during life and confirmed at post-mortem by Hannah in 1876. In 1880, Vigerdt made the first complete accurate description of a myocardial infarction, and in 1912 Herrick elaborated the clinical features of a sudden occlusion of a coronary artery and indicated for the first time that such an event was always fatal. If there was diversity of opinion on the cause of angina pectoris this was equally so concerning treatment. Heberden himself said that he had little or nothing to advance apart from quiet and warmth and spirituous liquors; he noted that opium at bedtime would prevent attacks at night. The first real advance in the treatment of angina pectoris came in 1867 from Thomas Lauder Brunton, with his observation on the action of amyl nitrite and his advocacy for its use for the relief of angina pectoris. In 1879 Wm. Morrell working at Westminster Hospital published a paper in the *Lancet* describing the effects of taking a solution of nitro-

glycerine in alcohol, he stated: "from a consideration of the physiological action of the drug and more especially from the similarity existing between its general action and that of Nitrite of Amyl I concluded that it would probably prove of service in the treatment of angina pectoris and I am happy that this anticipation has been realized." He cited three cases of undoubted angina pectoris who were treated with nitroglycerine with resulting reduction of frequency and severity of attacks.

Time has not permitted me to deal in full with the advances made in this century, but in ending I quote a few words from a dissertation read by A. Lawler before the Royal Medical Society in 1800, which are not inappropriate today: "Angina pectoris has seldom been completely cured yet still we must not despair as in time we may arrive at its true cause and administer effectual remedies."

# PATHOPHYSIOLOGICAL SESSION

Chairman: Professor W. Melville Arnott *Olim Praeses*

## THE PATHOLOGY OF ANGINA PECTORIS

W. F. M. Fulton, Glasgow

*Department of Materia Medica and Therapeutics, 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

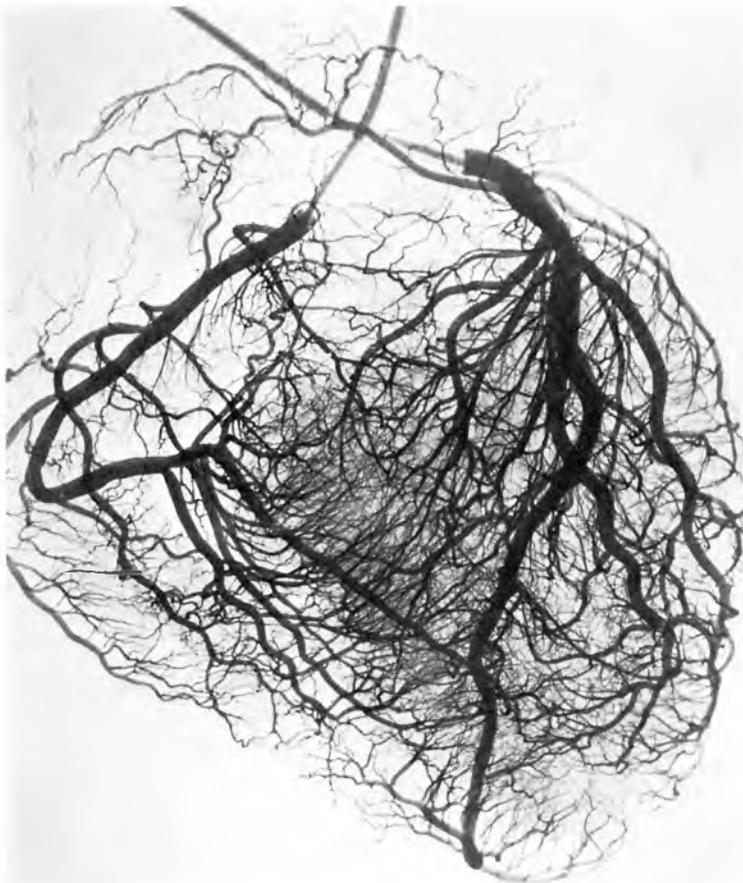
injection; the coronary arteries are outlined by calcification. Calcification is generally held to be a sequel not a cause in coronary disease. As Leary (1935) said, somewhat ambiguously: "calcification is merely of monumental character!"

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. (5/1)

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.

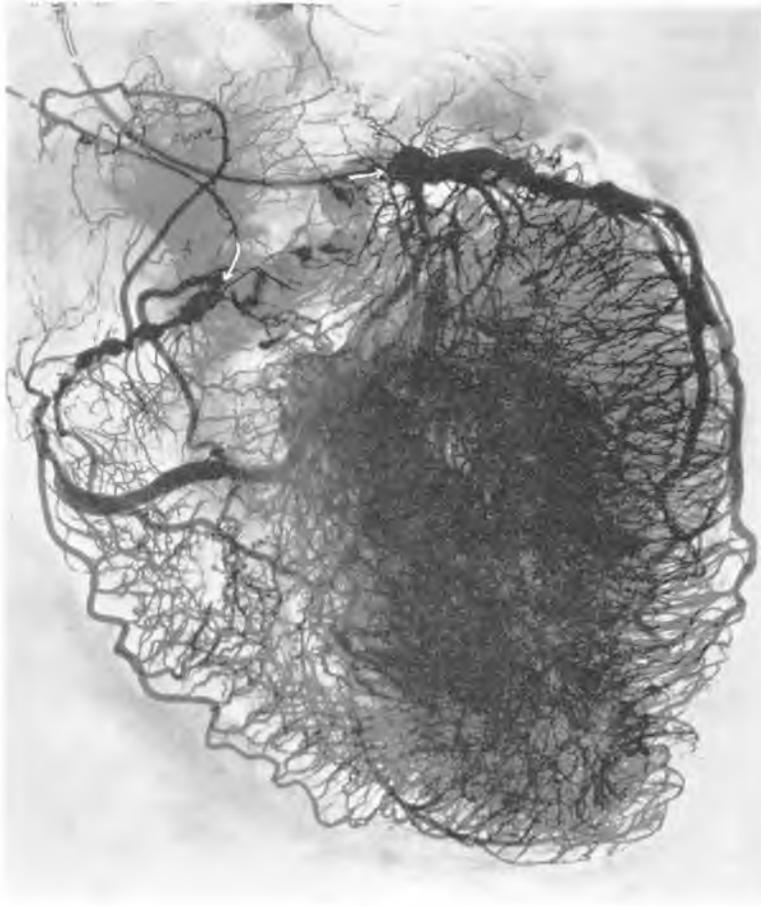
insufficiency, and there is no rule to the sequence of their manifestation. There is no surprise in this for the pathologist; for the ingredients of disease in the coronary arteries themselves are similar in each of the three settings.

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. ( $\times \frac{2}{3}$ )

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 cinearteriography 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 collateral 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  $\times 5$ .

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.

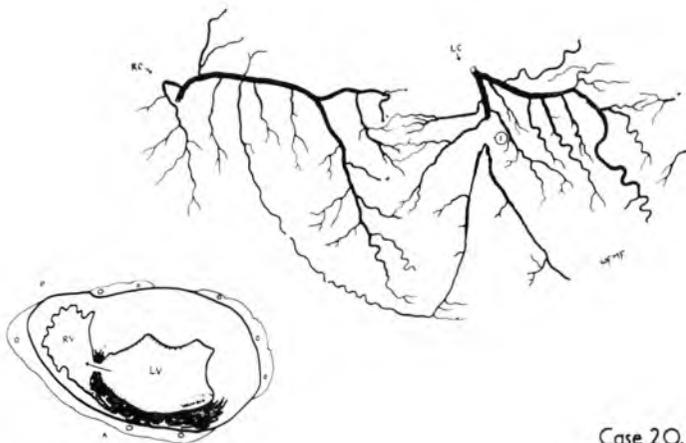
In this second case the situation is more complex because the first clinical episode of coronary artery occlusion was survived. This occlusion involved the anterior descending artery. Enlarged anastomoses carried blood flow from the right coronary artery across the interventricular septum to feed the 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 enlargement 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 stereoscopically. ( $\times \frac{3}{2}$  approx.)

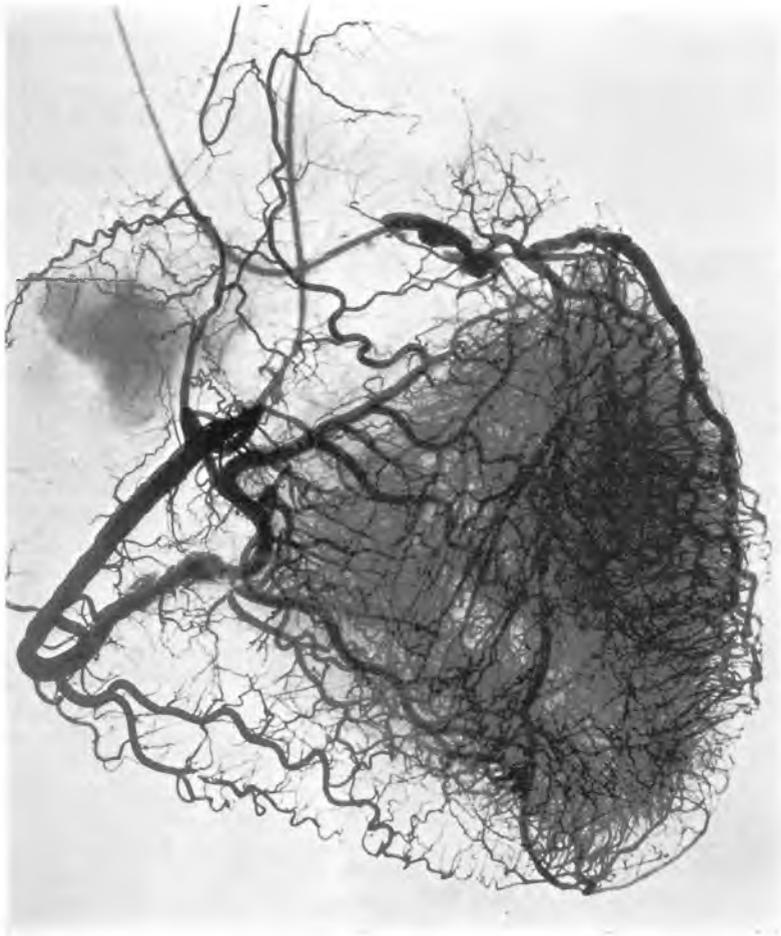


**Figure 4**  
 First case: Arteriogram of heart with acute myocardial infarction and no previous history of angina. Note complete occlusion of the anterior descending artery. The coronary arteries are otherwise unobstructed. Anastomotic changes are slight.  
 Reproduced from the British Heart Journal,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

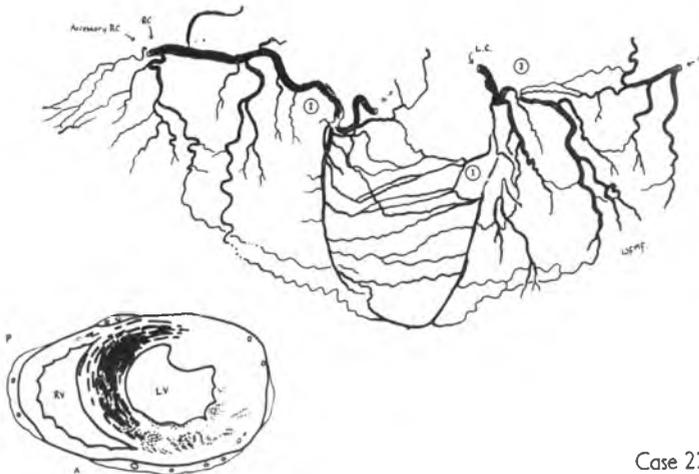


**Figure 5**  
 First case: Diagram of coronary circulation and myocardial damage. Solid black indicates acute myocardial necrosis.  
 Reproduced from Fulton, W., Coronary Arteries, 1965. By courtesy of Charles C. Thomas, publisher, Springfield, Illinois.

Case 20.



**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. ( $\times \frac{3}{2}$ )**  
 Reproduced from Fulton, W., *Coronary Arteries*, 1965. (By courtesy of Charles C. Thomas, publisher, Springfield, Illinois).



**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).

Case 22.

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 calibre 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. ( $\times \frac{4}{3}$ )**  
**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 } of the left ventricular wall is occupied by a network of wide-bore intercommunicating vessels derived from the subendocardial arterial plexus. ( $\times \frac{3}{2}$ )**  
**Reproduced from the British Heart Journal, 1964, 26, 1 (by courtesy of the British Medical Association .**

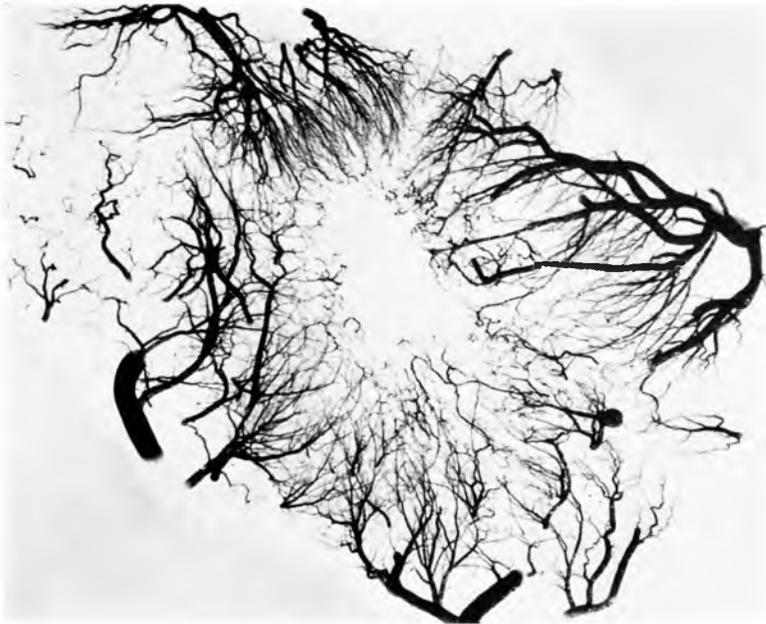


Figure 12  
 Normal: Arteriogram of 1 cm thick section through a normal heart showing the normal pattern of myocardial blood supply and the dimensions of normal subendocardial anastomotic vessels, for comparison with Figure 11.

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

Reproduced from the *British Heart Journal*, 1964, 26, 1 (by courtesy of the British Medical Association).

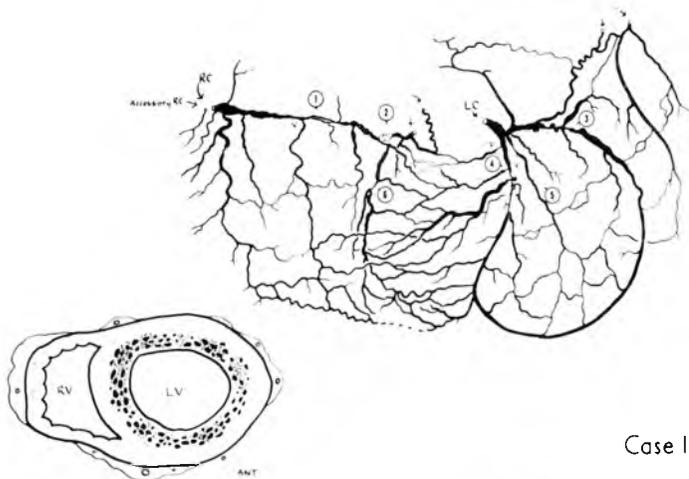
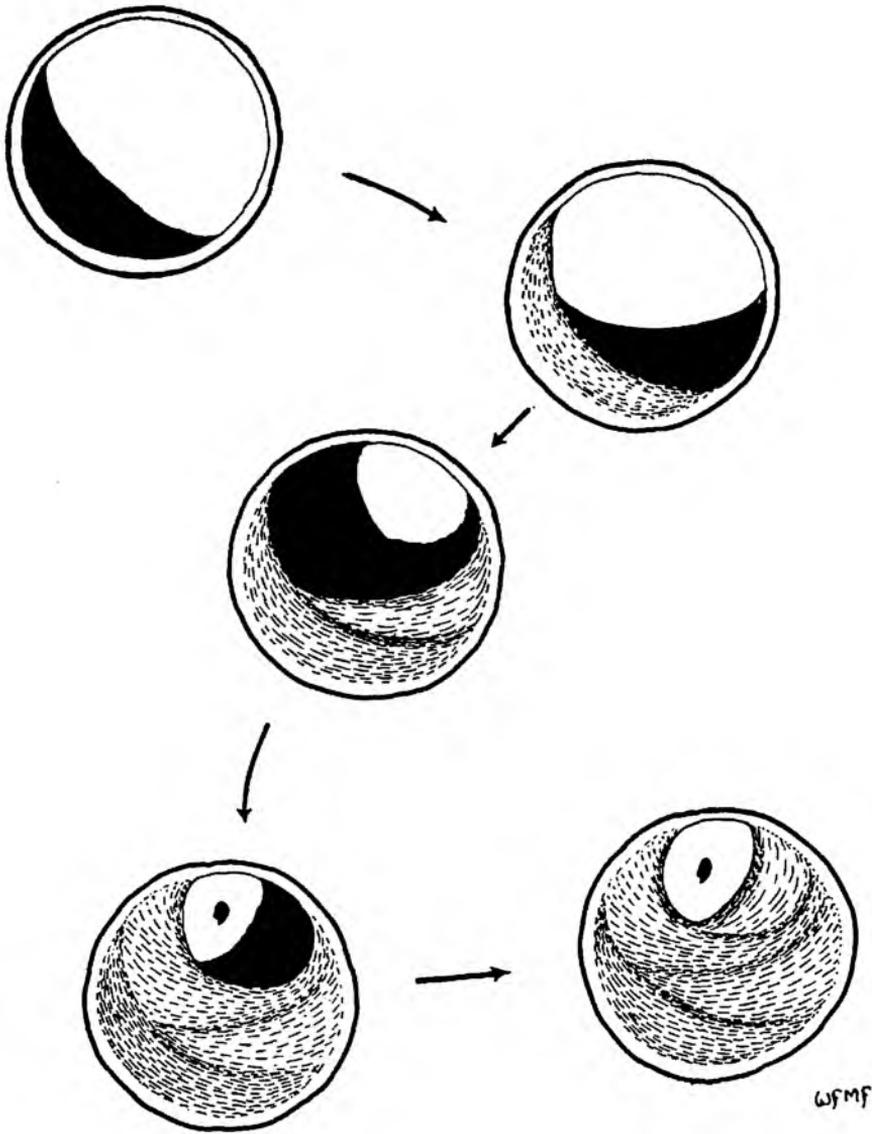


Figure 13  
 Third case: Diagram of the coronary circulation and myocardial damage. Solid black indicates acute focal necrosis and stippling old-standing replacement fibrosis.

