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A THESIS ENTITLED

A PATHOLOGICAL STUDY OF SUDDEN CORONARY DEATH IN GLASGOW

PRESENTED BY

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CONTENTS

SECTION I

SCOPE OF THE WORK

1 - INTRODUCTION

Ischaemic heart disease is the commonest cause of death in the Western Countries. No general agreement exists on the pathogenesis of atherosclerosis, which is the underlying cause of ischaemic heart disease. The mechanism by which those patients, with coronary arteries severely diseased for years, die suddenly is poorly understood.

Previous pathological studies have, however, suggested that the incidence of coronary thrombi is low in cases of sudden ischaemic death. Moreover, the triggering mechanism responsible for the sudden occlusion of the coronary arteries is in dispute, and it is not certain if there is any acute pathological lesion in the coronary arteries of these cases.

Glasgow and the west of Scotland have long had the reputation for a high incidence of coronary artery disease. Studies have shown that the highest mortality rates for ischaemic heart disease are in the north of Britain, with west central Scotland being the worst affected region (Fulton et al, 1978). A study was undertaken in the mid-1960's comparing the pathological changes of ischaemic heart disease in a hard water and a soft water area (Crawford and Crawford, 1967). It claimed to show more atheroma in the 30-44 year age group

in the soft water area. A greater susceptibility of myocardial ischaemic damage was also claimed in the soft water area. The areas used for comparison were London and Glasgow.

The present work which is based on the study of 130 cases of sudden death re-examines the question of whether an acute lesion is present in the coronary arteries of cases of sudden ischaemic death, to explain the moment of death. Every segment of the epicardial coronary tree was examined and the degree of atherosclerotic stenosis, if any, estimated. The extent and distribution of the atheromatous lesions in these cases were determined. The study also compared the incidence of these recent coronary events with a similar study of a similar group of cases, which was undertaken at the same time in the London area at the Department of Histopathology, St. George's Hospital.

2 - ACKNOWLEDGEMENTS

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3 - ASPECTS OF THE WORK DONE PERSONALLY

The general autopsies were personally performed in 70% of the total number of 130 cases of sudden death which form the basis of the present work. In all cases, however, the detailed examinations of the heart and coronary arteries were undertaken personally, and these included:

1. Post-mortem coronary angiography on the isolated hearts.
2. The nitro-blue tetrazolium test for the diagnosis of myocardial infarction.
3. Dissection, decalcification and re-x-raying of the whole epicardial coronary tree.
4. Histologic preparation and processing of sections of both the coronary arteries and myocardium, with the assistance of Mrs. C. Clapperton.
5. Microscopic examination of about 10,000 histologic sections of both the coronary arteries and myocardium.
6. Planimetry of about 7800 histologic sections of the coronary arteries.

SECTION II

BACKGROUND OF THE WORK

An Historical Note

There is no doubt that ischaemic heart disease occurred long before our time. Plaque-like lesions, similar to atheroma which is the underlying cause of the disease, were described in the arteries of the Egyptian mummies and it was suggested that three thousand years ago the old Egyptians suffered as much as we do now from arterial lesions identical with those found at the present time (Ruffer, 1911). Similar lesions were described in microscopic sections of the aorta of King Menpheteth, the 18th dynasty Pharaoh (Shattock, 1909).

Harvey in 1649, was familiar with ossified arteries and concluded that blood "does not pass with the same rapidity through occluded or impeded paths as it does meandering through open free patent ones" (Cited by Bedford, 1968). Yet the history of coronary heart disease really started with Heberden's account of angina pectoris in 1768. However, he had no inkling of the fact that the chest pain he described had any connection with the coronary arteries. In 1799 it was Jenner who related Heberden's angina to ossified coronary arteries. In 1809, Allan Burn was the first to try to prove the correctness of the myocardial ischaemic theory by a purposeful planned experiment (Herrick, 1942).

Since the 19th century, the history of the study of atherosclerosis falls rather sharply into two phases. The first was characterised by an exhaustive analysis of the morbid histology and was carried out largely by many German pathologists. The succeeding phase started at the beginning of the 20th century in the form of widespread and intensive biochemical and experimental studies, with the aim of understanding the relationship of cholesterol metabolism to atherosclerosis. In this phase Anglo-Saxon investigators have contributed, notably (Geiringer, 1951).

During the 19th century, experimental work was carried out by several workers, e.g. Von Bezold (1862), Samuelson (1880), Cohnheim and Schulthess (1882). Obstruction of the coronary arteries by ligatures, clamps or artificial emboli, promptly lead to fatal results (Herrick, 1912).

In 1844, Rokitansky described what we now call atheroma as a deposit on the surface of the vessel of a fibrinous material derived from blood. The deposition continuously increased in thickness by the addition of new strata. He described the deposition as undergoing atheromatous transformation which could be followed by calcification. In such lesions, Rokitansky described "pultaceous softening associated with fatty globules, cholesterin crystals and calcium salts" and stated that such softened plaques were likely to rupture through the force of blood (cited by Duguid, 1949).

Rokitansky was severely criticised by Virchow in 1853, on the basis that the material he had described was clearly subendothelial. Virchow considered that the lesion was based on "loosening" of the connective tissue ground substance of the intima as a result of "imbibition" of the constituents of the passing blood (cited by Woolf, 1982).

Virchow's ideas went unchallenged for a long time, until 1946 when Duguid revived Rokitansky's incrustation theory. Duguid noticed that many of the appearances classified as atheroma resulted from organisation of arterial thrombi (Duguid, 1946, and 1948). Duguid's view was shortly fully supported by others (Crawford and Levene, 1952, More and Haust 1957, and Movat, Haust and More, 1959), who confirmed the role of thrombosis by the identification of fibrin deeply within the intima. In 1965, Carstairs identified platelets and platelet antingens in human atherosclerotic lesions. However, although no general agreement exists on the pathogenesis of atherosclerosis, few would now deny that thrombosis superimposed upon pre-existing atherosclerotic lesions and leading to arterial occlusion is the most important complicating event in the natural history of atherosclerosis (Woolf, 1982).

The most common and dramatic way in which ischaemic heart disease may manifest itself is to cause sudden death of its victim. At the same time, it is by far the most frequent cause of sudden death (Crawford, 1977).

In Western Europe and the United States of America, cardiovascular diseases are the predominating causes of death and coronary heart disease is the cause of approximately two-thirds of the cardiovascular deaths in men and one third in women aged 55 years and over. With increasing age the proportion remains stationary in men but rises in women reaching 55 per cent at the age of 70 years (Vedin et al, 1973).

In Britain, the highest mortality rates from ischaemic heart disease in middle-aged men and women are in the north and west of the country. Scotland comes only second to Finland in having the highest rates in the world and the worst region is West Central Scotland (Fulton et al, 1978).

During recent years, deaths from ischaemic heart disease have apparently decreased significantly in the United States of America (Gillum, 1983), and a similar decline was also noticed in Finland (Salonen et al, 1983). Meanwhile in the United Kingdom, there is an argument about a decline in the rate of ischaemic heart deaths after 1973-74 (Heller et al, 1983), although the figures

show that the claimed decline is probably due to a peak in the years 1972-74 in all age groups and in fact the figures in 1979-80 are not less than in 1968 (Pedoe et al, 1983).

The term "sudden death" is open to considerable variation in its interpretation. Sudden unexplained natural death can be defined as death occurring either instantaneously or within twenty-four hours of the onset of acute symptoms or signs (Paul and Schatz, 1971). It has been suggested that cases of instantaneous coronary deaths differ in clinical and pathological aspects from other cases of sudden coronary deaths (within 24 hours). The instantaneous deaths have been described as occuring during or immediately after severe exertion and the hearts were said to show no acute lesions but to exhibit old coronary occlusions. Such individuals were thought to be dangerously prone to death from myocardial ischaemia (Friedman et al, 1973). Suggestion was also made regarding a relationship between the survival duration after the onset of symptoms and the presence of coronary thrombi, and it was claimed that the longer the time interval between the onset of symptoms and death the more the acute coronary lesions are present (Spain and Bradess, 1970).

On the other hand it has been claimed that in the vast majority of sudden ischaemic deaths, a significant acute lesion, particularly in the atheromatous plaque, with or without a severe degree of stenosis (more than 75%) in one or more of the major coronary branches, is a constant finding (Crawford 1977, Perper et al, 1975, and Baba et al, 1975). Death in such cases can be regarded as the result of spontaneous ventricular fibrillation in chronically ischaemic ventricles (Davies, 1982). The frequency with which mural and occlusive thrombi have been found in the coronary arteries varies markedly, probably due to varied thoroughness and techniques employed in examining the arteries. Some observers claim to find thrombi in almost 100 per cent of their cases, while in other series the figures have been as low as 25 per cent or even 8 per cent (Roberts and Buja, 1972). There is no doubt that the more carefully thrombi are sought the more frequently will they be found, and it is certain that tearing open the arteries longitudinally with coronary artery scissors will ensure a low yield (Crawford, 1977).

Sudden rupture or fissuring of a soft plaque seems to be the triggering mechanism responsible for the acute thrombotic occlusion of a vessel which has been diseased for years. However, this rupture is usually undetectable in most cases, unless serial or step sections are made (Falk 1983, Friedman 1975, and Friedman, 1973).

It must be said, however, that even the most meticulous search, supplemented by detailed microscopic studies, will leave a residue of cases, showing varying degrees of stenoses, where no recent event can be found. Crawford (1977) in his study of sudden deaths, showed that in 22 per cent of cases no recent event could be detected. He found that the constant feature of the pathology of these cases was the presence of severe and often multiple arterial stenoses. Another feature was that none of these hearts was the seat of recent infarction. On the other hand, all the cases he described with infarction were associated with recent events in the coronary arteries.

In cases with no recent or acute event, the exact mechanism of sudden death remains a mystery. Some alternative explanations have been discussed, including disturbances in the cardiac conductive system, and the role of platelet microthrombi or microemboli in the genesis of focal ischaemia (Schwartz and Gerrity, 1975, and El-Maraghi and Genton, 1980). Further possibilities, such as coronary artery spasm due to external or endogenous stimuli, lysis of a thrombus or stress whether physical or mental leading to increased myocardial requirements for oxygen or blood supply, have also been suggested. It is also possible that a period of systemic hypotension resulting from shock, surgical operation or certain drugs, could lead to a drop in blood flow through

narrowed coronary arteries below a critical level (Crawford, 1977 and Vincent et al, 1983). Unfortunately, none of these hypotheses can be adequately assessed in any way by pathologists.

Atherosclerosis in the pathogenesis of ischaemic heart disease.

The term "ischaemic heart disease" expresses precisely the state of structural and functional abnormality of the heart as a consequence of an inadequate blood supply. Other terms, such as "coronary thrombosis" or "myocardial infarction" emphasize one pathological feature which, important as it is, is not a constant finding. In the vast majority of cases (probably of the order of 98%), the lesions responsible for damaging the coronary arteries can be classified under the term "atherosclerosis" (Crawford, 1977).

Atherosclerosis, the correct translation is "porridge-like hardness" (Pickering, 1963), is defined as a "widely prevalent arterial lesion characterised by patchy thickening of the intima, the thickening comprising accummulation of fat and layers of collagen-like fibres, both being present in widely varying proportions (Crawford, 1960).

Atherosclerosis is one of the topics in pathology which seems fated to evoke prolonged, heated and often sterile controversy. Yet our knowledge of the processes involved in the atherogenesis is still very limited, and the various mechanisms playing a role in the initiation

and progression of atherosclerotic lesions are still largely unknown (Woolf, 1982). A major problem is that the disease progresses insidiously for many years before any symptoms develop, making it difficult to follow the early development of the disease in individual patients, and to relate causally the several types of lesions that have been described. For the same reason, identification of the risk factors for the disease has depended upon the relation of these factors to the clinical symptoms rather than on the extent and severity of the primary arterial lesion (Ross and Glomset, 1976).

The Fatty Dot or Streak

It would seem logical to approach the question of morphology and pathogenesis of atherosclerotic lesion by first describing the earliest lesion, and the sequence of changes that lead to the mature clinically significant raised fibrolipid plaques. However, there is controversy as to what constitutes the early lesion of atherosclerosis, and no agreement that what are called "early" atherosclerotic lesions inevitably develop into the characteristic plaque (Haust, 1971).

Aortic fatty streaking could be seen in 43 per cent of infants between the age of one and twelve months. In the coronary artery the fatty streaks appear in the proximal segments of the vessels about the time of puberty (Schwartz et al, 1967). However, lesions in the internal

elastic lamina were described, at or even before time of birth, in the form of stretching, splitting or fraying; as being the first visible manifestation of atheroma. These elastic lesions were thought to represent underlying foci of medial weakness, over which fibrous thickening later develops (Levene, 1956 a and b).

The fatty streaks show much less geographic and racial variation than do the raised lesions (Tejada et al, 1968). They appear as minute, round or oval, yellowish, sessile lesions, minimally elevated above the surrounding intima and cause no obstruction or clinical symptoms (Ross and Glomset, 1976). On light microscopic examination, the small fatty dot shows the presence of intracellular lipid droplets concentrated immediately under the endothelium or deeply within the intima, although a small amount of fat is distributed along the internal elastic lamina (Woolf, 1982). In larger lesions, the bulk of fat is still intracellular, but some cells disintegrate with an increase of the extracellular distribution of lipid (Haust, 1971).

