THE AETIOLOGY OF CORONARY THROMBOSIS.

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BY

ARTHUR WHITLEY BRANWOOD,

M.B., M.R.C.P.Ed.

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THE AETIOLOGY OF CORONARY THROMBOSIS.

Herrick is credited with having first drawn attention to coronary thrombosis as a condition which does not necessarily cause death. This was in 1912, yet the majority of the medical profession paid little attention to his observations until well after his second publication in 1919. It was not until 1930 that a reorganisation of the classification of heart disease, to include coronary thrombosis, occurred in the "International list of causes of death." Prior to 1930 there was no separate classification of diseases of the coronary arteries, though earlier literature contained many references to coronary vessel disease in relation both to angina pectoris and to cases of sudden death.

The history of the recognition of the disorder known as angina pectoris is connected with the names of three celebrated men:- Heberden, Jenner and Hunter.

On July 21st 1768 at the Royal College of Physicians, Heberden read a paper entitled "Some Account of a Disorder of the Breast." The name "angina" /

"angina" which he adopted cannot be regarded as altogether satisfactory since it was already in use to designate some affections of the throat with which the word's literal meaning - "a strangling" - is much more descriptive. In one sense, however, the term is fairly appropriate, since, as noted by Gairdner (1876), the words anxiety and anguish, expressive of two of the most prominent features of the disease, derive from the same Greek word as angina.

In 1773 John Hunter had his first attack of angina which was graphically described by his nephew, Everard Home. In 1776 he had a second attack and when convalescent he visited Bath. Here he was seen by his friend and pupil, Edward Jenner, who wrote to Heberden, giving his diagnosis of John Hunter's case and suggesting, for the first time, the probable association of disease of the coronary arteries with angina pectoris. In 1793 a post-mortem examination of John Hunter revealed the coronary arteries to be converted into "open bony tubes." This decided advance in the pathology of angina pectoris was communicated by Jenner to Parry who brought Jenner's views before the medical profession. These observers showed that angina pectoris was associated in most cases with an ossification, or some other form of obstruction /

obstruction by disease, of the coronary arteries of the heart. This was in 1799, yet William Stokes in 1854, discussing angina pectoris and sudden death, states that - "We may conclude that in the special group of symptoms described by Heberden and Parry, obstruction of the coronary arteries may or may not be present and as a cause of angina its action is remote and its existence unnecessary."

Jenner's communication to Heberden and Parry's publication of Jenner's work appears to have been over--looked by the majority of the physicians of the nineteenth century. Cases of sudden death following severe anginal pain, revealing at autopsy gross disease of the coronary vessels undoubtedly due to coronary occlusion, were attributed either to fatty degeneration of the heart, acute myocarditis, rupture of the heart, or to aneurysm of the heart, while angina pectoris, although the coronary arteries showed frank evidence of disease, was described as "neuralgia of the heart."

Hope, in 1831, discusses sudden death in cases of "softening of the heart" and states that there are two varieties of softening: "(1) Softening with increased intensity of redness - namely claret or violet /

violet coloured, denoting an excess of blood in the muscular substance and (2) softening with diminution of redness, namely faint yellow or fawn coloured and bespeaking a deficiency of blood." Laennec supposes softening of the heart to be "an affection sui generis, resulting from a derangement of nutrition", while Bouillaud contends that softening, in all its varieties of colour, is a result of inflammation. No mention is made of the coronary vessels by these two writers in their papers. Hope states that neuralgia of the heart or angina pectoris may originate from any cause, whether organic or functional, capable of irritating the heart or of rendering it morbidly susceptible to irritation; "and as structural disease of the organ has this effect more than any other cause, it is that on which the malady is most frequently dependent." The most violent cases of angina seen by Hope "have been connected with osseous, cartilagenous, steatomatous or other degeneration of the heart or great vessels and especially of the coronary arteries."

Stokes (1854) states of fatty degeneration of the heart causing sudden death that obstruction of the coronary arteries is often seen in this disease and that in certain cases it may assist in the production /

production of the fatty state of the heart - "but that we may often look on this condition as one of the adjuncts rather than the primary cause of the disease." In the chapter on angina pectoris he says that what--ever may be the immediate cause of the pain and sensation of approaching death, these are often en--countered in connection with some form of organic disease of the heart, namely:-

(1) Weakness and attentuation.

(2) Weakness with fatty degeneration.

(3) Some form of valvular disease, generally affecting the left side.

(4) Disease of the aorta, with or without obstruction of the coronary arteries.

Stokes enumerates the following conditions as causes of sudden death and predisposing to rupture of the heart:-

(1) Abscess in the wall of the heart.

(2) Apoplectic effusions into the substance of the heart, as described by Cruveilhier in his "Anatomie pathologique du corps humain."

(3) Muscular aneurysm.

(4) Fatty degeneration.

Of these he states that the last condition is the most frequent cause. Softening, fatty degeneration and /

and rupture of the heart must refer to myocardial infarction, a result of coronary vessel disease, yet Hope and Stokes mention the coronary arteries as secondary factors in these conditions, although disease of the coronaries had been mentioned as one of the causes of angina pectoris by both authors.

A vivid description of what almost certainly was a case of coronary thrombosis is Latham's account in 1876 of the death in 1842 of the celebrated Dr. Arnold of Rugby, at the age of 47 years. Latham referred to the case as one of spasm of the heart, and mentions environmental factors and heredity as playing a part in the aetiology of the condition. The following is an abstract of Latham's account:- "On my entering Dr. Arnold's room he said that he was sorry to disturb me so soon; and that he had not sent for me before, thinking that it would go off. He added 'I have had very severe pain since five o'clock, at intervals, and it gets worse I think'. The pain was seated at the upper part of the chest towards the left side, and extended down the left arm. He had been rather sick. His pulse I could scarcely feel. The tongue was clean. There was cold perspiration over his face. He then asked me what the pain was. I told him I believed it to be spasm of the heart. I asked /

asked him whether he had ever fainted in his life. 'No, never'. If he had at any time difficulty of breathing. 'No, never'. I then asked him if any of his family had ever had any disease of the chest. 'Yes, my father had; he died of it'. He enquired if disease of the heart was suddenly fatal. I answered that it was. 'Was it a common disease?' I said not very common. 'Where do you find it most?' 'In large towns I think'. 'Why?' 'Perhaps from anxiety and eager competition among the higher, and intemperance among the lower, classes.' Dr. Arnold died a little more than half an hour after I first saw him. The post-mortem examination showed a soft, flaccid heart muscle. There was but one coronary artery and that, considering the size of the heart, of small dimensions. It presented also a slight atheromatous deposit an inch from its orifice."

The association of coronary vessel disease and anginal pain, as shown so well by Latham, was again overlooked by other investigators, although such aetiological factors as heredity and higher grades of society were recognised as playing a definite part in cases of sudden death.

Thus Gairdner, in 1877, speaking of angina pectoris /

pectoris and sudden death, says "the condition of the nervous system and especially of the brain and spinal cord in angina pectoris opens up many very difficult and at present even insoluble problems connected with its ultimate pathology." On the other hand he says that it would seem premature to infer with Trousseau the existence of any distinct relation between epilepsy as a predisposing cause and angina pectoris. He does, however, quote the findings of Sir John Forbes who showed that in sixteen out of forty-five cases of sudden death characterised by angina pectoris, there were found disease and degeneration of the coronary arteries. Gairdner further states that among constitutional states gout is unquestionably the one which is most frequently related to angina pectoris; "indeed it would scarcely be too much to say that a large proportion of the suddenly fatal endings of gout in its irregular and atonic forms,more especially in the forms popularly termed gout in the stomach or gout in the heart, are of this character." He thinks that the pathology of these states is uncertain but enough remains after deduction to show:-

(1) That gouty persons and especially those who have had regular gout, degenerating after repeated attacks /

attacks with the irregular and atonic forms, are subject in an unusual degree to the causes of sudden death.

(2) That not only is death in such persons apt to be extremely sudden, but further, the course of the disease is liable to be disturbed by violent paroxysms of internal pain.

(3) That in certain cases the pain has distinctly the character of angina, while in other cases it seems to be associated with dyspeptic suffering and with disorders of the liver and kidneys.

(4) That in gouty subjects the heart and arteries are very prone to become disorganised and that the disorganisation is especially apt to assume the form which other observations show to give a predisposition to angina:- viz. calarious degeneration of the aorta and of the coronary arteries.

These cases of sudden death in sufferers from gout and attacks of so-called gout of the heart would seem to have been due to coronary occlusion.

In discussing the aetiology of angina pectoris and sudden death, Gairdner again quotes Sir John Forbes who found that only one-seventh of the cases recorded were below the fiftieth year of age and in respect of sex only one-eleventh were in women. It is possible, however, /

however, that his findings may have been greatly influenced by the mode of collection of the cases. The more severe cases would naturally attract more attention, especially if they were terminated by sudden death. Gairdner continues, that in a disease of this type, the symptoms of which are so purely subjective, the deaths of men of eminence, or men of a certain force and decision of character, would markedly impress physicians and would be recorded prominently, whereas other deaths would pass unobserv--ed or at least unrecorded. Another fact of importance in the aetiology is to be found in the Tables by Sir Gilbert Blane showing the rarity of angina pectoris in hospital practice. Gairdner states that in the higher ranks of society cases of extremely sudden death associated with symptoms as described by Heberden, and not of aneurysmal origin or connected with valvular disease of the heart, bear numerically a higher proportion to the whole field of disease than to the classes usually treated in hospital. Gairdner further states that there is a very general impression among physicians that sudden death from heart disease is frequently hereditary or at least is found /

found to cling as a tolerably well-marked characteristic in certain families, sometimes for generations.

Eulenburg, a year later in 1878, discusses angina pectoris as a disease of the nervous system and states that we do not here, or subsequently, include those cases due to circumstances hardly possible to recognise during life of ossification of the coronary arteries. He thus shows a slight recognition of the association of coronary vessel disease with anginal pain.

In the same year (1878) Schroetter described spontaneous rupture of the heart and acute myocarditis. His descriptions could only refer to myocardial infarction, a result of coronary artery occlusion. Of spontaneous rupture of the heart Schroetter quotes Morgagni who wrote at length concerning it and expressed the opinion that it could only occur where the muscle tissue was diseased. Schroetter states that disease of the coronary arteries is not in--frequently a cause of rupture and that it is very much commoner among men than among women. Discussing the symptoms he states that the patient may live for some days and the symptoms may begin with pain or a feeling of oppression in the chest, causing great anxiety, /

anxiety, the pain extending across the breast and down the left arm. Such attacks as these may be repeated until finally in one of them the patient suddenly dies. Schroetter also showed that the first evidence of acute myocarditis may be a rupture of the heart, or that a man, previously in good health, may begin to complain of pain in the region of the heart or of a feeling of oppression which may suddenly increase to the greatest agony. From Schroetter's histological descriptions of these lesions there can be little doubt that these correspond to infarction of the myocardium, yet no mention was made in his discussion of the coronary arteries.

Sir William Osler in his "Lectures on Angina Pectoris and Allied States" in 1897 mentioned many interesting points in the aetiology of angina pectoris, though many of his cases termed angina pectoris would now be called coronary thrombosis. He recognised the definite relationship between sudden death and disease of the coronary vessels and angina pectoris; and of the predisposing factors he says that men of muscular, even athletic, build who have been devotees of Bacchus and Venus form the largest contingent, while more wise men than fools are the victims /

victims of this disease. He emphasises the part heredity plays and states that true angina pectoris is an arterial incident and, since members of certain families show a special tendency to arterial degeneration, it is not surprising to find cases in father and son, or in brothers or even in representations of three generations. A very good example is the Arnold family. William Arnold died suddenly of spasm of the heart in 1801, his son, the celebrated Thomas Arnold, died in his first attack in 1842 aged 47. Matthew Arnold, the latter's distinguished son, was also a victim and died suddenly in 1888 aged 66 years.

Osler recognised four groups in his series of cases;-

(1) Sudden death without other manifestations of angina pectoris. Much more true of this type of "angina pectoris" (presumably coronary occlusion) is what Andral said of the fulmimant form of cholera - "it begins where other diseases end - in death." No inconsiderable proportion of sudden deaths in men of middle age and robust habits result from coronary artery disease and anatomically Osler showed that lesions of the coronary arteries are almost universally present: extensive arteriosclerosis, embolism, thrombosis /

thrombosis or, in some instances, the bursting of a small atheromatous "abscess" in one vessel.

(2) Death following the first well marked paroxysm - a man in full health, in the prime of life, may be seized with a paroxysm of angina and die within a few hours. This type, too, would seem to refer to coronary occlusion.

(3) Recurring attacks extending over a period of months or years. This group would be recognised as angina pectoris today. Osler states that the great majority of all cases of angina pectoris fall into this group.

(4) Rapidly repeated attacks over a period of days with the development of a state of cardiac asystole. This latter group, also, would be diagnosed today as coronary occlusion.

Sir William Osler recognised the disease to be due to lesions of the coronary arteries and, of his four types of angina pectoris, three were without doubt coronary thrombosis. Yet, in spite of Osler's masterly description of angina pectoris, his division of the disease into groups and the constant presence of coronary vessel disease, R. Douglas Powell, in Allbut and Rolleston's "System of Medicine" in 1910, discusses angina pectoris in three forms:-

(1) /

(1) In the first group are to be found cases in which the disease is a pure neurosis of the cardio--vascular system.

(2) Another class of case is associated with a diseased heart, either texturally damaged heart muscle or a valvular defect.

(3) A third group of cases contains well defined forms of disease in which the heart itself is the primary seat of the painful and often fatal symptoms. It includes certain cases of obstructive cardiac disease, especially cases of aortic or mitral narrowing, cases of textural degeneration and ischaemia of the heart, generally dependent on coronary narrowing.

These three forms of angina pectoris are somewhat vague and indefinite. Group 3 would appear to be the most serious and to correspond to coronary occlusion and angina pectoris as recognised today. Powell describes atheroma of the coronary arteries as causing the most important lesions of the cardiac muscle, viz. fatty degeneration, fibroid infiltration and aneurysm of the heart. He dismisses coronary thrombosis in a few words - "Thrombosis, embolism and aneurysm of the coronary arteries require but brief notice", and states that the symptoms of sudden occlusion of a branch of the coronary artery begin with /

with an anginal paroxysm which may be fatal at once, and that these acute phenomena almost invariably supervene upon chronic heart disorders already ascribed to degenerative changes.

A hundred and forty-two years had elapsed since Heberden's paper on angina pectoris and throughout that period the cause of sudden death associated with angina pectoris was the subject of much discussion and many divergent opinions. To summarize, Jenner in 1776 had suggested the association of disease of the coronary arteries with angina pectoris. His views were ardently supported by Parry in 1799. Hope in 1831 attributed sudden death to softening of the heart but stated that angina in its severest form was usually associated with degeneration of the coronary arteries. Stokes in 1854 mentioned fatty degenerat--ion of the heart as the most important cause of sudden death and that any changes in the coronary arteries were but secondary factors. Latham in 1876 recognised "spasm of the heart" as a cause of sudden death and associated the condition with disease of the coronary arteries. Gairdner in 1877 discussed angina pectoris in relation to the nervous system and mentioned the degenerative changes seen in the coronary /

coronary arteries associated with angina pain often seen in sufferers from gout. He stressed the part played by heredity both in angina pectoris and in cases of sudden death. Eulenburg in 1878 supported Gairdner's view that angina pectoris was a disease of the nervous system. Schroetter in the same year, described spontaneous rupture of the heart and acute myocarditis as causes of sudden death and mentioned disease of the coronary arteries as being very frequently the cause of the rupture. Osler in 1897 recognised the definite relationship between coronary artery disease and angina pectoris and sudden death. Powell in 1910,although stating that sudden occlusion of a coronary artery was characterised by anginal pain, dismissed the condition very briefly.

From 1910 until the inclusion of coronary thrombosis in the "International list of causes of death" in 1930 much work was done and many observat--ions were published on the clinical features of this disease. The first important and satisfactory account of the clinical features attending attacks of coronary thrombosis was published in 1910 by Obratzow and Straschesto. These Russian authors gave a true diagnosis in two of three cases they published. /

published. They emphasised a triad of symptoms - severe, lasting retrosternal pain; dyspnoea and orthopnoea; and,finally, gastralgia. All three of their cases had precedent angina pectoris. Obratzow and Straschesto called attention to the many features that are now recognised as important findings in coronary thrombosis, e.g. gallop rhythm, Cheyne-Stokes breathing, pericardial friction and distant heart sounds. They also noted the different clinical and pathological events that might result depending upon the size of the coronary artery involved. They indicated that softening and rupture of the infarcted area might result with haemopericardium. They ascribed the fever that was present in their second case to pericarditis and pleurisy. It is surprising that after such a comprehensive publication appearing in the German literature the condition was not more quickly appreciated on the Continent, although, in the following year, 1911, a similar report of four cases, of which two were diagnosed ante-mortem,were published by Hochhaus.

In 1912, Herrick's careful observations and persistent efforts drew attention to the facts that coronary thrombosis was a clinical entity, could be recognised during life, and need not end fatally. Curiously /

Curiously enough, this publication did not produce the expected result, for it aroused no interest. After a lapse of five to six years further papers appeared by Herrick and his associates in which the matter was taken up again. In fact that same year (1918) Levine and Tranter published a report of two cases of coronary thrombosis, one of which was diagnosed during life, although at that time Levine and Tranter were unaware of Herrick's previous work. During this time it was quite clear that Libman also had been familiar with coronary thrombosis as a condition differing from ordinary attacks of angina pectoris. In 1916, while discussing the various types of chest pain, Libman mentioned in passing that the diagnosis of a recent thrombosis could often be facilitated by the development of a slight temperature, moderate leucocytosis, and evidence of a patch of pericarditis, all coming on within a couple of days after the attack of severe pain.

Shortly after these publications an extensive literature appeared emphasising many of the same points that had previously been noted. Amongst the more important articles of a clinical nature were those by Gorham, Paullin, Levine, Longcope, Thayer, Wearn, /

Wearn, Gordinier, Hamman, Benson, and Wolff and White. These various publications brought the clinical features that are now considered to be diagnostic of coronary thrombosis before the medical public in America, so much so that in 1925 Christian stated that "coronary thrombosis is an easily diagnosable disease." Some of the above authors emphasised particular points that lead the way for a clearer understanding of the entire subject. Gorham pointed out the diagnostic importance and frequency of a pericardial friction rub, while Wearn, besides giving a very clear description of the symptoms and signs of the disease, called attention to a marked diminution in the height of the waves of the electro--cardiograph in his cases. Levine, in 1925, brought out the interesting observation that those patients who had hypertension and angina pectoris before the attack of coronary thrombosis might become free from anginal attacks if recovery was attended by a permanent and distinct lowering of the blood pressure.

While this extensive literature was appearing in America it is surprising that it was not until 1925 that this subject of coronary thrombosis, as a specific /

specific problem, began to be even considered in Great Britain. Mackenzie, in 1923, never made a clinical distinction between angina pectoris and coronary thrombosis.

In 1925, McNee described three cases of coronary thrombosis and stated that in sudden thrombosis of large branches of the coronary arteries there may occur, in patients who survive the immediate shock, a very remarkable clinical syndrome which deserves attention. This syndrome has the following features:-

(1) An agonising pain of varying distribution which lasts much longer than the usual attack of angina pectoris.

(2) Dyspnoea which may be extreme.

(3) A peculiar colour and appearance of the face.

(4) Immediate signs of acute cardiac failure.

(5) One sign which is inconstant but almost pathognamonic in association with a suggestive history or group of symptoms, i.e. a localised pericardial friction rub.

(6) Fever and a polymorph leucocytosis.

(7) Various abnormalities in the electrocardio--graph.

He stated further that the recognition of this clinical syndrome should be fairly easy in patients who have previously /

previously suffered from cardiac complaints such as angina pectoris. The real difficulties in diagnosis arise when coronary occlusion is the first evidence of cardiac disease in a previously healthy patient.

Gibson, in 1935, and Parkinson and Bedford in 1928, showed by their publications that they too had become aware of the problem of this disease. Campbell in 1929 emphasised the great frequency of coronary vessel disease in the population. The majority of his autopsy cases, many of them following surgical operations for widely different diseases, revealed a greater or lesser degree of coronary vessel disease.

In 1930 Carey Coombs compared the aetiology of angina pectoris and coronary thrombosis. He found that the age and sex incidence of the two groups corresponded closely with one another, and while angina of effort occurred principally in association with cardiovascular syphilis, high arterial tension, and senile degeneration of the heart, coronary thrombosis occurred in the second and third of these aetiological groups but rarely in the first.

It is therefore not surprising that prior to 1930 there was no separate classification of diseases of the coronary arteries and that cases of sudden /

sudden death due to coronary occlusion were termed "acute myocarditis", "fatty heart", "spontaneous rupture of the heart" or else the all-embracing term "angina pectoris". Coronary disease thus shows what appears to be a marked increase. Even this rather formidable array of deaths represents an under-statement rather than an over-statement of the actual picture, for it is common knowledge among clinicians that many cases of coronary disease are still un--diagnosed and are confused with disease of the stomach or gall-bladder. Denney believes that there has been unquestionably an increase in deaths from coronary disease while White finds the increase in coronary disease "appalling" and believes the most effective measure for prevention is "to call a halt on the world's mad rush of today." Cassidy, in a recent Harveian oration, stated that he had been impressed by the increasing prevalence of coronary disease especially in the last twenty years.

