HYPERTENSIVE AND ISCHÆMIC HEART DISEASE : A COMPARATIVE CLINICAL AND PATHOLOGICAL STUDY

BY

C. V. HARRISON AND PAUL WOOD

From the Departments of Pathology and Medicine, Postgraduate Medical School of London, Hammersmith Hospital

Received December 18, 1948

Hypertension and coronary sclerosis have been the subject of extensive study, yet they have many aspects that are still poorly understood. In the present work we have tried to ascertain how far they are dissociated and how far they overlap, and in particular we have studied their effects on the circulatory capacity of the coronary tree by injection and radiography.

Over a period of four years, from 1935 to 1939, we made a careful clinical study of most of the cases of ischæmic and hypertensive heart disease admitted to the wards of the Hammersmith Hospital. A total of 189 cases was analysed, of which 55 per cent were hypertensive, 30 per cent were ischæmic, and 15 per cent were mixed. Sooner or later some of these cases came to autopsy and so provided our chief material.

Each patient was classified in an arbitrary fashion, on clinical grounds, before the necropsy was made: those with angina pectoris or with myocardial infarction being considered to have ischæmic heart disease whatever the level of the blood pressure; those with high blood pressure and without angina or myocardial infarction being considered to have hypertensive heart disease.

The diagnosis of angina pectoris was made entirely on the history; that of myocardial infarction rested on well-known electrocardiographic criteria. Only patients with systolic blood pressures over 200 mm. and diastolic blood pressures over 100 mm., known to have been persistent, were included in the hypertensive series. In all there were twenty-seven hypertensive and fifteen ischæmic cases. In addition, twelve normal hearts were included in the pathological study to serve as controls.

In the hope of learning something about the factors governing cardiac enlargement, and in order to facilitate correlation between the clinical and pathological findings, an attempt was made to

divide the cases into subgroups. Subdivision of the fifteen ischæmic cases proved too difficult, however, and was finally abandoned in favour of Table I; for it was not clear whether a profitable subdivision should be based on the height of the blood pressure, on the duration of myocardial ischæmia, or on the duration of heart failure; moreover, the blood pressure was not known prior to myocardial infarction in some instances.

The twenty-seven hypertensive cases, which followed a simpler course, were subdivided according to their stage of development when death intervened as follows.

(1) No cardiac symptoms: Cases 24, 47, 60, and 69. Death was from pulmonary embolism in Case 24, from cerebral hæmorrhage in Case 47, and from uræmia in Cases 60 and 69.

(2) Effort dyspnœa only: Cases 23, 36, 39, 43, 44, and 65. Death was from cerebral hæmorrhage in Cases 23 and 44, from herniotomy in Cases 36 and 39, from pneumonia in Case 43, and from hæmatemesis from peptic ulcer in Case 65.

(3) Left ventricular failure: Cases 11, 13, 19, 41, 45, and 68. Death was from cerebral hæmorrhage in Case 11, from uræmia in Cases 13, 19, 41, and 45, and from bronchopneumonia in Case 68.

(4) Full course—death in congestive heart failure: Cases 8, 32, 38, 58, 62, and 63 followed previous manifestations of left ventricular failure; Cases 28, 48, 49, 50, and 53 had no such previous manifestations.

CLINICAL FEATURES

Owing to the arbitrary nature of the clinical grouping, the complaint was necessarily one of pain in those with ischæmic heart disease: in ten it was the presenting feature, but in five it was less evident than dyspnœa. For the same reason pain was not present in the hypertensive group, except in an

TABLE I
ISCHEMIC CASES

Case No.	B.P.	Duration of angina (months)	Duration of myocardial infarction (months)	Duration of L.V. failure (months)	Duration of congestive heart failure (months)	Weight of patient
17	—	nil	<1	<1	nil	12 st. 6 lb.
22	+	24	24	24	nil	6 st. 7 lb.
25	—	24	10	nil	nil	—
29	+	30	<1	nil	nil	—
30	+	nil	20	18	1.5	8 st. 7 lb.
37	—	1	1.5	2.5	2.5	—
40	—	nil	9	8	nil	13 st. 1 lb.
42	++	18	nil	nil	nil	9 st. 4 lb.
46	+	24	15	terminal	terminal	10 st. 0 lb.
51	+	nil	<1	terminal	terminal	12 st. 6 lb.
52	—	24	24	3	3	10 st. 2 lb.
55	+++	12	nil	36	terminal	12 st. 9 lb.
66	—	60	<1	<1	terminal	11 st. 0 lb.
70	—	12	<1	<1	<1	—
73	+	6	1	1	1	—

Note.—The blood pressure is recorded as + when it was in the region of 160–180/80–100 at its highest. In Case 42 it was higher than this, but only for a short time; Case 55 was originally classed as hypertensive, but had to be transferred to the ischaemic group owing to the development of angina. Case 37 was complicated by rheumatic heart disease with organic mitral incompetence.

atypical form which will be described later, but dyspnoea was invariable in those with cardiac symptoms.

There was a high incidence of rheumatic fever in both groups, four out of fifteen with ischaemic heart disease, and six out of twenty-seven with hypertensive heart disease. In two of each group the first attack had been in childhood, but in the remainder it had occurred in the third and fourth decades, and from the description might well have been rheumatoid arthritis. There was nothing else of significance in the previous history.

Personal and family history. The back-ground of these patients—their environment in childhood and later life, their private lives, their occupations, their relaxations, their habits and their reactions to the world in which they lived—seemed ordinary.

Cardiovascular disease was described in one or other or both parents in four of the ischaemic and in three of the hypertensive patients; but its exact nature, whether ischaemic or hypertensive, could not be ascertained.

Sex and age. There were twice as many males as females in the ischaemic group, whereas the proportion was equal in the hypertensive group. This difference is significant and well known. It was even more conspicuous in the larger clinical series. The sex distribution of the mixed cases was the same as of those with hypertension.

In the ischaemic group the average age for the men was 57 and for the women 68; in the hyper-

tensive group the figures were 59 and 55 respectively. The point of interest is the older age of women with ischaemic heart disease. This, too, is now well known.

Duration and onset. The average duration of life from the onset of cardiac symptoms was 1.9 years for those with ischaemic heart disease, and 2.2 years for those with hypertensive heart disease. Since the period during which these investigations were carried out was only about four years, and since only those cases that died were included in the series, these figures do not indicate the true prognosis of the diseases in question.

Seven of the ischaemic cases began with angina pectoris, four with dyspnoea on exertion. Of those with dyspnoea, one had rheumatic heart disease and another had hypertensive heart disease as well as occlusive coronary atherosclerosis. Thus only two of those with pure ischaemic heart disease started their symptoms with dyspnoea.

In the hypertensive group, on the other hand, seventeen out of twenty-three with cardiac symptoms complained first of breathlessness; the initial symptom was fatigue in four of the remainder, and dropsy in the other two.

Course. Six ischaemic patients recovered sufficiently after the onset of cardiac symptoms to resume work without distress. The duration of this improvement was six months to two years. The work undertaken was not light, and one of them worked as a navvy for a year after his first myocardial

infarction. Thirteen out of the fifteen ischæmic cases developed myocardial infarction sooner or later; the two that died without this development were complicated, one by polycythæmia vera, the other by hypertensive heart disease. Six patients had paroxysmal cardiac dyspnœa following myocardial infarction, and five of these later developed systemic congestion. Two others had heart failure with systemic congestion without evidence of preceding left ventricular failure.

In the hypertensive group recovery of function was rare after the onset of cardiac symptoms, and was observed in only two out of twenty-three patients. Both experienced acute pulmonary œdema on unaccustomed effort, and subsequently recovered to the extent that they remained free from all symptoms for several months, even though they carried out their normal duties. In the remainder the condition steadily deteriorated.

The full course of hypertensive heart disease was witnessed in six patients: effort dyspnœa progressed to left ventricular failure at rest, and this was followed by failure with systemic congestion. The average duration of life after cardiac symptoms appeared was two years and one month, the range being six to forty-eight months.