Ultrastructural study of fatty streaks showed that the lipid in the small lesions lay in the smooth muscles, whereas in more advanced lesions the lipid-containing cells are unidentifiable. It was suggested also that lipid is synthesised in the smooth muscles, which later on undergo transition into foam cells. The presence of cells with degenerative cytoplasmic changes may lead to

extravasation of lipid into the extracellular spaces and that, in turn, may serve as a stimulus for reactive fibrosis and progression of the lesion (Geer et al, 1961 and Ghidoni and O'Neal, 1967).

A defined role in the formation of fatty streaks and atherogenic sequence was proposed for the circulating monocytes (Gerrity, 1981 a and b). Monocytes were found to invade the intima of the lesion-prone areas, become phagocytic and accumulate lipid. Once a fatty lesion results, the lipid-laden foam cells migrate back into the blood stream. The ratio of penetrating monocytes to emerging foam cells decreases until a one-to-one ratio is achieved in the late lesions which do not progress further. Failure of the monocyte clearance system may result, at least partially, in further accumulation of lipid and advancement of the lesion.

At least three varieties of fatty streaks have been described by McGill (1974). The first, which occurs in childhood and adolescence, is found in all population groups, and the lipid is predominately intracellular. This type is not considered to be a predictor for the future development of raised lesions. A second variety occurs in young adults in the population groups with a high incidence of atherosclerosis. The lipid is usually extracellular, with increased extracellular connective tissue. It has been suggested that this type may constitute a precursor of the fibrolipid plaque. A third

type may be found in middle-aged and elderly subjects, in which there is a diffuse infiltration of the intima by lipids. At present, there is no evidence that this lesion grows into fibrolipid plaque (Cited by Woolf, 1982).

The Raised Lesion or Fibrolipid Plaque

This is the archetypal lesion of atherosclerosis which appears to be the most important factor in determining the clinical course of the disease (Tejada et al, 1968 and Deupree et al, 1973).

The lesion is usually eccentric and consists of a lipid-rich basal pool which is covered on its luminal aspect by a connective tissue cap. In some lesions the bulk is made up of fibromuscular tissue and the lipid portion is inconspicuous or even absent, giving the lesion a solid opaque appearance. In other plaques, the basal lipid, tissue debris and other plasma derived constituents, may be of massive proportion and separated from the lumen by a thin easily ruptured sheet of fibrous tissue. Indeed all gradations between these two extremes may be seen (Woolf, 1975 and 1982).

The simple fibrous plaque is thought to be found before the age of thirty, whereas other constituents such as fat, cholesterol clefts, necrotic debris and calcium do not appear before that age (Levene, 1956a). It has been suggested that the hard fibromuscular plaques are present in young patients, whereas the soft pultaceous lesions are

more likely to be seen in the older subjects (Leary, 1934a).

The "layered plaque" is a large eccentric lesion consisting of alternating zones of connective tissue and fatty debris, indicating that stenosis has built up gradually by successive episodes of thrombosis and incorporation of thrombus into the intima (Crawford, 1977 and Bouch and Montgomery, 1970). In severely affected lesions, the morphology of the plaque is complicated by the mural or the occlusive thrombi, and it is not always easy to determine where the thrombus ends and the underlying plaque, as it was before the thrombotic episode, begins (Woolf, 1982).

Aetiology

There are two classical theories regarding the aetiology of atheroma. The first is the "imbibition" or the infiltrative theory, which proposes that atheroma is due to accumulation of fats in the intima as a result of an invading stream of the circulating plasma lipoproteins. This is followed within a short time by proliferation of the connective tissue cells and an increase in the connective tissue ground substance (Virchow, 1856, Cited by Woolf, 1982). This invasion by the plasma lipoprotein is supposed to occur at sites of increased permeability (Anitschow, 1933, Cited by Friedman and Byres, 1963).

The second theory is the thrombotic or "incrustation" theory, which regards atheroma as an incrustation of fibrin which had become organised on the

vessel wall (Rokitansky, 1842, Cited by Duguid, 1946). Duguid (1946 and 1949), demonstrated that when a thrombus forms it will tend to retract after some time so that a channel will form which soon becomes lined with endothelium. When organisation follows, the subendothelial fibrin will be transformed into fibrous tissue by direct metamorphosis. Since this tissue is similar to, and continuous with, that of the original intima, it has the appearance of an intimal overgrowth. In some instances a complete organisation of the mass is brought about by this way; but more often fatty degeneration and softening takes place and thus the complete picture of the atherosclerotic plaque is produced.

More recently, much research has been devoted to the role of smooth muscle cell proliferation in atherogenesis. The "response-to-injury" hypothesis proposes that endothelial injury causes an immediate platelet response, platelets adhere to the subendothelial connective tissue, aggregate, and lose their granules. The platelet factor, supported by the plasma lipoproteins, leads to focal proliferation of the arterial smooth muscle cells. At the same time, lipid is deposited both in these cells and the surrounding connective tissue (Ross and Glomset, 1976). Using the cell marker technique for glucose-6-phosphate dehydrogenase, the "monoclonal" hypothesis suggests that each lesion of atherosclerosis is derived from a single smooth muscle cell which serves as a

progenitor for the remaining proliferative cells (Benditt and Benditt, 1973, Cited by Ross and Glomset, 1976).

Plaque Events

The most important event in the history of the plaque is thrombosis, which in the case of the coronary vessels may be lethal. The key factor preceding thrombus formation appears to be fissuring, splitting or rupturing of the soft lipid-rich plaque (Falk, 1983, Bouch and Montgomery, 1970, Friedman, 1975 and Constantinides, 1966). Plaque softening is a process of great importance which is still poorly understood. One suggestion is that it is due to the presence of unusual lipids (Brooks et al, 1971). The presence of small amounts of certain cholesterol esters produces different degrees of necrosis and inflammation. These lipids are regularly present in "necrotic" plaques and not in the predominately fibrous lesions (Harland et al, 1971). Another suggestion is that intimal necrosis may result from failure of an incorporated mural thrombus to retain a sufficient blood supply (Geiringer, 1951). This, in turn, leads to failure of the superficial and deep zones to link up, and to the consequent necrosis and the appearance of breakdown products including fat and calcium (Crawford and Levene, 1952 and Levene, 1956 a and b).

Plaque Rupture

It has been known to pathologists for many years that the thin fibrous cap separating the pool of soft extracellular fatty material and cholesterol clefts from the lumen of the artery may rupture, resulting in direct contact between the flowing blood and the atheromatous gruel (Leary, 1934a and b and Constantinides, 1966). When this happens, a number of events may follow separately, simultaneously or successively. These events include haemorrhage into the plaque, discharge of the atheromatous material into the lumen causing local obstruction or peripheral embolisation, mural thrombosis and occlusive thrombosis (Falk, 1983 and Davies and Thomas, 1981). In his study, Falk (1983) has shown that the fate of a plaque rupture depends on the degree of the pre-existing stenosis. If that is less than 75 per cent, the rupture will cause intimal haemorrhage without luminal thrombosis. But with stenosis in excess of 75 per cent, occlusive thrombosis occurs with increasing frequency.

The mechanism underlying sudden rupture of a soft atheromatous plaque has been disputed. It has been suggested that plaque rupture may constitute a link between hypertension or sudden severe physical exertion and coronary thrombosis (Crawford, 1977). It was also claimed that plaque rupture is the underlying fatal coronary event in older rather than younger persons

(Leary, 1934a). Other investigators suggest that probably when the process of softening goes up so far, no more than the normal bending and twisting of the arteries, which occurs during every heart contraction, is needed to tear the thin fragile cap (Ridolfi and Hutchins, 1977). Changes in the vascular tone, i.e. spasm, may also play a role in precipitating the plaque rupture (Hellstorm, 1979).

Plaque ruptures are not detected in many instances unless serial section studies are made (Friedman et al, 1973 and Constantinides, 1966). The ruptured fibrous cap is always very thin and usually heavily infiltrated with foam cells. At the site of rupture aggregated platelets can be identified and the thrombus formed may consist almost entirely of aggregated platelets. Fragments of the disrupted plaque may be found mixed with or deeply buried in the centre of the thrombus (Falk, 1983 and Friedman, 1975).

The frequent detection of plaque contents in the thrombus and the platelet aggregation at the site of rupture clearly indicate that the rupture has preceded and not resulted from thrombosis (Falk, 1983). Recent experimental and clinical observations make it likely that the complicating thrombotic response to plaque rupture can be suppressed to some degree by appropriate inhibition of platelet function (Folts et al, 1982 and Chesebro et al, 1982).

Plaque Haemorrhage

Haemorrhage within the substance of the thickened intima of atherosclerotic plaque is not infrequently seen. The plaque haemorrhage may occur in two ways. The first of these has been mentioned and occurs in association with rupture of an atheromatous plaque. In these circumstances, the resulting haemorrhage may be quite large, the blood forces its way under arterial pressure into the atheromatous cavity and may produce a lesion amounting to a minute dissecting aneurysm (Crawford, 1977). This type of lesion might be associated with thrombotic occlusion of the artery, or with a tiny mural thrombosis sealing the rupture site. Subsequently the clotted intimal haemorrhage will undergo degenerative changes with additional distortion of the already diseased arterial wall (Falk, 1983 and Crawford, 1977).

The second way in which intimal haemorrhage may occur is through rupture of the newly formed intimal vessels. Being thin-walled and somewhat sinusoidal in character, it is not surprising that ruptures and haemorrhages of these vessels might occur, especially in those parts of the plaque which suffer the greatest mechanical stress (Duguid, 1976, Cited by Woolf, 1982).

There is considerable difference in opinion regarding the importance of these haemorrhages in relation to coronary occlusion. It has been suggested that some

intimal haematomas are large enough to cause an important reduction in the size of the arterial lumen (Wartman, 1938). However, it seems unlikely that blood could escape from the capillaries into the intima at sufficient pressure and in sufficient amount against the full arterial pressure (Crawford, 1977). A second opinion is that intimal haemorrhages could precipitate coronary thrombosis through endothelial damage by the extravasated blood into the intima (Paterson, 1936 and 1938). This hypothesis was strongly opposed by Drury (1954), who showed that both intimal haemorrhage and coronary thrombosis, though may be found together, are independent complications of the atheromatous coronary artery.

Intimal haemorrhages were also suggested to play a role in the development of the early atherosclerotic lesions (Paterson et al, 1965). The "vascularisation theory" claims that lipid deposits are derived from the lipids of the extravasated blood, whether they are at normal or at elevated levels, whereas the fibroplasia is explained by the organisation of the clot. However, the evidence for these haemorrhages playing a significant part in the development of the early lesions is unconvincing (Woolf, 1982).

Thrombotic Occlusion of The Coronary Arteries

Although the role played by thrombosis in atherogenesis has been generally accepted, the frequency with which mural and occlusive thrombi are found in the coronary arteries of the victims of ischaemic heart disease is a matter of widely differing opinions. Some observers claim to find thrombi in almost nearly 100 per cent (Harland and Holburn, 1966 and Chapman, 1974), while in other series the figures have been as low as 30 per cent (Baroldi, 1965 and Schwartz and Gerrity, 1975), or even much less (Baroldi et al, 1979). The thoroughness and technique employed in examining the arteries play a major role in producing the variability of reported results. There is clear evidence to support this in comparing two studies from the same department (Branwood and Montgomery, 1956 and Bouch and Montgomery, 1970). In the earlier series, the incidence of thrombosis was found to be 59 per cent, but on repeating the same study using a totally different technique, the incidence was much higher (88%), and the authors stated that "the technique was undoubtedly a major factor in securing so high an incidence of occlusion."

It has been suggested that for the occurrence of fatal thrombotic occlusion of a coronary artery, the lumen must be reduced to one-quarter or less of its original cross-sectional area (Crawford, 1977 and Baba et al, 1975). Analysis of occlusive coronary thrombi reveals

that in the majority, free continuity can be shown between the lipid within the intima and thrombus within the lumen as the result of fissuring or rupturing of the intimal fibrous cap of the plaque (Davies, 1982 and Falk, 1983). Post-mortem coronary arteriography at pressures below those which occur in life often demonstrates free connection between the lumen and plaque, proximal to the occlusive thrombus (Davies, 1982).

The structure of occlusive coronary thrombi shows considerable variation in the different parts of a single thrombus. The oldest part of the thrombus is formed predominantly of platelets, and located usually in the most severely narrowed segment of the artery or immediately proximal to it. It is believed that as the lumen is progressively narrowed by platelet deposition, a critical point is reached at which the final closure is affected by the more rapid process of coagulation-thrombosis, involving the formation of a plug of fibrin strands, with entangled red and white cells in varying proportions. The process may be even more complicated as thrombus may cease and recur, thrombolysis may be active at some stages, or organization and recanalization may take place. In this way, the final occlusive thrombi may show evidence of more than one thrombotic episode (Crawford, 1977).