It would appear that for several years the incidence of coronary vessel disease has in reality been increasing and that it is now also occurring in younger /

YEAR.	MALE		FEMALE.		SYMPTOMS.		ELECTROCARDIOGRAM.				FAMILY HISTORY.											ON ADMISSION:		WEIGHT.	RESULT.		TOTAL CASES.
	-50 YRS.	51- YRS.	-50 YRS.	51- YRS.	PREVIOUS ANGINA.	SUDDEN "CORONARY THROMBOSIS."	ANTERIOR INFARCTION	POSTERIOR INFARCTION.	CORONARY VESSEL DISEASE.	NORMAL OR NO EVIDENCE.	NONE GIVEN.	NOT RELEVANT.	FATHER			MOTHER			OTHERS.			HIGH	LOW		RECOVERED	DIED.	
													CORONARY THROMBOSIS	CEREBRAL HAEMORRHAGE	UREAEMIA	CORONARY THROMBOSIS	CEREBRAL HAEMORRHAGE.	UREAEMIA	CORONARY THROMBOSIS	CEREBRAL HAEMORRHAGE	UREAEMIA						
1945	4	3	2	2	1	10	5	4	1	1	2	4	2	1		2			1			3	8	3	8	3	11
1944	2	8		2	3	9	5	4		3	5	4	1			1			1			5	7	1	9	3	12.
1943	3	8		3	4	10	4	2	4	2	3	4	1			1	2		3	3	1	7	7	2	5	9	14
1942	4	7	1	3	5	10	6	6	1		7	6	2			1	1					5	10	1	6	9	15
1941		4		2	1	5	1	1	1		5	1										3	3	1	1	5	6
1940	1	4		2	2	5	2	2		1	3	3						1	1			3	4	4	5	2	7.
1939	2	5		8	4	11	6	2	5	2	11	2	1				1					5	10	2	9	6	15
1938	1	2			2	1	2		1		1	2										1	2	1	2	1	3
1937		4		1	2	3	3	1	1		2	1	1						1			2	3	4	2	3	5
1936		1		1	1	1	2				1	1										1	1	1	2		2
1935		2				2	2					2										1	1			2	2
1934		2		1	1	2	2	1					1			1			1			1	2	1	2	1	3
1933		1		1	1	1						1		1								1	1		1	1	2
1932		3			2	1	3					3										2	1	1	1	2	3
1931																											
1930		1				1	1						1			1							1	1	1		1
1929																											
1928		1			1		1				1												1		1		1

TABLE I

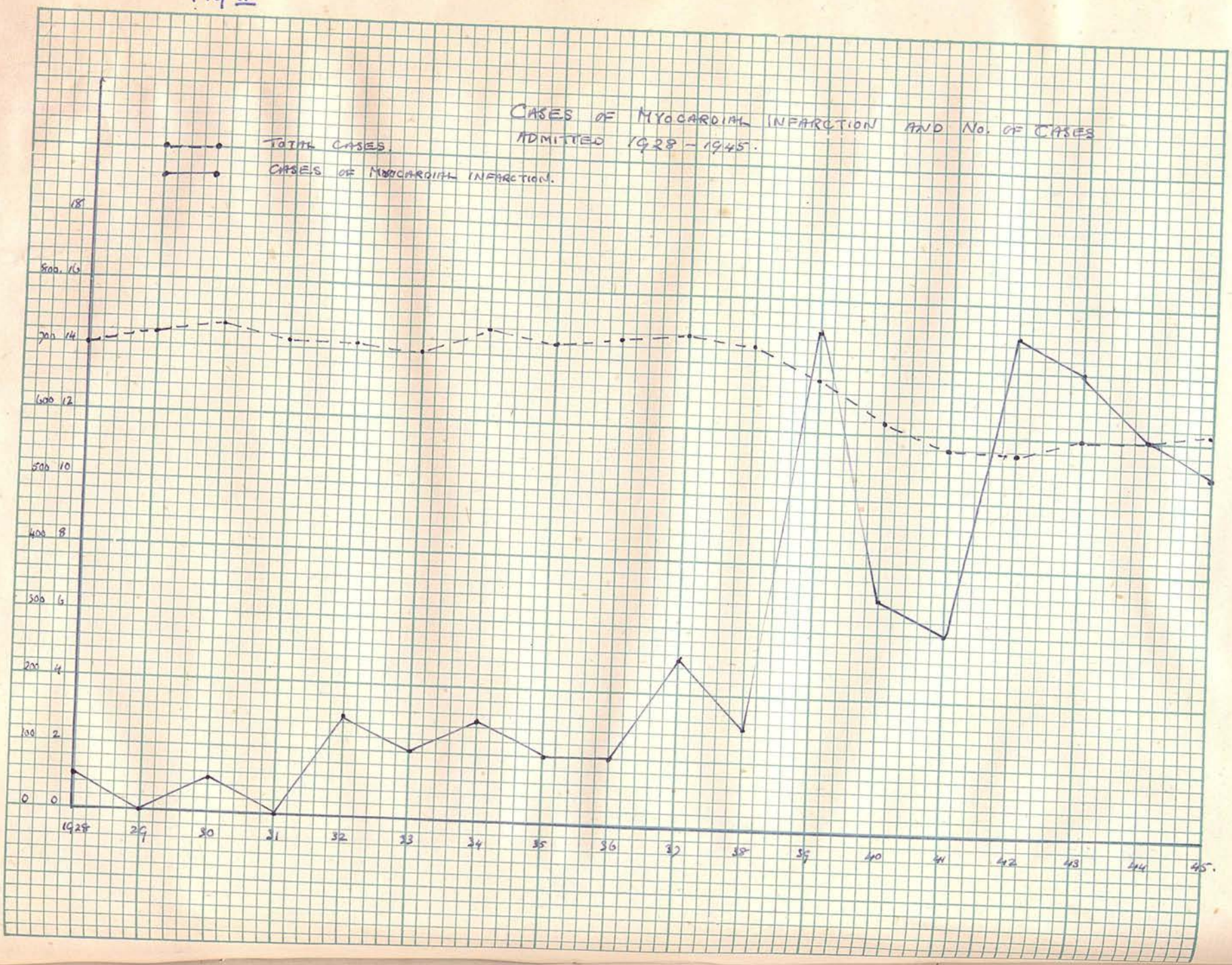
ANALYSIS OF CASES OF MYOCARDIAL INFARCTION

1928 — 1945.

FIG I


CASES OF CARDIAC INFARCTION. 1928 – 1945.
18
16
14
12
10
8
6
4
2
0
No. OF CASES.
1928
'29
30
31
32
33
34
35
36
37
38
39.
40
41
42
43
44.
45.
YEAR.

Fig II


CASES OF MYOCARDIAL INFARCTION AND NO. OF CASES ADMITTED 1928 - 1945.
TOTAL CASES.
CASES OF MYOCARDIAL INFARCTION.
18
16
14
12
10
8
6
4
2
0
700
600
500
400
300
200
100
0
1928
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45.

YEAR.	MYOCARDIAL INFARCTION.			TOTAL CASES ADMITTED.		
	MALE.	FEMALE.	TOTAL.	MALE.	FEMALE.	TOTAL.
1928	1	0	1	449	251	700
1929	0	0	0	465	251	716
1930	1	0	1	472	260	732
1931	0	0	0	464	246	710
1932	3	0	3	461	252	713
1933	1	1	2	456	248	704
1934	2	1	3	480	265	745
1935	2	0	2	462	264	726
1936	1	1	2	460	270	730
1937	4	1	5	463	260	723
1938	3	0	3	457	269	726
1939	7	8	15	411	284	695
1940	5	2	7	381	240	621
1941	4	2	6	329	264	593
1942	11	4	15	323	262	585
1943	11	3	14	336	265	601
1944	10	2	12	340	261	601
1945	7	4	11	342	263	605

TABLE II.

CASES OF MYOCARDIAL INFARCTION ADMITTED TO A GENERAL MEDICAL WARD (1928-1945) COMPARED WITH THE TOTAL CASES ADMITTED.

younger individuals. The cases of coronary occlusion, admitted to a general medical ward over a period of years, have been studied by the writer to determine:-

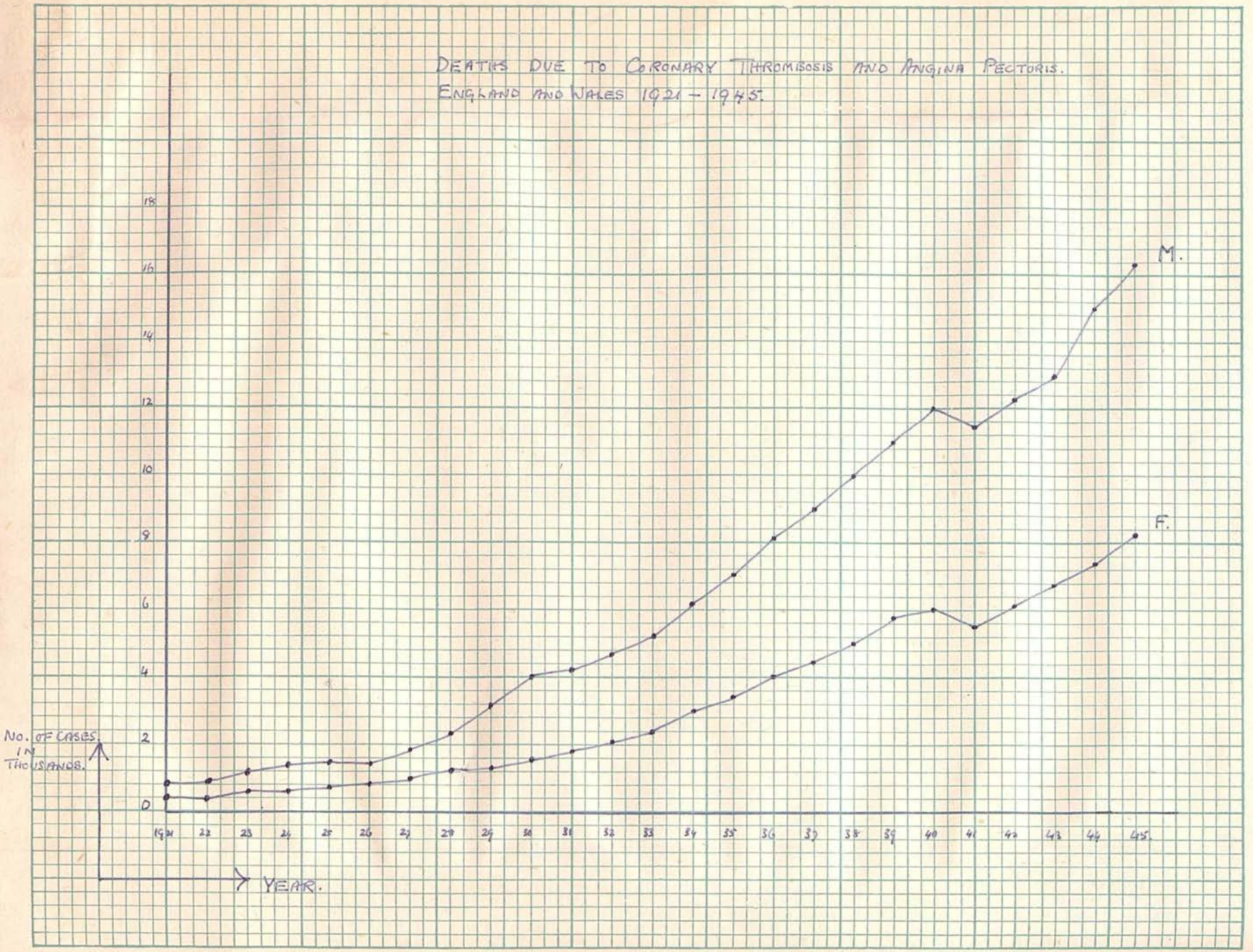
(1) Whether there has indeed been (a) an absolute increase in the number of cases and (b) an increased incidence of coronary thrombosis in younger people.

(2) Some explanation for this increase, if it occurred.

CASE MATERIAL.

Cases of coronary thrombosis which were admitted to a general medical ward during the period from 1928 to 1945 were studied. In all, a total of 102 cases diagnosed as coronary thrombosis were admitted. The main clinical features of these cases are shown in Table I. The diagnosis in the majority of the cases was confirmed by electrocardiogram or at post-mortem. It can be seen from Fig. I that there has been an increase in the cases of coronary thrombosis during the period 1928 - 1945 - from one case in 1928 to eleven and twelve cases in 1944 and 1945. Fig. II and Table II show the number of cases of coronary thrombosis compared with the total number of cases admitted over this period. It is interesting to compare /

FIG III


DEATHS DUE TO CORONARY THROMBOSIS AND ANGINA PECTORIS.
ENGLAND AND WALES 1921 – 1945.
18
16
14
12
10
8
6
4
2
0
M.
F.
No. OF CASES IN THOUSANDS.
1921 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45.
YEAR.

YEAR.	HEART DISEASE.		DISEASES OF THE CORONARY ARTERIES AND ANGINA PECTORIS.	
	MALE	FEMALE.	MALE.	FEMALE.
1921	24956	28754	743	343
1922	27565	32272	986	460
1923	26223	30663	1058	505
1924	28009	32641	1236	537
1925	29691	34368	1285	551
1926	30023	34442	1280	600
1927	33365	38744	1982	820
1928	35777	41251	2586	1108
1929	45018	51449	3376	1431
1930	42961	47142	4118	1766
1931	42670	49210	4145	1820
1932	43697	49418	4759	2145
1933	45662	52151	5743	2562
1934	46808	51706	6513	3079
1935	59277	54336	7475	3603
1936	53912	58493	8446	4026
1937	55429	59650	9350	4472
1938	56530	59904	10246	5163
1939	61208	64686	11919	5925
1940	65872	70388	12319	6311
1941	59811	62031	11706	5940
1942	57745	59191	12365	6356
1943	59180	61657	13679	6978
1944	61804	62339	15284	7531
1945	63047	65276	16728	8499

TABLE III.

DEATHS FROM ALL TYPES OF HEART DISEASE AND DEATHS FROM DISEASE OF THE CORONARY ARTERIES AND ANGINA PECTORIS.

compare these figures with those of the Registrar-General (Fig. III) - from under 1000 cases in 1921 in both men and women there were over 16,000 cases in 1945 in men and over 8000 cases in women. As the majority of deaths due to coronary vessel disease were, prior to 1930, classified as due to angina pectoris (for coronary thrombosis was not included in the "International List of causes of death" until 1930) the figures shown in Fig. III include both angina pectoris and coronary thrombosis. These figures of deaths due to coronary vessel disease show an absolute increase. The incidence of deaths from heart disease in general has also increased as can be seen in Table III. It is therefore justifiable to state that there has been an absolute increase in the incidence of coronary vessel disease during recent years, more than could be explained by the increase in population.

AETIOLOGY AND PREDISPOSING FACTORS.

Every disease has both exciting and predisposing factors in its causation. The exciting factors in the aetiology of myocardial infarction are of course well-known. They are:-

(A) /

(A) Involvement of the mouths of the coronary arteries by:-

(i) Syphilitic aortitis,

(ii) atheroma of the aorta,

(iii) the vegetations of subacute and acute bacterial endocarditis involving the aortic valve cusps.

(B) Plugging of the coronary artery by an embolus.

(C) Narrowing of the lumen of the coronary artery with subsequent thrombosis due to:-

(i) Atherosclerosis,

(ii) thrombo-angitis obliterans,

(iii) polyarthritis nodosa.

The commonest cause of myocardial infarction is the narrowing of the coronary artery due to athero--sclerosis with a superadded thrombosis. It is the aetiology of this condition that is under consideration. The predisposing factors in the aetiology of this disease are many and varied, yet it is only by a study of these that the explanation for the increase in incidence of "coronary thrombosis" will be found.

1. AGE INCIDENCE.

In this series the average age of all cases was 53.7 years, the average age for men being 53 years and for /

FIG IV.

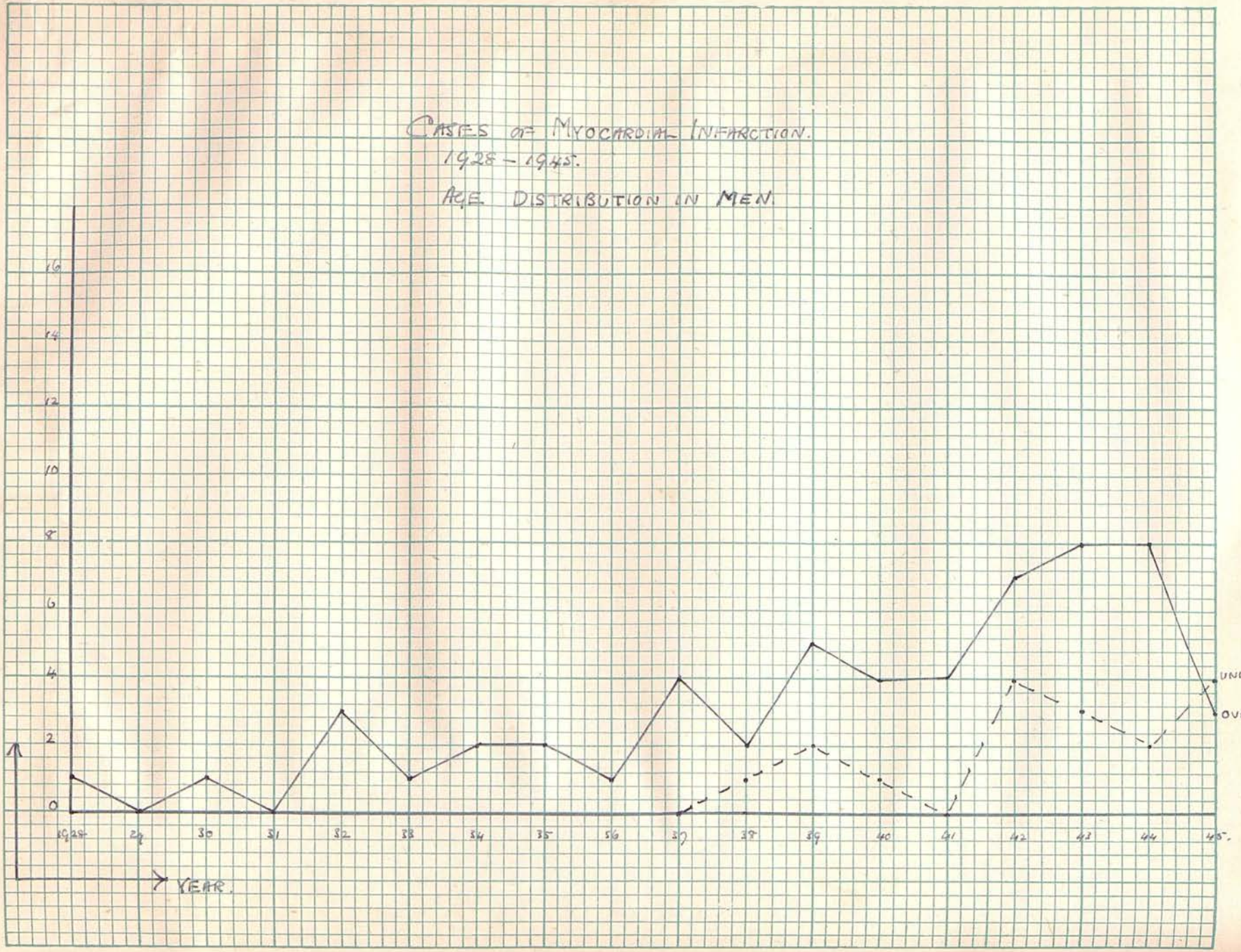
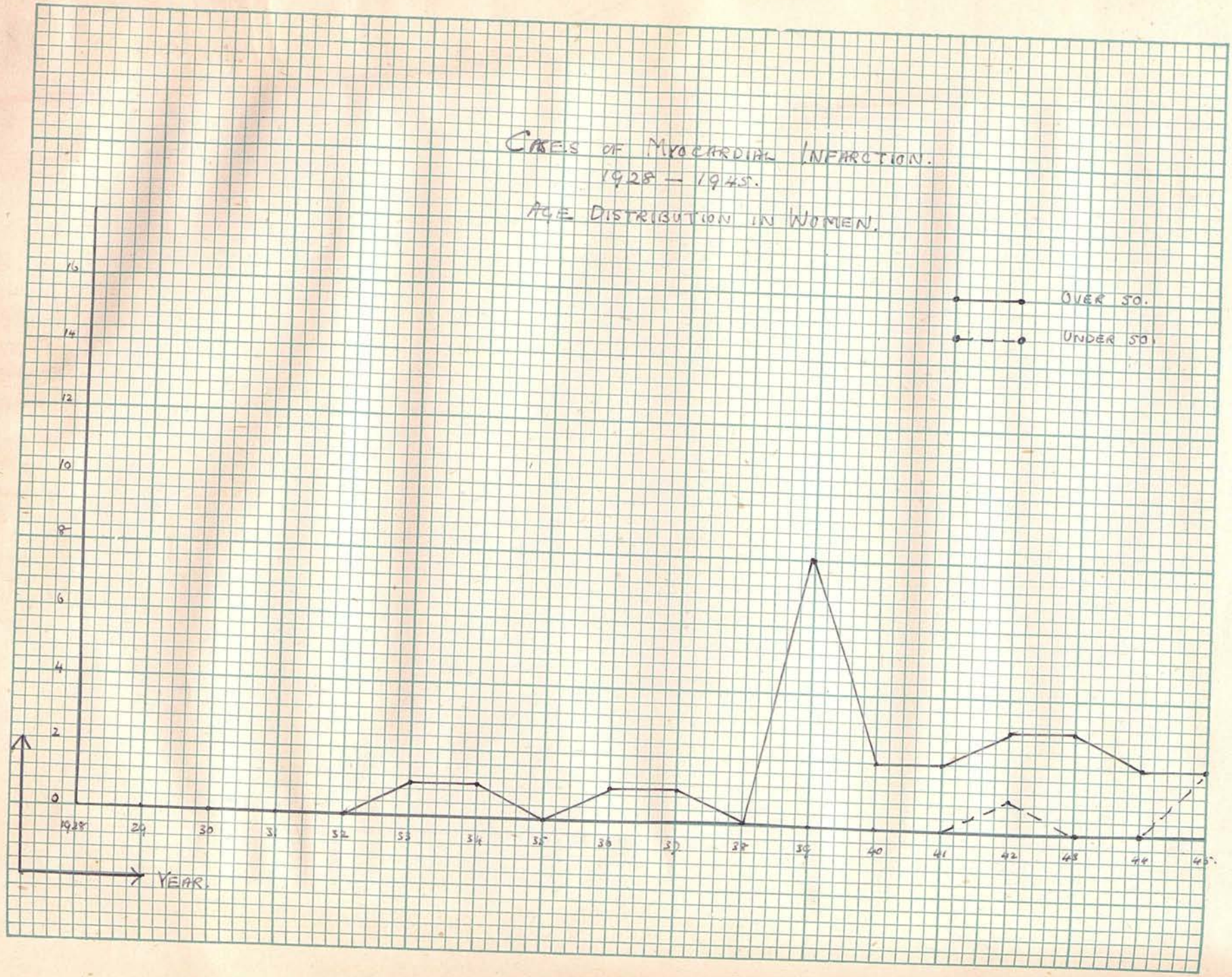

CASES OF MYOCARDIAL INFARCTION.
1928 – 1945.
AGE DISTRIBUTION IN MEN.
16
14
12
10
8
6
4
2
0
No. OF CASES.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45.
YEAR.
UNDER 50.
OVER 50.