Five cases gave no history of orthopnœa or paroxysmal cardiac dyspnœa, but after a period of effort dyspnœa developed heart failure with systemic congestion. Occasionally, the initial symptom was dropsy. The average duration of life from the onset of cardiac symptoms was two years and five months in this group, the range being six to eighty-four months.

Six patients died from non-cardiac causes at the stage of left ventricular failure—four from uræmia, one from cerebral hæmorrhage, and one from bronchopneumonia. The duration of cardiac symptoms in this group was twelve months (1 to 24 months).

Six patients died from non-cardiac causes at the stage of effort dyspnœa—two from cerebral hæmorrhage, two following herniotomy, one from pneumonia, and one from hæmatemesis due to peptic ulcer. The average duration of cardiac symptoms was two years and three months (1 to 84 months).

The remaining four cases had no cardiac symptoms. Two died with uræmia, one from cerebral hæmorrhage, and one from pulmonary embolism.

Thus the courses of ischæmic and hypertensive heart disease were similar in that left ventricular failure usually preceded failure with systemic congestion; they were dissimilar in that temporary recovery of function followed the onset of cardiac symptoms in about a third of the ischæmic cases, whereas steady deterioration characterized those

with hypertension. It is interesting and important that only one patient initially classed as hypertensive was transferred later to the ischæmic group because of the development of angina pectoris or myocardial infarction.

INCIDENTS IN THE COURSE OF HYPERTENSIVE HEART DISEASE

During the course of hypertensive heart disease certain events were observed that deserve special comment, for their significance was clinically obscure. Pathological studies clarified some of them.

Case 8. At one stage this man was severely constipated, and developed atypical chest pain followed by a lower blood pressure than usual, by a weaker cardiac impulse, and by left ventricular failure. The electrocardiogram showed low voltage QRS complexes and flat T waves in all leads. At necropsy, the heart showed marked left ventricular hypertrophy and weighed 695 g. In the skiagrams the coronary arteries appeared to be slightly smaller than those seen in other hypertensive hearts of similar weight, and their outlines were rather irregular; there were, however, no points of severe narrowing. The cardiac muscle showed patchy fibrosis at the base of the left ventricle posteriorly. The attack may have been due to temporary coronary insufficiency (Master *et al.*, 1947).

Case 19. For two years in this case there was frequent complaint of an ache behind the right shoulder, aggravated by exertion, and sometimes accompanied by a dull heavy ache in both arms. Latterly it was never mentioned. At autopsy, the left ventricle was hypertrophied and the heart weighed 480 g. Skiagrams showed coronary arteries of good size and with smooth outlines. There was no evidence of coronary narrowing nor of myocardial damage. It is concluded that the pain was not ischæmic.

Case 24. Six weeks before death this woman was seized with substernal pain, accompanied by pallor, sweating, cold skin, marked drop in blood pressure, and slight hæmoptysis. Serial cardiograms revealed the characteristic pattern of massive pulmonary embolism. The heart weighed only 340 g. The coronary arteries were larger than normal. There was no sign of coronary narrowing or myocardial damage. The presence of a relatively recent massive pulmonary embolism was confirmed.

Case 51. This man's symptoms began with acute pulmonary œdema after climbing some stairs. He was admitted with the diagnosis of acute myocardial infarction; but there was no convincing evidence of this. Cardiograms, however, were not obtained. The heart weighed 495 g. Skiagrams showed the coronary arteries to be narrowed with irregular

outlines. There was complete occlusion of the right recurrent branch, and a recent infarct at the base of the left ventricle posteriorly. The original diagnosis was correct and subsequent clinical judgment at fault.

Case 38. While in hospital this patient had an attack of severe substernal pain. Pallor and coldness of the skin were associated, and pericardial friction was heard later. But the blood pressure did not alter, and there were no electrocardiographic changes. The heart weighed 738 g. There was an organizing fibrinous pericarditis. Skiagrams showed the coronary arteries to be large with smooth outlines. There was no narrowing and no myocardial damage. Pericarditis was responsible for the pain.

Case 53. This woman had severe attacks of paroxysmal cardiac dyspnoea associated with syncope and substernal pain or choking. She also had attacks of left breast pain which radiated down the left arm and lasted two days. When the venous pressure was high she complained of præcordial tightness; this was twice relieved by venesection. The heart weighed 555 g. Skiagrams showed coronary arteries of good size with smooth outlines. There was no narrowing and no myocardial damage. Pain might have been due to transient coronary insufficiency associated with left ventricular failure.

Case 63. After partial recovery from left ventricular failure this man was pulled up on effort by a choking sensation in the throat accompanied by vague præcordial pain. Dyspnoea always preceded this sensation. Rest brought quick relief. The heart weighed 900 g. (the largest in the series). The coronary arteries were greatly enlarged and showed smooth outlines free from any points of narrowing. Histologically the myocardium was healthy except for a few microscopic points of fibrosis at the apex and base of the left ventricle. The fibrosis was focal and of the type frequently seen with myocardial ischæmia. The findings suggest that in spite of their enlargement the coronary arteries may have been inadequate to supply the enormous bulk of cardiac muscle, and pain may have been due to relative coronary insufficiency.

Case 65. This woman, during the last two months of her life, developed substernal pain on effort, radiating to the right side of the neck, to the axillæ, and passing down the inner sides of both arms to the elbows. It lasted ten minutes or so, and was associated with numbness and whiteness of the right hand for about twenty minutes. It was worse in cold weather, and was relieved by rest. The heart weighed 450 g. Skiagrams showed the coronary arteries to be of good size and free from narrowing. The myocardium showed no damage. Coronary spasm was probably responsible for the pain.

It is concluded that atypical thoracic pain in the course of hypertensive heart disease may be due to

relative coronary insufficiency associated with left ventricular failure, to coronary spasm, to massive pulmonary embolism, or to pericarditis.

MODE OF DEATH

Thirteen of the fifteen ischæmic cases died from the disease itself—ten of them abruptly and, in a sense, unexpectedly, and the other three slowly in congestive heart failure.

In contrast, only eleven of the twenty-three hypertensive cases with cardiac symptoms died from heart disease. Only two died suddenly—one with a dissecting aneurysm of the aorta, the other while under the influence of too much digitalis. The other nine died slowly in congestive heart failure, and continuous cardiograms at the time of death in three of them showed that the mechanism was not ventricular fibrillation or sudden standstill, but a slowly increasing depression of conduction.

SYMPTOMS AND SIGNS

Cerebral symptoms. Symptoms resulting from disturbances of the cerebral circulation, apart from Cheyne-Stokes breathing, which was associated with heart failure in both groups, were confined to the hypertensive cases, with the exception of one patient with ischæmic heart disease who had a stroke. The following conditions were noted: blurring of vision due to papilloedema (4 cases), sometimes progressing to blindness (2); severe headaches (6); mental deterioration (4); cerebral hæmorrhage (4); cerebral thrombosis (4); and hypertensive encephalopathy (1).

Renal symptoms. Nocturia occurred in five of the ischæmic and in twelve of the hypertensive cases. Uræmia developed in six of those with hypertension, but not in the others.

Peripheral vascular symptoms. Two of the hypertensive group exhibited the Raynaud phenomenon, and one intermittent claudication. Symptoms of peripheral vascular disease were not present in the patients with ischæmic heart disease.

Body-weight. In the ischæmic group body-weights ranged from 6 stone 7 pounds to 13 stone 7 pounds, and on the whole were average. Of the women, two were unduly obese and two were unduly thin; of the men only one weighed more than 13 stone.

In the hypertensive group, six patients were very obese, their weights ranging between 14 and 22 stone. In twelve cases there was considerable loss of weight (1 to 7 stone).

Cardiac rhythm. The rhythm was normal in ten of the fifteen ischæmic cases: permanent auricular

fibrillation was present in one, paroxysmal auricular fibrillation in three, paroxysmal auricular flutter in two, and paroxysmal tachycardia in one. These seven rhythm changes occurred in five different patients. The fact is stressed that permanent auricular fibrillation occurred in only one case; indeed it only occurred once in the larger clinical series of fifty-six cases.

In the hypertensive group the rhythm was normal in twenty-one instances; auricular fibrillation occurred in the remaining six and was permanent in five of them. Other rhythm changes were not observed. Permanent auricular fibrillation occurred in 10 per cent of the larger series.