It is this variation in the structure of occlusive thrombi responsible for a great deal of confusion in attempts to correlate the age of an occlusive thrombus in the artery, with the age of an infarct in the area supplied by that artery. The findings in a single random section through a zone of propagating thrombus may be quite misleading when the older zone has escaped observation. This may be interpreted as indicating that thrombosis occured secondarily to the infarction. Giving intravenous radio-labelled fibrinogen to patients admitted to hospital some hours after the onset of symptoms, the thrombus was found to be radio-positive at autopsy (Erhardt et al, 1976). However, it has been shown that the thrombus had a radio-negative head, but the more distal part was indeed radio-positive, confirming the later development by propagation (Davies et al, 1979).

Recanalization of a thrombosed coronary artery

There are two ways in which blood flow can be re-established through a segment of artery that has been occluded by thrombus. The first is a rapid one, which is likely to occur when the lumen has been obstructed rapidly by a thrombus with a high content of fibrin. The process is similar to the retraction of a blood clot in a test tube.

Once the blood flow is re-established, the retracted thrombus will be further compressed by the blood

force, and then it becomes incorporated into the vessel wall, forming a narrowed eccentric lumen (Crawford et al, 1961).

The second type of recanalization, by organization, occurs when the thrombus is less rapidly formed and contains lower proportions of fibrin and higher contents of cells and platelets. The process occurs over a period of weeks or months, and after some time the thrombus is converted into a plug of vascular granulation tissue. Later, the plug is converted into a fibrous cord with one or more channels passing through it. Regrettably, the recanalized channels are not immune from thrombosis; a sequence of events that may be designated "re-thrombosis" (Crawford, 1977).

Myocardial Infarction

The majority of incidents of ischaemic myocardial damage result from events in an atheromatous plaque. The immediate cause of acute regional infarction is thrombotic occlusion as a complication of coronary atherosclerosis (Harland and Holburn, 1966 and Davies et al, 1979). The controversy over the role of coronary thrombosis has resulted from different usage, mainly by pathologists, of the term myocardial infarction. Some use it for every type of myocardial necrosis, ranging from microscopic foci to larger visible lesions. Others use the term only for a single area of necrosis visible to the naked-eye in the

distribution of one major coronary artery (Davies, 1982). Two distinct varieties of acute myocardial necrosis may be seen in relation to coronary atherosclerosis. A localised "regional" type, and a diffuse subendocardial "laminar" one. The latter is less common and may occur in association with regional infarcts.

I. Acute Regional Myocardial Infarction

In this common form, a well defined area of necrosis involves the full thickness of one regional segment of the left ventricle which may extend to the adjacent parts of the right ventricle. The area of necrosis is usually some centimeters across, and confined to the area supplied by one major coronary artery. A far less common form is still regional, but not full thickness, being confined to the subendocardial zone (Davies, 1982). These forms of infarction or necrosis are said to be consistently related to acute thrombotic occlusion of the supplying coronary artery.

The size of the regional infarct depends on the variations in the anatomy of the subtending artery, as well as the extent of the available intercoronary anastomoses (Davies et al, 1979). The cutting off of the blood supply is said to occur abruptly and to be complete, or usually so, though it need not be permanent. Gradual impairment of blood supply may lead to piecemeal cell death and replacement fibrosis, which is a quite different

pathological entity from infarction (Crawford, 1977).

II. Diffuse Subendocardial Infarction

This second basic type of myocardial necrosis is essentially subendocardial in location, with the central part of papillary muscles being usually affected. Variations in this type tend to be of extent rather than of location. It often takes the form of multiple small areas of necrosis or less commonly the whole subendocardium may be necrotic, when the terms laminar or circumferential infarction have been used. Lesser degrees of the latter form may show small foci of necrosis, with many only detectable on microscopy (Davies et al, 1979).

Using post-mortem coronary angiography, Fulton (1965), showed the subendocardial infarction to occur in association with multiple severe coronary stenosis, or old occlusions, and he demonstrated the occurence of widespread anastomoses between the diseased arteries with a marked enlargement of the subendocardial vascular plexus. Diffuse subendocardial infarction occurs as a result of inadequate perfusion of the subendocardial arterial plexus precipitated by conditions of tissue hypoxia, such as heart failure, anaemia or carbon monoxide poisoning. It may be seen without significant arterial lesions in patients who fail to survive open cardiac surgery, in severe prolonged hypoxaemia or after severe

head injuries (Davies and Robertson, 1975).

Naked-eye Features of Myocardial Infarction

Although ischaemic death of the myocardium occurs within a few minutes of loss of blood supply, the visible changes of infarction do not appear until after eight hours or so. Accordingly, in patients who die suddenly within a few hours of coronary occlusion, no changes in the myocardium will be seen by naked-eye or using ordinary light microscopy (Anderson, 1980).

The first visible changes are blotchy congestion and pallor. After one day or so, a patch of softening may be felt, and during the next few days the affected tissue becomes pale and its colour changes from red to yellow due to leucocytic infiltration and small or larger haemorrhages may be seen. By the end of the first week, the yellow colouration extends throughout the infarct, and during the second week some thinning develops. During the third and fourth weeks the yellow colour changes into purple due to spreading of granulation tissue, and by the second month the infarct becomes paler as collagen is laid down. About three to six months, the lesion becomes a mature white scar (Crawford, 1977).

Such descriptions are of average findings and pathologists know to avoid the temptation of precise dating the time of the infarcts. Comparing the progression of events to that in experimental animals where the moment of arterial occlusion is precisely timed, is less informative as animals have a different metabolic rate, and the size of infarct is usually smaller. Furthermore, in man himself, the rate of progression varies according to the size of the infarct and quality of collateral circulation (Crawford, 1977). At the same time, it is impossible to pinpoint precisely from the clinical history, the time at which the infarction commenced, and sometimes well demarcated infarcts of at least one to two days maturity have been found in patients dying within a few hours of onset of pain (Knight, 1980).

Chemical Aids to the Recognition of Early Infarction

Many attempts have been made to develop chemical aids to the diagnosis of early infarction. Most depend on the reduction or loss of the enzyme activity in the necrotic muscles (Nachlas and Shnitka, 1963). Utilizing non-specific dehydrogenase reaction, methods have been described by Nachlas and Shnitka (1963), Ramkissoon (1966) and McVie (1970). In this method in which no substrate is added (the nitro-blue tetrazolium test), the reaction is dependent on both the enzymes and the endogenous substrates preserved in the myocardium. Viable

myocardium develops as a dark blue formazon staining, while infarcted areas remain relatively unstained. Failure of colouration of an infarct in the test may result from either enzyme or substrate depletion. This method is more sensitive for detecting recent infarction than other methods where a substrate is added, and it is claimed that it can detect infarcts that occurred eight hours before death (Nachlas and Shnitka, 1963), and can give positive results in experimental animals 5-6 hours after infarction (Anderson et al, 1979).

Microscopic Features of Myocardial Infarction

The earliest microscopic changes occur in the muscle cells and may be suspected after 6-8 hours from the onset of the infarction. The nuclei may be shrunken, while the muscle cells are slightly swollen, stain more deeply with eosin or acid fuchsin, and show blurring or loss of their transverse striations (Knight, 1980).

During the first twenty four hours the infarcted muscle shows the usual features of necrosis, oedema of the area occurs and inflammatory response is initiated in the adjacent viable tissue, presumably by products of autolysis. Over the succeeding few days, emigration of leucocytes into the area occurs and is followed by macrophages infiltrating into the dead tissue, which is progressively removed by combination of proteolytic enzyme liquefaction and macrophage activity. By the end of the

first week, granulation tissue extends into the area and in favourable conditions, replaces the dead muscles completely. From about the second week, collagen fibres appear and after the fourth week there is progressive fibrosis in the area. The process takes some weeks or even months depending on the size of the infarct. Eventually a pale fibrous scar remains (Crawford, 1977 and Anderson, 1980).

Summary

In summary therefore, debate and controversy still surround the mechanism by which victims of ischaemic heart disease die suddenly. Many believe that the incidence of thrombi and acute coronary lesions is low, and attribute the sudden death in the majority of cases to cardiac dysrhythmia. Others adopt the opinion that coronary thrombi are consequences rather than causes of myocardial infarcts. There is no doubt that understanding the pathogenesis of sudden ischaemic death has great implications on prevention and management of ischaemic heart disease.

SECTION III

MATERIALS AND METHODS

Aim of the Work

The present study is an attempt to understand the pathogenesis of sudden cardiac ischaemic death by examining the incidence of acute coronary lesions in cases dying suddenly in the Glasgow area. To achieve that object, morphologic changes were observed in the histologic blocks of 3 mm. cross sectional segments of the whole epicardial coronary tree. The degree of stenosis in the different segments of the coronary artery was estimated and the extent and distribution of atheromatous lesions were investigated. Setions from different areas of the heart were studied for signs of infarction using both the enzyme and histologic methods.

The incidence of the recent coronary events identified in the present work was compared with a similar study of a similar group of cases which was undertaken at the same time within the London area.

Case Selection

This study has included 130 cases of subjects under the age of 69 years, who died suddenly in the Glasgow area. At the early stage of the work, all cases of sudden death were included. However, later on and because of the enormous histologic work required, non-ischaemic deaths were rejected. Cases were collected until a number of 100 cases believed to die from ischaemic heart disease at the time of autopsy was reached.

Cases were selected at random, independent of the degree of coronary atherosclerotic damage. The hearts were obtained at necropsy from subjects who died suddenly within 24 hours of the onset of symptoms in the terminal illness. The series included only those who had not been under medical care and had not consulted their doctors within the last three weeks. In every case a post-mortem examination had been ordered by the Procurator Fiscal.

The study included those found dead, but known to be alive within the past 24 hours of death, and cases where death was witnessed by observers during the terminal episode. Cases with a history of angina or myocardial infarction were not excluded as long as they fulfilled the other criteria.

A report was always provided by a police officer that included a personal history, the circumstances of death and medical history which was obtained from the patient's medical records and supplied by his own doctor.

A full post-mortem examination has to be done on all cases, according to the Scottish law, by a member of the staff of the Department of Forensic Medicine and Science, The University of Glasgow. Significant pathological findings, including non-ischaemic cardiac lesions, were noted at autopsy. The brain was examined and sectioned in each case. Internal organs were thoroughly examined and specimens for histologic examination were taken from the different organs, when needed. Drug

screening was carried out in those cases known to be using drugs and in those with suspicious circumstances. That included the use of Gas Chromatography, Ultraviolet-Spectrophotometry and Mass Spectroscopy. Drug testing was performed by the highly qualified forensic scientists in this department. Blood and urine alcohol were also estimated whenever necessary.

Cases were considered as sudden ischaemic death when no other apparent cause of death could be found during the autopsy or the toxicological investigations and the coronary arteries showed a degree of stenosis of at least 75 per cent of the area of the lumen.

A control group of thirty patients was studied in whom an apparent non-ischaemic cause of death, whether natural or unnatural, could be identified.

Pathological Techniques

The hearts were removed unopened at necropsy and cut only after angiographic study of the coronary arteries. For this purpose, a simplified technique was employed (Crawford et al, 1961) which outlined the coronary arteries, at least as satisfactorily as more complex procedures, and has the great advantage of taking only about 15-20 minutes to complete and of leaving the arteries and the heart undamaged for subsequent dissection.

The heart was washed thoroughly to remove blood and blood clots. The proximal parts of the main right and left coronaries, about 1 cm long, were dissected free on

the ouside of the root of the aorta and ligatures were placed lightly around them. A mixture of barium-gelatine was prepared by dissolving 50 gm of gelatin powder (as solidifying agent), in 100 ml warm water till the mixture was homogenous. Then 800 ml of microdispersion of barium sulphate (Micropaque) was added and mixed well with the gelatin solution. The mixture was kept in a warm water bath during use and stock mixtures were stored in a cool room in a solid state, and reliquified when needed for injection by incubation in a warm water bath.

The mixture was injected first into the right coronary artery, using an ordinary 10 ml. syringe fitted with wide-bore cannula. Care was taken to ensure that no air bubbles were mixed with the injection medium. A maintained moderate pressure was required to ensure good filling, without risking rupture of the arteries. The filling was judged complete when the small branches of the arteries on the surface of the heart could be seen to fill, or when an increased resistance to the injection was noted. In most instances, about 2-3 ml. of opaque medium was required to fill one artery. The needle was then removed and the ligature tightened to prevent reflux. The heart was washed once more to remove any barium left inside the heart chambers.

The coronary artery injection in the present work was not performed under any specific pressure, as it seems

that it has no effect on judging the severity of stenosis. According to Wheatley's experience, changing the injection pressure does not alter the degree of coronary narrowing (Wheatley, 1983). However, injecting the coronaries under pressure below that which occurs during life might be helpful as a precaution against rupturing the arteries. On the other hand, failure of complete filling of the arteries by the injection media can lead to collapse of the histologic preparations and the eventual over-estimation of the degree of coronary stenosis.