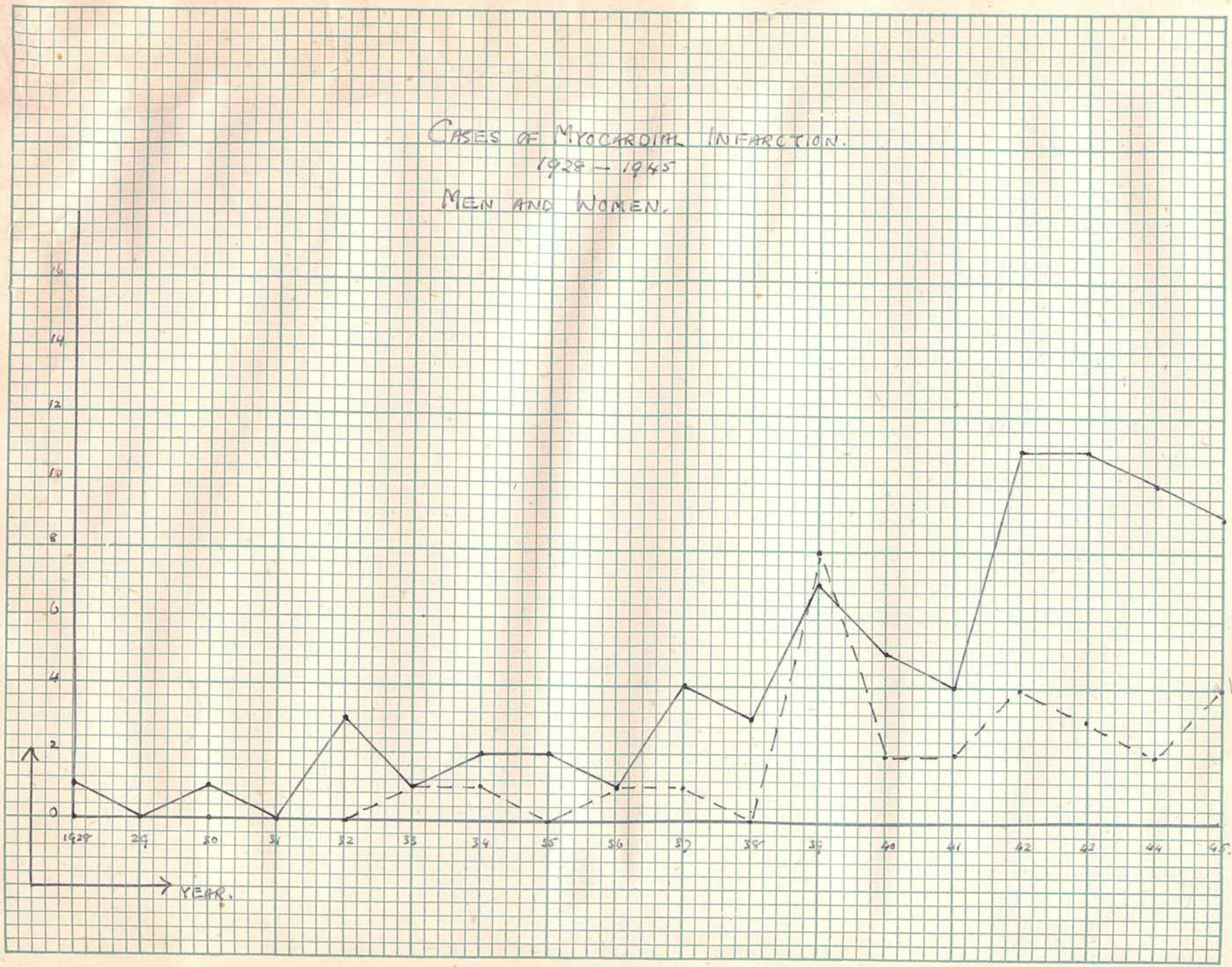
FIG V


CASES OF MYOCARDIAL INFARCTION.
1928 – 1945.
AGE DISTRIBUTION IN WOMEN.
OVER 50.
UNDER 50.
No. OF CASES.
0
2
4
6
8
10
12
14
16
1928
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
YEAR.

for females 62 years. The youngest male affected was 27 years and the oldest 80 years. The youngest female with coronary thrombosis was 47 years and the oldest 78 years. Fisher and Zukerman, in a review of 108 cases, found the average age to be 57.6 years, the youngest being 37 years and the oldest 84 years. Figs. IV and V show the age incidence of both sexes in the series under review. The cases of myocardial infarction are divided into (a) cases under 50 years and (b) cases over 50 years. It can clearly be seen that myocardial infarction, occurring in individuals under the age of 50 years, has been increasing during the past few years. No case under the age of 50 years was present in this series prior to 1936.

Lesser attributes myocardial infarction to a diminution in size and in number of the coronary arteries. He states that this is caused by a fall in the level of testo-sterone in the blood which occurs at the male climateric. On the basis of this theory he has treated cases of angina pectoris with testo-sterone and reported improvement in the symptoms of some of the cases with a change in the electro--cardiogram back to normal. His theory is open to two criticisms. Atherosclerosis occurs most commonly in /

FIG VI


CASES OF MYOCARDIAL INFARCTION.
1928 – 1945
MEN AND WOMEN.
16
14
12
10
8
6
4
2
0
NO. OF CASES.
1928
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
YEAR.
MEN.
WOMEN.

in older people, hence the development of coronary vessel disease and myocardial infarction, a result of atherosclerosis, is more likely to occur after the male climateric than before it. Secondly, some of the young men in this series under review who have recovered from an attack of "coronary thrombosis" have become the fathers of large families.

2. SEX INCIDENCE.

There were 73 males and 29 females in this series of 102 cases, thus giving a ratio of 2.5 males : 1 female. Fisher and Zukerman found a ratio of 2.7 males : 1 female, while Smith, Sauls and Ballew, in a study of 100 cases, found a ratio of 6.6 males : 1 female. The ratio given in the literature is usually about 3 men to 1 woman, although Falk declared that coronary disease was 4-6 times as common in men as in women. Fig. VI shows graphically the distribution of the sex incidence in the series under discussion.

No explanation has been given for this increased incidence of coronary thrombosis in males although hypertension, occupation and smoking may be possible factors, and will be discussed later. It has been suggested as a hypothesis, however, that as a result of /

of woman's child-bearing function, Nature has given her a cholerteral cleaning mechanism which may be an important factor against the development of coronary disease. Fellner, reporting his findings in autopsies on atherosclerotic subjects observed that, as a rule, women developed arteriosclerosis later in life than men, and that they also suffered a milder form of the disease.

The increased sex incidence of coronary thrombosis in men is due to other, or a combination of other, predisposing factors.

3. RACE.

All the cases in this series were Caucasian. Roberts has shown statistically that both angina pectoris and coronary thrombosis seem to affect the coloured races less frequently than the white. This fact is of interest, for hypertension is much commoner in negroes than in the white race, yet the incidence of coronary vessel disease has been shown to be less in coloured races.

4. WEIGHT OF THE PATIENTS. /

4. WEIGHT OF THE PATIENTS.

It is a usual belief that the heavy-set, over--weight, frequently athletic person is more susceptible to this disease than is the normal or underweight individual. In this series 23% were overweight. This figure refers to all the patients in the series. If this result is taken in respect of the patients who survived, then 33% were overweight. The height and age of the individual were used to determine the normal weight, and ± 20% has allowed for normal variation. Any patient who was more than 20% the normal weight was classified as overweight. The percentage of over--weight patients was determined in 102 consecutive cases, excluding " coronary thrombosis", and it was found that 20% of these individuals were overweight. The figure of 23% for overweight patients with myocardial infarction is therefore not statistically significant. Other workers, however, claim that obesity is a factor in coronary thrombosis. Reisman and Harris state that the patient's body build is an aetiological factor in coronary occlusion. Levine feels that those people who are underweight and in good health at the age of 40 years have a better expectancy of life than the average correct-weight person. Smith, Sauls and Ballew found 35% of

patients /

patients in their series of 100 cases to be obese.

Coronary thrombosis having been established, however, obesity may diminish the chances of recovery, because of:-

(i) fatty infiltration of the myocardium with resultant weakening of the heart and decrease in its reserve power, thus increasing the risk of cardiac failure;

(ii) the development of hypostatic pneumonia, a condition to which obese patients, when bed-ridden, are very prone.

There is no evidence, however, in this series that obesity plays any part in the aetiology of the disease.

5. TOBACCO AND ALCOHOL.

In this series 20% of the patients could be classified as heavy smokers, 30% did not smoke at all and the remaining 50% smoked in moderation only. It is interesting to compare these figures with those obtained from a similar number of cases of peptic ulcer, and with an equal number of cases excluding peptic ulcer patients and those suffering from coronary vessel disease. In the peptic ulcer group, 42% /

	SMOKERS.			NON-SMOKERS.
	HEAVY	MODERATE	TOTAL	
Control series	14%	42%	56%	44%
Peptic ulcer series	42%	42%	84%	16%
Coronary thrombosis series	20%	50%	70%	30%

TABLE IV.

PERCENTAGE OF SMOKERS AND NON-SMOKERS IN THE CONTROL, PEPTIC ULCER AND CORONARY THROMBOSIS SERIES.

42% of the patients were heavy smokers, while only 16% did not smoke at all and the remaining 42% smoked in moderation.

In the control group, 14% were heavy smokers, 44% did not smoke and 42% smoked in moderation. These figures are seen more clearly in Table IV.

If the figures in the coronary thrombosis series are compared with the control series,then 70% of the patients with coronary thrombosis smoked (20% of them heavily),while 56% of the control series smoked (14% of them heavily). These figures are statistically significant.

Alcohol would seem to play no part in the causation of coronary occlusion. 12% were heavy drinkers and 16% confessed to being not teetotal but only drinking in moderation. Smith, Sauls and Ballew noted that smoking played an inconclusive part in coronary occlusion. In their series 17% smoked excessively and 12% did not smoke at all. Alcohol was found to play little if any part in causing coronary occlusion.

The finding that smoking, in this series, is significant compared with a control series is support--ed by the results of other workers. Observations made /

made among workers in the tobacco industry, as well as among habitual smokers, suggest that an excessive occupational contact with tobacco, or nicotine in the form of dust or spray, or an environmental exposure to these agents in the form of smoke, may be aetiologic--ally related to the development of thrombo-angitis obliterans, as well as to hypertension and arterio--sclerotic changes, especially of the coronary arteries. (Aschoff; Hilpert; Strauss; Anitschkow; Koelsch; English, Willius and Berkson; Wright and Moffat; Moyer and Maddock; and Weicker). While the clinical and statistical findings of the above workers (such as occurrence of angina pectoris, tachycardia and coronary sclerosis) are not entirely conclusive, it may be mentioned that Adler and Hensel by the administration of nicotine to rabbits, produced arteriosclerotic lesions. Raab proposed that nicotine exerts such an effect by mobilising adrenalin, thereby making adrenalin the directly active agent. This suggestion is supported by the observations made by Staemmler in rats subjected to chronic nicotine poisoning. Both workers assume that nicotine is the harmful agent in smoking. Staemmler found, in an appreciable proportion of rats thus treated, medullary adenomatous hyperplasia of the suprarenal, in addition to a sclerosis of various organic arteries resembling that /

that seen in chronic adrenalin poisoning as described by Schmiedl.

Smoking, on the other hand, may play no direct part in the aetiology of coronary thrombosis. Smoking, and especially excessive smoking, may be a manifestation of nervousness. It may indicate that the patient is of a "highly strung", nervous, emotional temperament, and this factor may play a part in the causation of coronary thrombosis.

6. OCCUPATION.

The medical wards from which these cases were collected formed part of a hospital draining a large mining and agricultural community. In this series of cases it was found that:-

34.5% were miners,
27.5% industrial workers,
20% clerks and officials,
10.4% retired,
7.6% engineers,

while of the total admissions to the hospital in one year:-

24.4% were miners,
27.1% were industrial workers,
26.0% were clerks and officials,
8.5% were retired,
14.0% were engineers.

These /

These figures, however, do not give an accurate picture of the incidence of coronary thrombosis in the community for:-

(1) they refer only to the cases in this series - i.e. the "hospital class" of patient;

(2) no account is taken of any change in employ--ment, and the previous work may have had a bearing on the disease.

It is interesting to compare these figures with those of other workers. Hedley analysed 5,116 deaths due to coronary occlusion on the basis of the patient's occupation, and he found the occupational mortality per 100,000 to be:-

154 for professional men,

144 for proprietors, managers and officials,

128 for clerks and salesmen,

107 for manual workers.

Smith, Sauls and Ballew, reviewing 100 cases of coronary thrombosis noted that 67% were business-men of executive type or those engaged in small businesses which demanded excessive individual effort. The frequent occurrence among commercial travellers was also noted. They suggested that those who work hard and have irregular living habits are more vulnerable to this disease; 10% of their cases were physicians.

Masters /

Masters, Dack and Jaffre produced figures which are at variance with the above. In their series:-

35.5% were manual workers,
19.5% were housewives,
11% were businessmen,
10% were retired,
9% were professional men,
9.5% were clerks,
5.5% were stone workers.

The explanation of their figures may again depend on the locality of the hospital and the class of patient admitted.

Finally, the Registrar General's figures of death rates from coronary disease by age and social conditions in England and Wales 1930-1932 were:-

Class	I	100%
	II	64.2%
	III	38.2%
	IV	28.5%
	V	26.2%

The Registrar General sums up the position by stating that the figures seem to show that general cardio--vascular failure is more likely to occur without anginal symptoms amongst those engaged in manual occupations; /

occupations; but whether this is due to the coronary arteries being maintained in a more healthy condition, or to the greater demands made on the heart by physical exertion, or to nervous, dietary, or other peculiarities associated with professional or sedentary occupations, is a matter for surmise.

Denny suggests that the early appearance of sclerosis of the coronary arteries in certain individuals is most commonly attributed to nervous and emotional strain. Little attention has been paid to the fact that the disease is rare in men in occupations requiring daily physical effort, and most frequent in those with sedentary occupations. This suggests that physical inactivity predisposes to coronary disease. The opinions of two other workers are of interest in this respect. Rathe found that people living in rural areas were affected as often as those in urban areas, while Paul White says of angina pectoris - "it is encountered more in communities where the strain of life is great and a hurried existence a habit." Finally, Sir William Osler says of angina pectoris - "It is not a disease of the working classes. The life of stress and strain, particularly worry, seems to predispose to it and this is perhaps why it is so common in our profession."

It /

FIG VII

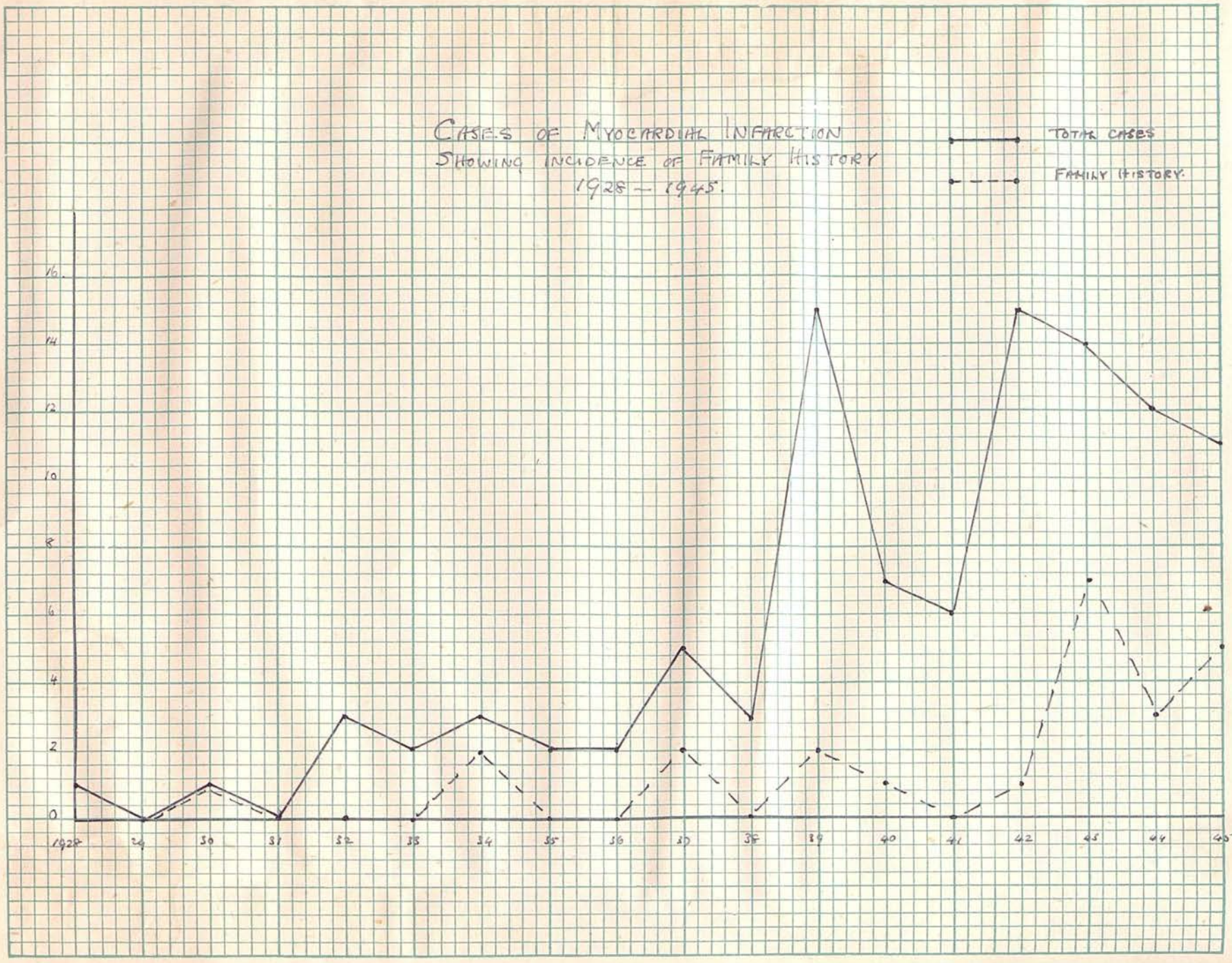
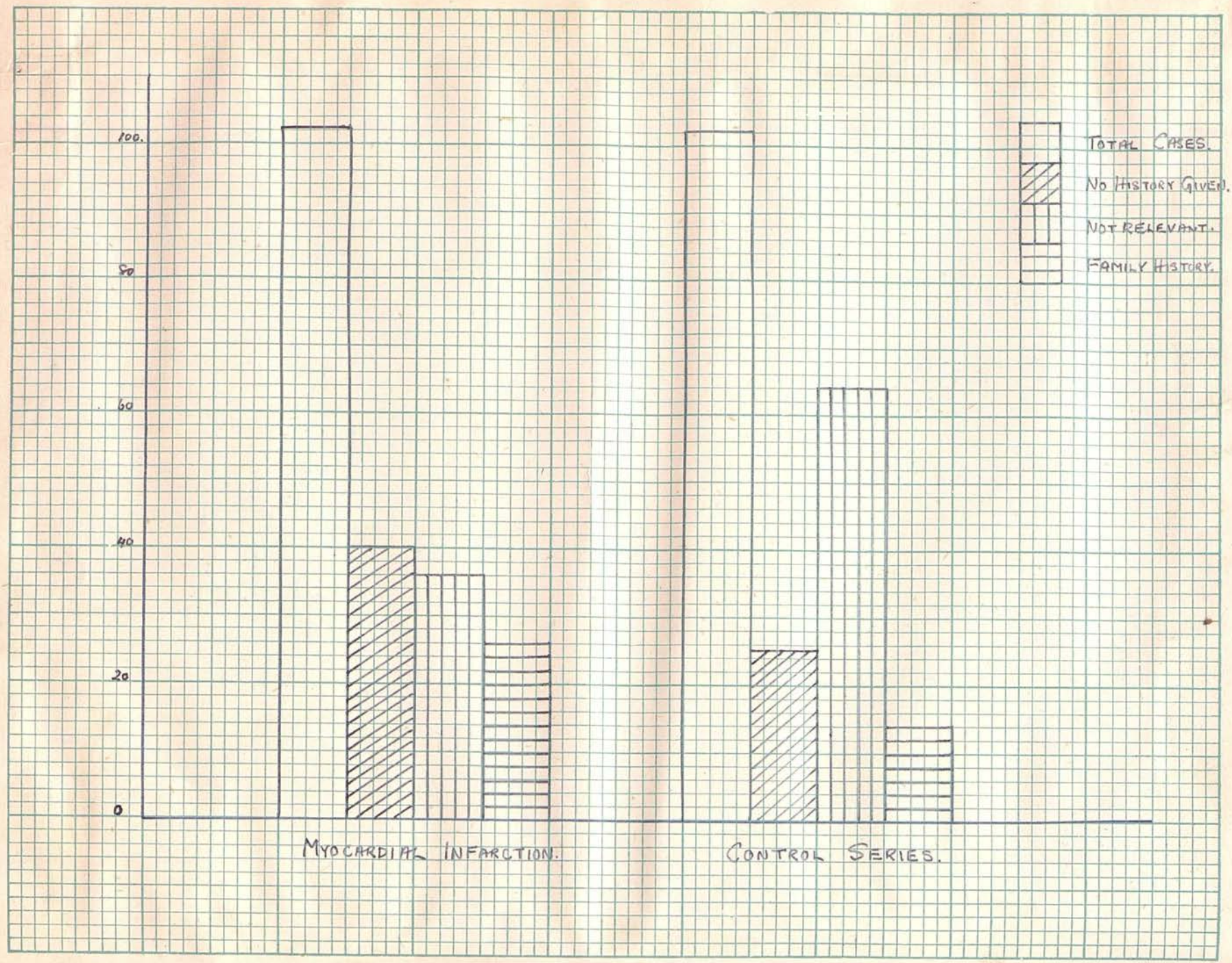

CASES OF MYOCARDIAL INFARCTION
SHOWING INCIDENCE OF FAMILY HISTORY
1928 – 1945.
TOTAL CASES
FAMILY HISTORY.
16
14
12
10
8
6
4
2
0
1928
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

Fig VIII


100.
80
60
40
20
0
TOTAL CASES.
NO HISTORY GIVEN.
NOT RELEVANT.
FAMILY HISTORY.
MYOCARDIAL INFARCTION.
CONTROL SERIES.