Case 17



**Figure 14**  
**Diagram of the thrombogenic origin of atherosclerotic 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 layers. This in turn would have been the fate of the layer of thrombus which has formed upon its surface.

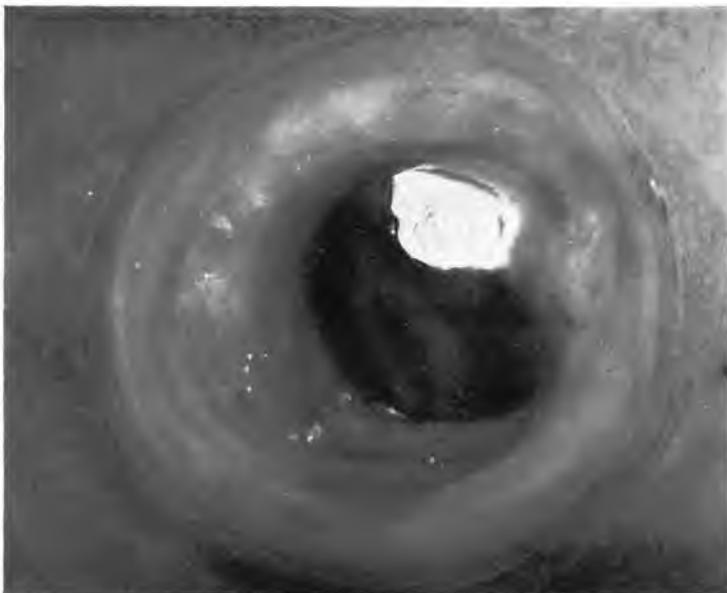
So far I have considered angina as an expression of coronary artery disease. There are of course many other factors extrinsic to the major coronary arteries which may impede blood flow within the heart wall, impair the quality of the blood delivered, or increase the requirements of the myocardium. The 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 disease; 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 peculiar 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. ( $\times 15$ )

## 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 coeur, 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.

# EXPERIMENTAL STUDIES ON THE MYOCARDIAL COLLATERAL CIRCULATION

(Abridged)

**J. Russell Rees**

*Cardiac Department, Westminster Hospital, London*

I want to talk about the measurement of collateral flow that Dr. Fulton has so clearly demonstrated. It is not possible to assess this after myocardial infarction in man, and as at present collateral vasculature of the dog resembles that of man we have used this animal to study collateral flow rates immediately following infarction, the changes which accompany recovery, and the effects of drugs and sympathetic blockade.

The infarcts are produced in two ways – anterior by ligating the anterior descending coronary artery at operation, and posterior by wedging a catheter in a large branch of the circumflex artery. The latter is inserted via the left carotid artery. In either case moderate sized infarcts result, with the expected electrocardiographic and enzyme changes, and an overall mortality of about 20 per cent collateral flow is determined by the clearance of radioactive xenon 133 injected into the vessels of the infarct via a fine catheter, and measured with an external scintillation counter.

Before producing infarction, we usually measure the normal myocardial blood flow by the same method – measuring the clearance of xenon 133 injected in solution through a catheter, which does not interfere with normal flow, lying in the mouth of the left coronary artery. In a normal heart the radioactive xenon diffuses rapidly through the myocardium and is then gradually removed over the next two to three minutes.

With the aid of a computer the clearance can be measured in several ways, the clearance rate (K) calculated, and the myocardial blood flow derived in ml/mm/gram. By contrast, in an infarct 3 days old clearance may take as long as 20 minutes, because of the low rate of collateral flow. Estimates of collateral flow immediately after infarction have varied from negligible to adequate, and the current continental and Russian view, recently supported in the *Lancet*, has been of interest to us. It is suggested that collateral flow after infarction is at first adequate, but then

falls to zero within a few hours as a result of harmful sympathetic vasoconstrictor reflexes which may be reversible. If this were so, there would be important therapeutic implications.

In both types of infarcts in our study we found that immediate collateral flow was established at about a quarter to a third of normal myocardial blood flow. There is usually a slight rise in collateral flow in the first hour and then a slow fall to the original level, but there is no evidence that it ever falls to zero. Occasionally this fluctuation is very marked. In one instance, the collateral flow was initially quite low, then rose to the highest we recorded, and finally fell until death from ventricular fibrillation after 5 hours. We have no idea what causes these fluctuations which are unrelated to blood pressure.

We have now recorded collateral flow just before or after resuscitation from ventricular fibrillation on five occasions, and found that it was always very low, ranging from .05 to .15 ml/min/gram of infarct. This is about —15 per cent of the normal value for the heart, a rate which is obviously dangerously inadequate. Two of these animals were successfully resuscitated with subsequent improvement in clearance.

We have examined the effects of general and local sympathetic blockade as well as surgical sympathectomy without demonstrating any beneficial effect on collateral flow, but it does increase slowly on successive days after recovery from myocardial infarction. There is usually little change over the first 3 days, but then it begins to rise and by about the 8th day reaches approximately  $\frac{2}{3}$  of the normal value. However this does not always happen. After an initial high level of collateral flow, the rate may fall and this may be followed by the death of the animal.

There are of course marked individual variations, but the usually inadequate early collateral flow is established through the fine interarteriolar anastomoses which we know do exist in the

normal heart of both dog and man, and the subsequent increase by the 4th day is due to progressive enlargement of some of these channels. After 10 days, there are often quite large anastomoses around the obstruction in the artery, around the apex in the septum. How responsive is this collateral vasculature during recovery? We are perhaps most interested in the capacity for vasodilation, and for this reason we tested dipyridome, the most active coronary dilator drug at present available. Under its influence, collateral flow increases, only slightly at first, but substantially more as the infarct ages. This response though considerable remains less than in normal myocardium. Our results show that collateral channels are almost maximally dilated in the first hours of infarction, but the greater increments in collateral flow caused on subsequent days indicate that the collateral vessels are then no longer fully vasodilated.

We have also found that collateral flow varies with the systemic blood pressure so that reductions in flow accompany the hypotension of shock and large doses of barbiturate. Conversely the use of pressor drugs is accompanied by an increase in collateral flow. The action of nitrites in angina is likely to remain controversial until we can decide where in the myocardium angina rises, and until we can measure blood flow at this focus. Meanwhile it may be unwise to dismiss the possibility that nitrites act in part by increasing flow.

In fact our studies support the alternative view that an important function of glyceryl trinitrate is to reduce the myocardial oxygen requirement, even though there is a transient initial increase in external cardiac work. This increased efficiency of energy utilization is not a specific effect of the drug but the normal consequence of increasing cardiac output at the same time as a fall in blood pressure takes place. What of the effect on flow? In the normal heart it is easy to demonstrate a biphasic action on myocardial blood flow. The initial increase is, however, transient and would easily be missed in studies in patients, which are harder to control.

When we measured the effect of glyceryl trinitrate on blood flow to the ischaemic myocardium we found an increase of collateral flow in 4 out of 6 animals given the drug 6 hours after infarction. The increase was slight, transient and less than in normal animals, but nevertheless occurred in the most unfavourable setting that could be devised. In those animals that responded the mean increase was 25 per cent.

We were fortunate to come across a natural occurrence in one dog which closely resembled the situation in a patient with ischaemic heart disease and previous infarction. Though spontaneous myocardial infarction in dogs is rare, this animal had a large anterior infarct showing fibrosis and new vessel formation. The anterior descending artery was sclerotic and much narrowed. In this animal we were able to measure collateral flow to an ischaemic zone with an old infarct and recent (induced) coronary obstruction. Not surprisingly the flow rates were a good deal higher than in the other dogs. They were in fact sufficient to prevent further infarction, and it is of particular interest that glyceryl trinitrate and dipyridamole increased the collateral flow.

Most studies of the glyceryl trinitrate in patients have been started too late to detect any vasodilator effect, which animal studies show to be over within 3 minutes of giving the drug. But with appropriate timing an increase in myocardial blood flow may be found even in patients with angina. In one such, a single tablet of glyceryl trinitrate taken sublingually increased the myocardial flow rate from  $\cdot 61$  to  $\cdot 70$  ml/min/gram.

#### *Conclusion:*

In experimental myocardial infarction collateral blood flow is immediately established at a rate of about one quarter of the normal resting value. It usually rises to a maximum after 2 hours, but is then liable to a slight and gradual reduction. Occasionally, for reasons not at present apparent, large fluctuations occur. Neurone blockade has no effect either in preventing infarction or in increasing collateral flow.

At any time during the early days after infarction, flow may fall below the potentially dangerous level of about  $\cdot 15$  ml/min/gram of infarct (15 per cent of the normal resting value) when ventricular fibrillation may occur.

On average, collateral flow begins to increase spontaneously after 4 days, and normal levels may be attained 10 days after infarction. For a few hours the collateral vessels are only slightly responsive to vasodilator drugs, presumably because they are already maximally dilated, but they begin to respond some days before the spontaneous rise in collateral flow.

Finally, though glyceryl trinitrate has other effects, perhaps of greater importance, it may cause a modest increase in collateral flow to the ischaemic myocardium.

# FIRST DISCUSSION

## Chairman: Professor W. Melville Arnott

*Dr. W. A. Alexander:* I do not think it inappropriate at this time to recall that I met Sir Thomas Lauder Brunton in London in the Spring of 1914 at a dinner of the London University of Edinburgh Club, in my capacity as a Senior President of the Royal Medical Society at that time. During the evening I had the pleasure of sitting beside him and my recollection of him, is of a man of small stature with grey-white hair and a trim beard, he was venerable in my eyes but actually he was only 70 years of age. I remember his keen interest in what was happening in Edinburgh, especially in the Royal Medical Society. The occasion and the man remain vivid in my memory.

*Dr. Walter Sommerville (Middlesex Hospital):* Dr. Russell Rees has presented in a very impressive and easy to understand fashion, what happens when a ligature is placed around the artery of a dog. He has also referred to what happens when a human individual has an occlusion in an artery. When he had operated on his animals, what became of them? Did they lie gently? Did they move around in cages? I ask this because in very carefully controlled observations on animals Epstein and his group found that if one applied ligature to a coronary artery and then divided the group of animals into two, one of them being kept at enforced rest and the other at enforced exercise, subsequently examination of the latter group showed a profuse collateral circulation in relation to the group that was kept at rest. The implication of this being that if a ligature is tied round a dog's coronary artery the animal should be allowed to run around in order to increase its collateral circulation. The counterpart of this has very often been cited in man and is one of the main supports of the doctrine that after he has had acute cardiac infarction he should get up out of bed and walk.

*Dr. Rees:* Our animals are neither forcibly exercised nor rested, they were allowed to walk around their cages as they wished. One third of them died

but it was not possible to tell which ones were likely to die, though of course they did have the lower flow rates. I don't think the amount of exercise they took affected their outlook, though I quite agree that it is possible to protect animals by making them anaemic, by pre-exercising them, and by pre-treating them with vasodilator drugs. The basic collateral vasculature of man and the dog is similar from that in these animals, though of course the situation will be more complex from one to another.

*Dr. Oliver (Edinburgh):* I think that the most interesting aspect of the excellent communication was his account of the single dog who was found at thoracotomy to have an infarct. He showed that after he had ligated the coronary artery the collateral flow was appreciably higher in this dog than it had been in other dogs who did not have an infarct. My first question, therefore, is: Has he tried to produce the same situation by ligating coronary arteries in dogs previously made hypoxic or dogs in whom he thinks he may have in some way produced a rather better than normal collateral circulation, and if so, how did they respond? The second question is: To what extent did this dog, in fact have coronary artery disease and what was the nature of the disease? I think this is relevant in terms of the suggestion that glyceryl trinitrate and dipyridamole both had a dilating effect. It has been suggested that it would be inappropriate to use vasodilator drugs in such a situation, and what is more one would not expect to see much dilatation or improved flow if there were very advanced coronary disease. You did describe that there was coronary disease of some nature in the anterior descending artery. I would think that before we jump to the conclusion that these drugs can improve collateral flow in such a situation, we have to be careful, perhaps in relationship to Dr. Gorlin's lecture yesterday that we should know exactly to what extent there is disease of the coronary arteries. Therefore, my

third question is: If this dog had extensive coronary disease and therefore extrapolating to the human would he expect that there might be an improved collateral flow when such drugs are used?

*Dr. Rees:* We have carried out a similar experiment in this type of situation, we ligated arteries 3 months before performing flow measurements and then measured collateral flow within the territory that we had rendered ischaemic and we also produced fresh infarcts adjacent to it and measured collateral flow in those regions. In both types of experiments collateral flow was greater than in those dogs who had previously had normal hearts, and I am quite sure that previous coronary disease does produce an increase in the collateral vessel and does protect the animal against subsequent coronary arterial obstruction. I think there is some evidence in this which also applies to man. As to the use of vasodilator drugs, I believe it can be shown that even in severe coronary disease a vasodilatation will occur, and there is good evidence that these drugs might work, even in acute myocardial infarction.

*Dr. Gorlin:* From our experience with coronary arteriography study of metabolism of the heart in patients with coronary heart disease, we have been struck by two points and in seeking help, I might address these to both of the speakers. The first is that we have seen no necessary association between having a severe obstruction and the development of an appropriate collateral circulation, and I would like to ask Dr. Fulton why he thinks this patient can develop a profuse collateral response and another one does not. I would be specific and ask him if he finds any variation in the size of the normal collateral channels, that are potentially present in the absence of disease, that may influence what happens when a patient subsequently develops atherosclerosis. My second comment is, that we have never seen the collateral pathways completely compensate metabolically under conditions of stress. Almost invariably we have seen the production of lactic acid by the myocardium even in the presence of profuse collaterals supplying the post obstructive region and we would wonder whether the patency of collaterals in a sense depends on function of metabolic demands: in other words, the bombardment of this area by some form of by-product of ischaemia and this may be essential in keeping these areas open.

Perhaps Dr. Rees might want to comment because of the variations he showed in the different responses in different dogs, whether the activity is different on given days or whether the by-products of the myocardium differed on different days.

*Dr. Fulton:* The first point about variations in collateral circulation in the normal: there is a certain variation but it is very hard to know what factors may be involved in this, I have noticed that in some instances there has been decreased collateral circulation in the presence of anaemia in the history, and this has previously been shown to be the case in experimental work as well as in observation. In regard to inadequacy of collateral circulation, it may well be that in some instances, this is based on an inherent tendency for collaterals to develop in one individual to a greater extent than another. I would make the point that in man, I think, that the rate of development of collaterals is very much slower than under the experimental conditions in the dog as Dr. Rees has so elegantly described. I think one would probably have to increase that period very considerably, I would also make the point in regard to the collaterals of dog and man, that in man it is deeper vessels rather than superficial and one does not see on the surface of the heart a development of collaterals such as he described within a short time of coronary occlusions, in fact, after years there may still be no comparable degree of superficial network although in all instances I did see deep network development of very considerable extent, I cannot answer why it should be in one instance the collaterals seem more adequate than another, I certainly would go along the whole way with your statement that you never found full compensation on the basis of my pathological studies because I do believe that the collateral circulation always follows the stimulus as I have said and I think that if it came to within an approach probably never exceeding or equalling the normal adequate circulation, this would make sense.

*Dr. Rees:* I would like to answer Dr. Gorlin's question about stressing these animals, I would agree that their response is inadequate, you can show after 3 months that the collateral supply at rest is the same as in the adjacent normal muscle. You cannot exercise these animals because they are anaesthetized if you give them dipyrindanole you may get a three or four fold increase in the

normal adjacent muscle but only 50 to 100 per cent increase in the ischaemic tissue, so the capacity is certainly restricted.

*Dr. P. Turner (St. Bartholomew's Hospital):* We are very interested in the role of adrenergic blockade on cardiovascular function and I would like to ask Dr. Russell Rees a question on his experiment with bretylium, there is I think a misapprehension to feel that pre-treatment with bretylium necessarily reduces the effects of the heart to sympathetic stimulation as far as circulating catecholamine are concerned it may increase the sensitivity of adrenergic receptors and I would like to ask him whether he feels that perhaps under the circumstances of his experiments with his animals there may be an increased circulating level of catecholamine and that it might be better to look at the effects of alpha and beta adrenergic receptor blockade rather than simple bretylium pre-treatment and if so whether he has done these experiments.

*Dr. Rees:* I was under the impression that bretylium and bethanidine would deplete an animal if given in sufficient dosage, but I don't know about that. We also performed a sympathectomy, and infiltrated with protein and I agree there may still be circulating adrenaline in those situations. As regards beta blockade, we have not done any intensive studies along the lines of procaine blocks but looking at one or two animals from day to day, up to 10 days there is a reduction of myocardial blood flow of a minor degree.

*Chairman:* Does reactive hyperaemia such as occurs in skeletal muscle occur in myocardium, with its blood supply reduced or occluded for a time insufficient to cause necrosis?

*Dr. Rees:* We have seen this on some occasions when the myocardium has been unexpectedly and dangerously atoxic for a while, but it does not seem to be a very common occurrence and we have not studied it specifically.