An antero-posterior x-ray was taken using an X-ray cabinet at a distance of 40 cms (50 KV exposure for 3 minutes). 18 x 24 cm x-ray films were used. The procedures were repeated for the left coronary artery and a second X-ray taken. The X-ray films were developed and the course of the artery followed, any stenosed segment being located and the extent of the intercoronary anastomosis studied. The degree of stenosis in each of the main arteries was scored as shown in the (Figure 1).

A mid-ventricular 1 cm. thick transverse slice was then cut. The site of the cut could be changed according to the site of an infarct if any has been detected naked-eye. The slice was rinsed under running cold tap water to remove blood and tissue juices from the cut surfaces and it was then incubated for 30 minutes at room temperature in a bath of solution consisting of 30 ml.

Figure 1

CODE NO

ANGIOGRAPHY

	L	LAD	LD	LC	LM	R	PD
N							
TO							
?THR							
S1							
S2							
S3							

Scoring the degree of stenosis in each of the main coronary arteries.

nitro-blue tetrazolium (1 mg/1 ml.), and 70 ml. of Sorensen phosphate buffer (0.1M,ph 7.4) (Nachlas and Schnitka, 1963). A very small quantity (pinch) of sodium succinate was added to compensate for the loss of endogenous substrates from the normal heart muscle, especially when the post-mortem interval exceeded 6 hours. A quantity of the solution sufficient to completely cover the myocardial slice was added. During the incubation the slice was gently agitated and turned in the solution, to ensure that there was no contact between the slice and the bottom of the container.

Viable muscle developed a dark blue formazon pigmentation, (Figure 2) whereas any infarcted areas remained relatively unstained. Recent and older fibrotic lesions were also clearly demonstrated by this staining reaction (Figure 3).

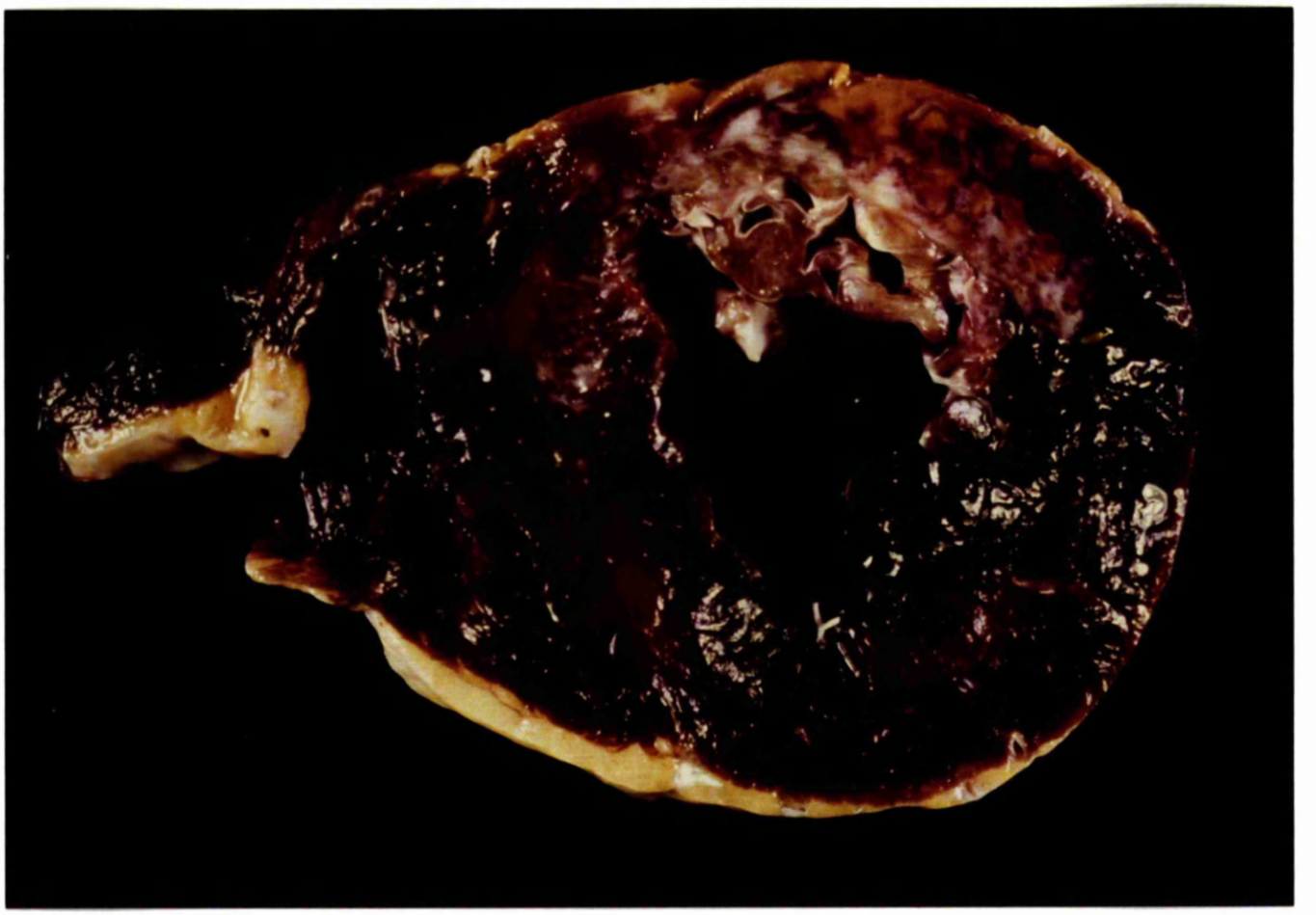
The myocardial slice was divided into 17 parts as shown in the (Figure 4); 5 anterior, 5 posterior, 2 lateral, 2 septal and 3 for the right ventricle. The reaction in each part was recorded in the endocardial, myocardial and epicardial zone, as shown in Table 1.

The heart was then fixed in formalin for further detailed study. Seventeen blocks were then taken in the same manner from the heart slice and processed for histological examination, using hematoxylin and eosin. The results of the microscopic examination were recorded without reference to the result of the enzyme test, as shown in the Table 1.

Figure 2

The nitro-blue tetrazolium test showing a normal heart slice.

Figure 3



Recent myocardial infarction involving the posterior wall of the left ventricle with also areas of old scarring in the same region.

Figure 4

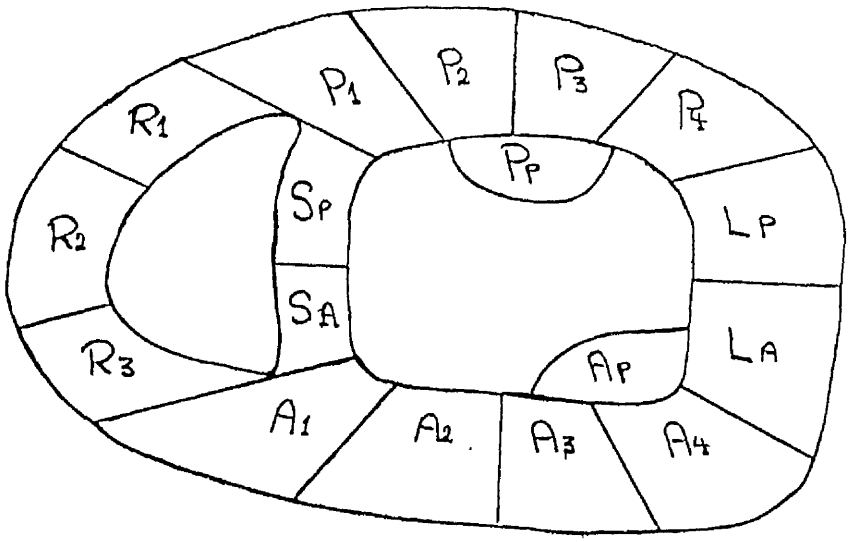


Diagram showing the way the heart slice was divided into 17 parts for the enzyme and histologic tests.

CODE NO

		MACRO			MICRO					
		N	F	I	N	F	GI	EST	>12H	PLAE
A1	E									
	M									
	P									
A2	E									
	M									
	P									
A3	E									
	M									
	P									
A4	E									
	M									
	P									
SA	E									
	M									
	P									
SP	E									
	M									
	P									
PI	E									
	M									
	P									
P2	E									
	M									
	P									
P3	E									
	M									
	P									
P4	E									
	M									
	P									
LP	E									
	M									
	P									
LA	E									
	M									
	P									
PP										
AP										
R1										
R2										
R3										

TABLE 1 Recording of the findings in the different areas of the heart by the enzyme test and histology.

The major epicardial branches were then dissected from the heart and placed in formic citrate decalcifying solution, made of 1300 ml 20% sodium citrate and 700 ml concentrated formic acid, for five days and then re-X-rayed as before.

Histological blocks, cut transversely, were then made every 3 mm. of the epicardial coronary arteries, including the posterior descending branch of the right, the diagonal branches of the left anterior descending and the left marginal branch of the left circumflex artery. Each block was labelled according to the code as shown in the Figure 5. The blocks were processed for histological examination using haematoxylin and eosin staining.

Plaque fissuring was diagnosed when the intimal cap was disrupted, resulting in a free continuity between the atheromatous material and the lumen and was accompanied by luminal thrombosis, mural thrombosis or intimal haemorrhage. Luminal thrombosis was diagnosed when a fresh thrombus was demonstrated inside the arterial lumen. Luminal thrombi were divided into major, occupying more than 50% of the lumen, and minor occluding less than 50% of the lumen. Mural thrombosis was identified when a fresh thrombus with fibrin and platelets was detected within the intima, whether accompanied by plaque fissuring or not. Intimal haemorrhage was diagnosed when plaque rupture was associated with a few red cells inside the intima.

Figure 5

CORONARY ARTERY DISSECTION

CODE NO.

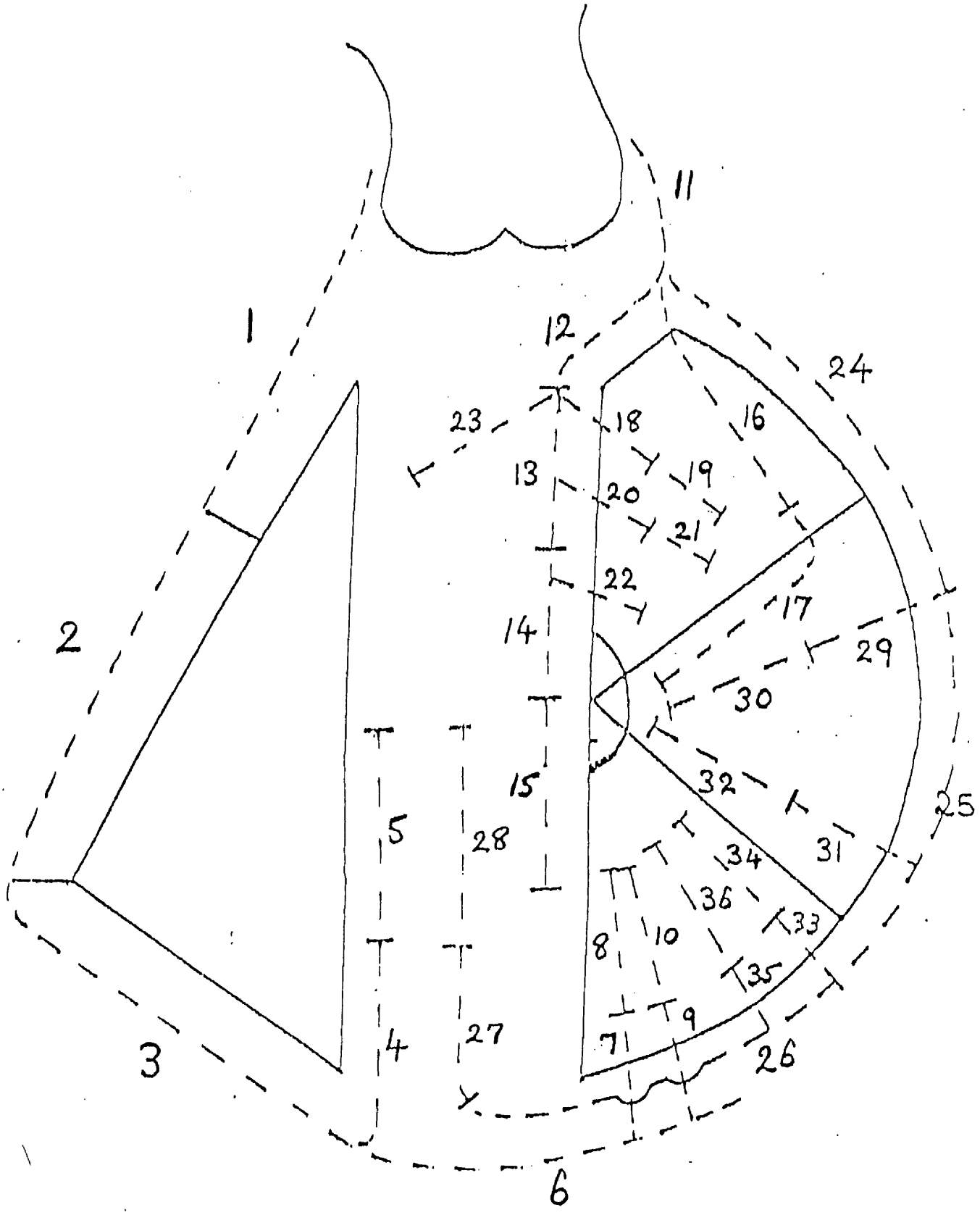


Diagram showing the method used for labelling the coronary blocks for histological examination.