It would thus appear that the majority of investigators believe coronary occlusion to be more common in individuals whose occupation and mode of life subject them unduly to the stresses and strains - emotional and nervous - of modern civilisation. Actual figures are so contradictory and are open to such numerous sources of error that no reliance can be attached to them. Of the figures given, those of the Registrar General are the most accurate, as they cover all occupations and all grades of society.

7. FAMILY HISTORY.

Patients suffering from coronary occlusion usually give a family history of some manifestation of cardiovascular disease. It would appear that the incidence of a family history of cardiovascular disease is greater in this group than in the case of patients suffering from other conditions.

Fig. VII shows the incidence of cardiovascular disease (in coronary occlusion; angina pectoris; cerebral haemorrhage and uraemia, a result of nephro--sclerosis) in the relatives of the cases in this series.

Fig. VIII shows the relation of family history of /

of cardiovascular disease in the cases under review as compared with a control group of cases. It can be seen that a family history of cardiovascular disease occurred twice as commonly in the cases of cardiac infarction as in the control series.

This result is open to two sources of error:-

(1) Not all the patients in this series, or in the control group, remember the causes of death of their relatives.

(2) Patients who suffer from coronary thrombosis are more liable to recall cases of a similar nature which occurred in their family, especially if these cases ended in sudden death.

Nevertheless it would appear that patients with coronary thrombosis show a higher incidence of deaths from cardiovascular disease in their families than do the rest of the population.

8. MODE OF ONSET.

In this series 70 cases were suddenly taken ill. Of these, 64 had the sudden onset of the characteristic praecordial pain associated with collapse and shock. 30 cases complained of symptoms suggestive of angina pectoris prior to the onset of the myocardial infarct.

The /

The remaining 8 cases were admitted suffering from sudden onset of severe dyspnoea, collapse, palpitations or syncope and vomiting. Clinically, this latter group showed the leucocytosis of between 1200-1800 occurring 2-3 days later as described by Richter, and the elevation of the B.S.R. which appeared later than the leucocytosis and persisted longer, thus confirming the work of Rabinovitch, Shookhoff and Douglas; Burak, Beikel, Mazar and Sciclonoff; and Hoffmann. A few cases showed the transient glycosuria first described by Jensen. All the cases in this "painless" group showed electrocardiographic evidence of recent myocardial infarction, or the infarction was demonstrat--ed at autopsy, and the cases have been included in the coronary thrombosis of sudden onset in Table I. Fisher and Zukerman found, in their series, approximately the same ratio of the sudden onset of coronary thrombosis to those with a previous history of angina pectoris (79: 36) as in this series (64 : 30).

9. (a) TIME OF ONSET; (b) STATE AT ONSET.

(a) In 80 patients in this series the attack of coronary thrombosis occurred during the day, in 22 at /

at night. (b) 42 cases suffered the attack during exertion and in 60 patients the attack appeared when at rest.

10. COMPLICATING DISEASES.

12 of the cases had suffered from chronic bronchitis, 9 from cholecystitis and 8 from diabetes mellitus. 51 of the patients (50%) were known to have had hypertension, although only 40 cases had high blood pressure on admission. This will be discussed separately.

11. HYPERTENSION.

51 of the cases under review (50%) were known to have suffered from hypertension prior to the onset of the myocardial infarction. Of these cases 30 were females and 21 were males. There would appear to be no relationship between the mortality rates and the previously existing high blood pressure. In fact, patients whose blood pressure remained moderately high or normal, during the attack, would seem to have the best prognosis, the level of the systolic pressure indicating the degree of shock, the output of /

of the heart, or the power of contraction of the left ventricle.

These findings are of interest when compared with the results of other workers. Smith, Sauls and Ballew had 41 hypertensive patients in their 100 cases, while Master, Dack and Jaffre showed the incidence of hypertension in women with coronary occlusion to be 32% higher than in men, thus supporting the figures in this series. Fisher and Zukerman found 65.5% of women with coronary thrombosis to have hypertension while only 39.25% of the men in their series had high blood pressure. In this series and in the cases described by Fisher and Zukerman the women with hypertension were invariably elderly.

Pre-existing hypertension is a common finding in cases of myocardial infarction, yet high blood pressure <u>per se</u> cannot be the only aetiological factor in the production of coronary occlusion, for hypertension is as frequent, as severe and as long-lasting in women as in men, yet the sex distribution of coronary thrombosis shows a greater incidence in men. Negroes suffer from hypertension more frequent--ly than do white people, yet they show a significantly lower incidence of coronary artery disease (Roberts). It /

It has been postulated therefore that, if high blood pressure were the major determining factor in produc--ing coronary thrombosis, there would be proportion--ately more cases of coronary thrombosis (1) among women than among men, and (2) among negroes than among the white population.

12. TYPE OF INFARCTION.

The cases in this series on whom electrocardio--graphic examinations were performed showed:-

Anterior infarction	45	cases.
Posterior infarction	23	cases.
Coronary vessel disease	14	cases.
No evidence of infarction	9	cases.

These results are in keeping with the findings of other authors (anterior infarction to posterior infarction as 1.9 : 1), the anterior infarction being about one and a half to twice as common as the posterior infarction. This is due to the descending branch of the left coronary artery usually being the vessel occluded. Some structural defect or other abnormality in the artery, or increased bulk of the myocardium of the left ventricle as compared to the right ventricle, may explain the predominance of anterior /

anterior infarction. These factors will be considered more fully in the next section.

13. ATHEROSCLEROSIS AND THE CORONARY ARTERIES.

Certain predisposing factors in the causation of atherosclerosis must be considered in the aetiology of coronary occlusion. These points may be of importance if there are associated structural or other abnormalities of the coronary arteries. Athero--sclerosis will be discussed first.

Hueper, in a review of the aetiology of arterio--sclerosis and of atherosclerosis, supports the original thesis that the fundamental and general causal mechanism of degenerative arterial disease is an impaired nutrition and oxygenation of the vascular wall, resulting in endothelial damage, increased intimal permeability, and the infiltration of plasma into the sub-intimal tissue, followed by the prolifer--ation of endothelial cells and the degeneration of the muscular and elastic elements of the media. If the plasma contains persistently or transiently pathologically large amounts of cholesterol, or physico-chemically related substances forming emulsions with the plasma, there occurs a retention of this material in the proliferating endothelial cells /

cells with the ultimate formation of atheroma, thus representing a special morphological variety of arteriosclerosis. The second morphological type of arteriosclerosis, on the other hand, is caused by highly excessive contraction or relaxation of the arterial wall through the action of hypertonic or hypotonic agents respectively, giving rise to the development of primary medial necrosis and calcific--ations. Hueper states that when the arteriosclerotic process is found restricted to one kind of artery, the type of the arteriosclertogenic agent, its affinity for certain organic vessels and the intensity of its action or its dose, combine in accounting for such a distribution. The various aetiological agents, causing arteriosclerotic changes by inter--fering with the nutrition and oxygenation of the vessel walls, may bring about this result by one of the following three mechanisms:-

(1) Clinically inert agents such as cholesterol, polyvinyl alcohol, methyl cellulose and pathological large molecular protein complexes present in the plasma, impair the gaseous and nutritive exchange in the interface of blood and vascular wall.

(2) Hypertonic agents cause vaso-constriction and result in a reduction of the blood flow in the vasa /

vasa vasorum, as these are compressed by the contract--ing media and intima. This results, especially in the inner portions of the vascular wall, in ischaemia and anoxaemia, accompanied by an accumulation of metabolic waste products. The ensuing injury to the vascular tissues, especially to the sensitive endothelial lining, leads finally to the development of an increased permeability with subsequent infiltration of constituents of the plasma, thereby preparing the way for secondary degeneration.

Of the many hypertonic agents mentioned, renin and hypertensin are probably the most important in causing a generalised vaso-constriction, but as regards the coronary arteries, the actions of adrenaline and nicotine demand further study. The presence of medullary adenomas (pheochromocytomas) of the supra-renal as well as the repeated and prolonged administration of adrenaline for therapeutic purposes - resulting in the production of paroxysmal hypertension - have been found to be accompanied by, in many instances, the occurrence of a severe and generalised atherosclerosis. (Paul; Biebl and Wichels; Kremer; Raab; Erdheim; and Jergesen). Similar changes have been elicited in the aorta and in the coronary arteries of rabbits by the repeated injection /

injection of adrenaline by many investigators. (Josue; Thorel; Schultz; Ficher-Wasels; and Stief and Tokay). These experimental atherosclerotic lesions are spotty and circumscribed. The main objection to these results is that rabbits develop spontaneous atherosclerosis. This fact must be considered when interpreting the results of these experiments.

Aschoff; Hilpert; Strauss; Anitschkow; English, Willius and Berkson; and Wright and Moffat have shown that workers in the tobacco industry develop, as well as thromboangeitis obliterans, arteriosclerotic changes, especially in the coronary arteries, while Adler and Hensel produced arteriosclerotic lesions in rabbits by the administration of nicotine. Raab proposed that nicotine is the harmful agent in smoking and exerts such an effect by mobilising adrenaline. This theory is supported by the work of Staemmler, who showed that rats, subjected to chronic nicotine poisoning, developed adenomata and hyperplasia of the supra-renal medulla.

There is experimental evidence that nicotine and adrenaline cause atherosclerosis, especially of the coronary arteries. It is tempting to associate these results with emotion, nervousness and worry, as predisposing factors in the aetiology of coronary thrombosis. /

thrombosis. Smoking may play a direct part in the causation of the disease, or may merely indicate an underlying nervous temperament. All these factors may be associated with excessive production of adrenaline, for short or prolonged periods, and the subsequent development of atherosclerosis.

(3) Hypotonic agents produce, by an excessive dilatation of the vascular walls, a compression of the collapsed vasa vasorum, a slowing of the blood flow and a lowering of the blood pressure, thus causing a stagnant anoxaemia in the vascular wall and an impaired gaseous exchange between the blood and the surrounding vascular tissues. Histamine, acetyl choline, nitrites, carbon monoxide and lowered oxygen pressure are important hypotonic agents.

Heinlein; Meesen; and Ruhl have demonstrated that in chronic histamine poisoning the media of the coronary arteries is replaced by connective tissue, and the myocardium contains numerous areas of necrosis and haemorrhage. These changes have been attributed to stagnant anoxaemia resulting from the circulatory failure.

Hall, Ettinger and Banting; and Heinlein have shown that a similar mechanism is apparently responsible for the arteriosclerotic changes found in /

in the coronary vessels of animals treated with acetyl choline.

Hueper and Landsberg have investigated the effects of chronic nitrite poisoning on rats. Rats which were subjected for a period of 5-7 months to increasing amounts of erythrol tetranitrate showed at the end of that time extensive arteriosclerotic lesions in the arteries of the heart, brain, lung and kidney. It is interesting that similar vascular changes (coronary sclerosis, medial degeneration and calcification of cerebral arteries) have been observed by Meixner and Mayrhofer; Fischer; Lowy; Laws and Ebright in chemical workers exposed to nitrites who showed during life the symptoms of chronic nitrite poisoning, viz. excessively low blood pressure, attacks of angina pectoris, mental deterioration and diarrhoea. Many of these workers died suddenly, often at a relatively early period of adult life, with the symptoms of coronary thrombosis.

Carbon monoxide does not produce arteriosclerosis, although degeneration of the media and proliferation of the intima are present in the cerebral vessels after repeated carbon monoxide poisoning.

Experimental studies conducted on animals by Buchner and Luft suggest that an excessive exposure

to /

to a reduced oxygen pressure with resulting anoxaemia, causes arterial and myocardial degenerative lesions. These observations are of particular importance from the standpoint of aviation medicine, especially as sudden deaths from coronary thrombosis have been observed by White in comparatively young pilots. Hazardous occupations, exposing workers to chronic nitrite poisoning and to lowered oxygen tension, would probably appear to be important factors in the development of arteriosclerosis and coronary vessel disease.

Men and animals, when exposed to the hypertonic and hypotonic agents mentioned above, in industry or experimentally, develop arteriosclerotic lesions. Yet the coronary arteries in the majority of cases show a more advanced degree of atherosclerosis than do the arteries elsewhere. This would indicate some difference in the structure between the coronary artery and arteries of a similar calibre. This structural difference may predispose the coronary artery to early development of atherosclerosis with later the sudden onset of coronary occlusion.

The degree of atheroma present in the coronary arteries of men compared with the degree of atheroma present in other arteries, and the structure of the coronary /

SEX.	AGE.	HEART WEIGHT in Gm.	STATE OF VESSELS. AORTA	CEREBRAL	RENAL	CORONARY ARTERIES.
Male	72	420	Atheroma	Atheroma	Arteriolosclerosis	Markedly atheromatous. Occlusion descend--ing branch of left coronary.
Male	64	400	Atheroma	Atheroma	Healthy	Markedly atheromatous. Occlusion left coronary at origin.
Male	66	410	Slight atheroma	-	Mild arteriolo--sclerosis	Very atheromatous. Occlusion and descend--ing of left coronary.
Male	48	430	-	-	-	Very atheromatous. Thrombus in left descending branch.
Male	56	410	Atheroma	Atheroma	Mild arteriolo--sclerosis	Markedly atheromatous. Occlusion right coronary and descending branch of left.
Male	39	380	-	-	-	Marked atheroma of origin of descending branch of left.
Male	54	360	Atheroma	Atheroma	Arteriolosclerosis	Marked atheroma of left and right coronary. Occlusion of right.
Male	62	420	-	-	-	Occlusion left coronary by atheroma at origin
Male	49	300	-	-	-	Occlusion left coronary. Atheroma in most of its course.
Male	52	360	-	-	-	Very atheromatous coronary arteries. Occlusion right.
Male	57	440	-	-	-	Atheroma left;coronary occlusion descend--ing branch.
Male	59	500	-	-	Arteriolosclerosis	Very atheromatous coronaries with occlusion of left at origin.
Male	70	360	Atheroma	Atheroma	Arteriolosclerosis	Very atheromatous coronaries. Occlusion left descending branch.
Male	68	400	Atheroma	-	Mild arteriolo--sclerosis.	Atheroma at origin of left coronary. Occ--lusion of descending branch.
Male	67	390	Mild atheroma	-	-	Atheroma left and right. Coronary occlusion left and right coronaries.
Male	47	420	-	-	-	Atheroma of left. Coronary occlusion of descending branch.
Male	61	440	-	-	Mild arteriolo--sclerosis	Atheroma of both coronaries. Occlusion of left at its root.
Male	58	420	-	-	-	Markedly atheromatous left coronary. Mild in right. No occlusion.
Male	60	380	Atheroma	-	-	Very atheromatous coronaries. Occlusion of left branch.
Male	65	360	Mild atheroma	-	-	Very atheromatous coronaries. Markedly narrowed left. No occlusion.
Male	46	400	-	-	-	Atheroma left. Coronary occlusion of descending branch.
Female	70	400	Atheroma	Atheroma	Arteriolosclerosis	Marked atheroma both coronaries. Occlusion of left and right.
Female	68	380	Atheroma	Atheroma	Mild arteriolo--sclerosis	Marked atheroma both coronaries. Narrowing of left. No occlusion.
Female	65	390	Atheroma	-	Mild arteriolo--sclerosis	Very marked atheroma both. Occlusion of left coronary.
Female	71	380	Atheroma	Atheroma	Arteriolosclerosis	Very marked atheroma of both coronaries. Narrowing of right. Occlusion of left.
Female	66	340	Atheroma	-	Mild arteriolo--sclerosis	Marked atheroma of both coronary arteries. No occlusion.
Female	69	290	Atheroma	Atheroma	Arteriolosclerosis	Very atheromatous coronary arteries. Occlusion right coronary.
Female	64	300	Atheroma	-	-	Marked atheroma of both coronaries. Occ--lusion of left and right.
Female	67	295	Atheroma	Atheroma	Arteriolosclerosis	Very atheromatous coronaries. Occlusion descending branch.
Female	68	310	Atheroma	-	Arteriolosclerosis	Very atheromatous coronaries. Occlusion of left and right branches.

TABLE V.

CONDITION OF AORTA, CEREBRAL, RENAL AND CORONARY VESSELS IN CASES OF MYOCARDIAL INFARCTION.

coronary arteries compared with the structure of other arteries of a similar size, must now be consider--ed to determine any possible correlation between them.

(i) Atheroma.

Of the 102 cases in this series, 47 died and, of these, 30 came to post-mortem. Table V shows the distribution of arterial lesions in these cases in the coronary, aorta, renal and cerebral vessels. The coronary arteries showed atherosclerosis in every case. This would appear to be but a manifestation of general--ised arteriosclerosis in patients over the age of 60, while in the younger patients the coronary lesion is an isolated finding. The heart was hypertrophied in all cases. This may indicate either a pre-existing hypertension or myocardial fibrosis, a direct result of coronary atherosclerosis.

Other workers have shown that in patients over the age of 60 years the most massive and advanced atheromatous lesions are generally found in the distal third of the aorta and in the iliac arteries. Similar lesions in the arteries of the heart, brain and lower extremities therefore appear to be mainly local manifestations of a process elsewhere. From a study of the vessels of soldiers, however, who died of /

of coronary occlusion while in training, French and Dock found that cases of coronary disease without tibial, cerebral or aortic lesions, which seem exceptional after the sixth decade, are the rule in men under 40. Levine and Hiondle suggest that the same may occur in men apart from those in training in other occupations. Coronary occlusion is almost inevitable and often is manifest in the twenties or even in the teens in cases of congenital xanthanatosis without gross atherosclerotic lesions elsewhere. (Muller; Bloom; Kaufmann and Stevens; Engelberg and Newman). The level of the arterial pressure is a very important factor in determining the site of severity of atherosclerosis. (Dock; Hueper). This fact supports the statement that the relative incidence of myocardial infarction is many times higher in cases of hypertension than in normal persons, although hypertension as mentioned previously is not the only factor in these cases. This of course may be due to the greater O_2 needs of the left ventricle when maintaining high arterial pressure, as well as to the greater severity of atherosclerosis in the hypertensive person. Pulmonary atherosclerosis is rarely seen without right ventricular hypertrophy and other evidence /

evidence of long-continued pulmonary hypertension. It may be seen in young people with mitral stenosis and faultless arteries. Arteriosclerosis is much more frequent and severe in the legs, where the vessels must withstand additional pressure due to gravity when sitting or standing, than in the arteries of the arms. In the aorta it is much more severe near the bifurcation than near its root. Hamilton and Dow found in the dog that the systolic pressure was much higher and the pulse much steeper in the region of the bifurcation than in the thoracic part of the aorta. This apparently is true in man, as the femeral pressure is higher than the brachial, and offers the most reasonable explanation for the localisation of severe atherosclerosis. There is no evidence that the pressure in the coronary vessels has a different level to that in the carotids (although the coronaries are the first branches of the aorta), therefore the frequency of coronary atheroma, as compared with atheroma in other arteries, cannot be accounted for by pressure differences alone, as in the case of the tibial and radial arteries.

(ii). Structure of the coronary arteries.