Of the six patients with auricular fibrillation, four had heart failure; or, putting it in another way, four out of eleven patients with heart failure had auricular fibrillation. Again, out of sixteen hypertensive patients without heart failure, only two had auricular fibrillation.

Contrasting the two groups it is seen that auricular fibrillation is more common in hypertensive than in ischæmic heart disease.

Cardiac impulse. The character of the cardiac impulse was described as forceful or thrusting in only three of the fifteen patients with ischæmic heart disease. Usually it was impalpable. In the hypertensive group, on the other hand, it was described as heaving in nineteen. This difference is considered significant and important.

Valves. Apart from one patient with organic mitral incompetence, due to concomitant rheumatic heart disease, there were no valve lesions in the ischæmic group. Aortic incompetence, however, occurred in four of those with hypertensive heart disease. It might be better described as an aortic leak, and appeared to be due to dilatation of the aortic ring resulting from high blood pressure. There was no peripheral vascular evidence of reflux and the diastolic blood pressure was not lowered. Seven patients had a mitral systolic murmur, and two had a soft mitral diastolic murmur. Both types of murmur were attributed to dilatation of the left ventricle.

Fundi. Apart from one patient with a combination of hypertensive and ischæmic heart disease and one with a single small exudate, the fundi were normal in the ischæmic group. In those with hypertension, on the other hand, marked hypertensive retinopathy with papilloedema, exudates, and hæmorrhages occurred in seven instances, exudates and hæmorrhages without papilloedema in one, and either exudates or hæmorrhages alone in two others.

It may be concluded that significant changes in the fundi are part of the hypertensive picture and do not occur in association with ischæmic heart

disease in the absence of diabetes (there were no such cases in this series).

Peripheral arteries. In eight out of the fifteen ischæmic cases the peripheral arteries were hardened. Eleven of the twenty-seven patients with hypertension had similar vessels; in the remainder the arteries were unduly firm and rubbery, but could not be described as hard.

X-ray appearances. The hearts of ischæmic cases were enlarged only when there was evidence of past or present failure, hypertension, or some other form of heart disease. Since only one patient had permanent auricular fibrillation it is not possible to comment upon the effect of this rhythm on the size of the ischæmic heart; for in that one case there was concomitant rheumatic heart disease with organic mitral incompetence. No instance of cardiac aneurysm was observed, but absence of pulsation in the region of the infarct was sometimes noted. Following heart failure (all those with failure had myocardial infarction), an enlarged cardiac shadow was always seen, the left ventricle being mainly involved.

In the hypertensive group the largest heart shadows were those associated with congestive failure. Cases without symptoms, or with effort dyspnoea only, showed slight to moderate enlargement of the left ventricle.

It is concluded that uncomplicated ischæmic heart disease does not cause cardiac enlargement, that uncomplicated hypertension causes hypertrophy of the left ventricle, and that heart failure is responsible for maximum cardiac enlargement in both groups.

Electrocardiograms. In the ischæmic group cardiographic changes were those of myocardial infarction when present. The features indicated anterior infarction in the first instance in seven, and posterior in four. Two showed signs of both anterior and posterior infarction, and two had normal curves.

In the hypertensive group sixteen out of twenty-four showed left axis deviation with depression of the RS-T segment in lead I, and of these eight also showed inversion of the T wave in lead I, and three inversion of the T wave in leads I and II. Two patients had left bundle-branch-block. Two had left axis deviation without other changes. In the remaining four there was no axis deviation but there was inversion of the T wave in lead I (Case 49), in leads I and II (Case 8), in leads II and III (case 69), and in leads I, II, and III (Case 19). All those with heart failure showed significant changes.

It is concluded that left axis deviation with depression of the RS-T segment with or without inversion of the T wave in lead I, or in leads I and II, is the

typical cardiographic pattern of severe hypertensive heart disease: this pattern was not observed in a single case of myocardial ischaemia. In cases of old-standing anterior myocardial infarction with persistent inversion of the T wave in lead I, there was no depression of the RS-T segment.

The hypertensive pattern with T I inverted was found in a third of the hypertensive group and in two out of twenty-eight mixed cases in the larger clinical series.

Blood pressure. The average blood pressure of six ischaemic cases prior to myocardial infarction was 180/95: after infarction the average pressure in eleven cases was 125/80. In the majority many readings were obtained: the highest average figure following infarction was 160/110. In two patients the blood pressure was taken immediately after an attack of myocardial infarction and was found to be elevated: in both these cases it dropped slowly following the initial rise and did not reach its lowest level until the third or fourth day. This delayed fall of blood pressure following myocardial infarction, with or without an initial rise, has been observed repeatedly in other cases in the clinical series. Attention is drawn to this fact and also to the frequency of moderate elevations of blood pressure found in ischaemic heart disease prior to myocardial infarction, elevations that are rarely accompanied by enlargement of the heart. Of fifty-six cases in the clinical series the blood pressure was less than 165/95 in 74 per cent.

The blood pressures of the hypertensive cases were necessarily high owing to the arbitrary classification employed. The average range was 245/140–190/115. The highest individual figure was 300/170, and the lowest 110/80. There were several features of interest.

First, there was no case in which the blood pressure was observed to drop as a result of heart failure. A terminal fall was common, but heart failure had often preceded this by weeks, months, or years.

Secondly, when the blood pressure fell much, there was usually an obvious cause. This was hæmorrhage in one case, shock from a strangulated hernia in another, massive pulmonary embolism in a third, and impending death in two others.

Thirdly the onset or cessation of auricular fibrillation, which was observed in Case 38, did not effect the blood pressure, whether there was heart failure or not (when there was fibrillation the pressure recorded was that at which most of the beats came through, and not the maximum pressure which was always higher).

Fourthly, two patients usually had normal pressures when at rest in bed, whether in heart failure or otherwise; but when up and about the figures

climbed to over 200/110 with or without heart failure. One of these patients lived for seven years following the onset of cardiac symptoms—a record for the series.

Renal function. No case of pure ischaemic heart disease was complicated by serious impairment of renal function as judged by urine concentration and by the urea clearance test. In the whole ischaemic group there was only one case with bad renal function, and that was a case with associated hypertensive heart disease. Even albuminuria was very rare apart from heart failure.

The hypertensive cases, on the other hand, frequently showed considerable impairment of renal function, and six of them died with uræmia. Twelve out of twenty-seven had less than 44 per cent of normal renal function as judged by the urea clearance test. Albuminuria occurred in all but one; granular casts were found in seven; there was considerable impairment of urine concentration in ten.

It may be concluded that impairment of renal function is a feature of the hypertensive state, and is unrelated to ischaemic heart disease.

Blood count. There was not a single case with anæmia in the ischaemic group, but there were two with polycythæmia. In contrast to this, nine hypertensive patients were anæmic, the red cell count being under 4,000,000 per c.mm., or the hæmoglobin being under 60 per cent.

DIFFERENCE BETWEEN ISCHÆMIC AND HYPERTENSIVE HEART DISEASE

The chief differences between ischaemic and hypertensive heart disease are shown in Table II. The evidence is based on the clinical features alone, and will be reviewed later in the light of the autopsy findings which were not known when the table was compiled.