Each histologic section was examined under the microscope and coded for the presence of intraluminal thrombosis, intramural thrombosis, plaque fissuring or intimal haemorrhage, without knowledge of the clinical data, or whether the case was a test or control.

The distribution of the various recent coronary events, if any, along the coronary tree, with the degree of the pre-existing stenosis at the site of the recent lesion, was noted. The findings were compared for each segment in all cases. Old lesions, represented by recanalisation of the coronary lumen, were recorded for each segment, if present, and their distribution was compared with those of the recent lesions.

Each histologic section was measured using a quantitative microscope. The microscope was attached to a magnetic plate which was connected to a computer programmed for measuring purposes. By moving a cursor on the magnetic plate, a light dot could be seen moving under the microscope, and through the cursor the light dot was directed to measure the wanted areas. Each measurement was recorded in the computer. The degree of stenosis was estimated by measuring the area within the internal elastic lamina (component C1), which was presumed to represent the original lumen, and the area of the existing lumen (component C2). On relating C2 to C1, the degree of the reduction of the arterial lumen in proportion to its original was estimated and the degree of stenosis was calculated.

Thrombi, when present, were measured (component C3), and their size was expressed as a percentage of the lumen before thrombosis has occurred. All the measurements were taken without knowledge of the clinical data.

The extent and distribution of the atherosclerotic lesions in each case was assessed by taking the worst stenosis figure in every segment of the coronary tree and this could then be displayed as a histogram (Figure 6). The figures were then compared for all cases and an average percentage of stenosis for each segment was estimated for each age group and for all the cases. To get a more detailed picture of the extent of atherosclerosis in each segment, cases were divided according to the degree of stenosis in each segment into those of less than 25%, 26-50%, 51-69%, 70-85%, 86-95% and those of more than 95% stenosis. The distribution of the different cases, according to the degree of stenosis in each segment, was estimated. The extent of stenosis in each two of the major arteries, when the third artery was severely affected by the disease at one or more of its segments, was also looked at.

Cases where the three major vessels were stenosed to greater than 70%, 80% and 90% were noted, and cases with two of the main arteries were narrowed to more than 70% were also estimated. In addition cases with limited areas of stenosis affecting only one or two segments of the coronary tree, with the rest of the vessels being relatively free, were noted.

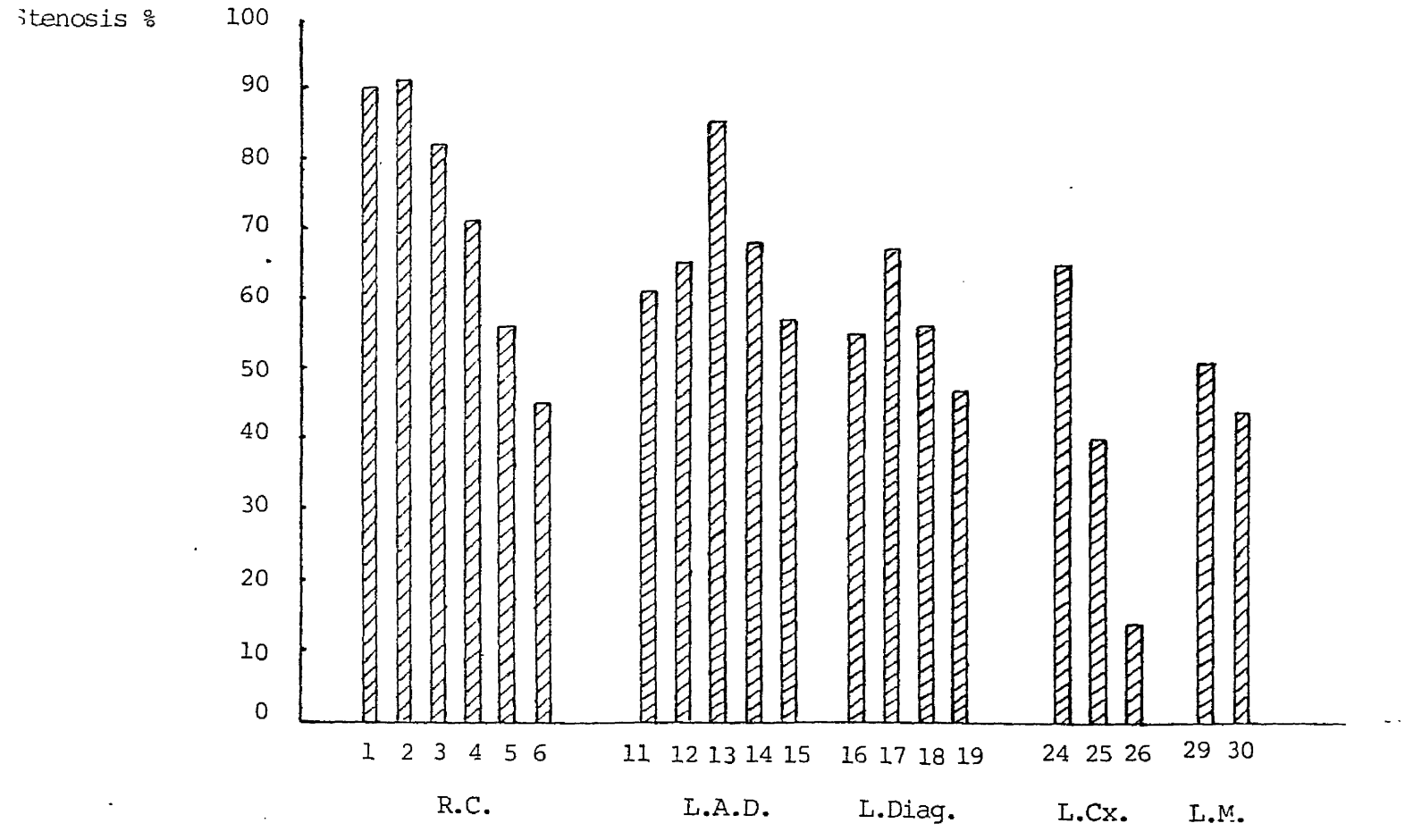


Figure 6 An example of Scoring the Degree of Stenosis of Different Segments of Coronary Tree for One Case.

SECTION IV

RESULTS

From 100 test cases, 92 showed a significant degree of stenosis of the coronary arteries (more than 75%), an acute pathological lesion in the arteries or both. In eight cases, however, there was no recent pathological event in the coronary arteries to explain the moment of death; and the stenosis was less than 75% of the lumen. These cases had been diagnosed as "sudden ischaemic death" at the time of the post-mortem where no other apparent cause of death could be found, and the post-mortem coronary angiography suggested a significant degree of atheroma.

Among the 92 cases, 81 had an acute coronary artery lesion (88%). Eleven cases, however, had a severe degree of stenosis (more than 75%) in one or more segments of the coronary tree, but did not show any recent patholgical event in the arteries. Three of these cases showed recanalisation of one of the arteries, suggestive of old occlusions.

The distribution of the 92 cases, according to the age and sex is shown in Figure 7.

Plaque fissuring (Figure 8) was demonstrated in 59 of the 92 cases (64%). In 48 cases, fissuring was found in one coronary branch, in 7 cases in two branches, and in 4 cases in the all three major branches. In 32 cases a rupture had occurred in one or more segment of the right coronary, in 27 cases in the left anterior descending branch, and in 15 cases in the left circumflex artery (Tables 2a and 2b).

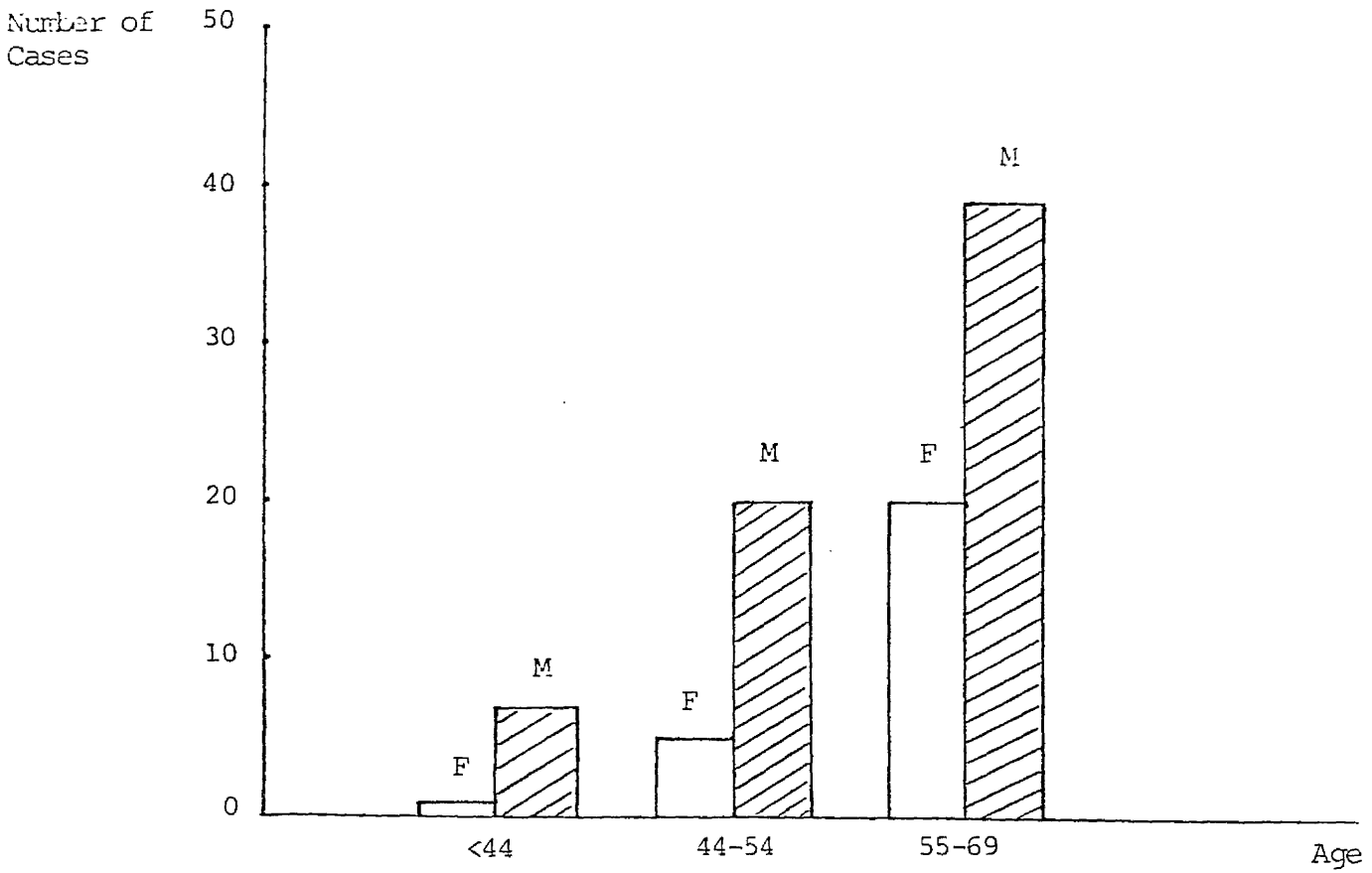
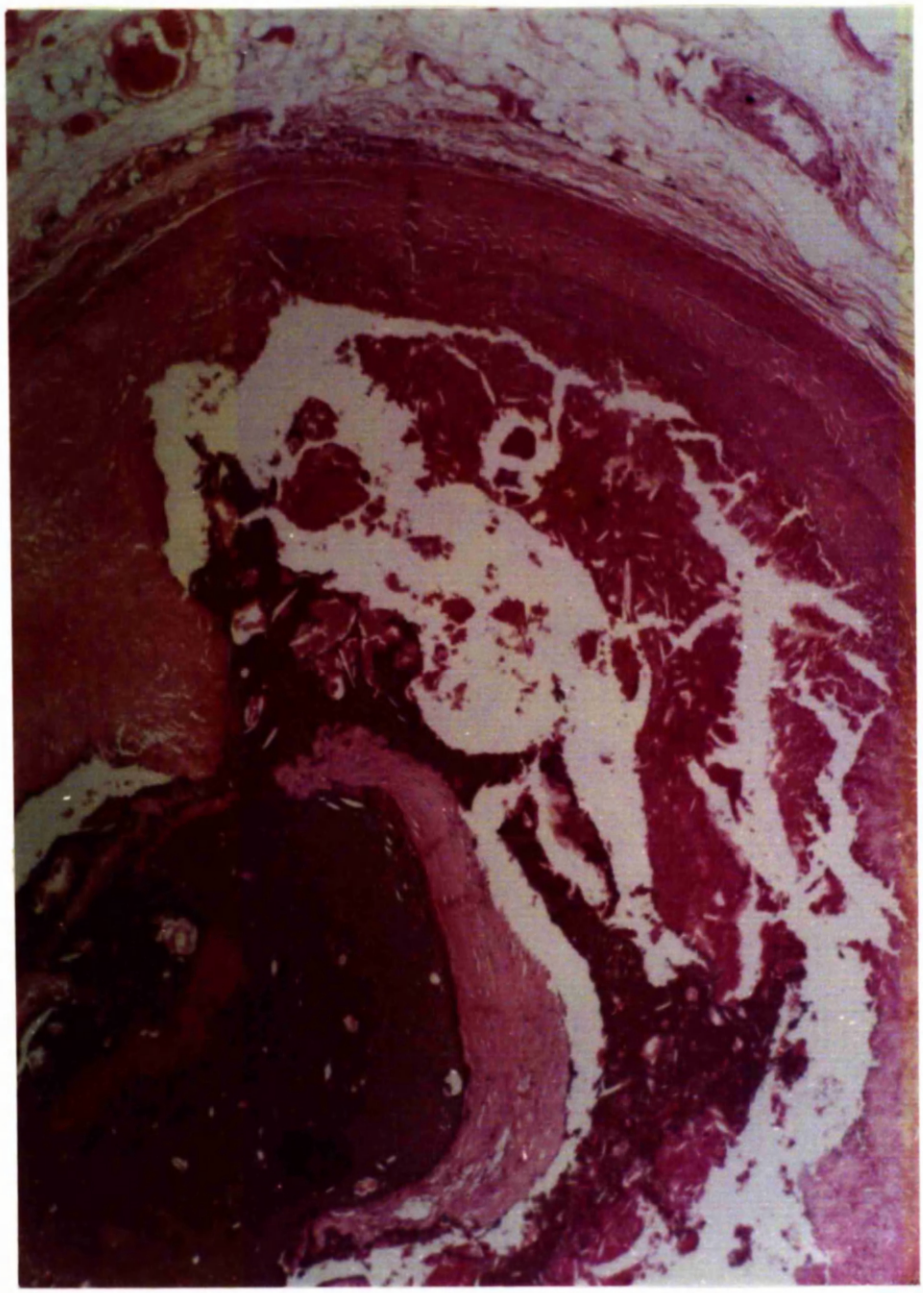