Sections of coronary arteries were examined from 25 male and 25 female cases which came to autopsy, in /

AGE.	DIAGNOSIS.	ANTERIOR DESCENDING BRANCH.		CIRCUMFLEX BRANCH.		RIGHT CORONARY.	
		1 cm.	3 cm.	1 cm.	3 cm.	1 cm.	3 cm.
26	Subarachnoid Haemorrhage	1.4	1.6	1.3	1.1	1.8	1.6
		1.2	1.5	1.1	1.3	1.4	1.2
		1.6	1.4	1.2	1.5	1.5	1.5
40	Fractured ribs. Haemothorax.	2.6	2.2	2.0	2.5	2.9	2.4
		2.0	2.6	2.4	2.4	2.5	2.8
		2.1	2.6	2.1	2.1	2.4	2.8
43	Weil's Disease.	2.4	2.6	2.9	2.6	2.1	2.3
		2.2	2.5	2.5	2.4	2.5	2.5
		2.6	2.6	2.7	2.8	2.2	2.1
34	Hodgkin's Disease	3.4	3.6	3.1	3.4	3.6	3.0
		3.8	3.9	3.5	3.0	3.1	4.0
		3.7	3.7	3.5	3.8	3.3	3.6
18	Miliary T.B.	3.2	4.0	3.8	3.7	4.0	3.7
		4.0	3.6	3.4	3.7	3.6	3.9
		3.2	3.8	3.5	3.2	3.8	3.6
36	Mitral Stenosis.	3.9	3.4	4.0	4.4	4.5	5.0
		3.0	3.2	4.4	4.2	4.2	4.2
		3.4	3.2	4.5	4.0	4.7	4.1
54	Multiple Myeloma.	5.0	5.2	4.7	4.6	4.4	4.2
		4.2	4.6	4.9	4.8	4.6	4.6
		4.8	4.4	4.7	4.8	4.6	4.3
24	Subacute Bacterial Endocarditis	4.2	4.8	5.2	4.4	4.2	4.6
		5.0	4.6	4.5	4.6	4.5	4.7
		4.8	4.4	4.7	4.8	4.3	4.7
38	Cerebral Tumour	5.8	5.6	5.8	5.0	5.6	5.6
		5.4	5.5	5.7	5.8	5.6	5.2
		5.6	5.3	5.8	5.4	5.8	5.4
40	Perforated Peptic Ulcer	5.9	5.8	5.4	5.0	4.6	5.0
		5.2	5.4	4.6	5.5	4.6	5.0
		5.3	5.8	4.8	5.2	4.2	4.8
60	Bronchial Carcinoma	6.0	6.2	5.0	5.4	5.0	5.2
		5.3	5.5	5.1	5.3	5.1	5.6
		5.4	5.2	5.3	5.6	4.9	5.0
38	Ruptured Appendix	6.0	6.4	5.6	5.4	5.5	5.3
		5.0	5.4	5.4	5.8	5.7	5.5
		5.5	5.6	5.6	5.7	5.6	5.4
66	Fractured Femur. Multiple Injuries	6.8	7.0	5.8	6.2	6.4	6.4
		6.1	6.2	6.4	6.1	6.2	6.5
		6.5	6.6	6.6	6.5	6.1	6.6
68	Prostatic Hypertrophy. Acute Pyelonephritis	6.4	6.6	6.8	6.6	6.2	6.4
		6.3	6.2	6.4	6.2	6.6	6.2
		6.5	6.4	6.6	6.5	6.4	6.4
12	T.B. Meningitis	6.6	6.0	6.6	6.8	6.5	6.1
		6.2	6.4	6.8	6.6	6.6	6.3
		6.5	6.3	7.0	6.6	6.6	6.2
59	Cirrhosis of the Liver	7.4	7.8	7.0	6.6	6.8	6.6
		7.6	8.0	6.8	6.4	6.6	6.2
		7.2	7.4	6.9	6.6	6.4	6.6
64	Cerebral Haemorrhage	7.8	8.4	7.6	7.2	6.8	7.1
		8.0	8.0	7.4	7.6	7.0	7.4
		7.6	7.8	7.6	7.6	7.0	6.9
62	Gastric Carcinoma	8.2	8.6	7.4	7.8	7.6	7.4
		7.8	8.4	7.8	7.6	7.8	7.6
		8.2	8.4	7.6	7.4	7.6	7.7
48	Fractured Skull. Cerebral Contusion	9.4	9.2	9.0	9.0	8.6	8.6
		9.6	8.6	8.4	8.8	8.2	8.6
		9.0	8.4	8.2	8.4	8.4	8.2
46	Disseminated Sclerosis. Bronchopneumonia	9.6	9.0	8.6	9.0	8.4	8.4
		9.4	9.8	8.2	8.4	8.6	8.3
		9.2	9.4	8.4	9.0	8.2	8.5
53	Post-operative Peritonitis	9.8	9.4	9.0	8.4	8.6	8.6
		10.0	9.8	8.4	8.6	8.0	8.2
		9.6	10.4	8.6	8.4	8.2	8.6
60	Haematemesis. Peptic Ulcer	9.8	10.6	8.6	8.2	8.4	8.6
		9.8	9.6	8.4	8.6	8.6	8.4
		10.4	9.8	9.0	8.8	8.4	8.6
61	Carcinoma of head of Pancreas	10.1	9.8	9.4	9.4	8.6	9.6
		10.6	10.6	8.6	9.6	9.0	9.2
		10.4	10.0	9.2	9.2	9.0	9.4
29	Status Epilepticus	11.4	12.6	9.0	9.4	9.2	9.4
		10.6	10.4	9.8	9.6	9.8	9.7
		10.2	10.6	9.6	9.8	9.6	9.3
44	Bronchial Carcinoma	11.6	10.8	10.0	9.6	9.8	10.3
		12.2	11.2	10.6	10.4	10.0	10.0
		11.8	12.4	10.4	10.2	10.2	10.1

TABLE VI.

RATIO OF INTIMA TO MEDIA IN CORONARY ARTERIES
OF MALE CASES.

AGE.	DIAGNOSIS.	AVERAGE RATIO OF INTIMA TO MEDIA OF CORONARY ARTERIES MALES.
26	Subarachnoid haemorrhage	1.38 : 1
40	Fractured ribs. Haemothorax	2,35 : 1
43	Weils Disease	2.40 : 1
34	Hodgkins Disease	3.40 : 1
18	Miliary T.B.	3.60 : 1
36	Mitral stenosis	4.00 : 1
54	Multiple myeloma	4.55 : 1
24	Subacute bacterial endocarditis	4.60 : 1
38	Cerebral tumour	5.45 : 1
40	Perforated peptic ulcer	5.30 : 1
60	Bronchial carcinoma	5.50 : 1
38	Ruptured appendix	5.50 : 1
66	Fractured femur. Multiple injuries	6.40 : 1
68	Prostatic hypertrophy. Acute pyelo--nephritis	6.40 : 1
12	T.B. Meningitis	6.50 : 1
59	Cirrhosis of the liver	6.80 : 1
64	Cerebral haemorrhage	7.40 : 1
62	Gastric carcinoma	7.70 : 1
48	Fractured skull. Cerebral contusion	8.60 : 1
46	Disseminated sclerosis. Broncho-pneumonia	8.75 : 1
53	Post-operative peritonitis	8.90 : 1
60	Haematemesis. Peptic ulcer.	9.50 : 1
61	Carcinoma of head of, pancreas	9.60 : 1
29	Status epilepticus	9.90 : 1
44	Bronchial carcinoma	10.80 : 1

TABLE VII.

AVERAGE RATIO OF INTIMA TO MEDIA OF CORONARY VESSELS IN MALE CASES.

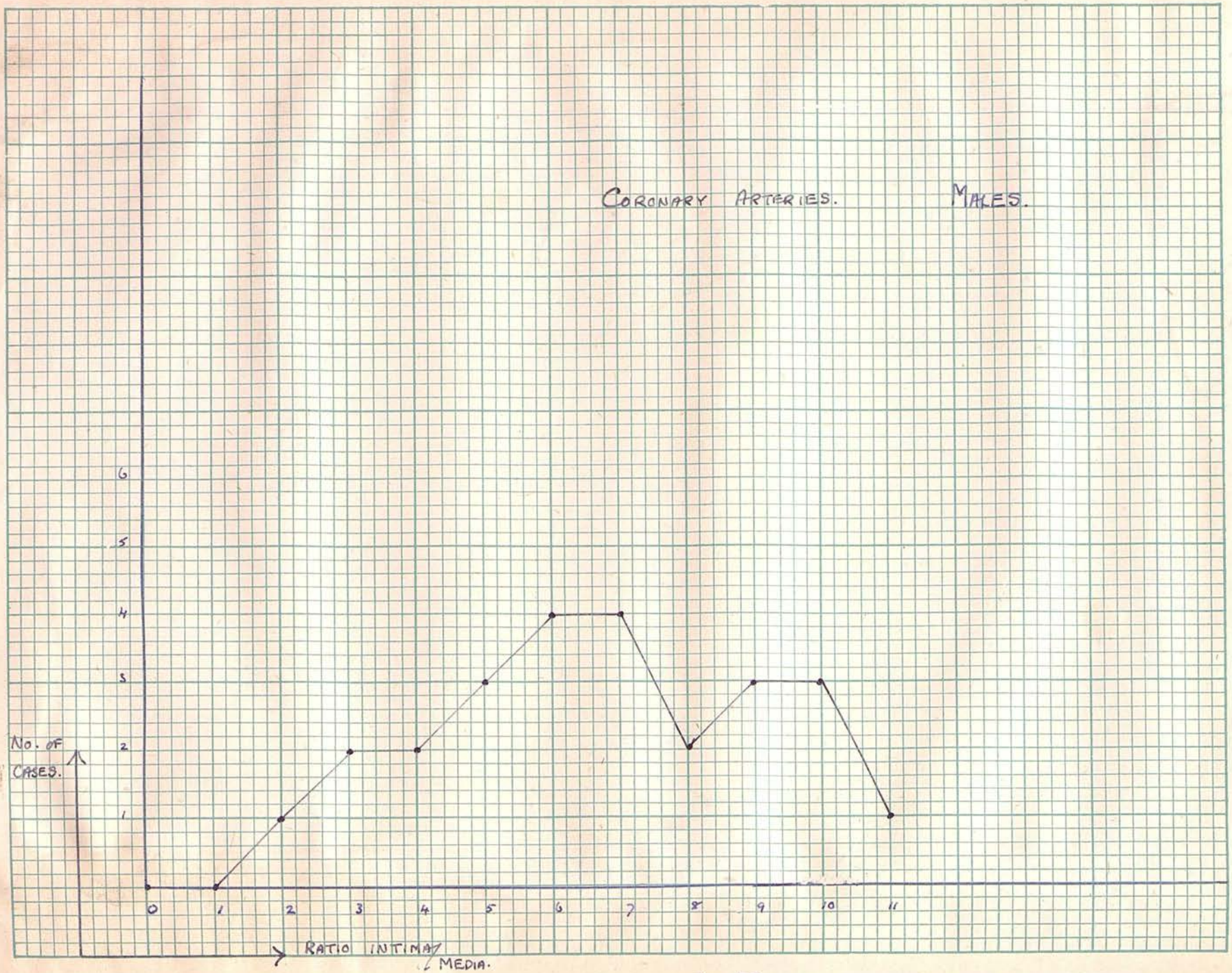

CORONARY ARTERIES. MALES.
No. OF CASES.
6
5
4
3
2
1
0
1
2
3
4
5
6
7
8
9
10
11
RATIO INTIMA / MEDIA.

FIG IX

AGE.	DIAGNOSIS.	ANTERIOR DESCENDING BRANCH		CIRCUMFLEX BRANCH.		RIGHT CORONARY.	
		1 cm.	3 cm.	1 cm.	3 cm.	1 cm.	3 cm.
48	Mitral Stenosis. Auricular fibrillation	1.1	1.2	1.0	1.1	1.0	1.2
		1.2	1.3	1.1	1.2	1.2	1.2
		1.2	1.1	1.0	1.0	1.1	1.1
16	T.B. Meningitis	1.4	1.2	1.2	1.2	1.4	1.2
		1.2	1.2	1.1	1.2	1.4	1.0
		1.3	1.5	1.0	1.0	1.5	1.1
14	Subacute Nephritis. Uraemia.	1.2	1.4	1.2	1.4	1.4	1.4
		1.1	1.2	1.1	1.2	1.2	1.5
		1.2	1.3	1.3	1.2	1.2	1.3
70	Carcinoma of Oesophagus	2.3	2.4	2.1	2.2	2.6	2.7
		2.4	2.6	2.3	2.1	2.4	2.2
		2.5	2.4	2.4	2.4	2.3	2.2
80	Cerebral Thrombosis	2.3	2.6	2.3	2.3	2.4	2.4
		2.4	2.4	2.4	2.3	2.1	2.1
		2.4	2.5	2.1	2.6	2.6	2.0
34	Post-operative Peritonitis	2.3	2.2	2.1	2.0	2.4	2.0
		2.4	2.6	2.6	2.4	2.6	2.6
		2.4	2.1	2.7	2.6	2.7	2.4
60	Carcinoma of Colon	3.2	3.4	3.8	3.6	3.5	3.7
		3.6	3.4	3.8	3.4	3.4	3.7
		3.4	3.4	3.4	3.6	3.7	3.2
44	Polycystic Kidneys. Uraemia.	3.7	3.8	3.6	3.6	3.2	3.3
		3.6	3.8	3.4	3.5	3.6	3.6
		3.8	3.6	3.8	3.7	3.4	3.7
61	Hypertension. Congestive Failure.	3.1	3.8	3.4	3.5	3.6	3.8
		3.6	3.7	3.6	3.6	3.6	3.3
		3.4	3.3	3.8	3.4	3.4	3.6
54	Carcinoma of Ovaries	3.4	3.6	3.3	3.6	3.4	3.2
		3.6	3.6	3.8	3.7	3.6	3.3
		3.8	3.7	3.2	3.3	3.7	3.5
52	Multiple Injuries	4.5	3.8	4.1	4.6	4.4	4.4
		4.7	4.4	4.2	4.0	4.0	4.6
		4.6	4.0	3.9	3.9	3.2	4.2
60	Phenobarbitone poisoning	4.7	4.6	4.2	4.6	4.2	4.6
		4.7	4.4	4.6	4.8	4.6	4.0
		4.6	4.6	4.4	5.0	4.4	4.4
68	Gallstones. Cholangitis.	5.2	4.6	4.2	4.1	4.6	4.3
		5.2	5.8	4.3	4.8	4.6	4.7
		4.6	5.0	4.4	4.5	4.0	4.2
65	Pernicious Anaemia	4.2	4.6	4.7	4.6	4.7	4.8
		5.0	4.0	4.3	4.7	4.3	5.0
		5.4	5.0	4.6	4.6	4.4	4.7
37	Mitral Stenosis	4.6	4.4	4.4	4.3	4.2	4.6
		5.0	4.7	4.6	4.6	4.7	4.7
		4.9	4.6	4.2	4.4	4.5	4.6
66	Cerebral Haemorrhage	4.9	4.7	4.2	4.2	4.5	4.8
		5.2	4.6	4.6	4.4	4.6	4.6
		4.6	4.9	4.8	4.6	4.6	4.6
60	Pulmonary Embolism	5.7	5.8	5.4	5.6	5.6	5.7
		5.5	5.0	5.6	5.8	5.8	5.6
		6.0	5.6	5.4	5.6	5.6	5.5
49	Carcinoma of Breast	6.0	6.2	5.5	5.4	5.4	5.7
		6.2	6.4	5.8	5.7	5.6	5.6
		5.6	6.0	5.6	5.8	5.9	5.8
65	Carcinoma of Stomach	6.2	6.4	5.8	5.8	5.4	5.6
		5.6	6.2	5.6	5.6	5.6	5.8
		5.8	6.0	5.6	5.4	5.6	5.4
30	Otitis Media. Cerebral Abscess.	6.6	6.5	5.8	5.6	5.4	6.0
		6.4	6.4	6.4	5.8	5.6	5.8
		6.2	6.6	6.6	6.0	5.4	5.4
57	Carcinoma of Cervix	6.9	6.6	6.4	6.5	6.8	6.0
		6.6	6.8	6.6	6.3	6.9	6.1
		6.8	6.9	6.0	6.0	6.8	6.3
28	Staphylococcal Septicaemia	6.9	7.6	6.8	6.4	7.0	6.6
		6.6	7.0	6.0	6.6	6.9	7.0
		6.8	7.4	7.0	6.6	6.0	6.8
34	Diabetic Coma	7.6	7.4	7.6	6.8	7.0	7.2
		7.4	7.6	7.0	7.0	7.6	7.6
		7.6	7.0	7.1	7.0	7.1	7.4
44	Intestinal Obstruction	8.0	7.5	6.6	6.8	6.6	6.8
		8.4	7.6	6.6	6.9	7.0	6.4
		7.6	8.2	7.0	7.0	6.6	6.6
70	Fractured Femur. Pneumonia.	8.0	6.9	6.0	7.4	7.6	7.6
		8.2	7.6	7.4	7.6	7.4	7.6
		8.4	7.8	7.6	7.3	7.6	7.4

TABLE VIII.

RATIO OF INTIMA TO MEDIA IN CORONARY ARTERIES OF FEMALE CASES.

TABLE IX.

AVERAGE RATIO OF INTIMA TO MEDIA OF CORONARY VESSELS IN FEMALE CASES.

AGE.	DISEASE.	AVERAGE RATIO OF INTIMA TO MEDIA OF CORONARY ARTERIES. FEMALES.
48.	Mitral stenosis. Auricular fibrillation.	1.15 : 1
16.	T.B. Meningitis	1.20 : 1
14.	Subacute nephritis. Uraemia.	1.25 : 1
70.	Carcinoma of oesophagus.	2.30 : 1
80.	Cerebral thrombosis	2.35 : 1
34.	Post-operative peritonitis.	2.35 : 1
60.	Carcinoma of colon.	3.5 : 1
44.	Polycystic kidneys. Uraemia.	3.6 : 1
61.	Hypertension. Congestive failure.	3.5 : 1
54.	Carcinoma of ovaries.	3.5 : 1
52.	Multiple injuries.	4.15 : 1
60.	Phenobarbitone poisoning.	4.5 : 1
68.	Gallstones. cholangitis.	4.6 : 1
65.	Pernicious anaemia.	4.5 : 1
37.	Mitral stenosis.	4.55 : 1
66.	Cerebral haemorrhage.	4.65 : 1
60.	Pulmonary embolism.	5.6 : 1
49.	Carcinoma of breast.	5.6 : 1
65.	Carcinoma of stomach.	5.8 : 1
30.	Otitis media. Cerebral abscess.	5.9 : 1
51.	Carcinoma of cervix.	6.55 : 1
28.	Staphylococcal septicaemia.	6.80 : 1
34.	Diabetic coma.	7.25 : 1
44.	Intestinal obstruction.	7.30 : 1
70.	Fractured femur. Pneumonia.	7.65 : 1

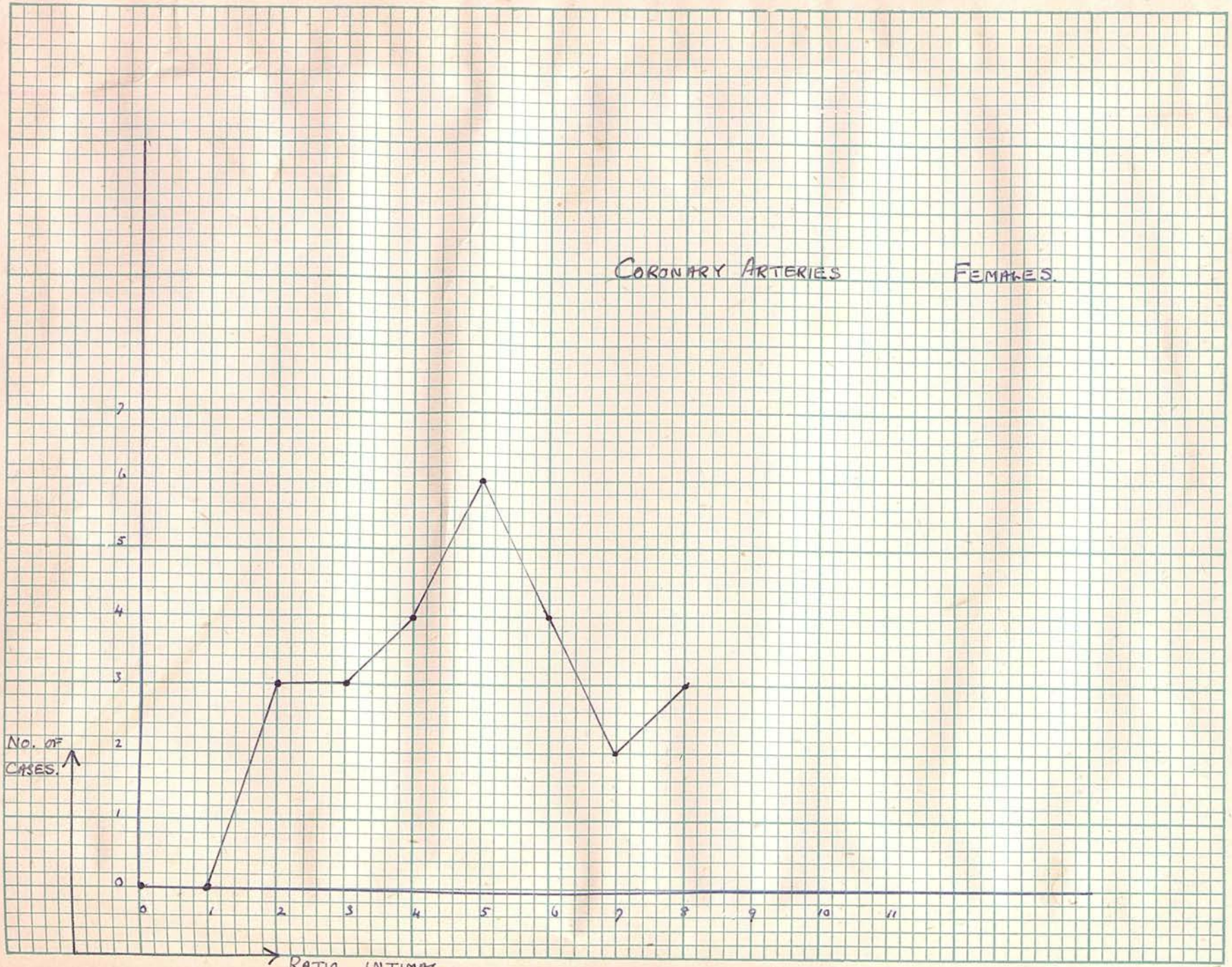

CORONARY ARTERIES
FEMALES.
NO. OF CASES.
0
1
2
3
4
5
6
7
0
1
2
3
4
5
6
7
8
9
10
11
RATIO INTIMA / MEDIA.

FIG X

in whom the cardiovascular system might be presumed to be normal. The sections were taken 1 cm. and 3 cm. from the origin of the descending branch of the left, circumflex branch and right coronary arteries. These sections were compared with sections from the cerebral and gastro-epiploeic arteries. Table VI shows the ratio of the thickness of the intima to the thickness of the media of the coronary arteries in male cases at 3 points in the same plane at the sites of section. It can be seen that the ratios of intimal to medial thickness are similar for each vessel in the one case. Hence it was decided to determine the average figure for the intimal to medial thickness ratio for the 3 coronary vessels, and so express the result as a single ratio in each case. This is seen in Table VII. The distribution of the ratios in the male cases is seen in Fig. IX. Tables VIII and IX show similar results for the female cases, and the distribution is seen in Fig. X. The average ratio of intimal to medial thickness for the male cases is 6.8 to 1; and for the female cases 4.2 to 1. The difference between the means is 2.4, and the standard error of the difference between the means is .89. This is significant.