PATHOLOGICAL FINDINGS

To obtain the desired pathological information, a technique had to be devised that would enable us to form an accurate estimate of the capacity of the coronary lumina during life, to trace the exact position of any vascular or myocardial lesions, and to preserve the tissues for histological study. It was decided that these requirements would be met by injecting the coronary arteries with a radio-opaque gel, followed by radiography and subsequent clearing of the whole heart after the method of Gross (1921). In order that the degree of vascular distension should be comparable with that obtained during life, all cases were injected at the known diastolic pressure of the patient. The only

TABLE II
THE CHIEF DIFFERENCES BETWEEN ISCHÆMIC AND HYPERTENSIVE HEART DISEASE

Feature	Ischæmic cases (15)	Hypertensive cases (27)
Complaint	Pain.	Breathlessness.
Sex	Male : female = 2 : 1.	Male : female = 1 : 1.
Age	Males av. 56.5 years. Females av. 67.8 years.	Males av. 59.2 years. Females av. 54.6 years.
Onset	Dyspnœa in 20%. Usually pain.	Dyspnœa in 75%. Sometimes fatigue or dropsy.
Course	Temporary good recovery in 40%. Myocardial infarction in 13 out of 15.	Temporary good recovery in less than 10%. Development of infarction necessitating change of classification—1 case.
Mode of death	Cardiac death 13/15 (abrupt 10/13).	Cardiac death in 11/23 (abrupt 2/11).
Symptoms from disturbances of the cerebral circulation.	Rare apart from cerebral thrombosis.	Blurring of vision: 4 Blindness: 2 Severe headaches: 6 Mental changes: 4 Cerebral hæmorrhage: 4 Cerebral thrombosis: 4 Six died with uræmia. Van Slyke less than 44% in 12 out of 27.
Renal failure	Very rare. Renal function tests usually good. Albuminuria rare apart from heart failure.	Albuminuria in all but one. Hypertensive retinopathy in 10 out of 27.
Fundi	Normal in all but one.	Anæmia in 9/27.
Blood count	Anæmia did not occur. Polycythæmia in 2.	
Rhythm	Permanent auricular fibrillation 1.	Permanent auricular fibrillation 5.
Cardiac impulse	Forceful or heaving in 3; usually impalpable.	Heaving in 19; usually located with ease.
Valves	Normal.	Aortic leak in 4.
Blood pressure	Average 180/95 before infarction. Average 125/80 after infarction.	Av. range: 245/140 to 190/115.
X-ray	Normal prior to heart failure.	Slight to moderate enlargement prior to heart failure.
Electrocardiogram	Always enlarged after development of heart failure. Normal or typical changes of myocardial infarction. The pattern described in the hypertensive column was not seen in a single case.	Considerably enlarged after development of heart failure. Left axis deviation with depression of the RS-T segment with or without inversion of the T wave, usually in lead I alone, sometimes in leads I and II, in 75%.

exception to this was in the case of normal controls in which the blood pressure was not known. In these cases a standard pressure of 90 mm. Hg. was used.

The apparatus (Fig. 1) consisted of a simple fluid column leading down from an adjustable container and connected to a mercury manometer. This was filled with warmed normal saline and served to wash out the blood from the coronary vessels and also to supply the required head of pressure for injection. The fluid column lead directly to a Y piece connected to two cannulæ for perfusing the heart, but was connected also to a shunt circuit containing two bottles, one to act as a pressure chamber and the other to contain the injection mass. When this circuit was shut off, the apparatus perfused saline through the coronary vessels; but when the direct circuit was closed and the shunt circuit opened, the saline displaced the air from the pressure chamber into the bottle containing the injection

mass, driving the latter into the cannulæ. The barium-gelatine injection mass was prepared according to the technique of Gross.

Procedure. At autopsy the heart was carefully dissected out, clots were dislodged and the heart weighed. It was then placed in normal saline and left at room temperature until it was injected a few hours later (usually three hours). The proximal parts of both coronary arteries were then defined and under-run with ligatures. Two cannulæ were then tied in, the whole manœuvre being carried out under water at 37° C. This warmed the heart to body temperature and also prevented any bubbles entering the coronary arteries. The heart was then perfused with normal saline at 37° C until the fluid issuing from the coronary sinus was relatively clear (about 1 minute). The circuit was then changed, and the warm gelatine mass injected at the same pressure. When the mass could be seen to have entered the fine arterioles in the pericardium, the

FIG. 1.—Apparatus used for injecting the coronary circulation with barium gel.
For description see text.

heart was placed in iced water until the gelatine had set, and then transferred to a bath of formol-saline for 24 hours. Stereoscopic skiagrams were then taken according to standard technique. The heart was then returned to formol-saline and left to fix for about ten days. Next, four routine blocks of myocardium were excised and frozen sections stained for fat. These were taken from the apices of the left and right ventricles anteriorly and from the bases of the ventricles posteriorly. Special blocks were also taken from other sites as indicated. The heart was then passed through increasing concentrations of alcohol from 30 per cent. to

absolute alcohol, in steps of 10 per cent, remaining about three days in each bath. By this means complete dehydration was obtained in about three weeks.

Old used alcohol was utilized for the lower concentrations, fresh absolute alcohol being employed only for the final one or two baths. This proved satisfactory and saved considerable quantities of alcohol. When the heart was dehydrated it was transferred to a bath of used methyl salicylate and later to fresh methyl salicylate. By this means the tissue was rendered relatively transparent. The coronary vessels, which stood out clearly owing to

the presence of the opaque injection mass, could thus be studied in detail and compared with their skiagrams.

Blocks for section were then taken from the major coronary vessels (8 or more) and from the myocardium (5 or more). The myocardial blocks were obtained from five standard sites: the anterior apical and posterior basal parts of the right and left ventricle, and the upper anterior part of the inter-ventricular septum. Additional blocks were taken from any other sites that showed anatomical changes. The blocks were washed in chloroform over night and embedded in paraffin.

RESULTS

Normal controls. Twelve normal controls, representing each decade of life from the third to the eighth, were examined by the standard technique (Fig. 3 and 7). In no case was there any evidence of heart disease or of high blood pressure either during life or at autopsy. The details of the cases are given in Table III. It is not proposed to discuss in detail the normal findings in injected hearts. This has already been done by Gross (1921) and in so far as the normal anatomy of the coronary tree is concerned, our findings are in agreement with his.

But we would add the important observation that coronary atheroma is compatible with an apparently normal lumen. In all twelve of this series the

skiagrams showed normal coronary outlines (Fig. 3), yet coronary atheroma was subsequently discovered in five, and was severe in three. In this connection it should be noted that the size of the coronary lumen in a paraffin section gives little or no indication of its real size during life. It was repeatedly noted both in normal and pathological hearts that where sections showed coronary narrowing, skiagrams might reveal no abnormality.

It is of course open to question how far such skiagrams reflect the state of the vessels during life; but we believe that, with the technique employed, they give the truest picture that can be obtained from an autopsy specimen. In contrast to the pathological cases, normal controls with atheroma showed no trace of myocardial fibrosis.

A second finding not emphasized by Gross was the relationship between the size of the coronary arteries and the size of the heart. Since all skiagrams were taken by a standard technique the plates are comparable as regards size. In all cases the three major coronary arteries (left anterior descending, left recurrent, and right) were measured near their origins. From their diameters their total cross-sectional area was calculated and plotted against the weight of the heart. The resulting graph (Fig. 2) showed a fairly close scatter around a straight line, and indicates that there is a direct relationship between the bulk of the cardiac muscle and its blood supply.

TABLE III
CONTROL CASES : SIZE OF HEART AND OF CORONARY ARTERY

Case No.	Age	Sex	Heart weight (grams)	Total coronary bore (sq. mm.)	Coronary atheroma (microscopic)	Cause of death
12	22	F	225	27.9	—	Subarachnoid hæmorrhage
35	23	F	213	38.1	—	Polyposis coli
21	24	F	165	18.9	—	Carcinoma of colon
76	34	F	280	29.7	—	Carcinoma of stomach
72	39	M	282	36.5	±	Acute appendicitis
77	47	F	190	32.3	—	Carcinoma of cervix uteri
1	54	M	265	20.0	+	Seminoma of testis
14	55	M	200	28.7	+	Carcinoma of œsophagus
10	56	F	308	32.0	—	Bronchitis
64	61	M	365	59.0	—	Carcinoma of lip
26	73	F	310	39.4	+	Primary carcinoma of liver
27	80	M	400	36.5	±	Cirrhosis of liver
<i>Hypertrophied controls</i>						
67	46	M	495	46.6	—	Cor pulmonale
71	60	M	495	41.8	—	Syphilitic aortic incompetence
54	71	F	585	51.5	±	Osteitis deformans. Heart block
20	60	M	643	44.4	—	Rheumatic mitral and aortic disease
59	64	M	850	71.6	±	Rheumatic aortic incompetence

FIG. 2.—Graph illustrating the linear relationship between the heart weight and the total cross-section of the main coronary vessels in normal controls, controls with hypertrophied hearts, and in cases of hypertensive heart disease.