*Dr. Friesinger (Johns Hopkins Hospital):* It is now relatively easy to put a flow probe electromagnetic tie around dog's circumflex artery beyond which you can put a snare which will stop flow completely and the dog is very sensitive insofar as the reactive hyperaemia is concerned. Occluding for a short time for one or two systoles, will show a reactive hyperaemia and with occlusions say for up to 30 seconds, since these unconscious dogs are not responding insofar as any reaction of

pain or any systemic haemodynamic change is concerned, very dramatic reactive hyperaemia occurs, overshoots three or four times, the resting flow, which persists for several minutes, are common.

# CORONARY BLOOD FLOW AND MYOCARDIAL METABOLISM IN ANGINA PECTORIS

(Abridged)

**Richard Gorlin**

*Harvard Medical School, Peter Bent Brigham Hospital*

It is interesting to note on this centenary celebration that we still are uncertain about the nature of anginal pain; we discuss the nitrites, we carry out experiments, yielding new data, and yet we are still really not quite sure how these agents act. I think it is desirable to review with humility some of Lauder Brunton's ideas about the actions of these drugs. At a major national meeting in America just one year ago, the observation was made that the blood pressure rises before pain occurs in attacks of spontaneous angina pectoris. Unfortunately the speaker failed to appreciate that Sir Lauder Brunton had suggested the use of amyl nitrite for this very reason, namely high blood pressure with angina. He thought that nitrites might reduce the pain of angina pectoris by lowering the pressure.

I would like to discuss some aspects of angina and myocardial ischaemia and present briefly our thoughts about the actions of nitroglycerine on the coronary circulation and the myocardium.

Anginal pain may arise not only as a function of deficient blood supply to a particular region of the heart, but also as a function of the distribution of collaterals supplying the same area from other coronary arteries. The situation is further complicated by the fact that the resistance blood vessels can constrict or dilate under various local influences and thereby alter the flow to a potentially ischaemic zone. Another complicating factor is the bombardment of an affected area by various efferent stimuli originating within the central nervous system. This can increase the force and speed of muscle contraction (so-called inotropic actions), and elevate the heart rate, thus increasing cardiac activity and so that energy requirements outstrip the blood supply of a potentially ischaemic zone. Then there are motor pathways which affect the arterioles of the coronary system and may cause them to react with either constriction or dilation, irrespective of the local effects of hypoxia. Finally – on the question

of the pain stimulus itself – we must always remember that a chemical reaction occurs in the presence of ischaemia which may produce various peptide substances (kallikrein and plasma-kinins). These have the ability to stimulate unmyelinated nerve fibres which may or may not be present in any given zone of the heart, depending on the degree of previous nerve damage and the patient's inherent nerve supply. Once these receptors are stimulated the impulse goes back to the central nervous system, but there are many slips between the cup and the lip. This pain can be augmented by impulses arising in other systems of the body or dampened if there has been some change in interpretation within the cerebral cortex. So all of these features must enter into our discussion of angina pectoris, irrespective of the objective assessment of myocardial ischaemia.

One way to learn something about the nature of myocardial ischaemia is to study cardiac metabolism. To do so, it is necessary to place a catheter in the coronary sinus. This is a simple and safe procedure, if done under proper conditions, by which blood samples can be obtained from various veins which course over the left ventricle. The metabolic exchanges of various substrates by the heart can then be studied by analysis of both arterial and coronary venous samples. The normal metabolism of the heart is essentially oxidative but when there is inadequate oxygen supply, the heart switches to glycolytic metabolism, with the result that lactic acid is generated as an end product and ultimately diffuses out into the blood stream. Thus, lactic acid concentration in the coronary sinus in excess of levels in the arterial blood is evidence of myocardial ischaemia. In normal subjects the heart extracts lactate and uses it as a fuel both at rest and during most stresses but ischaemic hearts can do this only at rest – when the oxygen supply is still adequate. In a patient who has coronary heart disease with greater than 75 per

cent obstructions in one or all three arteries, there is usually lactic acid extraction by the heart at rest. But, when cardiac activity is stimulated, the lactate concentration rises so that coronary venous concentration becomes higher than the arterial. When nitroglycerine is given, it relieves anginal pain, improves oxygen supply and burns off lactic acid production. On the other hand, isprenalin stresses the ischemic heart and increases lactic acid production.

In some marginal attacks we have recorded coronary vasoconstriction totally inappropriate to the situation. The first spontaneous observation of this phenomenon showed a normal coronary flow of 116 cc per minute per 100 grammes of muscle, which fell to 78 cc at the time of an anginal attack. Another patient had no pain, a blood pressure of 150/78, a pulse rate of 54, and a coronary flow of 71 cc, when the recording began. The patient then became hypertensive (180/110) and developed pain; the coronary flow *fell* to 51 cc. Nitroglycerine was given, the patient obtained relief of pain, the blood pressure fell to 130/73, the pulse rate dropped and the coronary flow *increased* to 88 cc per 100 grammes per minute. This phenomenon of a reduction in coronary flow associated with hypertension and coronary vasoconstriction has now been seen in three patients, each of whom developed a spontaneous attack of angina. Each also gave a prior history of apparently unprovoked attacks of anginal pain. These findings show that there is such an entity as coronary vasoconstriction, and that nitroglycerine appears to be effective in attenuating such an attack by tending to normalize the blood pressure and by augmenting coronary blood flow.

Bernstein and his collaborators at the Johns Hopkins Medical School have attempted to measure the effect of nitroglycerine on coronary blood flow alone. Finding that the blood pressure tended to fall after nitroglycerine administration, they gave it directly into the coronary artery so that systemic circulation would be unaffected by its peripheral dilator actions. Under these circumstances, different from how the drug is taken, they were able to demonstrate that coronary flow is augmented, that nitroglycerine is a coronary vasodilator in both normal subjects and angina patients. But is this its most important action? Several workers have found evidence of a beneficial and somewhat selective effect to augment collateral blood flow by collateral vessel dilation

and we have been able to confirm this by means of selective coronary angiography and radio-krypton studies of coronary flow.

#### *Summary*

It is our belief that nitroglycerine has actions on the coronary vasculature as follows. Coronary flow is increased by arteriolar dilation which is particularly important in the presence of induced vasoconstriction. There is also a profound effect to increase blood flow via the collateral circulation. As a result, blood is shunted towards the post-obstructive and poorly perfused areas of the myocardium.

# CARDIAC FUNCTION IN PATIENTS WITH ANGINA

Ottar Müller, Ullevål Hospital, University of Oslo

It is a great honour and pleasure for me to be invited to this meeting, commemorating the introduction by your former member, T. Lauder Brunton, of amyl nitrite as a potent remedy for anginal pain, one hundred years ago.

For some years, I have been interested in the haemodynamic consequences of coronary heart disease, the most common cause of anginal pain. That this symptom is due to an improper balance between the myocardial demand for energy and the supply available from the coronary circulation has been more or less generally accepted for a long time. This view seems, for instance, to have been held by Allan Burns in his book on cardiology printed in this city in 1809. The exact cause of the pain is still uncertain. It seems, however, to be linked to inadequate delivery of oxygen to the myocardium, either generally or locally. And metabolic studies (Cohen *et al.* 1965) have indicated changes probably due to hypoxia in patients with coronary heart disease not only during but also in the intervals between attacks of angina pectoris. If reduction of the coronary circulation and abnormal metabolism are common in these patients, it is reasonable to expect a reduction in ventricular function as well. However, one of the main symptoms of impaired left heart function, namely dyspnoea, has not been generally regarded as a feature of this condition (P. Wood 1953).

A number of investigations have been published in the last 10 years concerning the cardiac function in patients with coronary heart disease, but in my presentation today, I will concentrate mainly on my own investigations which have been carried out by means of right heart catheterization and include measurements of the pulmonary capillary venous pressures. These observations will also be discussed in the light of two other published studies, of R. Malmberg, 1964 and of Cohen *et al.*, 1965.

My investigations involved patients in whom the diagnosis of coronary heart disease had been established clinically with reasonable certainty, and in whom complicating factors such as valvular disease, hypertension, anaemia, and thyrotoxicosis have been excluded.

The investigations comprised studies both at rest and during light recumbent leg exercise (approximately 140 kgm/min for 5 min).

Figure 1 shows mean values of the main observed and calculated parameters in a resting state, for a control group with the same average age as two groups of patients, one consisting of 18 patients without recognised previous infarction and one of 61 patients with a history of infarction. The only parameter listed which deviated significantly from the controls was pulmonary capillary venous pressure.

REST Mean values

	Controls	A.P.	Infarct
O <sub>2</sub> -cons./M <sup>2</sup>	130.8	131.8	137.2
C I	3.49	3.52	3.29
Str. Index	49.5	52.8	47.9
PCVP	6.9	8.8	11.4
BP <sub>sys.</sub>		129	122
Heart rate	70.5	68.2	68.7

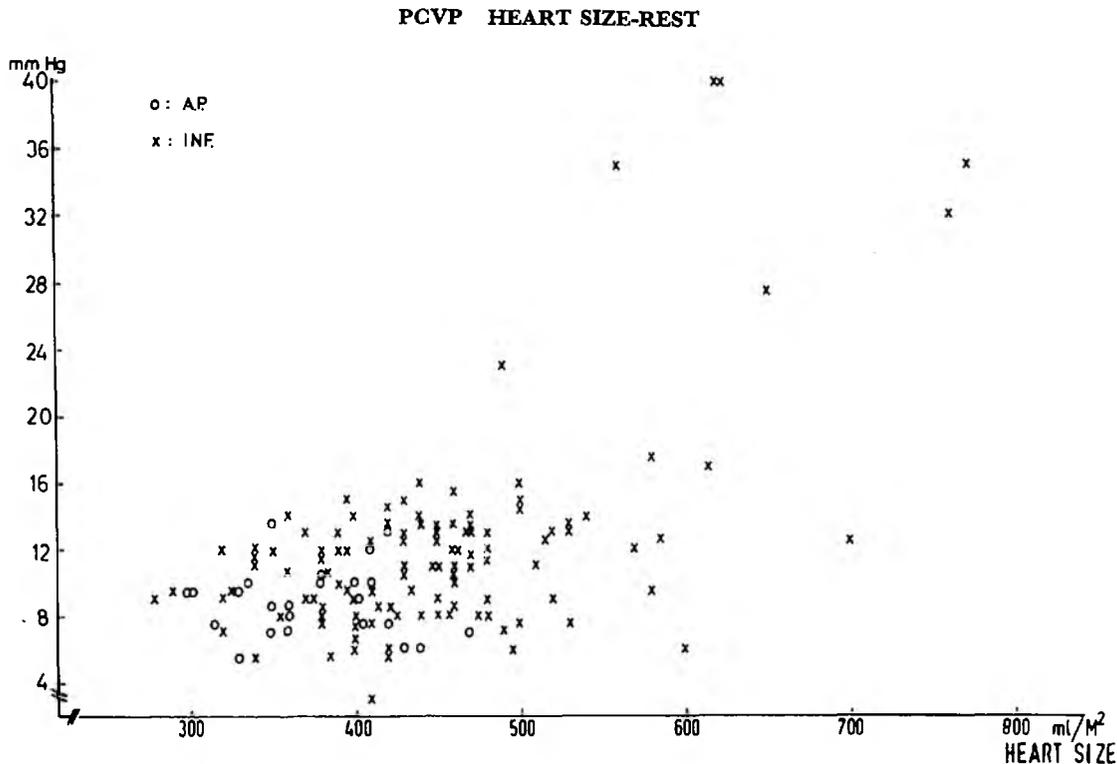
Figure 1  
Mean values for the three groups: Controls, patients with coronary heart disease without previous myocardial infarction and patient with previous myocardial infarction.

Figure 2 (on page 33) demonstrates individual pulmonary capillary venous pressure readings in the two groups of patients related to heart size assessed by x-ray. None of the patients without

previous myocardial infarction exceeded the normal upper limit of 14 mm Hg, although the group *average* was elevated. In the group of patients with a history of infarction, pulmonary capillary venous pressure varied with heart size, and one patient was in pulmonary oedema during the investigation. On the other hand, with decreasing heart size, pulmonary capillary venous pressure approached normal levels. Thus, investigated in this way, only a small proportion of patients with coronary heart disease will, as *individuals*, display distinctly abnormal cardiac functions and these will mainly be found among those with enlarged hearts.

Figure 3 illustrates the mean values obtained during the exercise test. The higher oxygen uptake in the infarct group reflects reduced efficiency and *not* a heavier load. Increase in cardiac output is here expressed as relative to increase in

**Figure 2**  
Pulmonary capillary-venous pressure at rest related to heart size (ml/M<sup>2</sup>). Patients with (Inf.) and without (A.P.) previous myocardial infarction.



**EXERCISE Mean values**

	Controls	A.P.	Infarct
O <sub>2</sub> -cons./M <sup>2</sup> dCO	350.5	319.6	367.2
dO <sub>2</sub> -cons.	7.7	6.9	6.2
Str. Index	59.8	58.9	52.1
PCVP	10.1	18.9	23.2
BP <sub>syst.</sub>		139	144
Heart rate	91.3	87.0	88.8

**Figure 3**  
Mean values for the three groups during light exercise.

oxygen uptake. Marked deviations from the controls were demonstrated, not only for pulmonary capillary venous pressure in both groups of patients but also for increase in cardiac output and stroke index in the group of patients with previous infarction. This was at least partly due to the patients with increased heart size. During the exercise test mean pulmonary capillary venous

pressure showed a more marked difference between patients and controls than at rest.

Figure 4 demonstrates individual pulmonary capillary venous pressure in the two groups of patients related to heart size. Only a small proportion of the patients' pulmonary capillary venous pressure values remained close to the normal limit of 15 mm Hg. A wide scatter was found and cases with greatly increased pressure were distributed regardless of heart size in both groups. With enlarged hearts, however, near-normal observations were lacking. It seems therefore that under the conditions of our exercise test, impaired left ventricular function may be revealed in varying degree by increased left ventricular diastolic, left atrial and pulmonary venous pressures in most patients in whom the diagnosis of coronary heart disease can be established by ordinary criteria. The exercise load used produced anginal pain in only a minority of the patients.

**Figure 4**  
**Pulmonary capillary-venous pressure during exercise related to heart size.**

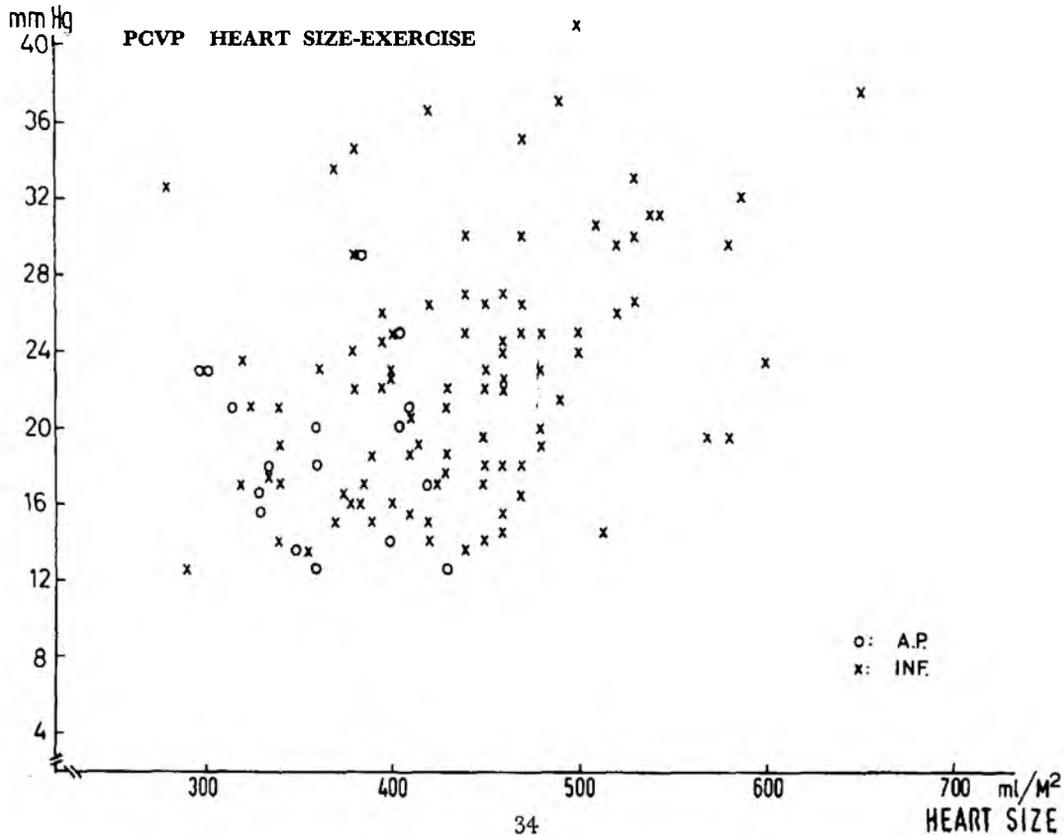
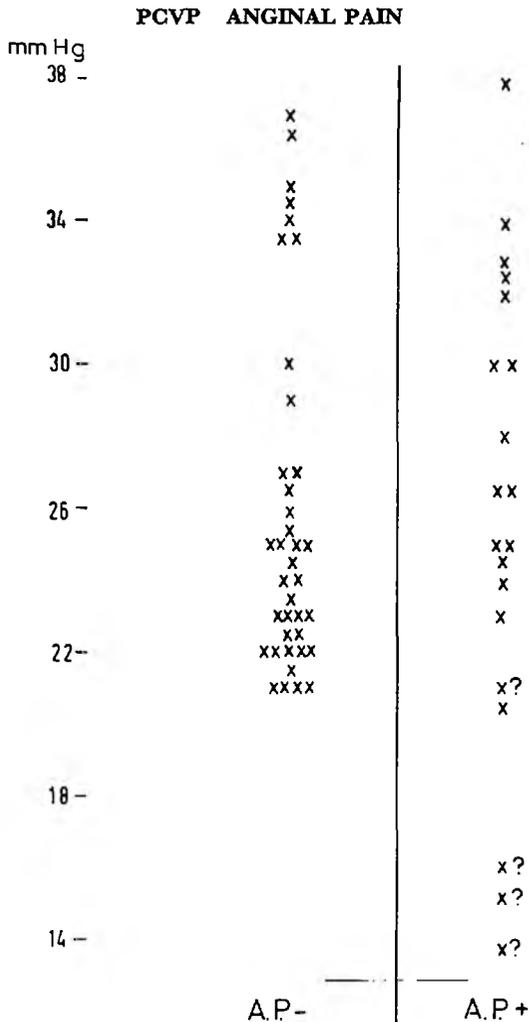


Figure 5 (on page 35) illustrates the pulmonary capillary-venous pressure values recorded during the exercise test in patients with anginal pain as the pain complaint and heart sizes of 500 ml/M<sup>2</sup> or below. The great majority of patients who developed typical anginal pain had markedly elevated pulmonary capillary venous pressure, while most of the patients with atypical sensations in the chest had only slightly or moderately elevated pressures. On the other hand, a number of patients developed markedly increased pulmonary capillary venous pressure but denied any discomfort. A further group, *not marked in the figure*, had neither unpleasant sensations nor markedly increased pulmonary capillary venous pressure. Observations indicating impaired left ventricular function in patients with coronary heart disease, especially during anginal pain and when exposed to stress have been obtained by several groups of investigators. Abnormal increases in pulmonary capillary venous pressure on exertion and particularly when this precipitates anginal pain have been reported by Malmberg

(1964). Ross and co-workers (1962) observed increased left ventricular end-diastolic pressure during spontaneous angina, while Benchimol and Dimond (1963) recorded, tracings indicative of altered left heart function by apex cardiography.