The cerebral and gastro-epiploeic arteries were examined in a similar manner and ratios of intimal thickness /

AGE.	DISEASE.	CEREBRAL ARTERY (MIDDLE) 1 cm.	CEREBRAL ARTERY (MIDDLE) 3 cm.	GASTRO EPIPLOEIC. 1 cm.	GASTRO EPIPLOEIC. 3 cm.
43	Weil's Disease	.08	.04	.09	.06
		.07	.06	.08	.05
		.08	.05	.08	.06
34	Hodgkin's Disease	.08	.05	.09	.10
		.06	.06	.09	.11
		.08	.06	.10	.09
18	Miliary T.B.	.10	.09	.11	.16
		.10	.10	.15	.17
		.11	.10	.15	.18
26	Subarachnoid Haemorrhage	.11	.10	.14	.16
		.12	.10	.15	.16
		.09	.11	.14	.14
40	Fractured ribs. Haemothroax	.16	.11	.11	.14
		.10	.10	.12	.15
		.10	.10	.16	.16
36	Mitral Stenosis	.14	.16	.14	.14
		.16	.15	.16	.15
		.14	.14	.16	.16
54	Multiple Myeloma	.15	.17	.16	.16
		.15	.14	.17	.16
		.16	.12	.16	.17
38	Cerebral Tumour	.13	.16	.14	.16
		.14	.12	.16	.17
		.15	.14	.18	.18
40	Perforated Peptic Ulcer	.16	.20	.20	.24
		.19	.21	.19	.20
		.20	.18	.16	.18
24	Subacute Bacterial Endocarditis	.20	.22	.21	.20
		.21	.21	.20	.19
		.20	.20	.21	.16
60	Bronchial Carcinoma	.22	.26	.24	.22
		.24	.24	.21	.23
		.26	.24	.22	.22
38	Ruptured Appendix	.24	.23	.26	.24
		.24	.26	.27	.26
		.21	.24	.26	.27
12	T.B. Meningitis	.24	.26	.28	.30
		.24	.25	.30	.30
		.20	.24	.30	.30
59	Cirrhosis of the Liver	.30	.32	.28	.31
		.34	.31	.34	.32
		.35	.32	.30	.30
66	Fractured Femur. Multiple Injuries	.35	.34	.34	.34
		.36	.34	.36	.36
		.34	.36	.35	.34
68	Prostatic Hypertrophy. Pyelonephritis	.37	.35	.37	.50
		.36	.36	.36	.41
		.40	.37	.40	.40
64	Cerebral Haemorrhage	.41	.46	.45	.40
		.40	.45	.43	.41
		.45	.45	.46	.42
48	Fractured Skull. Cerebral Contusion	.48	.46	.46	.49
		.50	.47	.50	.49
		.51	.46	.49	.50
62	Gastric Carcinoma	.57	.52	.51	.52
		.54	.53	.52	.56
		.52	.54	.56	.57
44	Bronchial Carcinoma	.54	.51	.60	.65
		.54	.52	.61	.65
		.52	.56	.64	.62
60	Haematemesis. Peptic Ulcer	.60	.62	.70	.70
		.61	.64	.71	.71
		.60	.65	.70	.72
29	Status Epilepticus	.64	.62	.80	.80
		.64	.63	.84	.82
		.64	.64	.80	.84
53	Post-operative Peritonitis	.70	.74	.95	.96
		.74	.75	.95	.97
		.75	.76	.96	.94
46	Disseminated Sclerosis. Pneumonia	.80	.85	1.0	0.9
		.84	.86	1.1	1.0
		.84	.80	0.9	1.0
61	Carcinoma of head of Pancreas	1.0	1.1	1.1	1.1
		1.0	1.1	1.0	1.1
		0.9	1.2	1.0	1.0

TABLE X.

RATIO OF INTIMA TO MEDIA IN CEREBRAL AND GASTRO EPIPLOEIC ARTERIES OF MALE CASES.

AGE.	DISEASE.	AVERAGE RATIO OF INTIMA TO MEDIA OF CEREBRAL ARTERIES. MALE CASES.	AVERAGE RATIO OF INTIMA TO MEDIA OF GASTRO EPIPLOEIC ARTERIES. MALE CASES.
43	Weil's Disease	.06 : 1	.07 : 1
34	Hodgkin's Disease	.06 : 1	.09 : 1
18	Miliary T.B.	.10 : 1	.13 : 1
26	Subarachnoid haemorrhage	.11 : 1	.15 : 1
40	Fractured ribs. Haemothorax.	.11 : 1	.15 : 1
36	Mitral stenosis	.15 : 1	.15 : 1
54	Multiple myeloma	.15 : 1	.17 : 1
38	Cerebral tumour	.15 : 1	.16 : 1
40	Perforated peptic ulcer	.17 : 1	.2 : 1
24	Subacute Bacterial endocarditis	.21 : 1	.2 : 1
60	Bronchial carcinoma	.24 : 1	.22 : 1
38	Ruptured appendix	.24 : 1	.25 : 1
12	T.B. Meningitis	.32 : 1	.30 : 1
59	Cirrhosis of the liver	.25 : 1	.30 : 1
66	Fractured femur. Multiple injuries	.35 : 1	.35 : 1
68	Prostatic hypertrophy. Pyelonephritis	.37 : 1	.40 : 1
64	Cerebral haemorrhage	.44 : 1	.42 : 1
48	Fractured skull. Cerebral contusion.	.48 : 1	.49 : 1
62	Gastric carcinoma	.53 : 1	.58 : 1
44	Bronchial carcinoma	.53 : 1	.62 : 1
60	Haematemesis. Peptic ulcer.	.62 : 1	.71 : 1
29	Status Epilepticus	.63 : 1	.82 : 1
53	Post-operative peritonitis	.74 : 1	.96 : 1
46	Disseminated sclerosis. Pneumonia.	.85 : 1	1.0 : 1
61	Carcinoma of head of Pancreas.	1.0 : 1	1.0 : 1

TABLE XI.

AVERAGE RATIO OF INTIMA TO MEDIA OF CEREBRAL AND GASTRO-EPIPLOEIC ARTERIES OF MALE CASES.

AGE.	DISEASE.	CEREBRAL ARTERY (MIDDLE) 1 cm.	CEREBRAL ARTERY (MIDDLE) 3 cm.	GASTRO EPIPLOEIC ARTERY. 1 cm.	GASTRO EPIPLOEIC ARTERY. 3 cm.
60	Phenobarbitone poisoning	.06	.05	.07	.1
		.06	.04	.08	.08
		.07	.06	.09	.08
16	T.B. Meningitis	.05	.05	.07	.06
		.06	.05	.07	.07
		.06	.06	.07	.07
48	Mitral stenosis. Auricular fibrillation.	.08	.08	.06	.07
		.09	.08	.08	.09
		.06	.08	.09	.08
80	Cerebral thrombosis.	.10	.10	.09	.10
		.10	.12	.11	.10
		.11	.10	.10	.10
60	Carcinoma of colon.	.11	.12	.11	.12
		.12	.11	.12	.11
		.10	.11	.11	.12
44	Polycystic kidneys. Uraemia.	.10	.10	.12	.12
		.10	.10	.10	.10
		.12	.10	.10	.11
14	Subacute nephritis. Uraemia.	.14	.12	.16	.14
		.15	.13	.14	.14
		.16	.12	.12	.14
34	Post-operative peritonitis.	.15	.14	.16	.14
		.15	.16	.16	.15
		.16	.16	.16	.16
70	Carcinoma of oesophagus.	.16	.16	.16	.16
		.16	.17	.14	.16
		.16	.16	.16	.16
61	Hypertensive cardiac failure.	.17	.16	.18	.16
		.17	.16	.16	.16
		.16	.16	.16	.16
52	Multiple injuries	.20	.21	.20	.21
		.21	.20	.20	.20
		.22	.20	.20	.20
68	Gallstones. Cholangitis.	.22	.24	.22	.23
		.22	.24	.22	.23
		.22	.24	.22	.23
54	Carcinoma of ovaries.	.24	.23	.22	.23
		.22	.23	.22	.23
		.22	.22	.22	.23
66	Cerebral haemorrhage.	.30	.32	.30	.36
		.31	.32	.31	.36
		.32	.33	.32	.36
49	Carcinoma of breast.	.36	.37	.34	.34
		.36	.36	.34	.34
		.37	.38	.32	.34
65	Pernicious anaemia.	.36	.36	.40	.41
		.36	.36	.40	.40
		.36	.36	.40	.40
60	Pulmonary Embolism.	.41	.41	.40	.42
		.42	.40	.40	.42
		.40	.40	.41	.42
65	Carcinoma of stomach.	.42	.42	.40	.40
		.42	.42	.41	.41
		.43	.42	.41	.42
37	Mitral stenosis.	.51	.56	.50	.52
		.52	.57	.57	.53
		.51	.52	.52	.56
70	Fractured femur. Pneumonia.	.52	.56	.54	.57
		.53	.57	.56	.58
		.53	.56	.56	.59
57	Carcinoma of cervix.	.60	.60	.56	.56
		.61	.61	.58	.56
		.60	.62	.58	.56
28	Staphylococcal septicaemia.	.71	.70	.61	.66
		.72	.70	.66	.64
		.73	.71	.64	.65
44	Intestinal obstruction.	.84	.84	.64	.69
		.84	.80	.66	.66
		.84	.80	.68	.66
34	Diabetic coma.	.90	.94	.70	.78
		.94	.94	.78	.78
		.95	.94	.76	.79
30	Otitis media. Cerebral abscess.	1.0	1.0	.80	.85
		1.1	1.0	.80	.86
		1.0	1.0	.84	.86

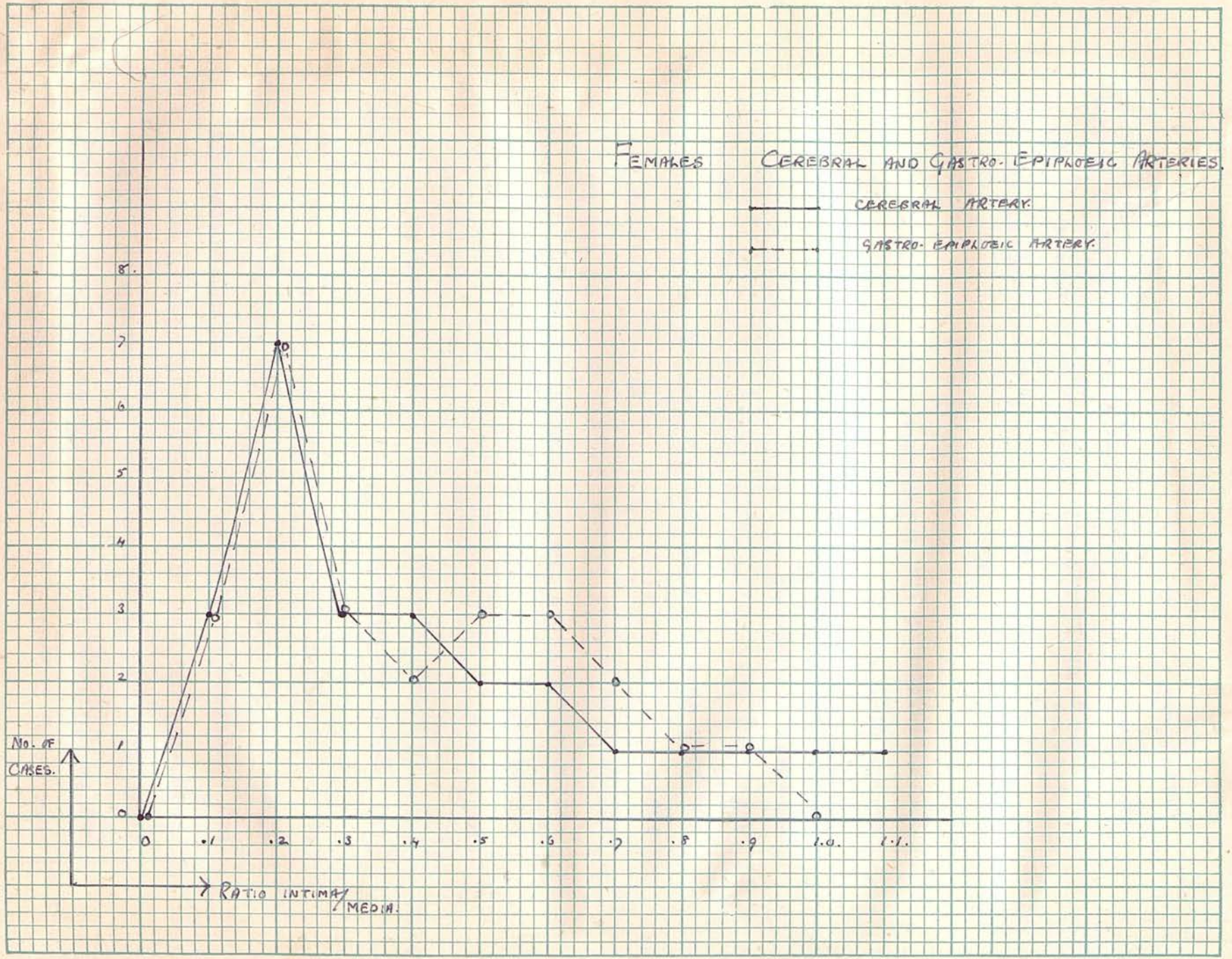
TABLE XII.

RATIO OF INTIMA TO MEDIA IN CEREBRAL AND GASTRO-EPIPLOEIC ARTERIES OF FEMALE CASES.

AGE.	DISEASE.	AVERAGE RATIO OF INTIMA TO MEDIA OF CEREBRAL ARTERIES. FEMALE CASES	AVERAGE RATIO OF INTIMA TO MEDIA GASTRO-EPIPLOEIC ARTERIES. FEMALE CASES.
60	Phenobarbitone poisoning	.05 : 1	.08 : 1
16	T.B. Meningitis	.05 : 1	.07 : 1
48	Mitral stenosis. Auricular fibrillation.	.08 : 1	.08 : 1
80	Cerebral thrombosis	.1 : 1	.1 : 1
60	Carcinoma of colon	.11 : 1	.11 : 1
44	Polycystic kidneys. Uraemia.	.10 : 1	.11 : 1
14	Subacute nephritis. Uraemia.	.13 : 1	.14 : 1
34	Post-operative peritonitis	.15 : 1	.16 : 1
70	Carcinoma of oesophagus	.16 : 1	.16 : 1
61	Hypertensive cardiac failure	.16 : 1	.16 : 1
52	Multiple injuries	.20 : 1	.20 : 1
68	Gallstones. Cholangitis	.23 : 1	.22 : 1
54	Carcinoma of ovaries	.23 : 1	.22 : 1
66	Cerebral haemorrhage	.31 : 1	.33 : 1
49	Carcinoma of breast	.36 : 1	.34 : 1
65	Pernicious anaemia	.36 : 1	.40 : 1
60	Pulmonary embolism	.40 : 1	.41 : 1
65	Carcinoma of stomach	.42 : 1	.41 : 1
37	Mitral stenosis	.52 : 1	.53 : 1
70	Fractured femur. Pneumonia.	.54 : 1	.57 : 1
51	Carcinoma of cervix	.60 : 1	.57 : 1
28	Staphylococcal septicaemia.	.71 : 1	.64 : 1
44	Intestinal obstruction	.83 : 1	.67 : 1
34	Diabetic coma	.93 : 1	.76 : 1
30	Otitis media. Cerebral abscess.	1.0 : 1	.84 : 1

TABLE XIII.

AVERAGE RATIO OF INTIMA TO MEDIA OF CEREBRAL AND GASTRO-EPIPLOEIC ARTERIES IN FEMALE CASES.


FEMALES CEREBRAL AND GASTRO-EPIPLOEIC ARTERIES.
CEREBRAL ARTERY.
GASTRO-EPIPLOEIC ARTERY.
8.
7
6
5
4
3
2
1
0
No. OF CASES.
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1.0. 1.1.
RATIO INTIMA/MEDIA.

FIGS XII

thickness determined as before. These results are seen in Tables X and XI in the case of the males, and XII and XIII in the case of the females. The distrib--ution of these ratios for both arteries in each sex is seen in Figs. XI and XII.

In the male cases the mean ratio for the cerebral arteries is 0.41 to 1 and the gastro-epiploeic 0.39 to 1, while the cerebral vessels in the female cases have a mean ratio of 0.38 to 1 and the gastro-epiploeic 0.40 to 1.

These results show that:-

(1) The ratio of the thickness of the intima to the thickness of the media of the coronary arteries is 10-15 times greater than that ratio in similar sized vessels, viz. the cerebral and gastro-epiploeic arteries, from the same case.

(2) The ratio of intima thickness to medial thickness of coronary vessels is greater in men than in women and this is statistically significant.

These results were obtained using a standard technique throughout. They are, however, open to criticism. The arteries were not injected before sectioning, therefore no account is taken of any varying degree of post-mortem contraction, or of any swelling of the intima due to post-mortem oedema, a result of autolysis. Nevertheless, it would appear that the intima of the coronary artery is thicker in

men /

men than in women, and is also thicker than the intima of other vessels of a similar calibre. These findings are supported by other workers. Studies of Spalteholz and Hochrein; Gross; Epstein and Kugel demonstrated the remarkable thickness of the coronary intima compared with that of the radial, tibial, cerebral and viseral arteries, even in the infant. They also emphasised the increase in thickness in age, and the variability in depth of the intimal layer from place to place in the same artery in different persons of the same age. A similar structure is found in arteries such as the occipital or penile which must lengthen or shorten with motion or turgescence. The peculiar intima of the coronaries which adapts the epicardial branches to the changes in distance between points of fixation during the cardiac cycle and which are relatively unsupported, suggests the possibility that here lies one of the chief causes for susceptibility in the development of atheroma. Dock has shown that the intima of the coronary arteries lying on the epicardium - already known to be thicker than that of any artery of a similar calibre elsewhere in the body - is much thicker in males than in females, and that this anatomical peculiarity is easily demonstrable in newborn infants.

It /

It would thus appear that the coronary arteries differ in structure from vessels of a similar size. This structural difference is due to the intima in the coronary artery being thicker than the intima in arteries of the same calibre. The intima of the coronary artery is thicker in males than in females, and, as this difference can be detected in infancy, it is not related to the variation in heart weight in the two sexes.

Can there be any correlation between this structural difference of the coronary artery and the incidence and development of atheroma?

Winternitz et al. have demonstrated a remarkably extensive pattern of circulation in the aorta of the cow. When the vessel is injected with India ink from the proximal end, with the branches and distal end ligated, the adventitial circulation becomes evident at once. These vessels in the specimen are seen to penetrate the media for a great distance, and at times actually to connect with the lumen of the vessel through very small orifices in the intima. This pattern of circulation in the walls of the blood vessels is demonstrated with facility in men. The Thesbian and coronary circulation of the heart, as described by Wearn suggest that this circulatory pattern /

pattern may be present in the walls of the coronary arteries. This is, in fact, the case; very minute vessels are encountered arising independently from the wall and running to the adventitia where they anastomose in the rich adventitial plexus. In a recent public--ation Paterson, in studying a series of coronary arteries in which thrombosis had occurred, discusses haemorrhage in the intimal tissue and describes small vessels in the intima arising from the lumen. These findings support the work of Hueper who states that the fundamental and general causal mechanism of degenerative arterial disease is an impaired nutrition and oxygenation of the vascular wall resulting in endothelial damage. This defective nutrition may be caused by excessive contraction or relaxation of the arterial wall through the action of hypertonic or hypotonic agents. It can be seen that, due to the greatly thickened intima of the coronary artery, any change in calibre of the vessel - be it constriction or dilatation - must constrict the vasa vasorum in its wall and thus impair the nutrition of the vessel wall. This predisposes to the mechanism of production of atheroma, as was described at the beginning of this section when Hueper's theory was discussed. As the coronary artery has such a thickened intima and so

very /

very little media, it is difficult to imagine the vessel changing its calibre at all in response to hypertonic or hypotonic agents. Any such change in calibre would be due, most probably, to these hyper--tonic or hypotonic agents increasing the cardiac out--put and causing increased coronary blood flow, with consequent dilatation of the vessel and resultant compression of the vasa vasorum in the wall.

Adrenaline is a known vasodilator or vaso--constrictor and is said to produce atherosclerosis after prolonged administration in the experimental animal. Its action on the coronary vessels deserves further study.

The response of the coronary arteries to adrenaline depends on the species being examined and the technique employed. Both constriction and dilatation have been reported to occur after administration of the drug, but dilatation is the pre--dominant response. Melville reported that both adrenaline and ephedrine caused vasodilation of the coronaries and abolished the coronary vasoconstriction induced by posterior pituitary extract. Anrep and his co-workers, using direct flow and perfusion methods in hearts <u>in situ</u>, observed coronary vasodilation after adrenaline; and Gollwitzer found that sympathetic nerve stimulation as well as adrenaline resulted in increased /

increased coronary blood flow. Katz et al. noted that the coronary flow in isolated perfused cats' hearts decreased in some preparations in response to adrenaline but increased in others. In 23 dogs' hearts, however, the drug caused only coronary vaso--dilation occasionally preceded by a slight transient constriction. Essex and his collaborators, using trained dogs, with thermostromuhr units implanted on the coronary arteries, observed that adrenaline markedly increased coronary blood flow, the augmented blood flow being accompanied by an accelerated heart rate. These results of the response to adrenaline, however, cannot be employed as an index of the effects of sympathetic nerve impulse, or of adrenaline, on the calibre of the coronary arteries, for the dilatat--ion and increased blood flow may be a result of increased cardiac output and heart rate caused by the drug. It is usually stated that adrenaline, or sympathetic nerve stimulation, causes coronary vaso--dilation, whereas vagal impulses cause vasoconstriction. (Anrep and Segall; Kountz, Pearson and Kaing). This conception has recently been questioned by Katz and Jochrim, who found in the dog's heart - an organ similar at least experimentally to the human heart - that /

that the isolated coronary vessels responded to vagal stimulation by slight vasodilatation, but that stimulation of the sympathetic fibres, or perfusion with adrenaline, elicited either vasoconstriction or vasodilation. Katz and Lindner later showed that the only coronary vasoconstrictor fibres were thus adrenergic in character and ran in the sympathetic pathways.

It would thus appear that the media in the coronary arteries responds to adrenaline and may result in vasoconstriction or vasodilation. The change in calibre is most probably enhanced by secondary alterations in coronary blood flow due to changes in cardiac output resulting from the administration of the drug. Because of the greatly thickened intima of the coronary arteries, this dilatation and constriction must cause compression of the vasa vasorum, and may result in anoxaemia and endothelial damage with later development of atheroma. Other hypertonic or hypotonic agents probably act in a similar manner.

14. CORONARY OCCLUSION WITH INFARCTION OF THE MYOCARDIUM.

Once atherosclerosis has developed the stage is then set for the occurrence of coronary occlusion with resulting /

resulting infarction of the myocardium. The occlusion may be a result of the atheromatous plaque alone, or, thrombosis may occur in the narrowed lumen. The occlusion may develop suddenly, presenting a clinical picture of "coronary thrombosis" or slowly giving symptoms of angina pectoris. These points merit further study.

i. Thrombosis in general.

The most important factors favouring thrombosis are:- (1) injury to the lining of a blood vessel, (2) slowing or eddying of the blood stream, (3) alter--ations in the physical or chemical constituents of the blood.