HYPERTENSIVE GROUP

It soon became apparent that the pathological findings were totally different in the two types of case. Though the differences in morbid anatomy and histology between ischaemic and hypertensive heart disease are well known, the dissimilarity was emphasized by the skiagrams. The ischaemic hearts showed narrow coronary vessels with irregular outlines, and, as a rule, one or more complete occlusions (Fig. 6, 9, and 10). The hypertensive hearts, on the other hand, showed large wide coronary arteries with smooth outlines and no narrowing. There were a certain number that showed evidence of both hypertension and ischaemia.

This group comprised twenty-seven cases of clinical hypertensive heart disease, subdivided into four groups according to their severity (page 205). The main pathological findings are summarized in Table IV.

Heart weight. All but two showed cardiac hypertrophy, the mean cardiac weight for the whole group being 597 g. ± 149 g. It will be noted from Table IV that the degree of cardiac hypertrophy expressed as total heart weight is fairly closely related to the clinical severity of the disease judged by the functional state of the heart. In the cases that ran a full cardiac course and died in congestive failure, the mean weight was 729 g. In the cases that showed evidence of left heart failure but did not die a cardiac death, the mean heart weight was 585 g. In those with effort dyspnoea only the mean weight was 492 g. Finally, in the four cases with no cardiac symptoms, the mean weight was only 406 g.

In all cases the increased cardiac weight was mainly due to left ventricular hypertrophy. Right ventricular hypertrophy was difficult to estimate. Owing to the hearts being cleared intact it was not

TABLE IV
HYPERTENSIVE CASES: SIZE OF HEART AND CORONARY ARTERIES
Died without cardiac symptoms

No.	Age	Sex	Blood pressure	Heart weight (grams)	Total coronary bore (sq. mm.)	Coronary atheroma		Myocardial fibrosis		R.V. hypertrophy	Mode of death
						X-ray	Micro.	Retic.	Focal		
24	63	F	260/120	340	39.0	—	+	—	—	+	Pulmonary embolism
47	63	F	250/130	485	55.2	—	—	±	—	—	Cerebral hæmorrhage
60	46	F	280/140	470	63.0	—	±	+	—	—	Uræmia
69	21	F	250/130	330	25.3	—	—	—	—	—	Uræmia

Died with effort dyspnæa

23	44	F	225/130	425	41.1	—	—	+	—	±	Cerebral hæmorrhage
36	58	F	220/135	545	64.8	—	±	+	—	±	Herniotomy
39	68	M	210/100	525	62.0	—	±	—	—	—	Herniotomy
43	87	F	230/150	440	—	±	+	—	+	+	Pneumonia
44	49	M	290/140	570	60.8	—	+	—	—	±	Cerebral hæmorrhage
65	44	F	230/120	450	42.3	—	±	+	—	—	Hæmatemesis

Died with left ventricular failure

11	56	M	243/125	700	82.4	—	+	+	—	+	Cerebral hæmorrhage
13	67	F	260/125	447	41.1	—	±	+	—	—	Uræmia
19	42	F	260/160	480	40.6	—	±	—	—	—	Uræmia
41	64	F	280/145	575	—	+	+	—	—	±	Uræmia
45	54	F	260/120	660	53.8	—	±	—	—	+	Uræmia
68	67	M	200/125	650	—	±	+	+	—	—	Pneumonia

Died in congestive cardiac failure

8	60	M	250/150	695	—	±	+	+	+	+	
28	69	M	150/120	750	63.8	—	±	+	—	+	
32	50	M	170/115	670	51.7	—	—	+	±	+	
38	53	M	270/140	738	51.5	—	+	—	—	+	
48	51	M	220/125	710	—	±	+	+	±	+	
49	54	F	200/100	810	79.3	—	±	+	±	+	
50	54	M	190/140	820	—	+	+	+	+	+	
53	59	F	190/110	555	41.1	—	±	+	—	+	
58	66	M	210/140	810	78.1	—	±	+	—	+	
62	68	M	220/135	560	—	+	+	—	+	—	
63	60	M	180/110	900	76.1	—	±	+	±	+	

possible to dissect off the right ventricle and weigh it separately; moreover, after clearing, it was considered that estimates of hypertrophy were of doubtful value owing to shrinkage. An attempt was made to estimate the degree of right ventricular hypertrophy histologically and the results are given in Table IV. Hypertrophy was obvious in fourteen cases, slight in four, and absent or unrecognizable in nine. The incidence of right ventricular hypertrophy in the different groups is of interest. In the eleven cases that died in congestive heart failure,

right ventricular hypertrophy was present in all but one: this one was complicated by severe coronary sclerosis. It is assumed that this hypertrophy was due to the strain thrown on the right heart by failure of the left ventricle.

The same explanation may be given for cases of right ventricular hypertrophy in the second group; for although these patients did not die in congestive failure, they had evidence of left ventricular failure during life. In the other two groups there was insufficient left ventricular failure to account for

right ventricular hypertrophy. Case 43, however, was complicated by emphysema, and Case 24 by old pulmonary embolism. The remainder showed very slight, if any, hypertrophy. Apart from hypertrophy the myocardium appeared healthy in twenty-six cases. In the twenty-seventh (Case 62) there was macroscopic evidence of infarction.

Endocardium. One (Case 48) showed calcifica-

tion of the aortic valve of Mönckeberg type, not causing appreciable stenosis or incompetence. All other cases were free from valve disease.

Radiography

It will be most convenient to describe first the typical findings in this group and then to discuss the

FIG. 3.—Normal control. Case 76. Heart 280 g. skiagram of injected heart. Note size of coronary arteries and their smooth outlines. (All skiagrams are 0.6 of natural size and are comparable.)

exceptions. The most striking feature was enlargement of the coronary arteries (Fig. 4 and 5). In 20 this enlargement was conspicuous; the outlines of the coronary lumina were perfectly smooth and there was no suggestion of irregularity or focal narrowing. The degree of coronary enlargement appeared to increase *pari passu* with hypertrophy of the heart. When the three main coronary

arteries were measured in the same way as the controls and their total cross sectional area plotted against the cardiac weight (Fig. 2), a fairly close scatter around a straight line was observed, which proved to be a continuation of that previously described in controls. This strongly suggests that the size of the coronary arteries is dependent on the size of the heart, and that they enlarge in response to

FIG. 4.—Hypertensive heart disease. Case 47, died before cardiac symptoms arose. Heart 485 g. Note enlargement of heart and coronary arteries and the smooth outlines of the latter.

an increased demand. There is, however, an alternative explanation, namely that the coronary arteries are dilated by the raised pressure within them, or that the pressure at which they were injected caused them to dilate more than controls injected at lower pressure. The latter possibility is refuted by the fact that two hypertensive cases (Cases 49 and 53) injected at low pressure (because

the diastolic pressure had fallen some time before death) revealed coronary arteries as large as any injected at higher pressures.

To investigate the possibility that coronary dilatation was the direct result of raised blood pressure during life, we injected five cases of cardiac hypertrophy due to other causes, namely, rheumatic valvular disease (Cases 20 and 59), syphilitic aortic

FIG. 5.—Hypertensive heart disease. Case 49, died of congestive failure. Heart 810 g. Note enormous heart and coronary arteries and the smooth outlines of the latter.

regurgitation (Case 71), cor pulmonale (Case 67) and osteitis deformans (Case 54), all showed a degree of coronary enlargement similar to that seen in hypertensive heart disease (Fig. 2). It is concluded that coronary vascular enlargement is related to cardiac hypertrophy.

Seven out of the twenty-seven cases showed some evidence of occlusive coronary atheroma in the

skigrams. In four (Cases 8, 48, 43, 68) this was slight; constituting no more than minor irregularities of outline and relatively small calibre in relation to the size of the heart; there were no points of gross narrowing. In three of these cases the myocardium showed a few small foci of fibrosis: in the fourth no lesion was detected. Each of the other three (Cases 41, 50, 62) showed severe coronary sclerosis

FIG. 6.—Ischæmic heart disease. Case 66. Heart 565 g. Note narrow irregular, calcified coronaries with several occlusions.

with narrowing of the lumen, at least one complete occlusion, and evidence of myocardial ischæmia. Clinically it is interesting to note that Cases 50 and 62 died suddenly. Case 41 died in uræmia.