Figure 5

**Pulmonary capillary-venous pressures during exercise in patients who developed anginal pain during the exercise test (AP+) and who did not (AP-). Heart sizes  $\bar{x}$  500 ml/M<sup>2</sup>. See also text.**



In an interesting publication, Cohen *et al.* in 1965 reported the observation of abnormally reduced increases in left ventricular ejection rate and stroke volumes in patients with coronary heart disease during exercise and especially so in

the presence of anginal pain. All these investigations confirm that signs of impaired left ventricular function may be observed in different haemodynamic parameters, and that this impairment is a common occurrence in patients with coronary heart disease during exercise and most markedly during attacks of anginal pain. There are, however, marked discrepancies between some of the observations reported. Malmberg (1964), for example, in his study of 36 patients obtained a mean pulmonary capillary venous pressure during exercise which is very close to my figure, but with a markedly higher work load (mean oxygen) uptake *ca* 480 ml/M<sup>2</sup>, compared to *ca* 345 ml/M<sup>2</sup>, with higher heart rates (113 compared to 90), higher systolic blood pressures (182 compared to 142) and a higher proportion of patients with anginal pain (3/4 versus 1/3). Cohen and co-workers (1965) found a consistent rise in left ventricular end-diastolic pressure neither during exercise tests precipitating anginal pain nor during anginal pain provoked by other stimuli leading to higher heart rates than observed by me, but with moderate peripheral blood pressure levels. The reason for this conflict in observation is obscure. It seems, however, to be of some importance to know whether high left ventricular diastolic and high left atrial pressures are a common occurrence in patients with coronary heart disease.

Gorlin's group (Cohen *et al.* 1965) in one of their papers suggested that the observed increase in pulmonary capillary venous pressure depended on high systolic (peripheral) blood pressures, leading to increased work and high myocardial oxygen demand.

Malmberg's observations may support this assumption. Mean systolic blood pressure in his patients during anginal attacks was as high as 190 mm Hg. compared with 162 in patients without anginal pain and with more moderate increase in pulmonary capillary venous pressure during the exercise test. Systolic blood pressure levels seem, however, to explain fully neither the contrast between Malmberg and my own patients with regard to pulmonary capillary venous pressure, nor the great discrepancy between the observed left ventricular end-diastolic pressures of Cohen *et al.* and the pulmonary capillary venous pressure observed by me during exercise.

The other main determinant of diastolic ventricular and atrial pressure at a given ventricular

function and systolic blood pressure is stroke volume, and this parameter suggested by animal-experiments seems indirectly to influence myocardial oxygen consumption.

Stroke volume seems to vary remarkably from one investigation to the other.

Figure 6 illustrates mean stroke volume, peripheral systolic blood pressure, heart rate and pulmonary capillary venous pressure in my patients with markedly elevated pulmonary capillary venous pressure, arranged according to whether or not they developed anginal pain during the exercise test. There was a higher average peripheral blood pressure in the group of patients with angina during the test. On the other hand, patients without angina had a greater average stroke volume. The differences were, however, very slight – and systolic blood pressure in both groups moderate as exercise-pressures.

PCVP<sub>ex.</sub> 24 mm Hg. or above

	A.P. +	A.P. —
PCVP	27.3	28.2
H.R.	88	86
BP <sub>syst.</sub>	146	136
Str. Ind.	46.2	51.7

Figure 6

Mean values for patients with marked increases in pulmonary capillary-venous pressures during exercise. The two groups comprise patients who did (AP+) and did not (AP—) develop anginal pain during the test.

In Malmberg's series, patients with comparable pulmonary capillary venous pressure had an average stroke index of under 40 ml.; while in Cohen's study the group of patients who developed anginal pain during the exercise test had an average stroke index as low as 32 ml. In the group without anginal pain the figure was 38 ml., compared to 49 ml. in the control group.

These variations in stroke index from group to group of patients seem to me to offer a probable explanation of the differences in observed pulmonary capillary venous pressure and left ventricular diastolic pressure. Nevertheless, I agree with the view that systolic blood pressure may be of some importance as well.

#### Conclusion

Signs of impaired left ventricular function are obtainable from coronary heart disease patients

under stress, and especially during attacks of anginal pain. The manner in which this left ventricular impairment manifests itself seems, however, to vary with several haemodynamic parameters of which systolic ventricular pressure and – especially – stroke volume may be the most important.

#### REFERENCES

- Cohen, L. S.; Elliott, W. G.; Rolett, E. L.; Gorlin, R.: *Circulation* 1965:31:409.  
 Dimond, E. G. and Benchimol, A.: *Brit. Heart J.* 1963:25:389.  
 Malmberg, R. O.: A Clinical and Hemodynamic Analysis of Factors Limiting the Cardiac Performance in Patients with Coronary Heart Disease. Balder AB, Stockholm 1964.  
 Ross, R. S.; Schwartz, N.; Gaertner, R. A.; Friesinger, G.: *J. Clin. Invest.* 1962:41:1395.  
 Wood, Paul: Diseases of the Heart and Circulation 3. impr. p. 377. Eyre & Spottiswoode, London 1963.

# SECOND DISCUSSION

**Chairman: Professor W. Melville Arnott**

*Dr. Adams:* I would like to ask Dr. Gorlin whether the formation of polypeptides in the area of ischaemia has actually been demonstrated. He spoke of kallikrein, but is this based on actual demonstration? One would expect some of these substances to form in an area of injury where intracellular lysozymes liberate their hydrolytic enzymes.

*Dr. Gorlin:* This particular demonstration has not been made in cardiac muscle, which is known to contain kallikrein, and it is also known that kallikreins are good coronary vasodilators. The particular observations have been demonstrated a number of times in peripheral skeletal muscle and the inference has been made that maybe a similar mechanism applies within the tissues of the heart.

*Dr. Adams:* It might be possible to arrange experiments where one can demonstrate these things. If one can take blood from the coronary sinus in an experimental animal it should be possible to pass this blood over certain pharmacological test objects, such as a guinea pig's ileum, or a rat's uterus. Dr. Bain of the Royal College of Surgeons in London has described a number of elegant techniques by which it is possible to follow the formation or release of these substances in peripheral blood in a similar manner and to make comparisons with standard to obtain some idea of the concentration which might be present.

*Dr. Sommerville:* Dr. Muller, in your two groups, one was with A.P. minus, meaning angina pectoris, and the other had infarcts, do you mean that they were subject to angina or that the observations were made on people during an anginal attack? I appreciate that towards the end you showed some graphs in which pressures were actually taken in the course of an anginal attack, but earlier, you quoted mean values of cardiac out-put, stroke out-put and mean PCVP (pulmonary capillary venous pressure). Later on

you come to the infarcts and these patients showed much higher pressures. It was here that I found some difficulty, because your next slide demonstrated pulmonary capillary venous pressure related to heart size and as far as I could see the people with angina pectoris had smaller hearts and those with infarcts were all on the right side but in your conclusion you stated that people with cardiac infarctions had a higher pulmonary capillary venous pressure and a larger heart. Does the presence of an infarct make the heart big? Experience suggests that this is not so unless the infarct is of a very large size in which case there may be considerable replacement of cardiac muscle by fibrous and other tissues allowing the contraction of the heart to alter its behaviour and allowing the diastolic volume and pressure to increase; the result then is a large heart. Is what you are describing not so much a factor of cardiac infarction but of cardiac failure regardless of the cause?

*Dr. Muller:* The group called A.P. comprises patients with a typical angina pain with ECG changes on exercise, no history and no signs of previous infarction; no reference is made to anginal pain during the test except for the last slide which shows certain A.P. plus and A.P. minus lines. Of the patients with previous myocardial infarction one-fifth had heart sizes larger than 500 mm. per square metre; the rest had heart sizes within what is regarded as fairly normal limits. In my studies, I plotted the pulmonary capillary venous pressures against heart size to try and see the effects of heart size and ascertain whether the patients with previous myocardial infarction and small hearts behaved as patients without recognizable previous myocardial infarction. They did, in that they had fairly normal pulmonary capillary venous pressure but both groups rose on exercise.

*Dr. Friesinger:* Over the last 5 or 6 years in the course of catheterizing a number of patients with

the intention of visualizing the coronary arteries, opportunities were provided to measure left ventricular pressures. About two hundred patients who had angina pectoris or previous myocardial infarction were catheterized and some observations concerning this group are pertinent; particularly the 15 patients who showed good left ventricular systolic and diastolic pressure measurements early in the study before contrasting with other material or other manoeuvres were carried out. During the study they developed angina pectoris in these 15 patients, all of whom had a normal resting left ventricular, end-diastolic pressure was invariably elevated to a considerable degree; that is to say, more than 20 mm. Hg during the anginal episode, and this was irrespective of what the left ventricular systolic pressure was. In a number of these the left ventricular systolic pressure was considerably elevated, in excess of 180 mm. Hg, having been approximately 120 mm. Hg during the control measurements. However, in the majority of cases the systolic pressure was not appreciably elevated and there was little change in the heart rate in any of the 15 patients who were studied. These facts would fit in well with the suggestions that the left ventricular end-diastolic pressure increases where anginal pain is present. Of the remainder in this group the left ventricular end-diastolic pressure sometimes became elevated and remained elevated even in the absence of pain. In the cases where left ventricular end-diastolic and systolic pressures were elevated these may be the individuals in whom the spastic phenomenon to which Dr. Gorlin referred is primarily accounting for their anginal distress and hence resulting in such large systolic blood pressure elevations.

*Sir John McMichael:* May I add that many of these patients suffering from angina are also breathless and one or other symptom may predominate in their minds. They complain of pain or they complain of breathlessness or a feeling of tightness in the chest. It is often rather difficult for them to decide whether they are feeling tightness or compression or actual difficulty in breathing. Many years ago I was intrigued by Dr. Muller's observations that during these attacks of pain these patients seemed to have other manifestations of left ventricular failure, and we all know that they often develop exaggerated gallop rhythm during the actual attack.

*Dr. Gorlin:* I think the substrate underlying pain and conjunctive cardiac failure is myocardial ischaemia; the amount of myocardium which is afflicted by ischaemia will probably govern whether or not evidence of congestive failure occurs with a rise in left ventricular end-diastolic pressure. In our experience, as yet incompletely collated, those patients who did develop a rise in pressure, such as described by Drs. Muller and Friesinger were people who showed a remarkable output of lactic acid from the myocardium and who usually showed two or three vessel coronary involvement. Ischaemia was indeed diffuse and severe, therefore it would be no surprise if such a heart would go into failure with lack of oxygen and set off a pain mechanism. A corollary to this is the patient with aortic stenosis who, when asked to carry out the sort of work previously described, will also go into cardiac failure and his heart will show a restriction in coronary flow and an output of lactic acid from the coronary sinus. On the other hand, about twenty per cent of all our patients with angina pectoris have single vessel coronary involvement and therefore a small zone of myocardial ischaemia at only one site in the coronary vein and which is sometimes barely detectable by a lactic acid production. Such patients have had attacks of angina and such patients have not had a rise in end-diastolic pressure whilst in our hands. The final point that I would make concerns whether or not the blood pressure rises. We have seen one individual have two completely different levels of left ventricular end-diastolic pressure during two similar attacks of anginal pain; when the blood pressure was elevated the end-diastolic pressure was elevated, when the blood pressure was not elevated the end-diastolic pressure was not elevated. Thus I think we have a mixture of the diffuseness of the affliction of the myocardium; the fact that we have two unrelated but dependent symptoms or signs and then we have the final factor, that is the impedance against which the heart must contract which can of course aggravate any haemodynamic balance which may occur in this situation.

*Mr Hunter:* Has anyone investigated changes in the biochemistry of the cardiac muscle cells and the action of nitroglycerine?

*Dr. Gorlin:* In recent years I have seen only one report on work on the myocardium per se and this showed that there was uncoupling of oxidative phosphorylation in the liver and in the

myocardium. One of the problems as I understand it is the difficulty of working with a substance such as nitroglycerine which is insoluble in water in order to define its effect.

*Dr. Julian:* Could I ask something about the anomalies of propranolol when given to these patients who are on the edge of cardiac failure; is the drug likely to precipitate them into cardiac failure?

*Dr. Gorlin:* We have been very pleasantly surprised to see how infrequently clinical cardiac failure emerged with the use of propranolol. We would avoid using any adrenergic blocking agent in a patient who had massive cardiomegaly but fortunately this is rare in the patient with coronary heart disease. I don't know how it fits in with our previous conversation about the frequency of cardiac failure apparently occurring with angina attacks; maybe its effect is to abate the hypertensive response, maybe its effect is to abate the venous return to the heart through its venodilating action which may counteract its negative actions, it is also true that this is a dose response related effect. It is well known that one may give propranolol intravenously in a dose that will actually reduce cardiac size, cardiac filling pressure, leave the cardiac output no more than 5 to 10 per cent reduced and the lower blood pressure no more than 5 per cent and will still produce effective blockade of all adrenergic stimulation of doses. Give just a little bit more than an average dose say, more than a 10th of a mg. per kg., the cardiac size, increases end-diastolic pressure goes up and of course it is a two-edged sword, but if one pays attention to dosage and if one observes the patient closely, checks his weight gain, vital capacity and so forth, one is able to determine the right dose for a given patient.

*Medical Student (Edinburgh):* Are the nerve endings, which are supposed to be involved in this process of anginal pain, randomly distributed through cardiac muscle? Is there any relationship between cardiac ischaemia and the degree of anginal pain?

*Dr. Fulton:* I cannot give a definite numerical picture, but I can say that in the one patient an anterior infarct may be associated with intense pain, and in another with no pain at all, and this will apply equally to posterior infarcts.

*Roger Smith (Edinburgh):* Would Dr. Gorlin

comment on a possible role of coronary vasoconstriction per se in angina?

*Dr. Gorlin:* To clarify my views a little bit, what I developed yesterday in part was that in the presence of organic coronary atherosclerosis there are certain pain symptoms, particularly provocative symptoms, which are associated with progressive diffuse disease, namely the triad of nocturnal, prandial and unprovoked angina. If these occur together there is a high likelihood that the entire coronary muscular tree is involved as opposed to one coronary vessel. On the other hand, in our experience and other groups who have been doing coronary arteriography for diagnostic purposes, that there is a small group of people who have severe, frequently unremitting symptoms which by all the usual criteria, are indistinguishable from classical angina pectoris, yet coronary arteriography will reveal no lesion or suggestions of a lesion. One believes that there is another category of patients who have the anginal demonstrable form of cardiac disease, I use that word advisedly because there is no way of knowing whether these people with cardiomyopathy, whether they have some small vessel disease or whether there is something wrong with the vasomotor system of the coronary bed and whether, for example, this is Raynaud's disease of the coronary tree. We have one such patient whom we suspect might well have the Raynaud's phenomena, and she has Raynaud's in her fingers, she has attacks of pain and she has a morphologically normal coronary vascular tree. I think it is important for us to realise that all that is angina may not be atherosclerosis.

*Dr. Matthews (Edinburgh):* Once again Dr. Gorlin has referred to pain: what weight does he place upon the incidence of pain occurring during meals. I believe that this is an unusual variance of coronary disease in Britain, this might depend I suppose on who you were having a meal with, and it might depend on the food, does Dr. Gorlin share my view?

*Dr. Gorlin:* We have found that pain does not increase after a meal. There are many people who, when asked to carry out a form of exercise after a meal have great difficulty in doing it, without having pain, though it is an obvious fact that when the meal was a longer meal or a heavy meal, so that after a long heavy meal where more effort is involved the patient may suffer pain, although a light meal might not affect him.

When we studied such things as the gastrointestinal tract (with barium) we were surprised to find that the incidence of oesophagitis and the incidence of gall stones was not greater in these people who had this particular complaint than in any of the other groups.

*Student - Medical School:* Is it true that some people who have carried on walking when the pain comes on find relief with the continuing exercise?

*Dr. Gorlin:* I see many patients who are so well instructed by their physicians to stop when they develop pain, that they will not walk through their discomfort and for this reason my own personal experience with this has been very small. I have seen the usual individual who describes the pain which he felt at the first hole in the golf course, and after resting awhile he finishes his game without feeling further pain.