When atheroma has developed in the intimal lining of a vessel then irregularities are produced on its inner surface. The blood flow is impaired, blood platelets tend to adhere to, and accumulate on, the damaged parts. There is a further slowing of the blood stream and the formation of a thrombus with further narrowing or occlusion of the lumen. That this mechanism occurs in the coronary vessels in relation to the atheromatous plaque is not disputed. There is no evidence that any alteration in the constituents of the blood plays a part in these cases of /

of coronary thrombosis. The blood flow in the coronary vessel is dependent on the level of the systemic blood pressure, according to Rabnoff and Plotz, to the arithmetic mean of the blood pressure at the root of the aorta, and on pressure gradients within the vessel itself. Both these factors will influence the rate of thrombus formation and will be considered in more detail below.

ii. Evidence of collaterol circulation.

In this series 64 patients had the typical clinical features associated with coronary thrombosis, 30 had had angina pectoris prior to the onset of the infarct and 8 had silent infarcts (vide supra section 8). Of the total cases, 30 came to post-mortem; 3 of these had silent infarcts, 12 had had a previous history of angina pectoris and 15 had never manifest symptoms of angina pectoris prior to their coronary thrombosis.

In every case in which there were previous symptoms of angina pectoris the coronary arteries were markedly atherosclerotic, 4 cases had evidence of old occlusion with calcification of one coronary artery and recent occlusion due to thrombosis in the other vessel, the remaining 8 cases showed recent thrombus /

thrombus formation with occlusion of one vessel.

In the 15 cases of coronary thrombosis with no previous history, similar lesions were present:- gross atherosclerosis in all; previous occlusion with calcification and obliteration of the lumen of one coronary artery, and recent coronary occlusion due to thrombus in the other coronary vessel in 2 cases; recent occlusion due to thrombosis in 9; no actual occlusion, the lumen being merely pin-point, in 4 cases.

The myocardium in all the cases presented evidence of the recent infarction with old fibriotic lesions in the 6 cases that showed healed previous occlusion. In addition small areas of fibrosis were present in the myocardium in every case indicating old minute healed areas of infarction.

Atherosclerosis was present in both vessels in every case, yet only 12 patients gave a previous history of angina pectoris. This would suggest the presence of a collateral circulation and would explain the findings of old complete occlusion in the vessels of 4 cases of the angina pectoris group and in 2 cases of the coronary thrombosis group.

The presence of such a collateral circulation would be important in determining the absence of previous /

previous symptoms, the site and extent of infarction and the suddenness of death. Prinzmetal, Simkin, Bergman and Kruger demonstrated a collateral circulat--ion by using radioactive red cells and glass spheres of known diameters in perfusion experiments in human hearts, removed at post-mortem. They found an extensive collateral circulation existed between the coronary arteries in healthy hearts. Their studies revealed the diameters of these inter-coronary vessels ranged from 70-180 μ ; these diameters fall within the dimensions of arterioles as defined by Maximow and Bloom. In the series of normal hearts investigat--ed by Prinzmetal et al. the diameters of the inter--coronary connections did not appear to increase with age. This was confirmed by Blumgart, Schlesinger and Davis but disputed by Gross and Spaltelolz who found that there was increasing anastomoses with increasing age. All the above workers are agreed, however, that inter-coronary anastomoses increase in size in the presence of coronary atherosclerosis or cardiac hypertrophy. Hirsch described vascular segments in the human heart similar histologically to vessels found in the glomus bodies of the digits; these glomus structures were arteriovenous anastomoses. He suggested that these intra-cardiac glomus /

glomus bodies functioned as regulators between the internal arterial pressure and the intestitial pressure of the cardiac musculature acting upon the wall of the vessels. Most of this work has been of an anatomical nature and has not served to elucidate the physiological significance of these vessels during life.

iii. Function of collateral circulation.

Wiggers has emphasised that, although intra-cardiac anastomoses have been demonstrated anatomic--ally, the coronary arteries are physiologically end arteries. He has pointed out that the absence of pressure gradients between the coronary arteries precludes the functioning of inter-coronary anastomoses in the natural heart. When one of the coronary arteries is gradually occluded, the arterial pressure distal to the narrowing or occlusion diminishes, and thus establishes a pressure gradient which now allows blood to flow from the opposite coronary artery through the existent anastomotic channels. In this way a functioning collateral circulation develops, by the enlargement of the anastomic channels. This collateral circulation in cases of coronary occlusion has been demonstrated by radio opaque injections and retrograde flow studies.

When /

When one of the coronary arteries is acutely occluded in an otherwise normal heart, are the collateral channels, which are known to exist in the natural heart, functionless? It is well known that the infarcted area in otherwise healthy hearts is smaller than that supplied by the obliterated vessel. This has been demonstrated in man by Von Reckling--hausen and Zenner, and Fujinami and, in experimental work on dogs, by Hirsch and Spalteholz. Therefore the rim of viable tissue around the infarct must be supplied by collateral vessels from other arteries. If a small enough artery is obstructed, collateral circulation might be sufficient to prevent myocardial necrosis. Prinzmetal, Kayland, Margoles and Tragerman have shown that if one coronary artery was suddenly occluded in a normal heart an increase in blood flow in the opposite coronary artery resulted. There is evidence by Manning, McEachern and Hall that concomitant with a coronary arterial occlusion, vasoconstriction may occur in the unresolved coronary arteries. Sectioning of the stellate ganglion and upper five thoracic ganglion have been shown by Le Roy, Fenn and Gilbert to prevent a reduction in coronary flow following ligation of one of the coronary arteries. This factor, therefore, may greatly limit the /

the possible function of collateral channels immediately following an acute occlusion. Eckstein, Gregg and Pritchard have actually measured the retro--grade flow distal to the ligation of the descending branch of the left coronary artery in the dog. They found the flow decreased immediately after the occlusion and then increased slightly after several hours. It would thus appear that when one coronary artery is gradually occluded the pressure gradient so produced allows blood to flow from the opposite coronary artery through existent anastomotic channels and so establishes a functioning collateral circulat--ion. When a coronary artery is suddenly occluded, however, there is a reflex spasm of the other vessels and the retrograde flow in the distal segment only increases after several hours.

iv. Effects of inadequate collateral circulation.

The coronary arteries must supply the heart with whatever the amount of blood it needs. They must supply not only the normal-sized, but also the greatly hypertrophied organ; they must supply the muscle adequately not only when its work is sufficient for the needs of the resting body, but when the heart is called upon, as it often is, to do a greatly increased amount /

amount of work. When a coronary artery is occluded a corresponding area of muscle loses its blood supply, there is a state of absolute ischaemia with the clinical picture of coronary thrombosis. When the blood supply to an area of muscle is reduced, or when it is incapable of increasing sufficiently to bring an adequate supply to muscle called upon to perform an increased amount of work, there is a state of relative ischaemia with a clinical picture of angina pectoris.

Provided the collateral circulation is adequate a patient may develop atherosclerosis of the coronary vessels or even complete occlusion of one of them with no angina or symptoms of coronary thrombosis. The collateral circulation may be inadequate. In this latter case anginal symptoms will be present and, when occlusion occurs, those of coronary thrombosis. An inadequate collateral circulation may be due to:-

(a) Failure of development of collateral circulation.

It was stated above that although a collateral circulation is present in the heart, the absence of pressure gradients prevents such an inter-coronary anastomosis from functioning. When one of the coronary arteries is gradually occluded by atheroma the arterial pressure distal to the atheroma diminishes. Thus /

Thus a pressure gradient is established which allows blood to flow from the opposite coronary through the anastomotic channels.

(1) Heredity. There may be a deficient number of inter-coronary vessels. This may be hereditry and may partly explain the family history of coronary occlusion in these cases.

(2) Age. The collateral circulation in the heart has been shown by Gross to increase with age. Therefore a coronary occlusion occurring in a young patient may have a more serious result because of an insufficient number of anastomotic channels to maintain an adequate collateral circulation in the heart. This factor may be a possible explanation of the high mortality of coronary thrombosis met with in the younger age group in this series. 17 patients were under the age of 50 and, of these, 12 died following the infarct (90.5%), 85 were over 50 and, in this group, 35 died (41.4%). The standard error of the difference between the percentages is 5.8. This is statistically significant. Elderly patients are more prone to die from hypostatic pneumonia than are the younger ones, this makes the standard error therefore even more significant.

(3) Site of Infarction. If gradual occlusion or narrowing occurs simultaneously in both coronary arteries, /

arteries, there would be no pressure gradient and the function of the anastomotic channels between the arteries would therefore be limited following an occlusion of one of them. In this series arterial infarction was met with nearly twice as often as posterial infarction (vide supra - section 12). The anterior descending branch of the left coronary artery was most commonly the site of occlusion. There is no gross variation in structure or immediate anatomical relations between the left and the right coronary arteries that would explain this distribution of atheroma. The increased bulk of the myocardium and the greater oxygen needs of the left as compared to the right ventricle have been suggested by some workers as possible explanations. The greater the demand for blood, the greater will be the change in calibre of the vessel with secondary pressure effects in the vasa vasorum, resulting in anoxaemia of the intima. This may predispose to the development of atheroma in the left coronary more than in the right.

Another factor may be the relative variation in the anatomical distribution of the coronary arteries over the heart. Blumgart, Schlesenger and Davis in a study of 125 hearts of patients, who died from coronary /

coronary occlusion, found variations in the distribut--ions of the three main coronary arterial branches. These variations could be classified into three general groups: one with a balanced coronary circulation, and the other two with left and right coronary artery preponderance, respectively. In the group with the balanced coronary artery circulation, the right coronary artery supplied the right ventricle and part of the inter-ventricular septum, while the left coronary artery supplied the left ventricle and the remainder of the septum. In hearts with left coronary artery preponderance, the right ventricle was, to an important degree, supplied by the left circumflex and left anterial descending arteries. In the group showing right coronary preponderance, the right coronary artery supplied a significant portion of the septum and left ventricle. The group exhibiting right coronary artery preponderance comprised approximately 40% of the hearts, the balanced circulation group, another 40%, and the group with left coronary artery preponderance, 20%. It would appear that not only is the location of an occlusion in a particular vessel important, but that the rôle of that particular vessel in the blood supply of the heart is of great significance. Blumgart, Schlesinger and Davis found, in /

in the group with left coronary arterial preponderance, comprising only 20% of the hearts, the incidence of arterial occlusions was unusually high and the incidence of myocardial infarction was highest. These infarcts generally resulted in death. In such hearts the left coronary artery supplies a relatively large part of the myocardium, therefore the increased blood flow through that artery may predispose to the formation of atheroma as described previously. Due to this architecture of the coronary tree the collateral circulation which develops from the right coronary artery in these cases will be insufficient. In contrast, the authors found that all but one of the infarcts in the hearts with a balanced circulation were healed infarcts, and two-thirds of those with right coronary artery preponderance were likewise healed. This would suggest that the collateral circulation which develops in these two latter groups is adequate. It may, therefore, be concluded that the results of occlusion of the coronary arteries, with the development of an adequate or inadequate collateral circulation, are influenced by the original pattern of the coronary arteries in any particular heart. This coronary artery pattern may be hereditary.

(b) Obliteration of the Collateral Circulation.

An important factor which may possibly limit the functional /

functional capacity of the inter-coronary anastomosis may be obliteration of these channels by disease or spasm with resulting narrowing or occlusion. These collateral vessels are of arteriolar dimensions and may therefore be subject to disease as may arterioles elsewhere in the body. The vessels may be occluded by arteriolosclerosis or by functional spasm.

(1) Arteriolosclerosis.

Arteriolosclerosis is invariably present in patients who suffer from hypertension. In this series 50% of the patients were hypertensive. Arterio--losclerosis affects the arterioles throughout the body and in this series it was present in 16 of the 30 cases which came to autopsy, 53.3%. 12 of these 16 patients were hypertensive (95%). Arteriolosclerosis, affecting these inter-coronary arterioles may cause narrowing or actual occlusion, and seriously limit the functional capacity of these collateral vessels of the heart. This, therefore, may play a part in the causation of the infarction.

(2) Functional Spasm.

It is well recognised and has been emphasised by the writer that coronary thrombosis is common in the emotional, highly-strung, nervous individual or in the individual /

individual whose occupation or mode of life subjects him unduly to the stress and strain - emotional and nervous - of modern civilization. It is also well known that worry or fright will cause an elevation of the blood pressure, even in "normal" people. This elevation is brought about by an increased output of the heart and by arteriolar spasm, especially the latter, for, according to Poisseuilles' law, the pressure varies inversely as the fourth power of the radius of a minute vessel. Once a collateral circulation has developed in response to narrowing of the coronary vessel by atheroma, then its functional capacity may be severely impaired by arteriolar spasm. The blood flow, already slowed, distal to the narrowing of the coronary vessel, would be even more sluggish and thrombosis may occur in that segment of coronary artery between the atheroma and the arteriole which is in spasm; or thrombosis may occur proximal to the atheromatous narrowing due to a sudden slowing of the blood in the main vessel caused by the arteriolar spasm.

The time of onset of the infarct and the state of the patient at this time are important factors which may predispose to arteriolar spasm and hence initiate the thrombosis and myocardial infarction.

Time of onset. /

Time of onset. 80 patients in this series experienced the attack during the day, 22 when asleep at night. This would suggest muscular activity, emotion, mental effort, worry and other trials that beset man during his days activities play a part in initiating the attack. Nightmares, a condition from which patients with heart disease are prone to suffer, may have precipitated the attack at night in the 22 cases.

State at onset. 42 patients suffered the seizure during exertion, 38 when at rest and 22 when asleep. The exertion was mild in 20 of the cases (49%) such as walking, washing or dressing. It was moderately severe in 10 cases (24%) and very severe exertion in 12 (27%). The case records of 28 of these 42 patients, i.e. 66%, suggest that the exertion may have been associated with some degree of anxiety or mental stress:- hurrying to catch a train in 2, endeavouring to work against time in 10, pushing a car which had broken down in 1, pulling a signal lever in 1, cranking a car in 1, playing a game of bowls in 1, playing golf in 1, hewing coal in 6, returning from watching a football match in 2, and "rushing about the town" in 3.

In /

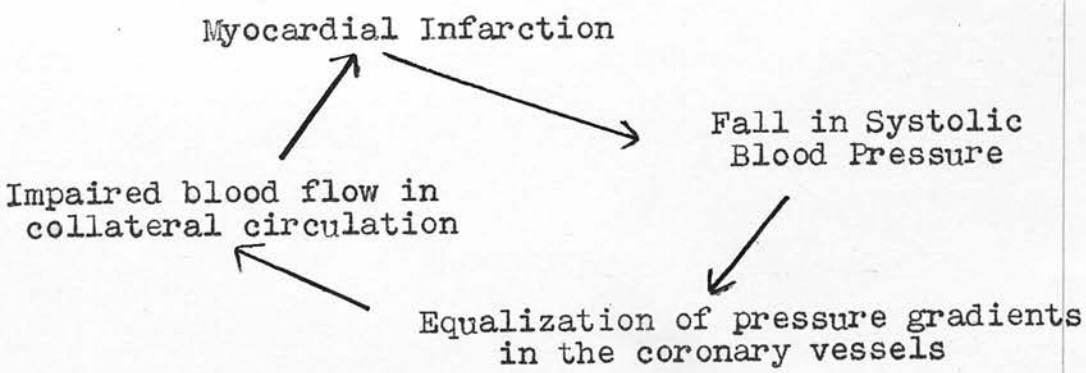
In the 38 patients in whom the attack occurred when at rest, 16 experienced the attack following a heavy meal (42%); 8 were reading; 6 were resting, although not asleep; and 8 were talking to their friends or relations.

Spasm of these inter coronary arterioles in response to excitement, worry, fright, etc., may well initiate thrombosis and myocardial infarction. The type of patient, and all the circumstances associated with the onset of the infarction, suggest that spasm plays a part in coronary thrombosis, there is no proof of this, however, and so it must remain a hypothesis.

(c) The effects of Myocardial Infarction on the collateral circulation. Myocardial infarction may affect the collateral circulation in two ways:- (i) by lowering the blood pressure; (ii) by causing reflex vasoconstriction of the collateral vessels.

(i) The Blood Pressure. When occlusion of a coronary artery occurs the resulting myocardial infarction may so weaken the contractile power of the heart that there is a fall in the level of the systolic blood pressure. This may further impair the blood flow, both in the unaffected vessel and also in the collateral /

collateral vessels. This fall in systolic pressure will therefore affect directly the local pressure gradients in the vessels of the heart and so will influence the size and extent of the infarction, thus a vicious circle is set up:-



The figures from the writer's series of cases support this. Of the total cases, 60% had a low systolic pressure on admission and, of this group, 58% died, while 40% had a natural or high blood pressure on admission and of this group 30% died. The standard error of the difference between the percentages is 9.7. This is statistically significant.

(ii).Reflex Vasoconstriction. Manning, McEachern and Hall have shown that concomitant with a coronary arterial occlusion, vasoconstriction occurs in the uninvolved coronary arteriesand in the inter coronary arterioles. /

arterioles. This vaso-constriction with reduction in blood flow can be prevented by sectioning the stellate ganglion and the upper five thoracic ganglia and has been demonstrated by Le Roy, Fenn and Gilbert.

This factor, too, may greatly limit the function of the collateral vessels immediately following an acute occlusion and therefore influence the size of the infarction and hence the prognosis.

CONCLUSIONS.

Although disease of the coronary vessels was not included in the "International list of causes of death" until 1930, many cases of sudden death due to coronary occlusion had been recognised by earlier workers. Some physicians, notably Jenner (1776), Parry (1799) and Osler (1897) recognised the definite relationship between coronary vessel disease and sudden death, while other workers, although mentioning thickening and calcification of the coronary vessels in their cases, attributed the cause of sudden death to rupture of the heart, aneurysm of the heart, acute myocarditis, fatty heart, and angina pectoris.

The /

The majority of these conditions were undoubtedly due to myocardial infarction resulting from coronary vessel occlusion. Irrespective of the divergent views held by these earlier physicians, all were agreed that heredity, the male sex, and certain occupations and modes of life were important factors in the causation of sudden death.

From the time of Herrick's publications in 1912 and 1919 and the inclusion of coronary thrombosis in the "International list of causes of death", coronary vessel disease has shown an enormous increase. Master suggests that this increase can be partly attributed to a lengthened span of life, ageing of the population, improved diagnosis and treatment of other diseases, accuracy in terminology, and populat--ion increase. The figures of the Registrar-General, however, and the United States Bureau of the census prove that this increase in deaths is real. Denny, White and Cassidy all state that they have been impressed by the increasing prevalence of coronary disease, especially in the last twenty years. The cases of coronary thrombosis in this series have shown an absolute increase in recent years. (Figs. I and II).

A study of the 102 cases here reviewed demonstrate that the structure of the coronary arteries, family history, /

history, sex, age, occupation, smoking and hyper--tension play a part in the causation of coronary thrombosis.

Structure of Coronary Artery.

The Fundamental principle in the causation of coronary thrombosis would appear to be an abnormality in structure of the coronary artery. The intima of this vessel is much thicker than the intima of arteries of a similar calibre elsewhere in the body. It is suggested that this intimal thickening is peculiar to arteries which must constantly lengthen and shorten, as do the coronary arteries during the cardiac cycle, and the occipital arteries, in which this intimal change is also found, during movement of the head and neck. Any of the factors which impair the nutrition and oxygenation of the vascular wall resulting in endothelial damage and predisposing to the development of arteriosclerosis, will in--variably affect the thickened intima of the coronary artery earlier, and to a greater degree than other arteries elsewhere in the body. It is probable that this endothelial damage is primarily due to ischaemia resulting /

resulting from obliteration of the vasa vasorum for, due to the greatly thickened intima of the coronary vessels, any change in their calibre must result in compression with obliteration of the lumina of the vasa vasorum. The greater the number of predisposing factors of arteriosclerosis, the greater and more severe will be the changes in the coronary arteries.

Heredity.

Heredity, as a predisposing factor of arterio--sclerosis and of coronary thrombosis, has been known for generations. It is therefore not surprising that this series of cases shows a family history of coronary thrombosis, cerebral haemorrhage or nephro--sclerosis exactly double that seen in a control group of patients. Heredity may also play a part in the distribution of the coronary arteries and on the number of inter-coronary anastomoses, and therefore predispose to occlusion.

Sex.

The one outstanding factor in cases of coronary vessel disease is that of sex. This has stared physicians in the face ever since this condition was first described by Heberden and Parry, yet little cognisance /

cognisance has been taken of it. One explanation of the great preponderance in the male sex is the structure of the coronary artery. The intima of the coronary artery is much thicker in the male than in the female. This difference is present in infants and would therefore imply an endocrinological cause. In this series, Fig. VI, shows that the incidence of coronary vessel disease has increased in both men and women during the last decade. The emergence of women in recent years from a sheltered life at home and their entrance into strenuous competition and strain in business and professional life may be, in part, responsible for this increase in incidence of the disease in women. The number of cases of coronary thrombosis that appeared in 1939 (Figs. I, II, VI) in both men and women, especially in the latter, may be due to the emotional strain associated with the outbreak of war.

Age.

As the intima of the coronary artery has been shown to increase in thickness with age, and as the onset of atheroma increases with age, it is not surprising that the majority of cases of coronary thrombosis occur above the age of 50. Myocardial infarction /

infarction has occurred more and more frequently in men under 50 years of age in the last decade (Fig. IV). This, too, may be explained by occupational strain. Age will also influence the prognosis for Gross has shown that there is an increasing collateral circulat--ion with increasing age.

Occupation.

Osler in 1897 stated of angina pectoris and coronary vessel disease - "It is not a disease of the working classes. The life of stress and strain, particularly worry, seems to predispose to it and this is perhaps why it is so common in our profession." The majority of investigators believe coronary occlusion to be more common in individuals whose occupation and mode of life subject them unduly to the stresses and strains - emotional and nervous - of modern civilisation. One factor causing athersclerosis in animals is the prolonged administration of adrenalin. Emotion, nervousness, and strain in business and at home will indoubtedly be associated with an increase in adrenalin in the blood. It is suggested that this adrenalinaemia produces changes in calibre of the coronary vessels by direct action on the media and by increasing the heart rate. This change in calibre results in compression of the vasa vasorum with resulting /

resulting ischaemia and anoxaemia of the intima of the vessel wall, and so predisposes to the development of atheroma in man as it does in animals. Because of the structure of the coronary artery the atheroma would appear primarily in this vessel, developing in the other vessels much later. This would explain the occupational incidence of coronary vessel disease (apart from hazardous occupations exposing workers to nitrite poisoning and to lowered oxygen tension, which are associated with a high incidence of coronary thrombosis) which has been an important factor in the disease in men, and might perhaps explain the occurrence of the disease nowadays in women.