Cleared specimens. All cases were subjected to "clearing" in methyl salicylate, the cleared specimens (Fig. 8) being compared with the skiagrams. This confirmed the conclusions drawn from the

latter and was of great value in selecting segments of the coronary vessels for histology. It did not, however, add any further information. Cleared specimens were not used for measurements owing to the shrinkage that occurs in the process of clearing.

Histology. Coronary arteries. Twenty-three cases (all but Cases 23, 32, 47, and 69) showed histological evidence of atheroma; yet the skia-

FIG. 7.—Normal control. Case 35. Heart weight 213 g. Cleared specimen showing white injection mass filling lumen of coronary arteries. Note the perfectly smooth outlines.

grams of sixteen of them exhibited normal coronary outlines, confirming the observation made in the controls that atheroma need not narrow the lumen. Atheroma in these cases was relatively slight and of patchy distribution. The seven cases that showed narrowing or irregularity of the arteries in the skiagrams all showed severe and generalized atheroma histologically. Two other features deserve com-

ment. In adult life normal coronary arteries have a well developed intima thicker than that of other arteries of similar size (von Glahn, 1936). In the hypertensive cases this layer tended to be thicker than in controls. Secondly, the media was hypertrophied.

An unexpected finding was polyarteritis nodosa in Case 32. This affected the majority of the small

FIG. 8.—Hypertensive heart. Case 36. Heart weight 545 g. Cleared injected specimen showing dilatation of coronary lumen and smooth outlines, indicating absence of occlusive coronary atheroma.

arteries throughout the body, but most of the coronary vessels were spared.

Histology. Myocardium. Evidence of hypertrophy has already been described. In addition, however, necrosis was seen in two cases. In Case 62 there were recent infarcts at both the apex and base of the left ventricle following severe coronary atheroma and thrombosis. In Case 41 there were numerous adjacent foci of infarction at the apex of the left ventricle, following thrombosis of the descending branch of the left coronary artery.

Fatty change. Fatty degeneration of slight or moderate severity was found in fourteen out of the twenty-seven cases. It did not appear to be correlated with the size of the heart, with the state of the coronary circulation, or with any other known factor, and we have therefore been unable to attach any significance to it.

Myocardial fibrosis was seen in the hypertensive cases in three forms, which we have called healed infarcts, focal fibrosis, and reticular fibrosis. The only example of a healed infarct was in Case 62 in which it was associated with an old coronary occlusion.

Focal fibrosis took the form of small foci (under 1 mm.) in which the muscle fibres had been replaced by collagen. In most cases replacement was complete, but occasionally necrotic muscle fibres were still visible. This lesion, which was seen with greater frequency and severity in the ischaemic group, occurred in seven of the hypertensive group (Cases 8, 32, 43, 48, 49, 50, and 63). The skiagrams of four of these (Cases 8, 43, 48, and 50) showed coronary narrowing, but in the other three (Cases 32, 49, and 63) the coronary arteries had uniformly wide lumina and smooth outlines. Case 32 had polyarteritis and since some of the smaller vessels in the myocardium were involved (but not the main coronary vessels) it is fair to assume that fibrosis was the result of occlusion of small vessels. Cases 49 and 63 died in congestive failure, and fibrosis might be attributed to relative coronary insufficiency; but we must point out that the vessels were large and free from any obstruction.

The third type of fibrosis, which we have called reticular, was always associated with gross muscular hypertrophy. It occurred in seventeen cases and took the form of an exaggeration of the normal interstitial reticular connective tissue fibres. In the normal heart these are extremely fine and can only be satisfactorily demonstrated by silver impregnation, but in cases of gross hypertrophy they thickened and became clearly visible as fine collagenous fibres surrounding the muscle fibres (Fig. 11). This form of reticular fibrosis tended to occur in foci and for this reason might be mistaken for

ischaemic focal fibrosis. We believe, however, that it is a separate entity for the following reasons. Firstly, it was not seen in any of our pure ischaemic hearts; secondly, it is limited to cases of gross myocardial hypertrophy; thirdly, we were never able to demonstrate any sign of muscle loss. We consider that it is a form of concomitant fibrous tissue hypertrophy.

Renal changes. The hypertensive cases were classified according to their cardiac condition, and though most were examples of essential hypertension, a few proved to be secondary to chronic nephritis. In practice the histological differentiation between nephritis and advanced arteriosclerotic kidney is extremely difficult, particularly since Ellis (1942) has shown that primary nephritis may persist with hypertension as the dominant clinical sign and arterial damage as the dominant renal change. In spite of these difficulties we have attempted to classify the kidneys in this series into hypertensive and nephritic. Seven (Cases 11, 19, 41, 47, 65, and 69) showed evidence of nephritis whilst the remaining twenty showed varying degrees of arterial damage, from a few hyaline vessels up to severe changes of the type classified as malignant hypertension. Six of the hypertensive group died in uraemia and four of these (Cases 19, 41, 45, and 69) were among those with histological evidence of nephritis. The other two (Cases 13 and 60) showed the histological appearances of malignant hypertension.

ISCHAEMIC CASES

There were fifteen cases in this group, and their main pathological findings are summarized in Table V.

Heart weight. The hearts were all hypertrophied except in Case 25. The mean weight for the whole group was $495 \text{ g.} \pm 76 \text{ g.}$, the range being 350–650 g. Such a degree of hypertrophy suggests that either ischaemic hearts may become hypertrophied during their course or that our cases were complicated by hypertension. It will be seen from Table V that eight cases had some degree of hypertension during life. The mean heart weight of these was 497 g., whilst the mean heart weight of those without hypertension was 494 g. Thus there is no correlation between heart weight and hypertension in this series. On the other hand, if the cases are divided according to the duration of cardiac failure, some correlation becomes apparent. Those with left ventricular failure for two months or more (6 cases) had a mean heart weight of $549 \text{ g.} \pm 56 \text{ g.}$; whereas those with terminal or no congestion (9 cases) had a mean heart weight of $459 \text{ g.} \pm 60 \text{ g.}$ The difference

TABLE V
ISCHÆMIC CASES

Case No.	Age	Sex	Blood pressure	Heart weight (grams)	Coronary* occlusion site	Myocardial†		Mode of death
						Fibrosis	Necrosis	
17	57	F	158/92	432	L.D.		L.V.A.	Syncopal
22	76	F	170/85	480	L.D.	L.V.A.	I.V.S.	Congestive cardiac failure
25	71	F	140/60	350	L.D., R.	L.V.A., L.V.P.	L.V.A., L.V.P.	Syncopal
29	43	M	172/120	480	L.D., L.C.	L.V.A.	L.V.A., O.M.	Syncopal
30	53	M	150/110	535	L.D., L.C.	L.V.A., O.M.		Syncopal
37	60	M	184/80	590	R.	L.V.A.	L.V.P.	Congestive cardiac failure
40	47	M	120/80	580	L.D., L.C.	L.V.A., L.V.P.	L.V.P.	Lung abscess
42	61	M	220/140	425			L.V.A.	Syncopal
46	55	M	190/100	400	L.D., R.	L.V.A.	L.V.P.	Hæmopericardium
51	65	M	95/60	495	R.		L.V.P., R.V.P.	Sepsis
52	53	M	120/80	480	L.D., L.C.	L.V.A.	L.V.A., L.V.P.	Congestive cardiac failure
55	71	F	175/105	630	L.D., R.		L.V.P.	Congestive cardiac failure
66	69	M	140/80	656	L.C., R.	O.M.	L.V.P., R.V.P.	Myocardial infarction
70	63	M	140/105	480	L.C., R.	L.V.P.	L.V.P.	Myocardial infarction
73	64	F	180/110	505	L.D., L.C., R.	L.V.P., L.V.A.	L.V.A., L.V.P.	Congestive cardiac failure

* L.D.=Left descending branch. L.C.=Left circumflex branch. R.=Right coronary.