Figure 7 Age and Sex Distribution in 93 cases of Sudden Ischaemic Cardiac Death

Figure 8



Section of the coronary artery showing plaque fissuring with the injection medium demonstrated inside the plaque.

TABLE 2 (a)

One artery	Two arteries	Three arteries
48	7	4
(81%)	(12%)	(7%)

Frequency of Plaque Fissuring in the Three Major Branches (Total number 59 cases)

TABLE 2 (b)

Right coronary	Left Anterior descending	Left Circumflex
32	27	15
(43%)	(37%)	(20%)

Distribution of Plaque Fissuring in the Three Major Branches (Total number 74 Ruptures)

A total of 80 incidences of plaque rupture were identified in the 59 cases; 35 in the right coronary, 30 in the left anterior descending, and 15 in the left circumflex branch. Figure 9 shows the incidence of plaque fissuring at the different segments of the coronary tree. The second segment of the right coronary, the second and third segments of the left anterior descending, and the second segment of the left circumflex branch were the parts most frequently affected by rupture. In general, the proximal parts of all branches, apart from the main left stem, were more affected than distal parts, with the second segment (the second 2 cm.) of the right coronary artery having the highest incidence of rupture.

Table 3 shows the distribution of plaque fissuring in the different age groups with the different recent pathological events accompanying the rupture, whether in the same segment or in another segment. In 39 cases, plaque rupture was associated with luminal thrombosis (Figure 10), in 6 cases it was accompanied by mural thrombosis (Figure 11), and in 14 cases intimal haemorrhages were found in association with the rupture. (Figure 12). In several cases, atheromatous material was discharged (embolised) into the lumen , (Figure 13) and fragments of the disrupted plaque could be identified buried deeply in the centre of the thrombus in many cases.

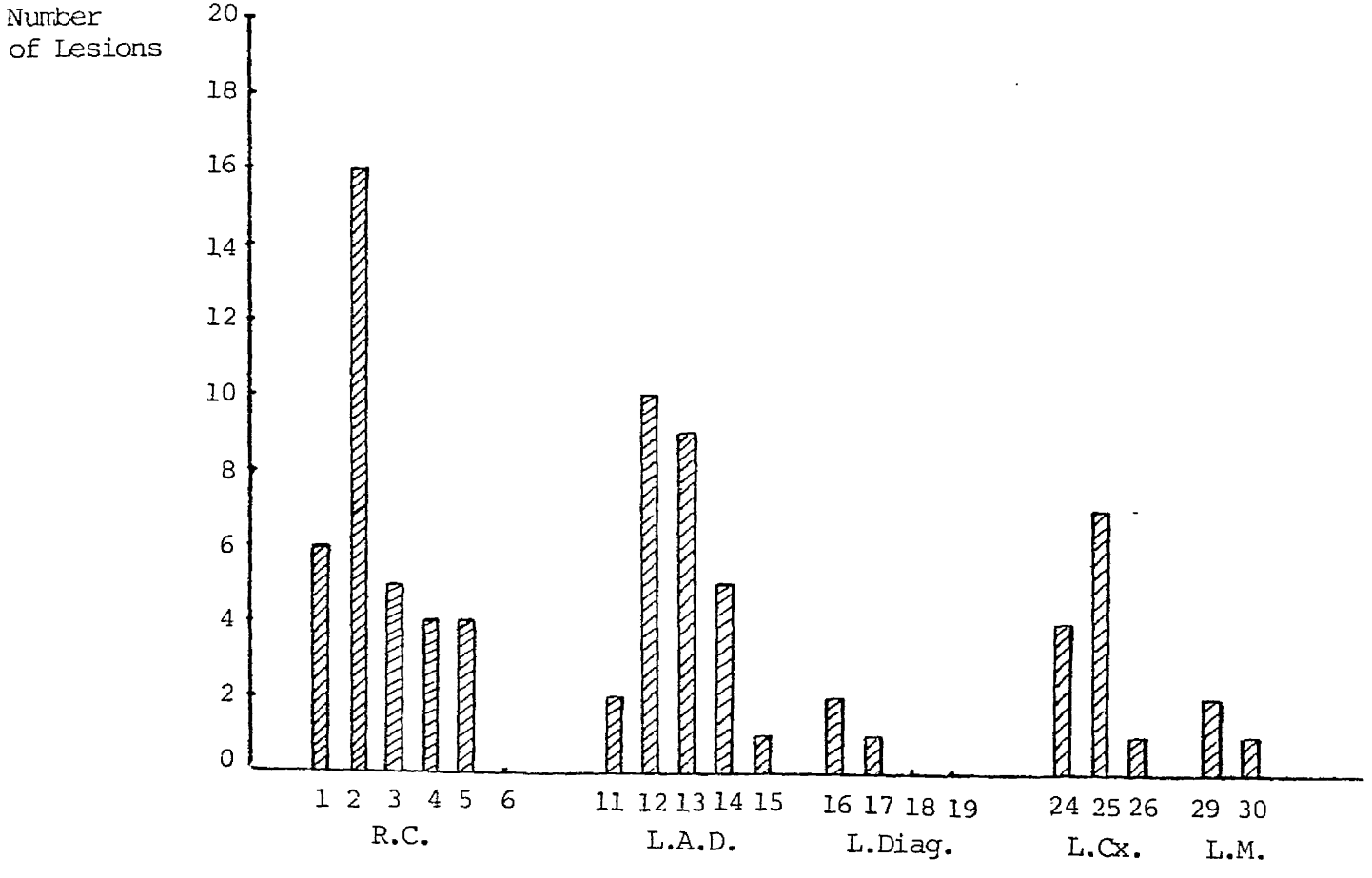


Figure 9 Incidence of Plaque Fissuring at Segments of Coronary Tree in 59 Cases.

TABLE 3

Males 55-69 (39 cases)			Females 55-69 (20 cases)			Males 44-54 (20 cases)			Females 44-54 (5 cases)			Under 44 (8 cases)		
29			13			12			3			2		
T	M	H	T	M	H	T	M	H	T	M	H	T	M	H
16	3	10	8	2	3	11	0	1	2	1	0	2	0	0

Distribution of Plaque Rupture and the Accompanying Acute Lesions in the Different Age Groups (Total number 59 cases).