*Dr. Friesinger:* We have had the opportunity on several occasions in the course of doing exercise electrocardiography on a relatively large number of patients and often found that an individual who while walking at a constant rate informed the physician observer that he was experiencing discomfort at a time when an ischaemic change was seen on his electrocardiogram but states that this is the sort of thing that he had often walked through; the exercises would proceed and his pain would disappear and the electrocardiogram would lose its ischaemic shift. This has been unusual in our experience but in the several observations we have noted that when the pain has disappeared the heart rate was less than that when the pain was present. On several instances where a reduction in blood pressure was obtained the blood pressure was a little bit lower as the exercise proceeds and as the pain disappeared. This has been seen in published reports showing electrocardiographic tracings and blood pressure recordings in which the authors also indicated that heart rates were slower and blood pressure lower after pain and ischaemic change subsides. It seems to me possible that in addition to opening up collaterals these patients are rather good at warming up, and after they warm up they do have more peripheral vasodilation, their blood pressure is lower and their heart rate is slower, hence although the foot pounds of energy which the man is expending be the same, his heart work has been reduced and this is the mechanism by which he is relieved of his pain.

*Dr. Simpson (Glasgow):* Our coronary patients are encouraged to play golf and I have one or two patients who can walk through their angina very easily without stopping over the first two holes, but they will not venture out on a cold day because they cannot walk through the angina on a cold day.

# THERAPEUTIC SESSION

Chairman: Sir John McMichael, F.R.S. *Olim Scriba*

## MODERN EPIDEMIC

(Abridged)

Professor J. N. Morris

*Department of Public Health, London School of Hygiene and Tropical Medicine*

All I have to say comes from prospective studies of ischaemic heart disease made in America and in this country since World War II. In Framingham, as in the other surveys, all those who already had signs of ischaemic heart disease were put aside, and the great majority who showed no evidence of it were followed up over the years. More men than women developed the disease during middle age. In this age group, there are three main manifestations of ischaemic heart disease – sudden death, classical myocardial infarction, and angina pectoris. When the total picture in Framingham was divided up according to these different modes of presentation, they found that in those who develop angina pectoris without classical infarction there is some excess of males in the thirties; near equality in the forties; in their fifties more women were affected than men. Many of these people of course do not come for medical care, they have these symptoms but ignore them.

Our own first study compared London Transport bus drivers and conductors. The total incidence of ischaemic heart disease was higher in the drivers. Sudden death as first clinical manifestation was just over twice as frequent among the drivers throughout middle age, with a ratio of 3-1 in the early part of middle age, falling to about 1½-1 in the latter part. But angina was commoner in the conductors than in the drivers.

Similar observations have been made in the Civil Service, comparing clerks and postmen. The total incidence and the sudden death rate was higher among the clerks, but angina was commoner in the postmen. Angina, unlike classical infarction and sudden death, is more common in physically active men. The same has been found in some American studies.

Has the incidence of angina pectoris increased through the years? There is no answer. Osler made the interesting observation that there are

far more cases outside hospital than inside, the disease being commoner in consulting practice. The particular problem of angina is that it is just a symptom, and that the reaction to placebo may be good. In a follow-up of 2,000 men in Chicago those who were nervous and preoccupied with bodily symptoms developed angina more commonly than the rest, while those who were not so nervous were more liable to develop classical infarction and sudden death. Cigarette smokers have twice as much ischaemic heart disease as non-smokers, including a higher incidence of angina.

It is clear that angina behaves differently from classical infarction in several respects. The most important of course is in prognosis. We have studied the Medical Sickness Society population of several thousand doctors, classified according to the way coronary disease first presented, following these cases for 15 years. 252 cases presented with infarcts, and 30 per cent died within a week of onset of the first clinical attack, many on the first day; at the end of the 5th year half the group were still alive, though some had died from other conditions. The 52 men having angina pectoris without recognized infarction had a far better early prognosis, very few dying in the first 5 years and 50 per cent surviving 10 years.

Coronary disease emerged from obscurity during the present century to become very common. Something like 1 in 5 men in this country now develop clinical ischaemic heart disease in middle age. It is the leading cause of death in middle age, nearly a third of deaths being certified to it. Ischaemic heart disease costs something like £50-£100 million per year in health service, social security payments and widows benefits; it is the greatest single cause of pensionable widowhood in this country. The monetary loss in wages and salaries per year to families of victims of the disease must now run to as much as £200-£300 million annually.

The greatest incidence of ischaemic heart disease is seen in developed countries with a high standard of living, an urban industrial, high consumption society. It has long been known that IHD is commonly associated with high blood pressure and raised blood cholesterol levels; epidemiological studies in recent years show that these two phenomena are apparent long before the heart disease, and in fact can be used to predict its occurrence and to identify high-risk individuals. In our own prospective study on London busmen, the men with raised systolic blood pressure at the initial examination (defined arbitrarily as the top quarter of the distribution) developed ischaemic disease more commonly than those with lower levels. These were casual readings and, meanwhile, the casual systolic pressure is a better predictor than any of the other 9-11 measurements of blood pressure at the intake examination. This has been found in at least one other investigation. Skin-fold thickness was measured at the initial examination; as in other such prospective studies, the men who were fatter developed ischaemic heart disease more commonly, but the excess was unimpressive. Casual blood cholesterol ranged from 115 to 385, mgm/100 ml. Men with high levels were far more liable to ischaemic heart disease than colleagues in the same occupation, of the same age, with low.

These prospective studies have shown the importance of two main factors - blood pressure and blood cholesterol. Blood sugar levels may also be important but there is not yet any published prospective study. When blood pressure and cholesterol readings are put together with other factors found to be important in this disease - occupation, age, family history, cigarette smoking, etc., it is possible to give all the men that we have studied a score implying cumulative risk, and a striking picture emerges. The incidence of ischaemic heart disease in the most susceptible group scoring badly in terms of B.P., cholesterol and several other factors is about twelve times that in the least, the men with most favourable B.P., cholesterol, family history, etc. However B.P. and cholesterol levels dominate the picture and the other 7 factors contribute only marginally, suggesting that much or more of their contribution is via these two. Does this offer possibilities for preventive action? Specifically, if high blood pressure or high blood cholesterol are successfully treated, will the heart disease be prevented? It is

impossible to answer these questions from the data available at present. A trial that hopes to provide the answer in regard to hypercholesterolaemia is now under way and will be described by Dr. Oliver.

# IS ANGINA PREVENTABLE?

**M. F. Oliver**

*Department of Cardiology, Royal Infirmary, Edinburgh*

Last week I looked through some of the earlier records of the hospital where you, Sir, and I and most of us here had our training. You may like to know that the interest in ischaemic heart disease which Lauder Brunton established 100 years ago is being actively perpetuated in the same ward. The area where we established the first major Coronary Care Unit in Britain a year ago is very probably the same as that where young Brunton made his classical observation concerning the use of nitride of amyl.

Prevention of ischaemic heart disease, whether we are considering angina or myocardial infarction, must be taken to mean the prevention of the *premature* onset of the disease. Death from a heart attack at an advanced age would not necessarily seem undesirable.

Intervention can be expected to produce the highest yield if it is made before symptoms of ischaemic heart disease develop. That we should direct our attention particularly towards the pre-symptomatic stage of the disease is emphasized by consideration of the immediate mortality following acute myocardial infarction. It has been shown by Bainton and Peterson (1963) and by Kannel *et al* (1963) that the majority of patients who die after their first myocardial infarct do so within an hour of the onset of symptoms. Thus, many victims never reach hospital and the mortality from acute heart attacks is considerably under-estimated from hospital statistics. These reports highlight the need to prevent the attack from occurring in the first instance, and in this talk I do not propose to consider what can be done about the prevention of angina once a patient has developed myocardial infarction. This is usually known as secondary prevention.

A far more interesting and fundamental challenge is – What can be done towards the primary prevention of angina and other presentations of

ischaemic heart disease? Professor Morris has already outlined with great clarity the principal risk factors associated with the development of ischaemic heart disease, and I propose now to return to these and consider which are amenable to control and prevention (Table I on page 44).

## *Control of risk factors*

Hyperlipidaemia is mostly controllable, either by the use of Atromid-S or a polyunsaturated fatty acid diet and I will consider the control of this risk factor in more detail shortly. It may also be partly preventable insofar as a rapid increase in weight is preventable and this is often associated with hypertriglyceridaemia.

The control of hypertension presents a major problem which is outside the scope of this talk. In the first place it is by no means certain, because of the unsatisfactory nature of the available drugs, that hypertension can always be controlled and certainly the side effects of these drugs are sufficiently serious to preclude their widespread use as a means of control of moderate hypertension in otherwise healthy men. In the second place, it has not been shown that adequate control even of severe hypertension is associated with fewer myocardial infarcts when comparison is made with patients whose hypertension has not been adequately controlled (Hodge *et al.*, 1961; Hood *et al.*, 1963). The principal reasons for reduction of overall mortality when hypertension is controlled are that there are fewer deaths from cerebrovascular accidents and from congestive failure, but there is no significant change in the incidence of deaths from ischaemic heart disease.

While most of the remarks which I am making apply equally to myocardial infarction as to angina, it is worth stressing that the pattern of cigarette smoking in patients with angina pectoris is quite different from that which one obtains from patients with myocardial infarction.

TABLE I  
**RISK FACTORS IN ISCHAEMIC HEART DISEASE  
 AND THEIR CONTROL**

*Well documented risk factors*

Hyperlipidaemia	—	controllable, partly preventable
Hypertension	—	partly controllable, seldom preventable
Cigarette smoking	—	<i>preventable</i>
Surgical or irradiation menopause	—	often preventable

*Less well documented influences*

Physical inactivity	—	<i>preventable</i>
A rapid gain in weight	—	<i>preventable</i>
Diabetes mellitus	}	— partly controllable, not preventable
Hyperuricaemia		
Thrombogenic tendency		
Psychogenic stress	—	not controllable, not preventable

TABLE II  
**SMOKING HABITS IN 118 WOMEN UNDER 45 YEARS WITH  
 CONFIRMED ISCHAEMIC HEART DISEASE**

	Total numbers	No. of non-smokers	Nos. of smokers and cigarettes day		
			1-14	15-24	25+
A.P.	58	23	21	13	1
M.I.	60	8	27	18	7

Comparison of non-smokers with heavy smokers (15 or more) indicates a significant difference between A.P. and M.I. ( $0.005 > P > 0.001$ ).

TABLE III  
**SMOKING HABITS IN 118 WOMEN UNDER 45 YEARS WITH CONFIRMED  
 ISCHAEMIC HEART DISEASE**

	Per cent who are non-smokers	Per cent who are cigarette smokers		
		1-14/day	15-24/day	25+/day
A.P. (58)	40	36	22	2
U.K. population*	47	37	13	3
M.I. (60)	13	45	30	12

\*Mean figure for women 21-35 and 36-55 derived from 1961 report of Tobacco Manufacturers Committee.

Professor Morris has already mentioned the experience of the Framingham study and I will only add to this by commenting that Doyle *et al.*, (1964) also showed a clear-cut relationship between heavy cigarette smoking and myocardial infarction in the Albany study but no such relationship existed between heavy cigarette smoking and angina. In Tables II and III, you will see similar findings in young women. During the last 15 years, I have seen 150 women, all under the age of 45 with symptoms suggestive of ischaemic heart disease; 58 of these had angina pectoris with myocardial ischaemia in their electrocardiograms and 60 had myocardial infarction. Examination of these tables indicates that women who get a myocardial infarct have different cigarette smoking habits from women who develop angina pectoris and also from women in the normal U.K. population. Various suggestions have been put forward for this difference. It is possible, although there is no good factual evidence, that cigarette smoking leads to a thrombogenic tendency. There may be a greater degree of coronary vasoconstriction, perhaps coronary spasm as described by Dr. Gorlin and as a result there may be less satisfactory formation of coronary collateral vessels in heavy cigarette smokers. A third possibility is that there are more arrhythmias in heavy cigarette smokers as a consequence of increased catecholamine and free fatty acid production; in this context, it would be interesting to try to document whether there is a higher incidence of sudden death and of immediate mortality following myocardial infarction in heavy cigarette smokers compared with non-smokers. One of the reasons for spending a little time considering cigarette smoking is that it may present a different problem so far as primary prevention is concerned when compared with the other risk factors which are perhaps more closely associated with the gradual development of coronary atherosclerosis.

There is a higher than usual incidence of angina pectoris and myocardial infarction in women whose reproductive life has ceased at an unduly early age. While a number of these women undergo premature hormonally-determined cessation of menstruation, surgery or irradiation are not uncommon causes. The removal of both ovaries, or their irradiation, can often be prevented.

Amongst the less well documented influences described in Table I, there are two which are in

theory entirely preventable. One is physical inactivity and the other is rapid gain in weight. The effects of preventing physical inactivity on the development of ischaemic heart disease have not been studied and there is no current trial to determine whether increased activity has a primary protective effect. Of course, this is a very difficult subject to study. It would be necessary to identify a large group of physically inactive men and to take a randomized proportion of these men and ensure that they became physically active consistently and continuously over a long period of time. It would be equally necessary to be certain that the remaining randomized half continued to be physically inactive. I think that this is impossible to do in any culture.

It has been suggested (Heyden, 1964) that a rapid gain in weight is associated with an increase in serum triglycerides but, of course, there is no good evidence as yet that an increase in serum triglycerides alone is an adverse risk factor. One has to distinguish the increased risk which is known to occur in patients with hypercholesterolaemia from that which has yet to be shown in patients with hypertriglyceridaemia. It is also important to emphasize at this point that obesity by itself is not to be incriminated as an independent risk factor. In the Framingham and Albany surveys, obesity only becomes a significant adverse influence when it is associated with hypercholesterolaemia or hypertension. My own experience in the small group of young women already mentioned confirms this view. On the other hand, obesity has been shown to increase the work of the heart and should therefore be avoided.

#### *Primary Prevention Trials*

The question proposed by the title of this talk – “Is Angina Preventable?” demands consideration of the principles of primary prevention trials. Prevention of atherosclerosis itself is the most important therapeutic challenge today and it is likely to remain so until more is known about the initiating pathogenic influences. Some progress could be made, however, if preventive trials are established in groups of men who can from existing evidence be regarded as having an increased risk of developing one of the symptom complexes of atherosclerosis.

Any trial of a preventive treatment in healthy men raises certain ethical questions. Is one justified in altering the habits by drugs or by diet of

men who regard themselves as entirely healthy in the hope that they will be protected from a disease which they may not ever get? While this view commands respect and is sometimes put forward against prevention trials, many doctors feel that there is a stronger moral argument in favour of such trials. It is necessary, therefore, to examine the design of primary prevention trials.

A number of risk factors have already been defined and discussed in detail. There can be two different and independent approaches to the control of these factors. One is to control one factor at a time and the other a number of factors simultaneously. Support can be advanced for both approaches. If it is assumed that there are four different risk factors amenable to control, satisfactory control of three simultaneously might lead to a reduction for the sake of the example of 30 per cent in mortality from ischaemic heart disease. Similarly, successful control of the fourth factor alone might also lead to a reduction of 30 per cent in mortality. Since the control of several factors simultaneously might theoretically neutralize the effect of controlling some singly – for example, the increase in weight which follows the cessation of cigarette smoking – it can be postulated that control of a fourth factor might lead to an even sharper fall in the attack rate. One can conclude, therefore, that the control of several factors simultaneously and of one singly are both rational and acceptable approaches towards the implementation of primary prevention trials. Par excellence, hyperlipidaemia is the risk factor most suitable for control alone.

#### *Control of hyperlipidaemia*

There are various approaches which can be made towards the establishment of trials to control hyperlipidaemia. Perhaps the most satisfactory is to identify those individuals in the normal population with the highest risk, to randomize these and treat half of them. Another possibility is to concentrate on those who have hyperlipidaemia together with other high risk characteristics, such as a family history of vascular disease and for example, to study the effects of correcting hyperlipidaemia in the brothers and sisters of young patients with myocardial infarction. Another possibility, which is less satisfactory because it entails a mammoth trial, is to take the whole of a given population, to randomize them all and treat half of them.

For a number of years, we have been studying here in Edinburgh various means of controlling hyperlipidaemia. I have personally taken the view that any major change in the usual diet is not likely to be a practicable approach to the control of ischaemic heart disease. I do not believe even if it could be shown that a fundamental change in the normal diet reduces the attack rate from ischaemic heart disease and this has not yet been shown, that the public will pay any more attention to these findings than they are presently doing to the incontrovertible evidence that cigarette smoking is associated with lung cancer and ischaemic heart disease. Thus, we have addressed ourselves to the problem of trying to find a means of controlling hyperlipidaemia without alteration of the diet. We have studied oestrogens and thyroid hormones and rejected them both because they are only partly effective or have intolerable side effects, and during the last six years have concentrated particularly on studying and appraising the effects of Atromid-S (Symposium on Atromid, 1963).

I do not want to take up time discussing Atromid-S but there are three major points which require attention. The first is that this drug reduces elevated serum cholesterol levels and also elevated serum triglycerides (Oliver, 1962). The second is that it leads to removal of cholesterol and lipid deposits from tissues; tuberous xanthomata disappear (Borrie, 1964) and lipaemic exudates resolve in diabetics (Cullen *et al.*, 1964). The third and perhaps the most important point is that the drug causes a large efflux of neutral sterols in the faeces (Ahrens, 1969). Thus, there is excellent circumstantial evidence that the drug not only lowers serum lipids and removes it from the tissues but that it actually promotes loss of cholesterol from the body – evidence which is lacking for diets containing polyunsaturated fats.

#### *The Edinburgh Primary Prevention Trial*

I have been so impressed by the effect of Atromid-S that two years ago I decided to take the plunge and establish a primary prevention trial using Atromid-S as a means for controlling hyperlipidaemia. This trial is jointly run by myself and Professor Morris, and with the close collaboration of Dr. R. A. Cumming from the Blood Transfusion Service. The majority of the men participating in this trial are blood donors

and all are volunteers. The age of the men is between 30 and 59 years.

The hypothesis which we are trying to test is that reduction of elevated serum lipids in healthy men leads to a decrease in the incidence of ischaemic heart disease. If after five or six years of study, we come out with a negative result, then I think this will in fact be a contribution since the air will be cleared, as it were, and presumably we can then disregard elevated serum lipid levels as a therapeutic problem. On the other hand, if the trial ends with a positive result then I believe that we may be able to say for the first time that ischaemic heart disease can really be prevented.