Smoking.

The incidence of smoking is greater in cases of coronary thrombosis than in a control series and this increase is statistically significant. Of the many toxic substances produced by smoking - such as nicotine, pyridine, carbon monoxide, methane and other hydro--carbons - nicotine has been shown to produce arterio--sclerotic lesions in animals. It has been suggested that in man nicotine exerts a similar effect by mobilising adrenalin. Hence smoking may play a direct part in the causation of coronary thrombosis.

It /

It may, however, merely indicate an underlying nervousness in the patient.

Hypertension.

Hypertension is a common finding in cases of coronary thrombosis. It occurred in 50% of the cases under review. High blood pressure per se is not the only aetiological factor, however, for, if it were the major determining factor in producing coronary thrombosis, there would be proportionately more cases of myocardial infarction among women and among negroes. It has been shown by Rabnoff and Plotz that the coronary blood-flow is proportional to the arithmetic mean of the blood pressure at the root of the aorta, and that the diastolic pressure is more important than the systolic pressure. All things being equal, an increase in diastolic pressure would be accompani-ed by an increase in coronary blood flow. Impaired nutrition and anoxaemia of the endothelial cells of the intima, with the later development of atheroma, could therefore only occur in these circumstances by alteration in calibre of the coronary vessels caused by the increased blood flow. Both Wearn and Dock, however, have stated that this coronary blood flow may not compensate adequately for the increased cardiac /

cardiac work which hypertension imposes, nor for the decrease in the maximal capacity of the capillaries relative to the mass of muscle fibres in the hyper--trophied hearts of patients with hypertension. The arteriolosclerosis, however, which develops as a result of hypertension will greatly limit the functional capacity of the collateral circulation of the heart and thus predispose to thrombosis and infarction. It will, however, maintain the pressure gradients in the coronary vessels once occlusion has occurred.

So that, although hypertension is a factor in the causation of coronary thrombosis, it is not one of the major determining factors.

Emotion.

From the time of John Hunter (in 1785) - who stated that his life was in the hands of any rascal who chose to annoy him - to the present day, where the highest incidence of coronary thrombosis is seen among men whose occupation and mode of life subject them unduly to stress and strain, and, particularly, worry, emotion would seem to have played the greatest rôle in the causation of coronary thrombosis. The emotional factor may precipitate the infarction by causing vascular spasm. Spasm of the inter-coronary arteries /

arteries will therefore slow further an already sluggish blood flow in the portion of the vessel distal to the atheroma and allow thrombosis to occur in this segment of coronary artery. This theory is borne out by the sayings of two men. W.J. Mayo picturesquely compared the belief of the ancients - that the heart was the seat of the emotions - with the modern idea that stern control of the emotions affects the coronary arteries of the heart, while Sir William Osler stated that in the worry and strain of modern life arterial degeneration is not only very common, but develops often at a relatively early age. For this he believes that the high pressure at which men live, and the habit of working the machine to its maximum capacity, are responsible rather than excesses in eating and drinking. Arteriosclerosis, creeping on slowly but surely "with no pace perceived", is the Nemesis through which Nature exacts retributive justice for the transgression of her laws. A man who has early risen and late taken rest, who has eaten the bread of carefulness, striving for success in commercial, professional or political life, after twenty-five or thirty years of incessant toil reaches the point when he can say, perhaps with just satis-
-faction: /

satisfaction: "Soul, thou hast much goods laid up for many years, take thine ease," all unconscious that the fell sergeant has already issued the warrant.

Collateral Circulation.

Once atheroma has developed in the coronary artery, thrombosis and occlusion of the vessel occur. The results of this occlusion depend on the previous formation of an adequate collateral circulation, these anastomotic channels are of the dimensions of arterioles and the effects of coronary occlusion may therefore be greatly influenced by the presence of such an adequate collateral circulation. This collateral circulation is produced between the two coronary arteries by pressure gradients, which opens up existing anastomotic inter-coronary arterioles. When atheromatous narrowing and occlusion occur in one vessel, the collateral circulation so produced may be adequate for the needs of the myocardium. If the collateral circulation is inadequate, then atheromatous narrowing or thrombosis will produce symptoms of angina pectoris or of coronary thrombosis due to myocardial ischaemia or actual infarction respectively.

The collateral circulation may be inadequate:-

(1) if the rate of development of atheromatous narrowing /

narrowing and occlusion exceeds that at which a collateral circulation can be developed;

(2) if occlusion and narrowing occur in both coronary vessels and therefore there is no pressure gradient to open up the anastomotic channels;

(3) if the pattern of the coronary arterial distribution is that of left coronary artery pre--ponderance; when narrowing occurs in this vessel the collateral channels developing from the right coronary artery will be inadequate to supply the great bulk of myocardium, previously supplied by the left coronary vessel;

(4) if occlusion occurs in the coronary vessel of a young patient with only a small number of inter-coronary anastomotic channels;

(5) if there are an hereditary small number of inter-coronary arterioles;

(6) if the collateral channels are obliterated by arteriolosclerosis in hypertensive patients;

(7) if there is vaso-constriction of the collateral vessels, such as may occur due to excite--ment or emotion. This is probably a common factor in precipitating coronary thrombosis;

(8) Once myocardial infarction has occurred, then /

then the fall in blood pressure and the associated vascular spasm of the collateral arterioles will affect the size of the infarction and hence the prognosis.

FACTORS INFLUENCING THE PROGNOSIS OF MYOCARDIAL INFARCTION.

Apart from such factors as the weight of the patient, intercurrent and complicating diseases, correct diagnosis and adequate and proper treatment, certain other points are of interest and may influence the prognosis. It would appear that the prognosis may be favourable, although the disease is grave, if coronary thrombosis occurs in an elderly individual, with a moderate degree of hypertension, with a posterior infarction and with no previous history of angina pectoris. This is supported by the results from the writer's series:- 90% of patients under the age of 50 years died, 41% over the age of 50 years died. Hypertension will produce arteriolosclerosis and therefore obliterate the collateral vessels; it will, however, maintain the pressure gradient in the coronary and collateral vessels following an infarct and therefore limit the size of the infarction. In the /

the 30 cases that came to autopsy, 16 had hypertension, 12 of them showed arteriolosclerosis, 75%; yet, 30% of the patients with a normal or high blood pressure on admission, died, as compared to 58% of deaths in patients with a low blood pressure on admission.

There will need to be a more adequate collateral circulation in the balanced coronary circulation and right coronary preponderance group than in the left coronary artery preponderance group. Of the total cases only 23 showed evidence of posterior infarction, and of these 10 died; 45 cases had evidence of anterior infarction, and of them 30 died, the other 7 patients had either electrocardiographic or post-mortem evidence of both anterior and posterior occlusion. The standard error for the posterior and anterior infarction group is 8.2. This is statistic--ally significant.

Patients who suffered from angina pectoris prior to developing a coronary thrombosis would appear to have an inadequate collateral circulation, therefore the prognosis should theoretically be worse than patients who develop an occlusion with no previous anginal symptoms. This, however, is not the case.

30 /

30 patients gave a previous history of angina pectoris and 20 died, 72 gave no previous history, and of these 27 died. The standard error for these two groups is 4.9. This is not significant. This result is understandable, for the collateral circulation must be inadequate for both angina pectoris and coronary thrombosis to occur.

Terrible as are some of the associated conditions accompanying coronary vessel disease, there is a kindly compensation, for in no other disease is the ideal death so often given. Caesar, when questioned at his last dinner party as to the mode of death most to be preferred, replied, "That which is the most sudden."

REFERENCES.

ADLER, J. & HENSEL, O. (1906) Deutsche Med. Wchnschr. XXXII, 1826.

ANITSCHKOW, N. (1933) Cowdry, E.V. Arteriosclerosis, 271.

— (1913) Virchow Arch. f. Path. Anat. CCXI, 193.

ANREP, G.V. (1936) Lane Medical Lectures Univ. Series, Vol. III, 199.

ANREP, G.V. & SEGALL, H.N. (1926) Heart. Vol. XIII, 239.

ASCHOFF, L. (1924) Lectures in Pathology.

— (1933) Introduction in Cowdry, E.V. "Arteriosclerosis".

— (1930) Beihefte Z. Med. Klink, XXVI, 1.

— (1939) Arteriosclerosis. J.A.M.A. CXIII, 1046.

— (1939) Klin Wchnschr. XVIII, 656.

BENSON, R.I. (1926) Arch. Path. & Lab. Med. II, 876.

BIEBL, M. & WICHELS, P. (1925) Virchow. Arch. f. Path. Anat. CCLVII, 182.

BLANE, G. (1876) Med. Chir. Trans. IV, 133.

BLOOM, D., KAUFMANN, S.R. & STEVENS, R.A. (1942) Arch. Dermat. & Syph. XLV, 1.

BLUMGART, H.L., SCHLESINGER, M.J. & DAVIS, D. (1940) Am. Heart J. XIX, 1.

BOUILLAUD, J.B. (1825) Traité Clinique des Maladies du Coeur.

BUCHNER, F. & LUFT, V.C. (1936) Beitr. z. Path. Anat. XCVI, 549.

CAMPBELL, /

CAMPBELL, J.S. (1929) Quart. J. Med. XXII, 247.

CASSIDY, Sir M. (1946) ~~Haverian~~ Harveian Oration. Lancet II, 6426.

CHRISTIAN, H.A. (1925) North. Western. Med. (Dec.)

COOMBS, C.F. (1930) Quart. J. Med. XXIII, 233.

CRUVEILHIER, J. (1829) Anatomie Pathologique du Corps Human.

DENNY, F.P. (1936) New Eng. J. Med. CCXIV, 769.

DOCK, W. (1943) North. Carolina Med. J. IV, 457.

— (1946) J.A.M.A. CXXXI, 875.

— (1941) J. Ex. Med. Vol. 74, 177.

EBRIGHT, G.E. (1914) J.A.M.A. LXII, 201.

ECKSTEIN, E.R., GREGG, D.E. & PRITCHARD, W.H. (1941) Am. J. Physiol. CXXXII, 351.

ENGELBERG, H. & NEWMAN, B.A. (1943) J.A.M.A. CXX, 1167.

ENGLISH, J.P., WILLIUS, F.A. & BERKSON, J. (1940) J.A.M.A. CXV, 1327.

ERDHEIM, J. (1930) Virchows Arch. f. Path. Anat. CCLXXVI, 187.

ESSEX, H.E., WIGRIA, R.G.E., HERRICK, J.F. & MANN, F.C. (1940) J.A.M.A., XIX, 554.

EULENBURG, A. (1878) Cyclop. of Pract. Med. Vol. XIV, 32.

FALK, O.P.J. (1942) J. Missouri. M.A. Vol. XXXIX, 162.

FELLNER, Quoted by Falk.

FISCHER-WASELS, B. (1905) Munchen Med. Wchnschr. Vol. LII, 46.

FISCHER- WASELS, /

FISCHER-WASELS, B. (1905) Deutsche. Med. Wchnschr. XXXI, 1713.

—— (1933) Frankfurt. Ztschr. f. Path. XLV, 1.

—— (1934) Geneva International Labour Office. II, 349.

FISHER, R.L. & SUKERMAN, M. (1946) J.A.M.A. Vol.CXXXI, 385.

FORBES, J. (1876) Cyclop. Pract. Med. Article Angina Pectoris.

FRENCH, A.J. & DOCK, W. (1944) J.A.M.A. Vol. CXXIV, 1233.

FUJINAMI, (1900) Virchows Arch. f. Path. Anat. IX, 447.

GAIRDNER, W.T. (1876) A System of Medicine. Reynolds, p. 535.

GIBSON, A.G. (1925) Lancet, II, 1270.

GOLLWITZER, M.K. & KRUGER, E. (1935) Arch. f. d. ges. Physiol. CCXXXVI, 594.

GORDINIER, H.C. (1924) Am. J. Med. Sc., Vol. CLXV, 250.

GORHAM, L.W. (1920) Albany Med. Ann. Vol. XLI, 109.

GROSS, L., EPSTEIN, E. & KUGEL, M. (1934) Am. J. Path. Vol. X, 253.

GROSS, L. (1921) The Blood Supply of the Heart.

HALL, G.E., ETTINGER, G.H. & BANTING, F.G. (1936) Canad. Med. A.J. Vol.XXXIV, 9.

HAMILTON, W.F. & DOW, P. (1939) Am. J. Physiol. Vol. CXXV, 48.

HAMMAN, L. (1926) John Hopkins Hosp. Bull. Vol.XXXVIII, 273.

HEBERDEN, /

HEBERDEN, W. (1772) Medical Trans. of College of Physicians. Vol. II.

HEDLEY, O.F. (1933-37) Public Health Reports. Vol. LIV, 972.

HEINLEIN, H. (1935) Virchow's Arch. f. Path. Anat. CCXCVI, 448.

HERRICK, J.B. (1912) J.A.M.A. Vol. LIX, 2015.

— (1918) Trans. Assoc. Am. Phys. May.

— & NUZUM, F.R. (1918) J.A.M.A. Vol. LXX, 67.

— (1919) J.A.M.A. Vol. LXXII, 387.

HILPERT, H. (1938) Klin. Wchnschr. XVII, 1300.

HIRSCH, S. (1942) Arch. de Biol. LIII, 513.

— & SPALTEHOLZ, W. (1907) Deutsche Med. Wchnschr. XX.

HOCHHAUS, H. (1911) Deutsch. Med. Wchnschr. Vol. XXXVI, 2065.

HOFFMANN, M.A. (1936) Minnesota Med. XIX, 512.

HOME, E. Quoted in Osler. Angina Pectoris and Allied States. 1897.

HOPE, J. (1831) A Treatise on the Diseases of the Heart and Great Vessels.

HUEPER, W.C. (1941) Medicine. Vol. XX, 397.

— & LANDSBERG, J.W. (1940) Arch. Path. XXIX, 643.

— (1945) Arch. Path. XXXIX, 54.

JENNER, E. (1827) Baron's Life of Jenner.

JENSEN, J. (1937) J. Missouri M.A. XXXIV, 77.

JERGESEN, F.H. (1933) Arch. Path. XVI, 340.

JOSUE, /

JOSUE, Mo. (1903) Compt. Rend. Soc. de Biol. LV, 1374.

KATZ, L.N., LINDNER, E., WEINSTEIN, W., ABRAMSON, D.I. & JOCHRIM, K. (1938) Arch. Internat. de Pharmacodyn et de Thérap. LIX, 399.

KATZ, L.N. & JOCHRIM, K. (1939) Am. J. Physiol. CXXVI, 395.

KATZ, L.N. & LINDNER, E. (1939) J.A.M.A. CXIII, 2116.

KOEBSCH, F. (1936) J.A.M.A. CVIII, 888.

KOUNTZ, W.B., PREASON, E.F. & KAING, K.F. (1934) J. Clin. Invest. Vol. XIII, 1065.

KREMER, D.N. (1936) Arch. Int. Med. Vol. LVII, 999.

LAENNEC, R.T.H. Traité de L'Auscultation, 2nd Ed.

LATHAM, P. (1876) New Sydenham Society, Vol. I, 453.

LAWS, G.C. (1898) J.A.M.A. XXXI, 793.

LE ROY, G.V., FENN, G.K. & GILBERT, H.C. (1942) Am. Heart J. XXIII, 637.

LESSER, M.A. (1942) New Eng. J.M. Vol. CCVI, 51.

LEVINE, S.A. & TRANTER, C.L. (1918) Am. J. Med. Sc. Vol. VIII

—— (1922) J.A.M.A. Vol. LXXIX, 928.

—— (1929) (Quoted by Richter) Medicine, Vol. VIII, 245.

—— & HIONDLE, J.A. (1945) New. Eng. J. Med. Vol. CCXXX, 657.

LIBMAN, E. (1919) Trans. Assoc. Am. Phys. Vol. XXXIV, 138.

LONGCOPE, W.T. (1922) Ill. Med. J. Vol. XLI, 186.

LOWY, /

LOWY, J. (1924) Die Klink der Berufskrankheiten. Vienna Heim. 392.

MACKENZIE, J. (1923) Angina Pectoris. Oxford Med. Publications.

MANNING, G.W., McEACHERN, C.G. & HALL, G.E. (1939) Arch. Int. Med. LXIV, 661.

MASTER, A.M., DACK, S. & JAFFRE, H.L. (1939) Arch. Int. Med. LXIV, 767.

— (1947) Am. H.J. Vol. XXXIII, 135.

MAXIMOW, A.A. & BLOOM, W. (1938) Text Book of Histology, 3rd ed.

MAYO, W.J. (1935) Proc. Staff. Meeting. Mayo Clinic, X, 393.

MEISSEN, H. (1937) Beitr. z. Path. Anat. u.z. Allg. Path. XCIX, 329.

— (1938) Klin. Wchnschr. XVII, 142.

MEIXNER, K. & MAYHOFER, A. (1921) Vierteljahrsschr f. Gerichtl. Med. LXI, 228.

MELVILLE, K.I. (1933) J. Pharmacol. & Exper. Therap. XLVII, 355.

MORGAGNI, J.B. Quoted by Schroetter.

MOYER, C.A. & MADDOCK, W.G. (1940) Arch. Surg. XL, 277.

MULLER, C. (1938) Acta Med. Scandinav. Supp. LXXXIX, 75.

McNEE, J.W. (1925-26) Quart. J. Med. Vol. XIX, 44.

OBRATRZOW, W.P. & STRASCHESKO, N. (1910) Zischr. f. Klin. Med. Vol. LXXI, 116.

OSLER, W. (1897) Lectures on Angina Pectoris and Allied States.

PARKINSON, J. & BEDFORD, D.E. (1928) Lancet, Vol. I. 4.

PARRY, C. /

PARRY, C. (1799) An Inquiry into the Symptoms and Causes of the Syncope Angiosa commonly called Angina Pectoris.

PATERSON, J.C. (1936) Arch. Path. Vol. XXII, 313.

PAUL, F. (1931) Virchow's Arch. f. Path. Anat. CCLXXXII, 256, 327.

PAULLIN, J.E. (1921) South Med. Journal. XIV, 16.

POISSEUILLES, J.L.M. Quoted by Fishberg. Hypertension and Nephritis, 4th Ed.

POWELL, R.D. (1910) System of Medicine. Allbut & Rolleston.

PRINZMETAL, M., SIMKIN, B., BERGMAN, H.C. & KRUGER, H.E. (1947) Am. Heart J. , XXXIII, 420.

PRINZMETAL, M., KAYLAND, S., MARGOLES, C. & TRAGERMAN, L.J. (1942) J. Mt. Sinai Hosp. VIII, 933.

RAAB, W. (1939) Ztschr. f.d. ges Exper. Med. CV, 657.

RABNOFF, O.D. & PLOTZ, M. (1946) Medicine. XXV, 285.

RATHE, H.W. (1942) J.A.M.A. CXX, 99.

RECKLINGHAUSEN, Von F.D. & ZENKER, F.A. (1891) Verhandl. d 10 Int. Med. Cong. Berlin,

REGISTRAR GENERAL'S REPORTS. (1930-32).

RICHTER, M.A. (1934) Chicago Med. Soc. (Feb. & March).

RIESMAN & HARRIS Quoted by Richter.

ROBERTS, S.R. (1931) Am. H. Journal. Vol. VII, 21.

RUHL, A. (1933) Arch. f. Exper. Path. u. Pharmakol. CLXXII, 568.

— (1929) Arch. f. Exper. Path. u. Pharmakol. CXLV, 255.

SCHMIEDL, /

SCHMIEDL, H. (1913) Frankfurt Ztschr. f. Path., XIII, 45.

SCHROETTER, L. (1876) Cyclop. of Pract. Med., Vol. VI, 259.

SCHULTZ, E. (1938) Herzen Klin. Wchnschr. XVII, 75.

SMITH, C., SAULS, C. & MALLEW, J. (1942) Ann. Int. Med. Vol. XVII, 681.

— — — (1942) Ann. Int. Med. Vol. XVII, 162.

SPALTEHOLZ, W. & HOCHREIN, M. (1932) Arch. f. Exper. Path. U. Pharmakol, CLXIII, 333.

SPALTEHOLZ, W. (1907) Vermandl d anat. Gesellsch. XXI, 141.

STAEMMLER, M. (1935) Virchow's Arch. f. Path. Anat. CCXCV, 366.

— (1936) Klin. Wchnschr. XV, 404.

STIEF, A. & TOKAY, L. (1935) J. Nerv. & Ment. Dis., LXXXI, 633.

STOKES, W. (1854) "Diseases of the Heart and the Aorta."

STRAUSS, L.H. (1936) Ztschr. f. d. ges Exper. Med., XCVIII, 603.

THAYER, W.S. (1923) International Clin. Vol. I, Series XXXIII.

THOREL, C. (1915) Ergebn. d. Allg. Path. U Anat. XVIII, 1.

TROUSSEAU, A. (1865) Clinique Med. English Translation. Vol. I, 602.

UNITED STATES BUREAU OF THE CENSUS VITAL STATISTICS. (1942) Vol. I.

WEARN, /

WEARN, J.T. (1923) Am. J. Med. Sc. Vol. CLXV, 250.

-- METTIER, S.R., KUMPP, T.P. & ZSCHIESTE, L.J. (1933) Am. H. J. Vol. IX, 143.

WEARN, J.T. (1940) Harvey Lectures. Vol. XXXV, 243.

WEICKER, B. (1940) Deutsches Arch. f. Klin. Med. CLXXXV, 393.

WHITE, P.D. Heart Disease. p. 609.

WIGGERS, C.J. (1936) The Physiology of the Coronary Circulation in Diseases of the Coronary Arteries and Cardial Pain.

WINTERNITZ, M.C., THOMAS, R.M. & LE COMPTE, P.M. (1937) Am. H. J. Vol. XIV, 399.

WOLFF, L. & WHITE, P.D. (1926) Boston Med. & Surg. J. CXCV, 13.

WRIGHT, I.S. & MOFFAT, D. (1934) J.A.M.A. CIII, 318.