T = Luminal Thrombosis

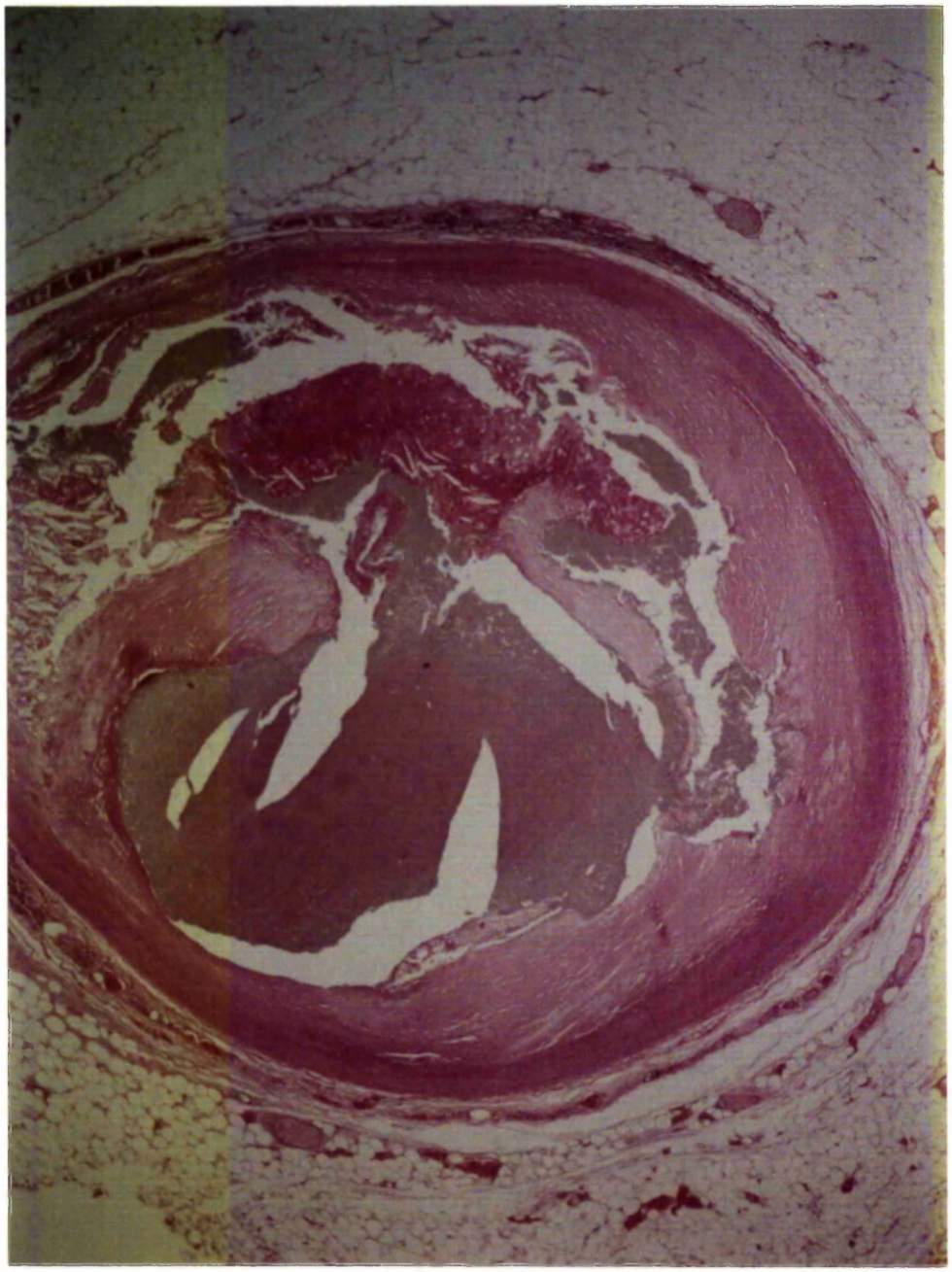
M = Mural Thrombosis

H = Intimal Haemorrhage

Figure 10

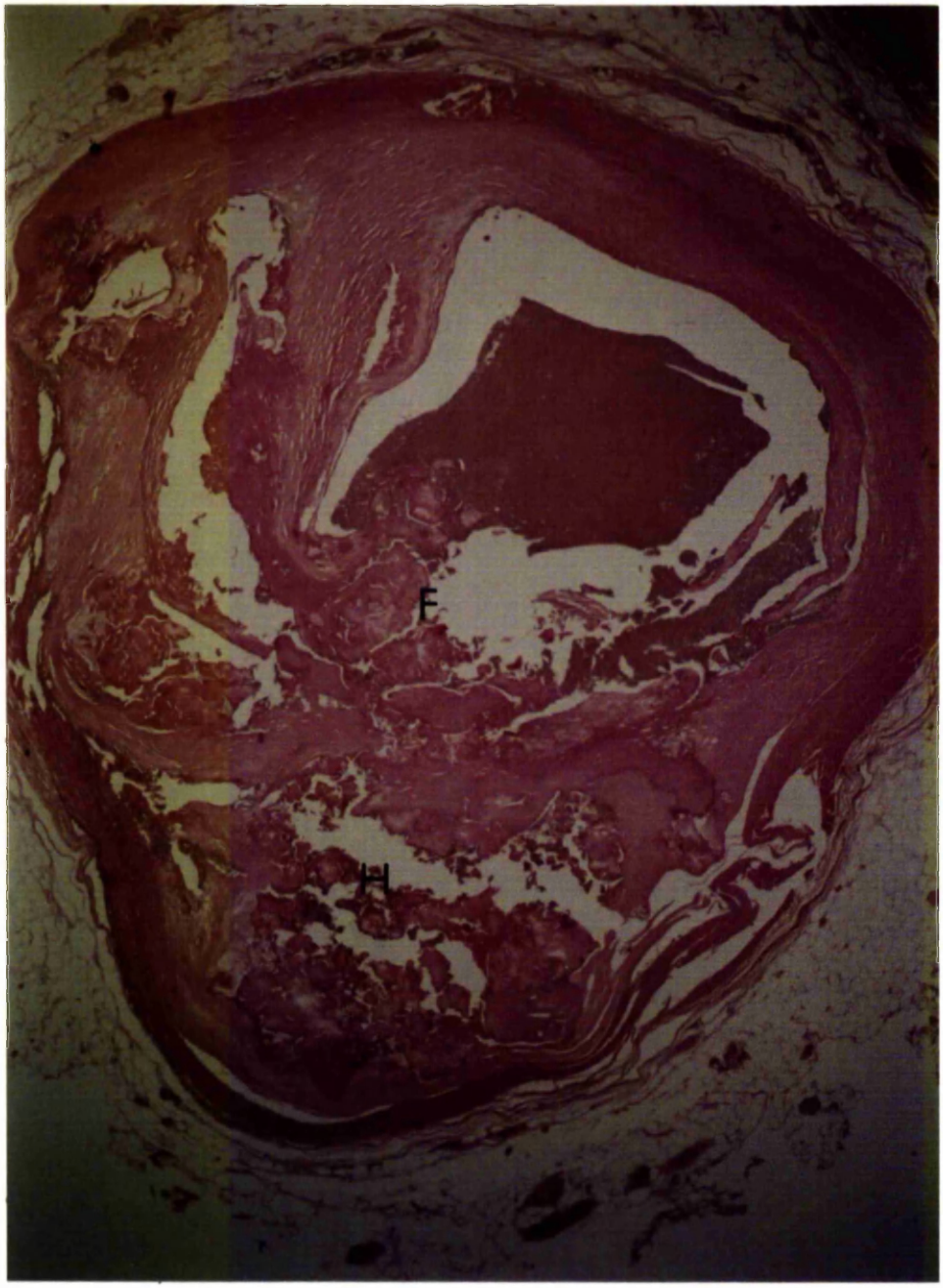
Plaque rupture accompanied by both intraluminal and intramural thrombosis. The affected vessel was stenosed to 88% and the luminal thrombus occupied 35% of the stenosed lumen.

Figure 11



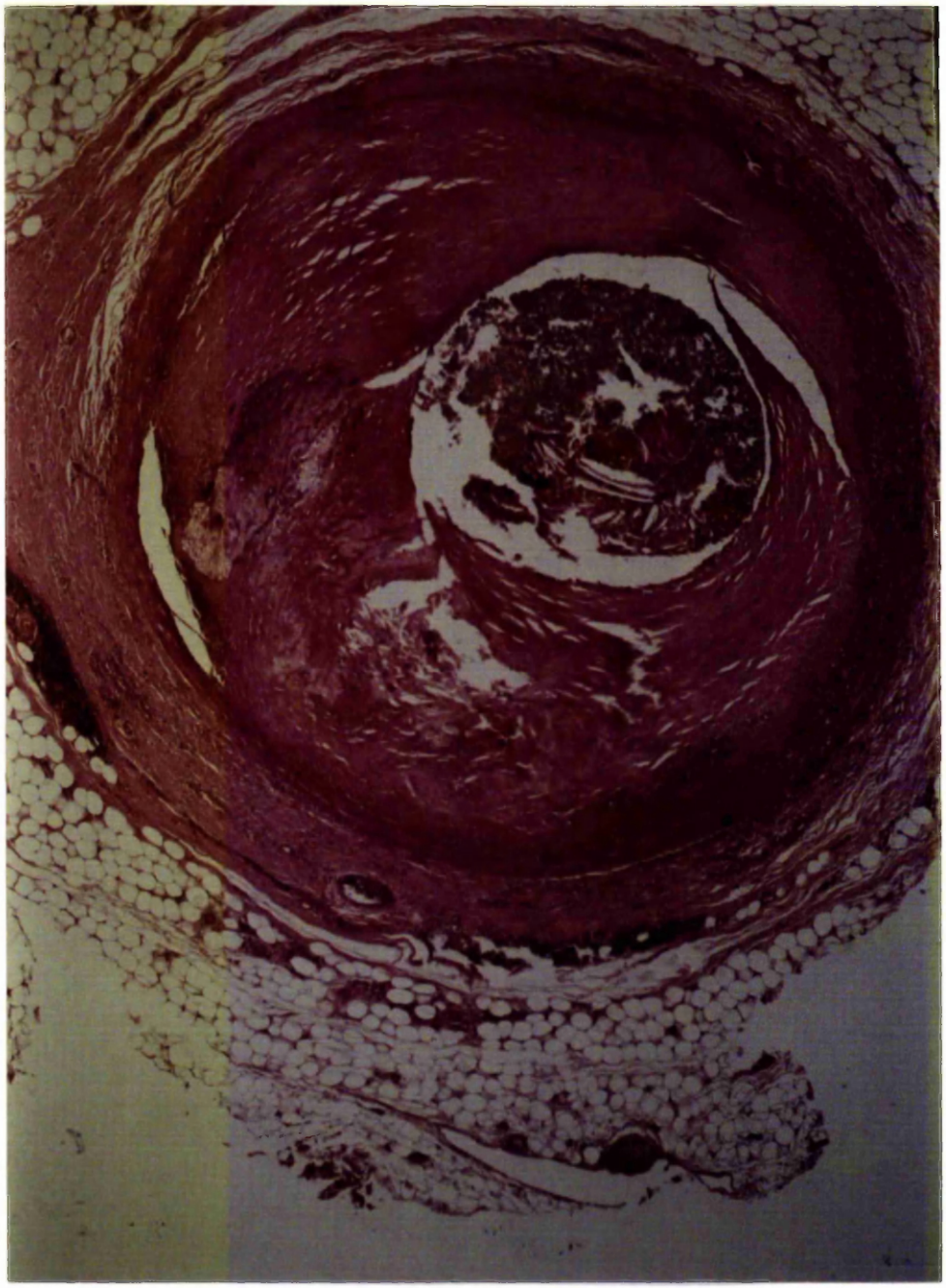
Plaque rupture associated with mural thrombosis; the coronary artery was narrowed to 65%.

Figure 12



Plaque fissuring (F) associated with intimal haemorrhage (H); the artery was stenosed to 65%.

Figure 13



Atheromatous material (embolus) partially occluding an artery (70% stenosis), and distal to a ruptured plaque.

Table 4 shows the degree of pre-existing stenosis at sites of plaque rupture, with relation to the associated lesion at the site of rupture. It demonstrates that thrombosis almost always accompanied the rupture when the previous stenosis was greater than 75% of the lumen, whereas in cases with lesser degrees of stenosis, the rupture was usually associated with intimal haemorrhage.

Table 5 shows the relation of the time interval between the onset of symptoms and death, with the presence of plaque rupture. There was no obvious difference in the incidence of rupture in the different groups.

Intraluminal thrombi were found in 61 cases (66%). Table 6 shows the incidence of thrombosis in the different age groups. In 39 cases, thrombi were associated with plaque fissuring, whereas in 22 cases no fissuring could be identified. (Figure 14) Mural thrombi were found in 6 cases in association with plaque rupture. Thrombi were absent in 25 cases (27%).

In 5 of the 61 cases with luminal thrombosis, more than one artery was involved. In 12 cases, there was more than one discontinuous segments whether in the same artery or in more than one vessel.

In all, 75 separate thrombi were found among the 61 cases. Forty-eight of the thrombi were occluding more than 50% of the lumen (major thrombi), and 27 were occupying less than 50% of the lumen (minor thrombi).

TABLE 4

Stenosis %		50%	50-64%	65-74%	75-84%	85%
	H	1	8	8	7	9
Ruptured Plaque	M	O	O	2	6	4
	T	O	2	O	8	25

Degree of Pre-existing stenosis at sites of Plaque Rupture and the Accompanying Acute Lesions (Total number 80 Ruptures)

H = Intimal Haemorrhage
M = Mural Thrombus
T = Luminal Thrombus

TABLE 5

15 minute (31 cases)	15-60 minute (11 cases)	1-6 hours (11 cases)	6-24 hours (11 cases)	Unknown (28 cases)
20 (65%)	9 (82%)	6 (55%)	6 (55%)	18 (64%)

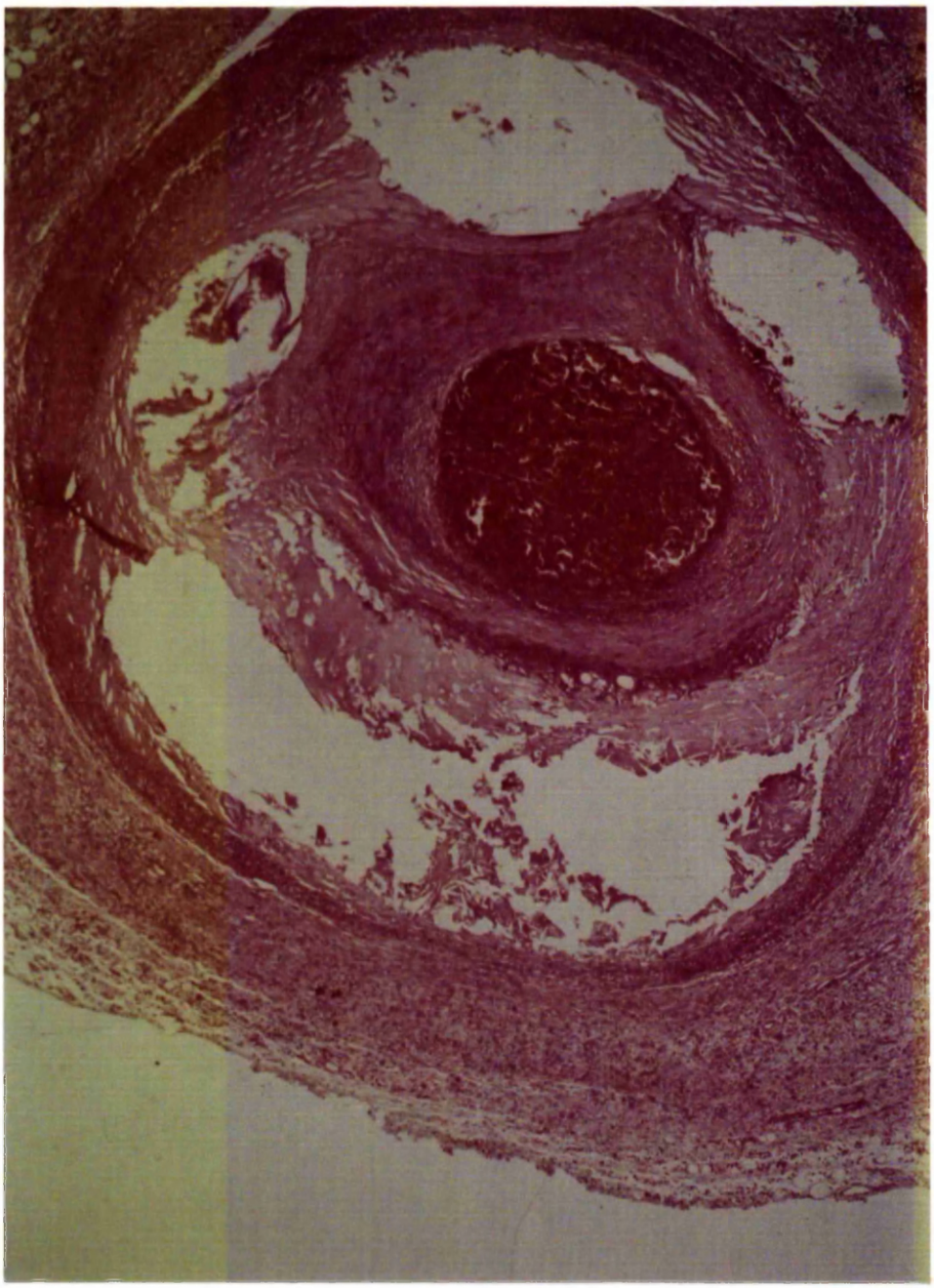
Relation of the Time Interval between Onset of Symptoms and Death with Occurrence of Plaque Rupture. (Total number 92 cases)

TABLE 6

Males 55-69 (39 cases)	Females 55-69 (20 cases)	Males 44-54 (20 cases)	Females 44-54 (5 cases)	Under 44 (8 cases)
22 (56%)	12 (60%)	17 (85%)	3 (60%)	7 (88%)

Distribution of Luminal Thrombi in the Different Age Groups.
(Total number 61 cases)

Figure 14



Intraluminal thrombus totally occluding an artery with 80% stenosis and distal to the site of rupture.