† L.V.A.=Left ventricle anterior. L.V.P.=Left ventricle posterior. R.V.P.=Right ventricle posterior. O.M.=Obtuse margin. I.V.S.=Interventricular septum.

is 90 g. and the standard error of the difference is 9.7 g. This correlation between duration of failure and heart weight is similar to our finding in the hypertensive group, and is further evidence that cardiac failure is an important factor in the production of myocardial hypertrophy.

Coronary arteries. The skiagrams (Fig. 6) and cleared specimens (Fig. 9 and 10) of the injected coronary vessels in the ischæmic cases showed a characteristic picture, quite different from that of the hypertensive group. The characteristic feature was the constant presence of severe narrowing or occlusion, usually both. There was, of course, some variation in the degree and extent of the lesions. In eight cases the whole coronary tree was affected and all the major arteries were narrowed and irregular in outline, often with deposits of calcium salts in their walls. Complete occlusions in both right and left coronary arteries were usually demonstrable.

In the other seven cases arterial narrowing was limited either to one vessel (usually the left) or to part of a vessel, whilst the rest of the coronary tree was relatively normal. In some of these cases the unaffected vessels were wider than normal. The mean heart weight was slightly higher (527 g.) in cases with localized coronary narrowing than in those with generalized coronary narrowing (460 g.). Out of four with no history of angina of effort (Cases 17, 30, 40, and 51), three were examples of localized coronary narrowing.

Coronary occlusion was commonly multiple as

previously indicated, though in one case it was incomplete, and in four it was single; there were eight cases with two blocks and two cases with three blocks. The distribution was as follows: out of twenty-six complete occlusions eighteen were in the left coronary artery and eight in the right. Myocardial infarction was found in thirteen out of fourteen cases with one or more complete occlusions. The case without complete occlusion had no infarct but only microscopic foci of necrosis. The other (Case 37) without infarction had a solitary occlusion of the right coronary artery, and showed only microscopic necrosis. Amongst the other thirteen cases there were fourteen healed infarcts and eleven recent infarcts, all but one involving the left ventricle. The areas affected were the apex anteriorly (11 cases), the base posteriorly (10 cases), the obtuse margin (3 cases) and the base of the right ventricle posteriorly (1 case). In each of these twenty-five infarcts the appropriate coronary artery was completely occluded. There was no correlation between the type of lesion present and the mode of death. Syncopal deaths were not particularly associated with recent thrombi or infarcts.

Anastomotic vessels, just big enough to be visible in the skiagrams, were noted in all cases. These occurred in relation to the distal parts of occluded vessels, and sufficed to permit retrograde filling of these vessels. They were better seen in the "cleared" specimens (Fig. 9 and 10).

Histology. Coronary vessels. With certain reservations histological study of the coronary

arteries confirmed the radiographic findings. In most of the skiagrams, however, no matter how irregular or narrowed the majority of the vascular lumina, some segments still looked normal both in calibre and in smoothness of outline; yet microscopically these parts also showed severe atheroma. A similar discrepancy was observed both in the controls and in the hypertensive cases, but it is

repeated for emphasis that even in manifest ischaemic heart disease, the appearance of atheroma in a section of a coronary artery does not necessarily indicate narrowing *in vivo* at that site. Again, it was quite impossible to tell from the skiagrams whether a focus of narrowing was due to atheroma or to a recanalized thrombus. On numerous occasions points of narrowing noted in the skia-

FIG. 9.—Ischaemic heart. Case 46. Anterior view showing small coronary arteries with irregular outlines, complete occlusion in right coronary artery, and anastomoses via pericardial vessels.

grams and in cleared specimens proved to be healed thromboses in which the recanalized lumen was as large as the adjacent narrowed atheromatous vessel. This may explain the occurrence of myocardial infarction in the presence of patent, though narrowed, vessels; for the absence of complete occlusion at autopsy does not prove the vessel was never blocked during life. These examples of organized recanalized thrombi were ones in which the histological diagnosis was unequivocal, but apart from these there were many others in which such an interpretation would be difficult to refute. In late cases of recanalized thrombosis, the fibrous tissue

replacing the thrombus fuses with atheromatous lesions so intimately that we were often unable to tell whether a given lesion was atheromatous or thrombotic. This difficulty was accentuated when atheromatous lesions showed undue vascularity of hæmorrhage as described by Winternitz *et al.* (1938). Both phenomena were observed in some sections or the coronary arteries in nearly every case. When the vasa vasorum were small the hæmorrhages were fresh, it seemed fair to assume that they were late effects of atheroma; but when the vasa were large and ran parallel with the coronary artery, and when blood in the plaque was represented only by groups

FIG. 10.—Ischæmic heart. Case 25. Showing recanalized occlusion of the descending left coronary artery and irregularity of outline in others.

A

B

FIG. 11.—Section of heart muscle. (A) *Hypertensive heart disease (Case 11)*, and (B) *Control* (both magnified $\times 108$) showing hypertrophy of interstitial connective tissue in myocardial hypertrophy “reticular fibrosis.” Silver impregnation.

of macrophages filled with pigment, it became impossible to decide whether or not there had been thrombosis. This similarity lends support to the hypothesis recently put forward by Duguid (1946) that what is ordinarily regarded as coronary atheroma is, in fact, the result of organized thrombi.

Myocardium. The histological appearances of the myocardium in the present series of cases conformed to the accepted descriptions of ischæmic heart disease, but there were two points that merit some discussion. The first is the time relation between coronary closure and myocardial infarction. In the majority of cases these corresponded. Recent infarcts were associated with recent thrombi and old infarcts with old thrombi. Furthermore, they were associated in position, the infarcts occurring in sites supplied by occluded vessels. We did not observe any cases in which infarction was due to the closure of a vessel supplying the infarcted area only by anastomoses, though this has been observed by Blumgart *et al.* (1940). We did, however, observe three examples (Cases 29, 46, and 55) in which recent infarction was unassociated with recent thrombosis in any vessel big enough to be visible macroscopically. In two of these (Cases 29 and 46) the symptoms of the fatal infarct arose at home whilst the patient was at rest, and the lesion cannot therefore be attributed to unusual circulatory demands beyond the capacity of the coronary supply. It is possible that a period of diminished cardiac output may have reduced the coronary flow sufficiently to have precipitated the infarcts, but there was no evidence available on this point. Coronary spasm can almost certainly be excluded on the grounds that the coronary tree was too rigid for this to be possible. These cases are of importance because they may represent the late counterpart of cases of sudden death in ischæmic heart disease where neither recent occlusion nor fresh infarction is demonstrable at autopsy. It is possible that such cases, which are common in forensic practice, might show infarction if they survived long enough.

The second feature noted in the present series was the development of minute foci of necrosis leading to focal fibrosis. These small lesions, usually just visible macroscopically, were encountered in ten of the sixteen cases, often in several sites in one heart. We were able to observe every stage of their development, and they showed exactly the same changes as do ordinary infarcts, but on a minute scale. It appears to us desirable that these lesions should be regarded as minute infarcts, and that the term ischæmic fibrosis should imply this. In most cases these small lesions were found to be related, both in time and site, to occluded coronary branches, but

this was not always so. Minute infarcts without demonstrable vascular occlusion presumably have the same pathogenesis as their larger counterparts.

DISCUSSION

Previous history. The high incidence of a history of rheumatic fever in both hypertensive and ischæmic groups is regarded as coincidental, for necropsy revealed evidence of rheumatic heart disease in but one case, and the known facts deny relationship. Thus, of 542 cases with granular kidney reported by Pitt (1887), 6 per cent had mitral stenosis. Of 403 clinical hypertensives analysed by Boas and Fineberg (1926), 8 per cent had mitral stenosis. Of 1000 hypertensive cases studied by Bechgaard (1946), 1 per cent had clinical evidence of mitral stenosis. Finally, in 122 hypertensive subjects under 50 years of age, Haloven and Salomaa (1947) found a history of rheumatic fever in 6.6 per cent, compared with an incidence of 9.8 per cent in 250 controls. Although figures from the paper by Pitt and by Boas and Fineberg, and also those given by Levine and Fulton (1928) show that about 40 per cent of cases of mitral stenosis have hypertension, it must be remembered that 33 per cent of men aged 40, and 43 per cent of women aged 40, have a blood pressure of 150/100 or above (Master *et al.*, 1943). Claims that the rheumatic process may involve the coronary vessels (Plesch, 1947) cannot be denied; but there is no statistical evidence implicating rheumatic fever as an important ætiological or contributory agent in the development of the common form of ischæmic heart disease.