The aim which we have set ourselves is to show a 5 per cent reduction in morbidity and mortality from ischaemic heart disease and at a 1 per cent significance level. In order to do this, it can be calculated that 80 infarcts are required in a control group and thus 40 infarcts in a treated group. It is difficult to be exactly certain about the annual attack rate in hyperlipidaemic men

in Britain but the Framingham figures probably apply and for men of the age with which we are dealing this is 1 per cent per annum. Thus, we will need to study 8,000 men in a control group for one year or better still, in view of the progression of the disease, 2,000 men over a minimum period of four years. The treated group must of course be the same size and thus the basic requirements for this study are 4,000 men and these have to be obtained from a population three times this size. This is because we are selecting hyperlipidaemic men – in other words, those above the top tertile. It is important to emphasize the magnitude of the trial and the fact that primary prevention trials cannot be undertaken with small numbers.

The design of the Edinburgh Ischaemic Heart Disease Prevention Trial is shown in Fig. I. Olive oil is used as a placebo; it is a monoene without effect at the dosage given on serum lipid levels. As you can see, we have an additional group in our study. This is 2,000 men in a

### EDINBURGH I.H.D. PRIMARY PREVENTION TRIAL

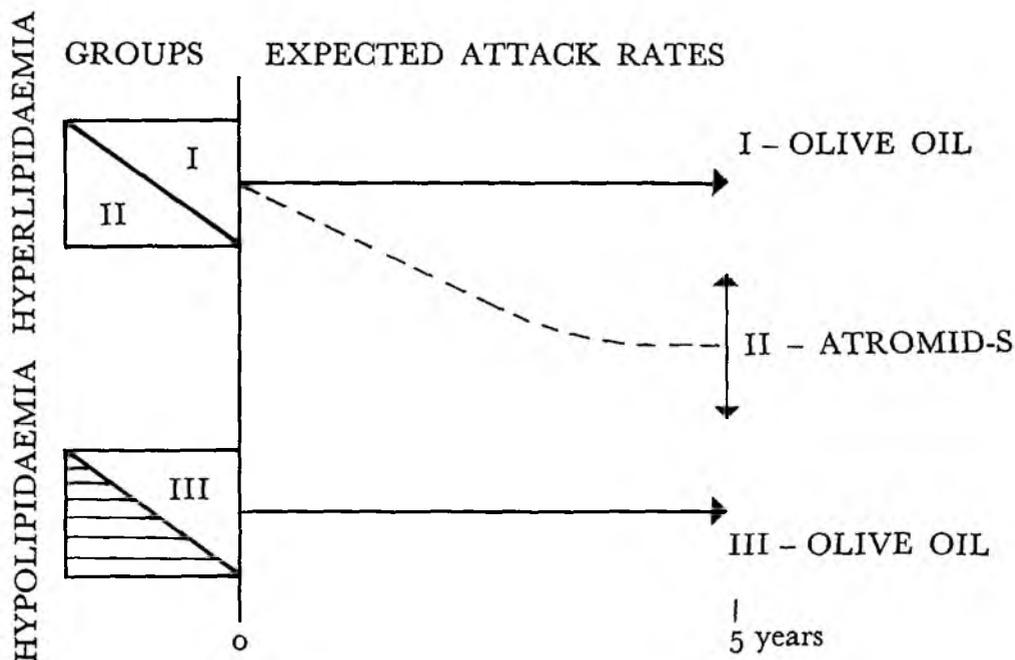


FIG. I

hypolipidaemic group also receiving olive oil. This third group acts as an additional control and also allows all the team to be blind so far as the selection of men is concerned. Thus, if a man asks why he has been selected for the trial and inquires whether he has a high serum cholesterol level, we can honestly answer that we do not know since we are looking at both ends of the "cholesterol population". I should add that none of the team know which man is receiving Atromid-S or olive oil, and so we are twice blinded in this study.

At present, 1,700 men have been enrolled from the Edinburgh area. We hope to obtain 4,000 men from this area but because of the difficulty in getting these large numbers, we are shortly going to extend the trial to Prague and Budapest where the exact design of this trial will be replicated. The statistical analysis from all three centres will be made in Professor Morris' Department in London. The establishment of this trial in two other countries may be of particular value in testing the practicability of its application in the future; if similar results can be obtained from three separate cultures, then they are all the more significant and impressive.

At present, there is little to say about our own study. Obviously, there are no results available. We have been delighted with the co-operation and interest of the participants. Since it is possible to measure Atromid-S blood levels, we know that we have a very high adherence to the treatment and we also know that we have achieved the expected reduction in serum lipids.

### *Conclusion*

I shall end by returning to the question which I set myself, "Is angina preventable?" I do not know the answer to this and I do not think that anybody else does yet. The only way, in my opinion, of finding out the answer is to establish primary prevention trials of the types which I have outlined.

# THIRD DISCUSSION

**Chairman: Sir John McMichael, F.R.S.** *Olim Scriba*

*Professor Donald:* The speakers have mentioned a number of factors, blood pressure, obesity and so on, but neither of them mentioned the question of family incidence of this disease which some of us hope, with good family histories might be favourable.

*Dr. Robertson:* I wonder if Professor Morris or Dr. Oliver has correlated the number of miles driven in motor cars to the incidence of coronary heart disease, and particularly driving in traffic as opposed to driving on the open road; after all, the incidence of this modern epidemic roughly correlates to the rise of the motor car. I was very interested in a recent article which described a test in which a cardiometer was attached to the driver of a motor car and whilst waiting at the lights a pulse of 150–200 was recorded; this was quite usual.

*Professor Hunter:* I would like to ask Dr. Oliver if it is a reasonable risk to give Atromid-S for 5 years to otherwise healthy people?

*Dr. Borchgrevink (Oslo):* Dr. Oliver, do you suggest that there may be a difference in response to what you call two different cultures, and do you think it might confuse the issue by bringing them into the study and possibly finding that the positive effects of the treatment in Britain, for instance, might differ from the results achieved effect in the other countries?

*Dr. Turner:* Would Professor Morris care to comment on the recent criticisms that have been made on the London Hospital pathological studies? I know most of you will be familiar with the work on the exceptionally good pathological material which apparently shows that the incidence of atherosclerosis has not changed very much and is certainly not commensurate with the apparent increase in coronary thrombosis. Dr. Robert Smith has recently published a book criticising this; he questioned whether there had in fact been this remarkable increase in clinical

coronary artery disease on the grounds that insufficient attention had been paid to the changing age population in the London Hospital pathological material; this is obviously of very great importance.

*Professor Morris:* Recent studies have confirmed that the family history is important. In two main studies, one of whole populations and another based in London, findings suggest that the chance of a person developing a coronary is strikingly higher where there is a family history of the disease. They haven't taken it any further yet in terms of explaining the mechanism because insofar as we know blood pressure, cholesterol levels and obesity are all important mechanisms in disease; so the genetic components of these do not begin to explain the very striking family history. In answering the question which Dr. Robertson put, I would say that it is a question of whether it is the sitting and driving or whether it is the nervous strain. We don't know, but perhaps the answers will come from monitoring as you suggest. Professor Hunter asked whether we think it is a reasonable risk to give Atromid-S to people over a long period of time. Yes. We have looked at this very carefully, Atromid-S has been studied as you know for at least 6 years and some 5,000 men in this country have been receiving the drug for 2 years or more; one case of agranulocytosis has been reported in a patient who was also receiving three other drugs, one of which was known to produce agranulocytosis before, and which occurred at a stage when maturation arrest would not be expected, that is to say, three days after the administration of Atromid-S. It appears to be non-toxic and it has no side effects so far as we can see other than that which one would expect from oil. We are rather impressed by the effects of the drug. There is a system within our survey which will show difficulties as they rise; if toxicity or if serious side effects occur they

will become rapidly evident and will stop the trial.

*Dr. Borchgrevink:* Might the application of the study in the two cultures confuse us? It could, but I think it is desirable that we should do it because it seems to me very important that if our study cannot be replicated in another culture then it is less meaningful and surely if we can reproduce the same results in other cultures they are likely to be more widely accepted.

# CHEST PAIN, EXERCISE ELECTROCARDIOGRAPHY AND CORONARY ARTERIOGRAPHY

(Abridged)

**G. C. Friesinger**

*Johns Hopkins Hospital, Baltimore, Maryland*

Over the last 6 or 7 years Dr. Richard Ross and I in the department of medicine at Johns Hopkins Medical School have had a continuing interest in objective methods which might be used in assessing the individual who comes to the physician complaining of chest pain. Angina pectoris is many things; it is a metabolic defect with lactate excess, it is a certain pathological picture, it is a group of individuals who are disposed to have certain things happen to them, but most of all angina pectoris is pain in the chest. It is pain in the chest as far as the patient is concerned, and this is the symptom on which the physician has to base important decisions concerning diagnosis, prognosis and treatment. The problem with chest pain is that it is a very subjective complaint, and a discussion with the patient is certainly the most satisfactory way to establish its cause. If the pain be typical in quality and duration as is described in Heberden's reports and later emphasized by Osler, one can confidently conclude that it is indeed angina pectoris, that the coronary arteriosclerotic process is severe, and that the prognosis – though varied – is more or less predictable. However, particularly in the current epidemic in Western societies certain serious diagnostic problems arise in individuals complaining of chest pain. There are two main reasons for this. One is that some other kinds of pain very closely mimic that of angina pectoris; oesophageal and musculoskeletal pains are two notorious examples. This is because the pain pathways that supply these structures are similar to those conducting pain from the heart. The other diagnostic problem arises in individuals who may have only very trivial causes for their chest pain, but tend to be overdiagnosed because of a rather hysterical sort of attitude on the part of both patients and doctors. The former are influenced by the lay press and awareness of the seriousness of chest pain, and the latter by

fear of "going out on a limb", so to speak, and missing a serious diagnosis. In addition there are other problems in patients with clear-cut ischaemic heart disease. Our ability to prognosticate is still inadequate and limited, and the means by which we can evaluate therapy are still not fully satisfactory. The objective methods which I am going to describe are first, functional evaluation of the individual and his complaint by exercise electrocardiography and second, anatomical assessment of the coronary circulation by selective coronary arteriography. The only question to be answered in this group of patients is, "Is ischaemic heart disease present?" Of approximately 800 whom we have seen over a 6 year period, 238 have gone through the entire gamut of investigations in an effort to answer this question. In the others we felt that more simple and perhaps less hazardous means of investigation were sufficient. The 238 individuals all had chest pain, which had been diagnosed by one or more physicians as angina pectoris, but they can be divided into two groups according to the history – those whom we concluded had ischaemic heart disease and the others in whom our history did not, clearly, suggest that it was present. The mean age in each group was 44. And, we felt that there were good and justifiable clinical reasons for full investigation of all these patients. None had persistent hypertension or X-ray cardiomegaly. I would like to review the methodology we have used, and emphasize that this was a prospective study. Our routine investigation included blood lipids, sugar, postprandial blood sugar estimations, exercise electrocardiography and selective coronary arteriography. Though one might argue about the need for arteriography, if it is done at all – the selective method provides the most information. Other studies were made on the basis of clinical indication, not routinely in all patients. We have considerable follow up information on every

individual obtained at annual intervals, either by seeing the patient again, or by letter from the referring physician. All information obtained during in-patient investigation, which usually took about 5 or 6 days, has been programmed in a computer for easy handling and correlation, the follow-up data being added as it becomes available so that we can continue to alter our "final" assessments. I believe it is very important to make a firm opinion on the history, without seeing the electrocardiogram, arteriogram or even perhaps the referring physician's letter. In this study two or more physicians specifically interested in chest pain - (in nearly all cases I have been one of them) took a history and recorded what they believed to be the cause of the pain. For the purposes of this study, "Typical" angina pectoris is defined as related to effort, relieved by rest, at least partly substernal in location and visceral in character. It can have other features as well but it must have these three characteristics, and the physician taking the history must be convinced of its ischaemic cardiac origin. If the pain is classified as atypical angina pectoris, this means that in the judgement of the clinician it is probably ischaemic myocardial pain but does not fulfil one or more of the criteria outlined. A third classification is "pain of uncertain origin", and in this case two or more clinicians, are uncertain whether the pain is cardiac in origin. There is a fourth category in which all clinicians associated with the study agree that the chest pain present does not arise from the heart. We even had 6 patients with no chest pain at all.

As regards the electrocardiogram we have devised light-weight electrodes which can be placed on the chest, so that 12 lead tracing can be obtained during exercise. Similar electrodes are now available commercially. Nearly all muscle "noise" can be eliminated by placing the arm leads below the clavicles, and this method together with normal chest and right leg leads provides a conventional electrocardiogram for interpretation. Other kinds of leads, which might be easier to apply can produce difficulties in interpretation; experience with Bi-polar leads, for instance, is too limited for complete reliability. I believe that our method increases the safety of the examination, since the electrocardiogram from multiple sites on the chest can be observed continuously during exercise.

The criterion which we have arbitrarily selected

to indicate ischaemic during exercise is a square or down-sloping T.S. segment depressed one or more millimetres from the baseline with a duration of 0.08 second or longer, and persisting for 3 or more beats. As regards the exercise load, the patient currently walks upon an escalator - ergometer (we used a bicycle previously) the load being adjusted to the heart rate response. Criteria for stopping the examination are:

1. The patient complains of fatigue or breathlessness.
2. The ECG shows ischaemic changes regardless of whether pain occurs or not.
3. Pain occurs, believed by the physician to be angina pectoris.
4. The heart rate reaches 90 per cent of the predicted maximum - which is a function of age, not conditioning.

The exercise electrocardiogram obtained under these conditions is interpreted by physicians not otherwise associated with the study. The coronary arteriogram is made by the selective technique and classified arbitrarily as follows:

0. No abnormalities on the arteriogram;
1. Minimal irregularities (we cannot attribute any clinical significance to this degree of arteriographic change even though on the basis of post mortem injection studies I am convinced that the least irregularity revealed by this crude method indicates appreciable narrowing - perhaps 20 or 30 per cent of the cross-sectional area of the lumen).
2. "Localized, severe narrowing" (a debatable degree of change and therefore in quotes).
3. Multiple narrowings.
4. One or more totally obstructed vessels.

This is not necessarily a progressive scale; many individuals in class 3 (multiple narrowing) are more severely ill than some in class 4 who have only one artery totally obstructed, and good collateral circulation.

We now come to the information derived from this study, which was designed to assess whether or not ischaemic heart disease was present and assess its severity by objective methods.

On the history, 91 of the 238 individuals had typical angina pectoris by the criteria defined, of these, half had a normal electrocardiogram. 40 had atypical angina pectoris, 66 had pain of uncertain cause and 41 patients did not have angina pectoris in our opinion. Regardless of classification, most patients had a normal electrocardio-

gram. Of the 91 individuals with typical angina pectoris all except 2 or 3 participated in exercise electrocardiography, and an adequate test was defined as one in which the heart rate reached 90 per cent of the maximum, or in which angina pectoris was objectively manifest by an ischaemic change on the electrocardiogram. Of those with an adequate test 57 showed ischaemic change, 15 did not. Arteriography in these same 91 patients revealed very severe changes in 77, a "severe localized narrowing" in 7, and no, or trivial change in the remaining 7. On the basis of all the information we have to date (and we have followed up some patients for 6 years) we have attempted to decide whether ischaemic heart disease is present or absent. In the 91 individuals originally classified on the history as typical angina pectoris we concluded that ischaemic heart disease was indeed present in 86. In 4 we decided (mainly on the basis of follow up information) that we were wrong in our initial historical evaluation, and that ischaemic heart disease was absent; in 1 we remain uncertain. It is interesting to note that 84 of these 86 individuals with "typical" angina pectoris had very severe arteriographic change.

The other group of great importance in assessing the usefulness of our method consists of the 41 individuals with chest pain not thought to be angina pectoris on the history alone. 2 out of 34 who had adequate exercise electrocardiogram by our criteria did have an ischaemic change; the arteriogram in 39 of the 41 showed no or trivial abnormalities but in 2 patients the changes were very severe. Follow up data in these 41 individuals have led us to believe that one individual does indeed have ischaemic heart disease, while the initial impression that it was not present seems to be borne out in 36, and in 4 we remain uncertain. At least 3 possible explanations can be offered for the 2 patients not diagnosed on the history. First, they may indeed have had angina, related to the changes seen arteriographically. Second, their symptoms could have been a mixture of ischaemic and non ischaemic. Third, they may belong to the 5 per cent of individuals in this group (mean age 44) with severe coronary changes, but no present or previous ischaemic complaints.\*

#### *Conclusion*

The arteriographic patterns seen in individuals with "typical" angina pectoris (by our definition) may vary considerably, although serious arteriographic change is nearly always found. 238

patients with troublesome chest pains thought to be due to ischaemic heart disease were evaluated by clinical and laboratory studies including exercise electrocardiography and selective coronary arteriography. The arteriographic study tended to provide the most definitive diagnostic data, but this is related in part to the fact that a relatively young age group was studied. Angina pectoris is virtually always associated with severe arteriographic change, but many persons have less marked disease arteriographically than post mortem studies would suggest. This is reasonable in light of the fact that we have studied a population in an early stage of their disease. The patterns associated with myocardial infarction are more variable than those seen in angina pectoris. Our early follow up studies suggest that coronary arteriography may increase our knowledge of the natural history of coronary artery disease and lead to more accurate diagnosis, better treatment and more reliable prognosis.

\*The patients in the clinical groups, atypical and uncertain pain had variable degrees of arteriographic abnormality - from class 0-4. It is likely that it is in these groups the arteriographic method is most helpful in clarifying clinical problems.

# PROGNOSIS OF ANGINA PECTORIS

**Christian F. Borchgrevink**

*From : Department VII, Ullevål sykehus Head : Professor dr. med. Einar M. Blegen*

Coronary heart disease expresses itself usually as angina pectoris or myocardial infarction. At least in Norway, angina pectoris is the more common form, particularly in people under the age of 65. The vast majority of patients with myocardial infarction is admitted to hospitals while the majority of patients with angina pectoris as the sole expression of coronary heart disease seeks a general practitioner if he sees a doctor at all. Therefore the incidence of angina pectoris in the population is less well known, than the incidence of myocardial infarction and consequently the exact prognosis is hard to give.

The large American studies on the prognosis of angina pectoris include a high percentage of patients who have experienced one or more infarctions, who have developed heart failure or who have cardiac enlargement. The prognosis in such patients is therefore unlikely to be the same as in patients with, so far, uncomplicated angina pectoris.

Although sudden death or an acute infarction will always hang as a Damocles sword over the heads of patients with angina pectoris (as it actually does over the heads of all of us) the prognosis is probably not as grave as generally accepted 30 years ago. Paul D. White states in one of his many papers that the average survival was thought to be less than 5 years. Such figures were usually derived from autopsy data. Zoll *et al.* (1951) found among 177 autopsied patients with angina pectoris that  $\frac{1}{3}$  had died within one year after start of symptoms, 50 per cent within 2 years, 75 per cent within 5 years and 90 per cent within 10 years. To me such figures only show that some patients die soon after developing angina pectoris and that some patients live for a long time. But as we do not know the number of living patients with angina, the figures tell very little about the exact prognosis.

As the results of the long-term studies, mainly from America, appeared, it was clearly shown that the prognosis although still grave, was at least somewhat brighter than generally felt. In 1943 White *et al.* published their experience with 500 patients with angina pectoris, followed for almost 20 years, and in 1956 Richard *et al.* published a follow-up study. This is a remarkable study as all patients were traced, the same can unfortunately not be said about the other large American studies. The survival curve is shown in Figure 1. Half of the patients were dead  $8\frac{1}{2}$  years after diagnosis was made. Some patients were still alive 30 years after diagnosis. Only 20 per cent of the patients had normal cardiac status at the time of diagnosis, and they showed a better prognosis as the group as a whole, a point I shall return to. 76 per cent of all the deaths were cardiac.

The largest study was published by Block *et al.* in 1952. Almost 7,000 patients were followed from 5 to 23 years. The average duration of angina pectoris prior to diagnosis was  $2\frac{1}{2}$  years and 25 per cent of the patients had experienced previous infarction.

Figure 2 shows the survival curve of the patients together with the corresponding curve of the normal population. It will be seen that there was a distinct higher mortality the first year after diagnosis. The 5 and 10 years' survival were 58.4 and 37.1 per cent respectively against 86.9 and 70.4 in the normal population. Almost 20 per cent of the patients could not be traced after 10 years.

Table 1 on page 56 shows that the survival rate falls with age. However, when adjusted for normal death, the effect of angina survival is the same in all on age groups. A similar observation was made by White *et al.*, i.e. that the excess mortality of patients with angina pectoris measured in numbers of lives is independent of age.

The study of Block *et al.* gives detailed information

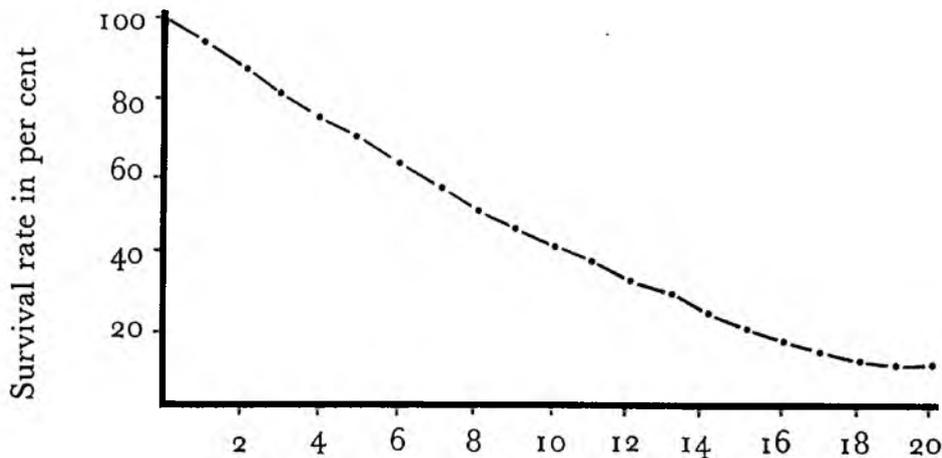


FIG. 1 Years after diagnosis (White *et al.* 1943)

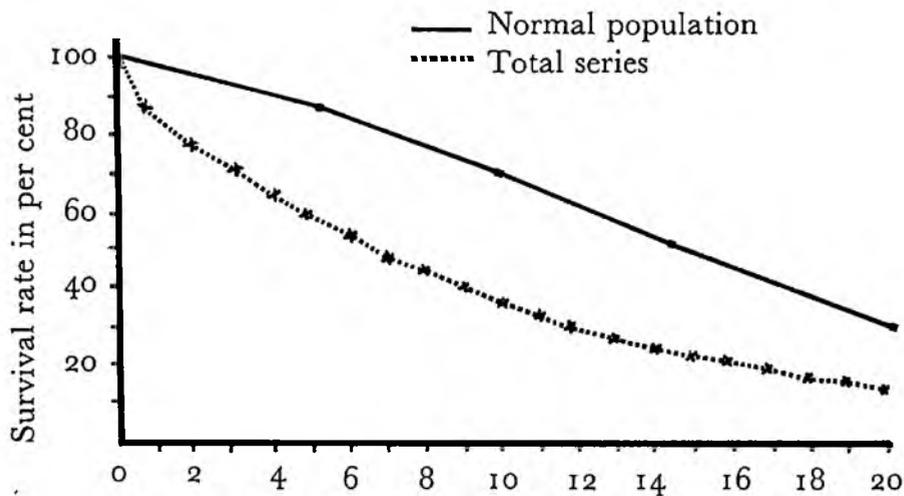


FIG. 2 Years after diagnosis (Block *et al.* 1952)

on factors influencing the prognosis as shown in Table 2. Patients with hypertension, abnormal ECG, cardiac enlargement or previous myocardial infarction have a more serious prognosis while angina pectoris connected with obesitas showed a better prognosis. They also made the observa-

tion that angina pectoris connected with malignant disease showed a poor prognosis, a statement I do not find unreasonable. This multifactorial influence on prognosis makes prognostic comparison from one series to another very difficult and almost meaningless, particularly when

Table 1

Age (Years)	Survival Rate in %			
	5 years Adjusted for Normal Death		10 years Adjusted for Normal Death	
<40	66	68	47	50
40-49	65	69	43	49
50-59	61	68	37	48
60-69	55	69	29	51
70-79	43	72	16	62

(Block *et al.* 1952)

Table 2

	Survival Rate In %	
	5 Years	10 Years
Total Series	58	33
Previous Infarction	46	26
Abnormal ECG	43	23
Cardiac Hypertrophy	41	20
Heart Failure	20	8
Hypertension, Group 3	22	1.3
No Cardiac Hypertrophy	64	39
Normal Blood Pressure	63	40

(Block *et al.* 1952)

evaluating effects of drugs on the long-term prognosis. This situation is similar to the one we are facing after myocardial infarction, which was clearly pointed out by our Chairman some years ago.

In 1960, Seim, from Norway, studied the prognosis of angina pectoris in 600 patients followed for 5 to 25 years. 99 per cent could be traced. The 5 and 10 years' survival was about 70 and 50 per cent, respectively slightly better than in Block's material. Figure 3 on page 57 shows that females have a better prognosis than males. Patients with normal ECG have a much better prognosis than patients with abnormal ECG, the 5 years' mortality being about 22 and 45 per cent respectively.

The problem of remission has been attacked by Riseman (1966), who has followed 122 patients with angina pectoris weekly for 6 months to 16½ years. More than half the patients showed remissions, defined as 2 months or more without pain. Half of these were free from pain for more than one year. In half the patients the remission

was spontaneous. 20 per cent of the patients had periods with exacerbations. It was impossible to beforehand to tell whether a patient would experience a remission or an exacerbation.

Life Insurance Companies' Institute for Medical Statistics at Oslo City Hospitals has made a study of 331 patients with angina pectoris without infarction. The majority attended an out-patient clinic, and the others had been admitted to medical departments. Table 3 shows the ratio of observed/expected deaths. This ratio falls with age which may be interpreted to mean that angina pectoris is more serious in young patients. However, if take the difference in the numbers of deaths between patients and the normal population there is actually very little difference between the age groups, confirming Block *et al.*'s and Richard *et al.*'s findings that the excess mortality in angina pectoris expressed as the number of deaths is independent of age.

Table 3

Age (Years)	Number of Deaths	
	Observed/Expected	Difference Between Patients and Population (per 1000)
35-54	5.5	30
55-69	2.3	34
>70	1.4	37

There seems to be little difference in the ratio whether the angina lasted a short or a long time before registration (Table 4). The duration of the observation period seems also to have little influence on the excess mortality (Table 5) on page 58. This is in contrast to the result of Block *et al.* who found a higher mortality in the first year. The discrepancy may perhaps be explained by Table 6 on page 58, which clearly shows a higher mortality the first year after myocardial infarction. 25 per cent of Block's patients had

Table 4

Duration of Angina Prior to Registration	Number of Deaths Observed/Expected
<6 Months	1.6
6-12 Months	2.2
1-2 Years	1.5
2-5 Years	2.9
>5 Years	2.8

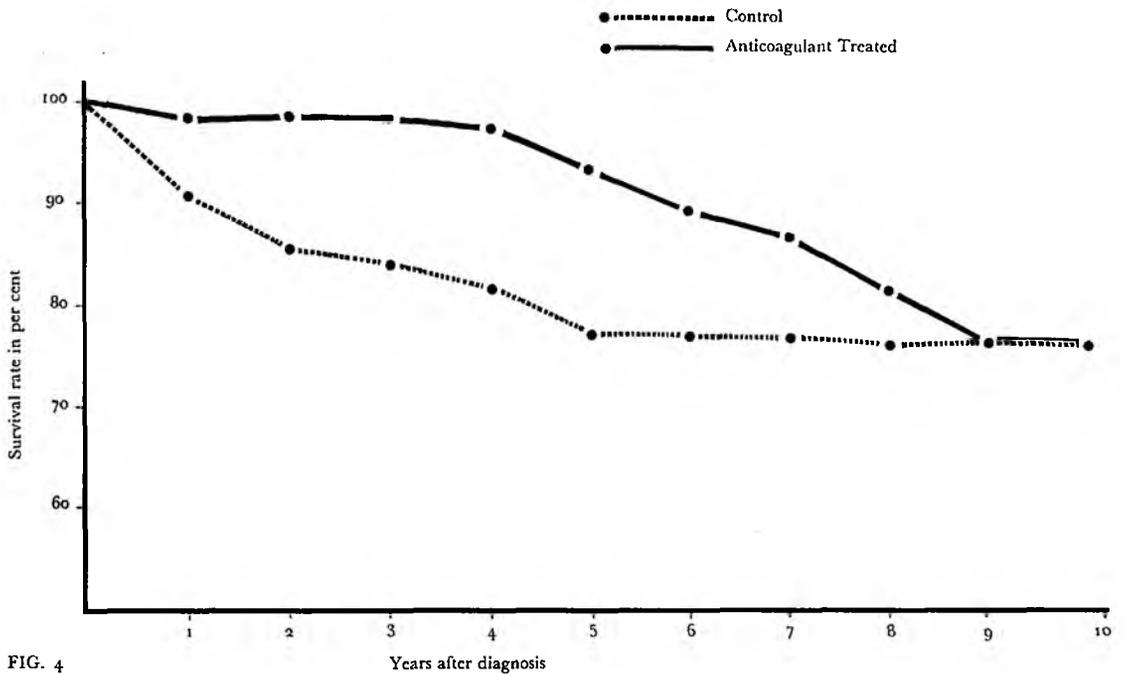
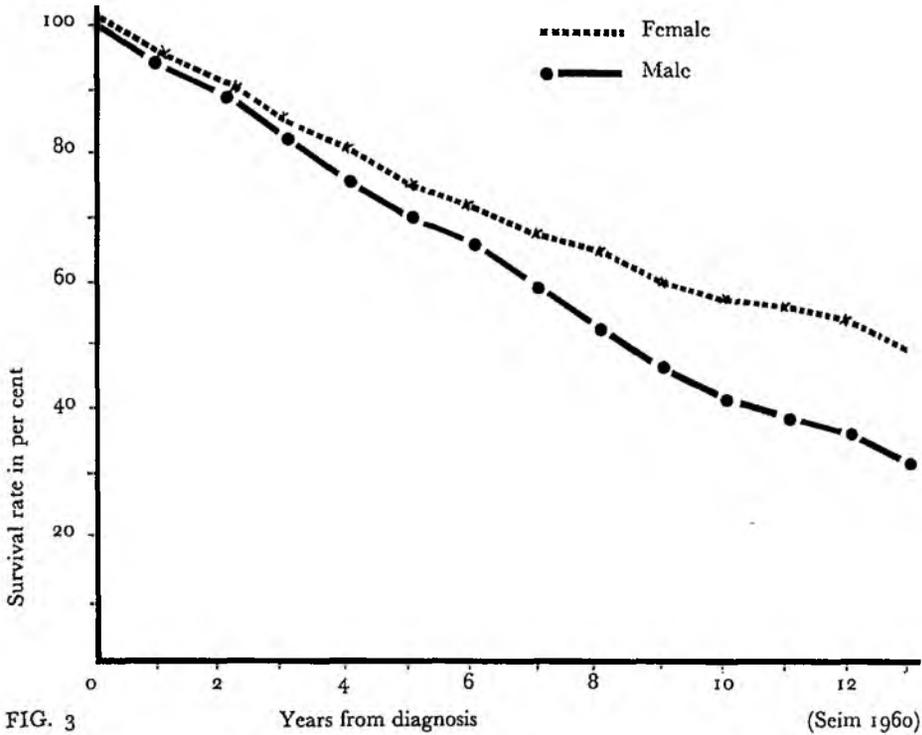


Table 5

Obs. Period	Number of Deaths Observed/Expected
<6 months	2.1
6-12 months	2.4
1-5 years	2.3
>years	1.8

Table 6

Age (Years)	No. of Deaths - Observed/Expected		
	Years after discharge from hospital		
	1	2-5	>5
30-49	10.6	7.2	4.5
50-64	6.0	3.4	2.8

## Patients with Myocardial Infarction

experienced infarction, and this fact may explain the high mortality in first year.

Table 7 shows that there was, perhaps surprisingly, no difference in prognosis between the patients with moderate or severe angina pectoris as White *et al.* have also pointed out.

By carefully reading the patients' history it turned out that the majority of the patients had angina on exertion while the minority did not, although they still got a diagnosis of angina pectoris.

Table 7

Angina	Number of Deaths Observed/Expected
Severe	2.2
Moderate	2.0

Table 8 shows that only angina on exertion is correlated with excess mortality while the patients with diagnosed angina pectoris without this symptom actually seemed to have a mortality lower than normal, indicating most likely that they did in fact not have coronary heart disease.

Table 8

Angina on Exertion	Number of Deaths Observed/Expected
Yes	2.6
No	0.5

The serum cholesterol level is a well known predictor of myocardial infarction in normal persons, and Table 9 shows that this holds true also for patients with angina pectoris.

Table 9

Cholesterol (MG%)	Incidence (3 years) of Myocardial Infarction	
	No Angina Pectoris	With Angina Pectoris
<249	0.8	4.9
250-299	1.9	8.1
>300	3.0	20.8

Westlund &amp; Nicolaysen 1966

May medical or surgical treatment influence the prognosis in patients with angina pectoris? As far as I know, there has been no dietary study on such patients. But recent experience in Norway where a strict cholesterol lowering diet reduced the rate of re-infarction in male survivors of acute infarction, makes it likely that such diet also would be of benefit to patients with angina pectoris.

Most of the drugs used in the treatment of angina pectoris are aimed at curing or preventing the anginal attack. Even if this goal is achieved we do not know whether these drugs actually prolong the life of the patients, as no large long-term study exists.

Several authors have reported on the long-term effect of surgical treatment. Hallen (1964) followed 90 patients employing the method of Beck, for 2½ years. The annual mortality was 7 per cent which does not permit any conclusion. Brofman (1960) observed 110 patients for 3-5 years, of whom 75 per cent survived 5 years. He compared his results with the study of Block *et al.* who found a 5 year survival rate of 58.4 per cent and concluded that his patients had benefited from the operation, a conclusion hard to accept because of lack of information on the similarity of the two groups.

It is difficult for me to discuss the prognosis of angina pectoris without mentioning the possible beneficial effect of long-term anticoagulant therapy. In 1957 we randomized patients with angina pectoris without infarction with normal blood pressure and heart size, into an anticoagulant group and a control group. After 18 months

one death has occurred in the treated group against 9 in the control group, a difference statistically significant at the 1 per cent level. I made a follow-up study last month and the Figure 4 shows the result. All patients are traced and followed for a minimum of  $7\frac{1}{2}$  years and a maximum of  $9\frac{1}{2}$  years or until death. 80 per cent of the survivors are still on anticoagulant therapy. The 5 year survival in the anticoagulant treated group was 93.2 per cent, which is definitely higher than in any report in the literature and statistically significantly higher than in the control group where the survival was 77 per cent. Beyond the first years the interpretation of the curves is difficult and comparison between them is of little meaning. Anticoagulant therapy was started in the control group  $1\frac{1}{2}$  to 2 years after the start of the study as we did not feel justified in withholding this therapy from the patients. The 10 year survival rate was the same in the two groups (75 per cent) but now we have no control group for comparison. I would guess that Mr. Chairman would disagree with me, but I still think that the most likely interpretation of these results is that anticoagulant therapy is of value in patients with angina pectoris when given within a year after the first symptoms.