Family history. Platt's suggestion that essential hypertension may be a hereditary disease transmitted as a Mendelian dominant with a rate of expression of over 90 per cent (Platt, 1947) cannot be easily dismissed. Thus it may be calculated from Berchgaard's findings in over 1000 hypertensive subjects that the incidence of high blood pressure in the parents was about 75 per cent (Bechgaard, 1946), and the author considered that about 20 per cent of his cases were renal in origin—a group in which the hereditary factor has been shown to play no part.

The hereditary aspect of ischæmic heart disease has been less frequently studied, and has been rarely separated from the hypertensive group. General opinion, however, strongly favours hereditary predisposition.

Age and sex. Our figures bear out the well-known difference in sex and age incidence. The ratio of males to females is usually given as about 4 : 1 in ischæmic heart disease, whereas it is close to 1 : 1 in essential hypertension. It is also recognized that the preponderance of males in ischæmic

heart disease is proportional to the age of the groups studied. Thus it is overwhelming in those under 40; 8 to 1 in those between 40 and 49; 4 to 1 in those between 50 and 59; 2 to 1 in those between 60 and 69; and the sex ratio is equal in those over 70 (Hedley, 1939; Gordon *et al.*, 1939).

Clinical features. The steady downhill course of hypertensive heart disease was well illustrated, and contrasted sharply with good temporary recovery in at least one-third of the ischaemic cases. This latter behaviour may be attributable to coronary thrombosis with or without infarction, followed by improvement in the collateral coronary circulation.

More than half the hypertensive group died from non-cardiac causes, chiefly uraemia or cerebral haemorrhage. Only two died suddenly. On the other hand, ten out of fifteen ischaemic cases died abruptly. This confirms the well-known fact that ischaemic hearts are peculiarly liable to develop ventricular fibrillation, but it also demonstrates that hypertensive hearts are not.

Of great interest was the rarity with which cases initially classified as hypertensive later developed angina pectoris or myocardial infarction. The pathological studies provide a ready explanation for this, for they show that the typical hypertensive heart has smooth distended coronary arteries. It is not denied that about 66 per cent of ischaemic cases have a blood pressure over 150/90, (Master *et al.*, 1936), or that nearly 50 per cent have a blood pressure at least 160/100 (Riseman and Brown, 1937); but we agree with the latter authors that systolic pressures over 200 are rare. It must be repeatedly pointed out that about half of the population between the ages of 50 and 60 have blood pressures of 150/100 or above (Master *et al.*, 1943), and it is therefore misleading to quote similar figures in ischaemic heart disease, which involves particularly this age-group, as evidence that coronary disease is intimately related to hypertension. The difference in the quality of the cardiac impulse in the two groups and in the size of the heart as viewed fluoroscopically, was most impressive.

The pathological findings proved conclusively that the hypertensive electrocardiographic pattern showing left axis deviation with depression of the RS-T segment with or without inversion of the T wave in lead I was not due to coincident coronary disease nor to myocardial fibrosis, but appeared to closely related to the size of the left ventricle. Likewise, auricular fibrillation and bundle-branch-block occurring in hypertensive heart disease could not be ascribed to ischaemic fibrosis. Admittedly, bundle-branch-block was twice as common in ischaemic as in hypertensive heart disease in the

clinical series, occurring in 10 per cent and 20 per cent of the cases respectively.

PATHOLOGICAL FEATURES

The most striking observation in the injected hearts was the basic difference in the coronary pattern between the hypertensive and ischaemic series and the lack of overlap between them. It is probably true that hypertension does predispose to coronary sclerosis, but our findings suggest that the relationship has been overstressed. Confusion may have arisen on account of the frequency at autopsy of enlarged hearts with atheromatous coronary arteries—it being assumed that the hypertrophy indicates previous hypertension and atheromatous coronary arteries indicate ischaemia. Either of these assumptions may be false. Our observations show that in coronary sclerosis cardiac failure can produce myocardial hypertrophy to an average weight of 550 g. irrespective of a raised blood pressure. This has been observed by Bartels and Smith (1932) and by Davis and Blumgart (1937), and Eyster (1927, 1928) has suggested that stretching of the heart by dilatation is the essential stimulus to hypertrophy. In spite of this, the assumption is still commonly made that a heart weight of over 500 g. indicates hypertension. Another source of error is the assumption that atherosclerosis must cause coronary narrowing. Stewart *et al.* (1935) showed that this was not so and our present findings confirm this. It is not suggested that atheroma does not lead to ischaemia but we believe that by ordinary examination it is very difficult to estimate whether or not the vessels are narrowed during life.

Our observation that the coronary arteries enlarge as the heart hypertrophies confirms the previous findings of Gross (1921), Russow (1936), Fishberg (1937) and Sagebial (1934), but in addition they strongly suggest that the degree of coronary enlargement keeps pace with the needs of the heart and that "relative" ischaemia is not a cause of cardiac failure in hypertension. The concept of relative ischaemia has probably arisen from the finding of myocardial fibrosis unassociated with appreciable coronary sclerosis. Such fibrosis may be of the type which we have called reticular and which we believe to be a form of fibrous tissue hypertrophy and not an indication of muscle destruction. This was also the view of Stadler (1907). Alternatively, there are undoubtedly cases of focal myocardial fibrosis indistinguishable from healed infarcts but unassociated with any coronary occlusion. Such cases have been observed by Blumgart (1940, 1941), Gross and Sternberg (1939), Ravin and Greeves (1946) and by Holyoke (1945), as well as by us. We suggest that it is more reasonable to attribute them to a diminu-

tion of coronary flow during a phase of cardiac failure than to postulate either relatively small coronary arteries or spasm.

SUMMARY AND CONCLUSIONS

Comparative clinical and pathological studies have been made on twenty-seven cases of hypertensive heart disease and fifteen cases of ischæmic heart disease. There were twelve controls.

Hypertensive cases were characterized clinically by even sex distribution, dyspnœa, steady deterioration, retinopathy, cerebral symptoms, impairment of renal function, anæmia, auricular fibrillation, and by clinical, radiological, and cardiographic evidence of left ventricular enlargement before the onset of heart failure. Only one case originally classified as hypertensive developed subsequent angina pectoris or myocardial infarction. Death was rarely abrupt.

Ischæmic cases were characterized clinically by an unequal sex distribution favouring men, the older age of women, the infrequency of early dyspnœa, the absence of anæmia, of retinopathy and of cerebral symptoms, good renal function, normal rhythm, normal heart size before failure, good temporary recovery, and by abrupt death.

At autopsy the hearts were investigated by injection of the coronary arteries followed by stereoscopic radiography and dissection and histological examination. The following conclusions were drawn.

Moderate degrees of coronary atheroma do not necessarily cause narrowing.

The size of the coronary arteries varies directly with the heart weight in both normal and hypertrophied hearts irrespective of the cause of the hypertrophy.

The coronary arteries vary sharply between hypertensive and ischæmic cases: in the former they are large with smooth bores, in the latter they are narrow and frequently occluded.

In hypertensive cases the heart weight varies with the degree of failure during life and not with the height of the blood pressure.

The coronary size increases as the heart size increases and there is no evidence to indicate relative ischæmia of the ventricular muscle.

In severely hypertrophied hearts the normal fibrous tissue increases in thickness.

In ischæmic cases cardiac hypertrophy is the rule and can be correlated with the duration of failure.

Myocardial infarction can occur in the apparent absence of coronary occlusion, and is probably then due to circulatory failure.

We are deeply indebted to Dr. Duncan White for his kindness in taking stereoscopic skiagrams in all cases. We also wish to thank Mr. J. Baker and Mr. J. Griffin for the many hundreds of slides they prepared and Mr. V. Willmott for the photographs.

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