#### *Conclusion*

How is one to conclude? The prognosis of angina pectoris is as unpredictable as life itself. Some patients die soon after their first attack, some go on living almost for ever. It is extremely difficult if not impossible to give an exact prognosis in the individual patient, but as a group it is probably fair to say that they have roughly a 50 per cent chance of surviving for 10 years. If they already have experienced a myocardial infarction, if they have hypertension, cardiac enlargement or abnormal ECG the prognosis is poorer. If they have no complication to their angina their chances of surviving for 10 years are probably about 75 per cent. The prognosis is independent of age, and severity and duration of the symptoms. It is better when the angina is combined with anaemia, obesitas or thyreotoxicosis, while it is worse when it is combined with valvular heart disease. On the whole the prognosis of angina pectoris is similar to the prognosis of survivors of myocardial infarction.

The majority of the patients have had angina pectoris for several years before the diagnosis was made. If we had been able to register the patients

from their first symptom this might have influenced the prognosis. It is, however, difficult to say in which way.

It is not impossible that cholesterol lowering diet and/or intensive anticoagulant therapy may improve the prognosis in patients with angina pectoris.

# PANEL DISCUSSION

**Saturday 22nd April**

Chairman – Dr. D. G. Julian.  
Panel – Richard Gorlin  
Ottar Muller  
G. C. Friesinger  
C. F. Borchgrevink  
Sir John McMichael, F.R.S.

## *The Management of the Patient with Angina Pectoris.*

*Chairman:* I thought that we might concentrate this discussion on the more controversial aspects of treating angina but I realise that almost the only uncontroversial aspect is the use of short term nitrites. It is a tribute to Lauder Brunton that this seems to be the only form of treatment on which we would probably all agree. Much more controversial is the use of long-action nitrites. Should one employ these clinically?

*Dr. Friesinger:* I myself prescribe a long-acting nitrite but I must be confident that the angina is at a stable phase. My usual practice is to have the patient keep a log; he is asked to describe the effects he is experiencing with the drug. He is told to take the drug for three weeks and then discontinue it for three weeks, continuing in this fashion for some length of time. I see him every few months, review the log and decide whether it is worth the expense. I believe that the adequacy of the dose is an extremely important point and in my opinion some manufacturers of long acting nitrites recommend the wrong dose; it is too small. As I review the log I look for the side effects resulting from the pharmacological action, such as headache and postural hypertension to establish the adequacy of the dose.

*Dr. Fulton:* It is my impression that most clinicians utilise short-term nitrites and apparently with good effect. They are difficult to evaluate because of the placebo effect of treatment and the varying degree in which a patient experiences

angina over the sort of period that one may conduct a trial; published work confirms this. As far as long-term nitrites are concerned, I have not found that they have more to offer than the repeated use of short-term nitrites.

*Question:* Has anyone used aerosol inhalers for a more accurate delivery of dose and if so, with what sort of results?

*Dr. Muller:* I have tried one type of aerosol inhaler containing nitroglycerine in a few patients and found very similar effects to those achieved with amyl nitrite.

*Dr. Oliver:* In relation to sustained release of nitroglycerine as distinct from other long-term nitrites could the panel tell me whether they are convinced that any nitrites do not cause peripheral vasodilation?

*Dr. Friesinger:* I must see peripheral vasodilation before I am satisfied, but what form the drug takes seems unimportant to me. One must titrate the dose to the patient to the point where peripheral vasodilation is occurring, and I think that in the prophylaxis of attacks this is a necessary guide line.

*Question:* Has nicotinic acid or nicotinamide been tried?

*Sir John McMichael:* Nicotinic acid treatment has been extensively tried and is said to lower blood cholesterol but I do not think the results have been dramatic in angina.

*Chairman:* Propranolol has created the most interest recently and I would like to ask if anyone has found this to be effective in the treatment of angina?

*Dr. Fulton:* The published reports by others would suggest that it is. A proportion of my patients have benefited from treatment with the drug and so have others in whom angina has been associated with tachycardia. In some instances some individuals are more satisfactorily treated with propranolol than with nitrites

although of course there is no objection to using both concurrently. Those who do use both have found that they have been able to reduce the nitrite requirements.

*Chairman:* Do you think there are any dangers in giving propranolol?

*Dr. Fulton:* I have not noted many problems and would have thought the dangers are quite small if the dosage is gradually built up for the individual patient who was not in some unusual state, who simply had angina pain without severe cardiac failure. There has been very little evidence that anyone has run into much trouble this way. The curious thing is that the dosage which has surely been used for the relief of angina has been far in excess of the dose which is accepted as being sufficient to produce full beta-adrenergic blockade.

*Dr. Friesinger:* It is a useful drug but I do not think that one can generalise. It seems to me that in patients in whom the tachycardiac response or the elevation of blood pressure seems undue for the amount of effort that they are performing, this drug should be very useful.

*Dr. Muller:* I have only had experience with propranolol with regard to its possible ability to precipitate left ventricular failure. I tried propranolol on sub-normals and on exercise found increased left heart diastolic pressures. In patients with coronary heart disease there was no increase in these pressures, so I gather that there must have been a balance between the positive and the negative effects of these patients; they did not seem to go more into left heart failure without it.

*Sir John McMichael:* I understand that the drug was something we had in reserve for use when anginal pain appears to be quite uncontrollable by ordinary means.

*Dr. Lassers:* Yesterday Drs. Gorlin, Friesinger and Muller talked about the elevation of left ventricle end-diastolic pressure and wedge pressures on exercise in patients with angina. There is at least some evidence that the apex cardiogram correlates with these parameters. Has Dr. Friesinger had any experience with apex cardiography and how it correlates with other parameters in the diagnosis of ischaemic heart disease, and secondly, I should like to ask the panel what work has been done with the apex cardiography and the effects both of propranolol and nitrites?

*Dr. Friesinger:* You are of course quite right in saying that the apex cardiogram, that is the amplitude of the (a) wave can be a reasonable guide to the elevation or the degree of elevation of left ventricular end-diastolic pressure. In a number of patients in whom we have carried out these exercise tests we have obtained apex cardiograms before and after exercise and in a number of them at a time when they were undergoing catheterisation with a catheter in the left ventricle. We obtain an apex cardiogram and correlate directly the reading that we get from the ventricle with the apex cardiographic signal obtained simultaneously from the chest. In this way, one can get a linear correlation between the left ventricular end-diastolic pressure and the signal from the apex cardiogram, provided that the elevation of the left ventricular end-diastolic pressure(?) is mainly due to an (a) wave kick. If all the parameters of the left ventricular end-diastolic pressure are elevated – the early as well as late – and there is not a large atrial component contributing to the final diastolic volume – hence the left ventricular end-diastolic pressure, then the correlation tends to be not so good. It is indeed a useful sort of thing to look at when the correlation is good and the patient has a normal apex cardiogram on exercise; if it becomes abnormal you obviously have good evidence to indicate that he has gone into a kind of ventricular failure.

*Chairman:* Would there be a good case for digitalising our angina patients?

*Dr. Muller:* I have no experience whatsoever of the digitalisation of patients with angina. Some have reported good effects and others to the contrary. In a recent study of the effects of intensive digitalisation of patients with coronary heart disease, the author found he could produce an exercise test which precipitated anginal pain and on repeating this test 50 per cent of his patients did not complain of pain, and this seemed to be correlated to improved left ventricular function as was seen by cardiac catheterisation.

*Chairman:* Can we now deal with anticoagulants? Perhaps Dr. Borchgrevink would tell us whether his controlled group were in fact receiving small doses of anticoagulants.

*Dr. Borchgrevink:* I would first like to make one general comment and it is that anticoagulants therapy is prophylactic when given to survivors after myocardial infarction to prevent further infarctions and it seems odd to me that 90 per cent

of the publications dealing with anticoagulant therapy are primarily concerned with preventing second and third infarctions when the first infarction is fatal in about forty per cent of cases. If people use long-term anticoagulants after myocardial infarction it seems illogical not to use it prophylactically in patients with angina whom they know are more prone to develop myocardial infarction. In our study we gave intensive treatment to half the patients and the remainder what we thought to be moderate in terms of P & P test used at that time. The first group were treated at fifty per cent to sixty per cent intensity and the second at twenty per cent intensity, the former being more successful of the two. I drew the conclusion that if we are going to use anticoagulant therapy our treatment should be intensive.

*Dr. Fulton:* I have already put forward the suggestion that in the majority of instances clinical coronary heart disease is due to thrombosis, although the evidence is very hard to come by; one does not know just what is the position at the onset of clinical illness which then goes on for quite a long time before there is any pathological examination. The clinical evidence of sudden onset of anginal symptoms, (by sudden, I mean that one day the patient has no angina and the following day he could recall an experience of angina) which has apparently entered his life. In the course of time this often passes as having been gradual in onset because it was not very severe, but I think that very often this was thrombosis right at the onset of the symptoms. Accordingly, one would feel that if anticoagulant therapy is going to benefit this situation the earlier it is used the better, and of course, prophylactically.

*Sir John McMichael:* I have examined the published papers on the use of anticoagulants and noted flaws in some of the trials which were carried out. There were faults in the selection of patients and often it was seen that control cases were found to be much worse than expected. It was said that patients bled from overdosage of anticoagulants whilst at the same time they produced new thromboses. After trying this form of treatment and having looked at all the depressing evidence we decided to give it up.

*Dr. Borchgrevink:* I think this complex of bleeding with thromboses occurring at the same time is not as confusing as it seems. Thrombosis as you know, consists of two parts: the white head consisting of platelets and the red tail which is more or less

clotted blood. The anticoagulant therapy we use, and that includes heparin, does not influence the formation of the white head; it can only delay or inhibit the formation of the red tail. That means that even with ideal anticoagulant therapy making the blood unclottable a white head may still form and occlude the lumen.

*Chairman:* May we now discuss surgery? Do the participants believe that internal mammary implantation in the myocardium is an effective way of supplying blood to the myocardium?

*Dr. Fulton:* I have not seen the original angiocardiographs of these studies, but the published statements in some studies would suggest that forward flow through the internal mammary has been achieved into areas distal to coronary occlusion. The unfortunate thing about some of the earlier cases has been that in the course of time the artery which was grafted has again become occluded. From the pathological point of view it would seem to me that there must be opportunity for introducing new blood supply into the coronary circulation in the presence of coronary artery disease. The coronary arteries of man and of mammals have been designed to supply the heart muscles from without, inwards. In the presence of disease the deep vessels may be greatly dilated and intercommunicating to the point at which entry of blood into any one part of that system could in fact be distributed to all parts of the left ventricular wall, and this occurs in man. At the moment it would seem that the difficulties of supplying new blood to the system are technical rather than absolute. In principle I can see that there should be a good future for such procedure.

*Dr. Friesinger:* We have carried out very few surgical procedures in the Sir Johns Hopkins Hospital; about twenty five patients have been operated on for ischaemic heart disease in the last five years. We consider that this is an investigative surgical procedure whose worth is not known, but on reviewing the data up to the present time it would seem that surgical morbidity and mortality are low; the theory on which surgery is based seems relatively sound. A small group of patients who are incapacitated because of angina of long duration and which can be demonstrated on a severe anatomic basis can be subjected to these procedures, but one must follow up results over a number of years before one can give a true opinion as to its value.

*Chairman:* Would Dr. Rees give his opinion on

the effectiveness of surgery in terms of providing a new blood supply?

*Dr. Rees:* The main problem is which patients should we select to undergo surgery and what would be the effect on the prognosis if to some extent we improve the collateral flow in the area of the myocardium. I believe, without question, that it is possible to improve the blood flow to an area of ischaemic myocardium by implanting a systemic blood vessel into that area but whether or not one then improves prognosis by doing so is still not proven. If an improved prognosis can be obtained by subjecting the patient to surgery then perhaps we could extend the procedure to those patients who have not suffered a first infarction and hopefully prevent infarction occurring. This would mean those patients who have severe disease which has been demonstrated by arteriography and whose myocardium has not yet become necrosed or scarred.

*Chairman:* Would you say something about the mortality risk and technical difficulties?

*Dr. Rees:* There are two things involved, the first is the type of patient you are dealing with and the other concerns technical aspects of surgery. Firstly, the mortality is going to be directly proportional to the care with which you select your patients. If you limit surgery to those patients who have angina decubitus, that are in degrees of heart failure, and who have previous infarctions, then your operative mortality may be as high as two or three per cent, as suggested in the Bigelow and Effler reports. Secondly, technical aspects of bringing one vessel from one place and from another; the only thing that has been proven statistically is that you can implant the internal mammary artery into the anterior wall of the left ventricle with a patency of eighty per cent. Whether or not bringing a graft from the posterior aorta or bringing up a splenic artery or implanting both internal mammary arteries is useful remains to be proven. They may be useful anatomically but there are other ways in which one can pick up an artery from the chest wall, such as by using both internal mammary arteries, bringing one up through the diaphragm or posteriorly using the intercostals.

*Chairman:* Do you regard a previous infarction as a contraindication to surgery?

*Dr. Rees:* No. In approximately one hundred patients on whom surgery had been carried out, Vineberg reported 60-65 per cent had had prev-

ious infarctions so that the patient who has ischaemic muscle and is suffering pain, not necessarily from scar tissue, would still be a candidate even though he had had a previous infarction.

# SUMMING UP

**Sir John McMichael, F.R.S.**

*Director, British Postgraduate Medical Federation, London*

This symposium has indeed been full of interest. All the speakers have given us a great deal to think about, increased depth of understanding has emerged from the transatlantic communications of Drs. Gorlin and Friesinger. They have shown where our clinical assessment, even with electrocardiographic help, can fall short of full comprehension. Until we can sharpen up our precision in assessment of these patients, a great deal of what we have been doing up to now has contained a fraction of guesswork.

Professor Morris gave an excellent paper on the epidemiological side – the extraneous environmental factors which may be influencing the situation, and Dr. Oliver approaches the problem by study of the “milieu interieur” – the recognisable biochemical factors which may contribute to the development of this disorder. The therapeutic point of view and the mode of action of drugs by Dr. Rees added knowledge gained at Westminster. We also heard the excellent report of the studies by the Oslo group who have tried very creditably and very hard to see whether or not one can really prevent thrombosis. We go away sadder, and wiser men, realising how much there remains to be found out. I would not like to close without mentioning the excellent historical introduction so ably given by Mr. Hunter, and by Miss Leach who set us a background of knowledge about the time of Lauder Brunton whom we commemorate. We still think that the nitrites are the sheet anchor in the treatment of Angina Pectoris, so that our commemorative occasion has indeed been very appropriate. Quite apart from the scientific programme I think you will all admit that those of us who are senior graduates of this great school can feel justifiable pride in the performance of the present generation of students running this distinguished medical society. I would like particularly to mention Dr. Roger Smith who has been the organising secretary of the occa-

sion and who has indeed put in an enormous amount of work in arranging this programme and its quite spectacular success. Mr. Hunter, Mr. Irving and Miss Reid have also played a full part in the organisation. If this Royal Medical Society has contained many of the great men of the past, it contains great men and women of the future as well. We thank them all for what they have done to make it such a splendid occasion and I have been privileged indeed to play a little part in it.





A Complete and Integrated Medical Course

## A companion to medical studies

Editors-in-chief: R. PASSMORE & J. S. ROBSON

**Volume 1. Anatomy, Biochemistry, Physiology and Related Subjects.** 1968 (Reprinted 1969). 1142 pages, 1075 illustrations. Cloth £6 6s, limp 95s.

'The contributors, the editorial board and the editors-in-chief are to be congratulated on their foresight and abilities in providing so successfully a single textbook capable of educating and stimulating the medical student and a book which is forward-looking enough to help equip him for life and practice in the 20th or 21st centuries.' *British Medical Journal*.

**Volume 2. Pharmacology, Microbiology, General Pathology and Related Subjects.** 1970 (Reprinted 1970). 836 pages, 420 illustrations, 30 plates (14 colour). Cloth £6, limp 90s.

'This book maintains the very high standard set by the first volume . . . There is a freshness of approach in this book which makes it highly attractive, and medical students today are fortunate to have it. It is also a very good buy.' *The Lancet*.

**Volume 3. Medicine, Surgery, Obstetrics, Therapeutics and Social Medicine.** Autumn 1971. 1500 pages, fully illustrated. Cloth about £8, limp about £5 10s.

Other books for students

<b>Lecture Notes on Haematology</b>	
Hughes-Jones	30s
<b>Lecture Notes on the Infectious Diseases</b>	
Warin & Ironside	25s
<b>Lecture Notes on General Surgery</b>	
(3rd edn.)	
Ellis & Calne	45s
<b>Immunology for Students of Medicine</b>	
(3rd edn.)	
Humphrey & White	60s
<b>Histology (6th edn.)</b>	
Ham	£7 10s
<b>Introduction to the Anatomy and Physiology of the Nervous System</b>	
(2nd edn.)	
Bowsher	20s
<b>Fluid Therapy (2nd edn.)</b>	
Taylor	30s
<b>Practical Neurology (2nd edn.)</b>	
Matthews	50s
<b>Handbook of Medical Treatment</b>	
(12th edn.)	
Chatton	63s

BLACKWELL SCIENTIFIC PUBLICATIONS

OXFORD AND EDINBURGH

MEMBERSHIP  
MEANS



Founded 1902

To GRADUATES of SCOTTISH MEDICAL & DENTAL SCHOOLS

- SECURITY & UNLIMITED INDEMNITY AGAINST DAMAGES & LEGAL COSTS THROUGHOUT UNITED KINGDOM AND OVERSEAS
- ADVICE ON ALL PROFESSIONAL AND ETHICAL PROBLEMS

THE  
MEDICAL & DENTAL DEFENCE UNION

Joint Secy. (Medical)  
JAMES PATTERSON  
M.C., B.A., M.B., Ch.B.

OF  
SCOTLAND

Joint Secy. & Treasurer  
C. C. MILLAR  
T.D., C.A.

105 ST. VINCENT ST., GLASGOW

041-221 8381