(Figure 15). Thirty-five cases had major thrombi in one or more of their coronaries, compared with 26 cases who had minor thrombi. Table 7 shows the distribution and the size of the largest thrombus in the 61 cases with luminal thrombosis. Considering the 75 incidences of thrmbosis, the distribution was 30 in the right coronary (40%), 32 in the left anterior descending (43%), and 13 in the left circumflex branch (17%).

Figure 16 shows the distribution of luminal thrombi in the different segments of the coronary tree. The second segment of the right coronary artery, the second, third and fourth segments of the left anterior descending branch were the most frequently affected by thrombosis. The second segment of the right coronary artery (second 2 cm.), had the highest incidence of thrombosis, and the proximal parts of the major arteries, excluding the left main stem, had more thrombi than the distal parts.

Table 8 shows the relation between the duration of survival and the presence of coronary thrombi. No obvious difference in the incidence of thrombosis was noticed between the different groups.

The degree of the previous stenosis in the segments with the largest thrombus is shown in Table 9. Only one minor thrombus (occluding less than 50% of the lumen) was found when the pre-existing stenosis was less than 50%.

Figure 15

Fresh minor thrombus (A)adjacent to an older organised thrombus (B); the vessel was stenosed to 75%.

TABLE 7

Size of Largest Thrombus Per Case (% of lumen)	Number of cases	Coronary Artery R.C.	L.A.D.	L.Cx
1-24	12	3	6	3
25-50	14	7	5	2
51-75	12	5	6	1
76-100	23	9	7	7
Total	61	24 (39%)	24 (39%)	13 (22%)

Size and Distribution of Luminal Thrombi in 61 cases of Sudden Cardiac Ischaemic Death.

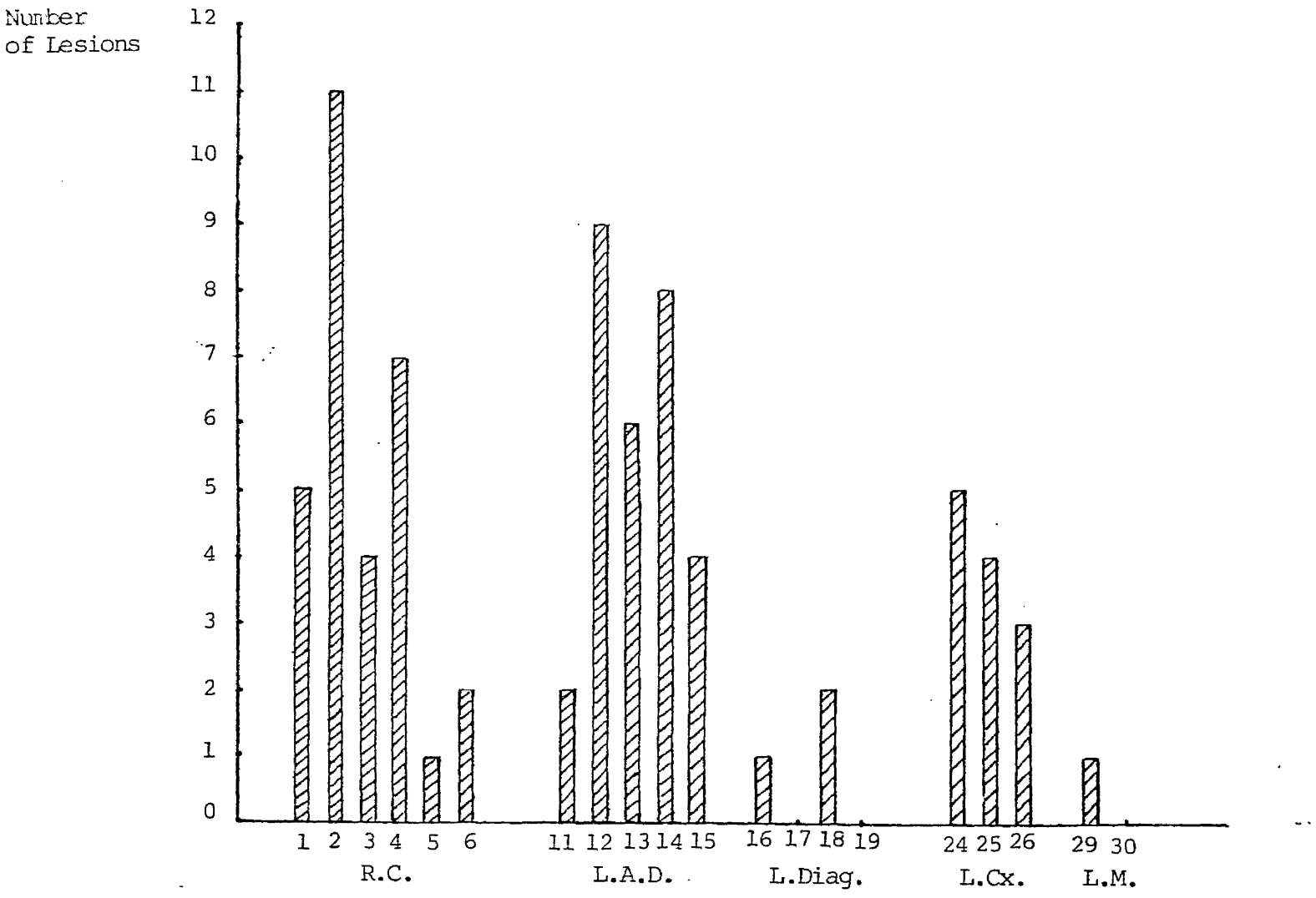


Figure 16 Incidence of Luminal Thrombosis at Segments of Coronary Tree in 61 Cases.

TABLE 8

15 min. (31 cases)	15 - 60 min. (11 cases)	1 - 6 hrs. (11 cases)	6 - 24 hrs. (11 cases)	Unknown (28 cases)
20 (65%)	7 (64%)	8 (73%)	8 (73%)	18 (64%)

Relation of the Time Interval between Onset of Symptoms and Death with the Presence of a Thrombus. (Total number 92 cases)

TABLE 9

Stenosis %	50%	50-64%	65-74%	75-84%	85%
Number of Major Thrombi (>50%)	0	0	2	8	29
Number of Minor Thrombi (<50%)	1	0	0	4	17

Degree of Pre-existing Stenosis at site of largest Thrombus per Case (Total number 61 cases).

Two cases had major thrombi (occupying more than 50% of the lumen) in asssociation with previous stenosis of 65 to 74%. Table 10 shows the degree of the previous stenosis in the segments of all the separate instances of thrombi (75 instances). Two minor thrombi were found at a site with a previous stenosis of less than 50%, and another two were found when the stenosis was 50-64%. Three major thrombi were found with previous stenosis of 50-64%, and another three at 65-74% stenosis.

Recanalisation, representing old lesions, (Figure 17) was found to occur in 27 cases; three of these cases had no recent pathological lesion in the coronary arteries. Table 11 shows the incidence of recanalisation in the different age groups. In two cases, recanalisation was found in all major three arteries, and seven cases showed recanalisation in two branches. Recanalisation was found in the right coronary in 15 cases, in the left anterior descending in 11 cases, and in the left circumflex in 11 cases (Tables 12a and 12b).

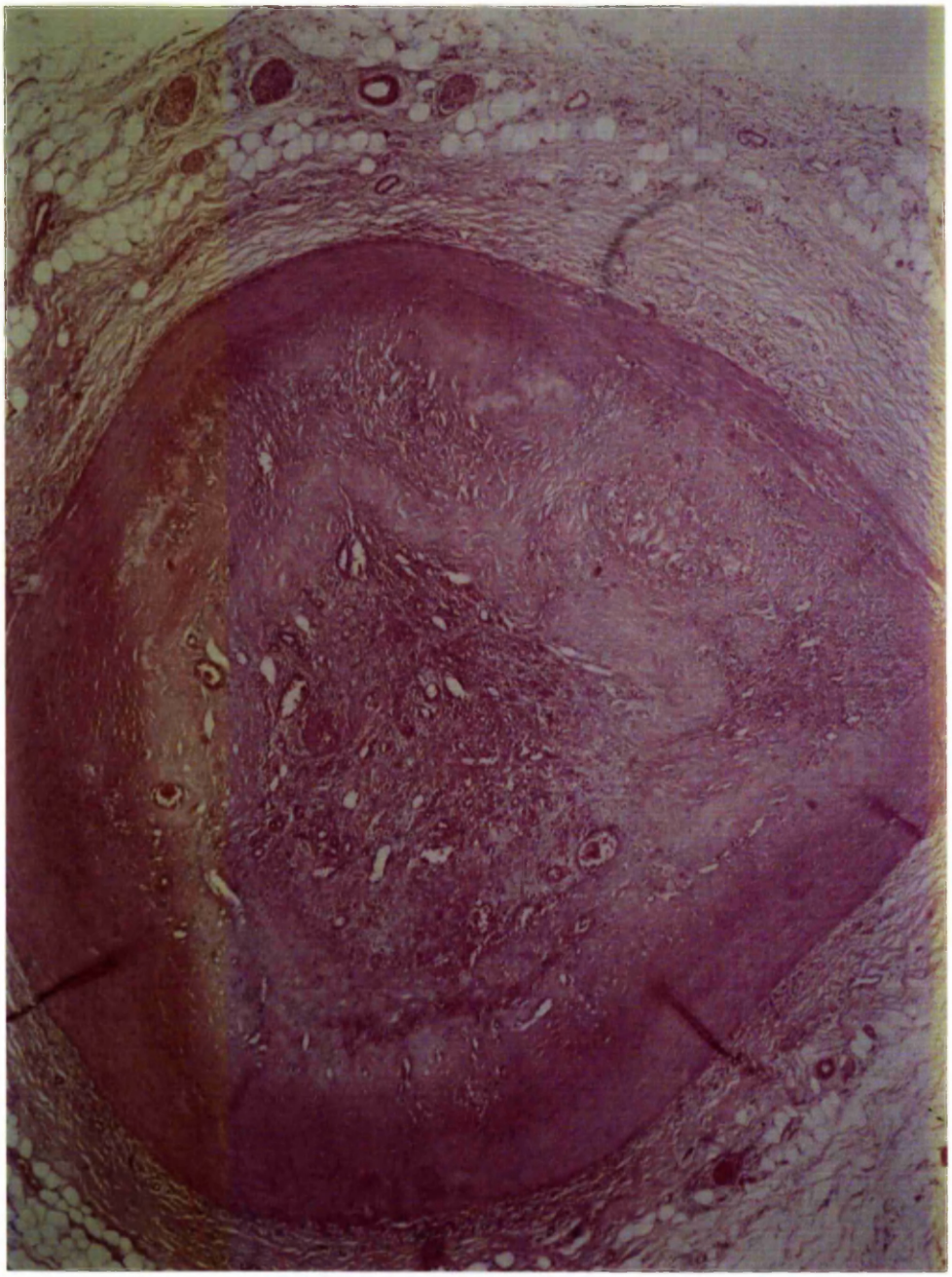
Distribution of recanalisation (old occlusions) in the different segments of the coronary tree is shown in Figure 18. The fourth segment of the right coronary, the first segment of the left diagonal, and the first segment of the second diagonal, were the most commonly affected sites with recanalisation. Unlike with fissuring and thrombosis, the proximal parts of the main branches did not show a high incidence of recanalisation.

TABLE 10

Stenosis %	50%	50-64%	65-74%	75-84%	85%
Number of Major Thrombi (50%)	0	3	3	10	32
Number of Minor Thrombi (50%)	2	2	0	5	18

Degree of Pre-existing Stenosis at sites of all Separate Instances of Thrombi (Total number 75 thrombi).

Figure 17



Coronary artery, occluded by an organised thrombus, showing recanalisation.

TABLE 11

Males 55-69 (39 cases)	Females 55-69 (20 cases)	Males 44-54 (20 cases)	Females 44-54 (5 cases)	Under 44 (8 cases)
14 (36%)	6 (30%)	5 (25%)	1 (20%)	1 (13%)

Distribution of Recanalisation (Old Lesions) in the Different Age Groups (Total number 92 cases)

TABLE 12 (a)

One artery	Two arteries	Three arteries
18	7	2

Frequency of Recanalisation in the Three Major Branches (Total number 27 Cases)

TABLE 12 (b)

Right coronary	Left anterior descending	Left circumflex
15 (40%)	11 (30%)	11 (30%)

Distribution of Recanalisation in the Three Major Branches. (Total Number 37 lesions).

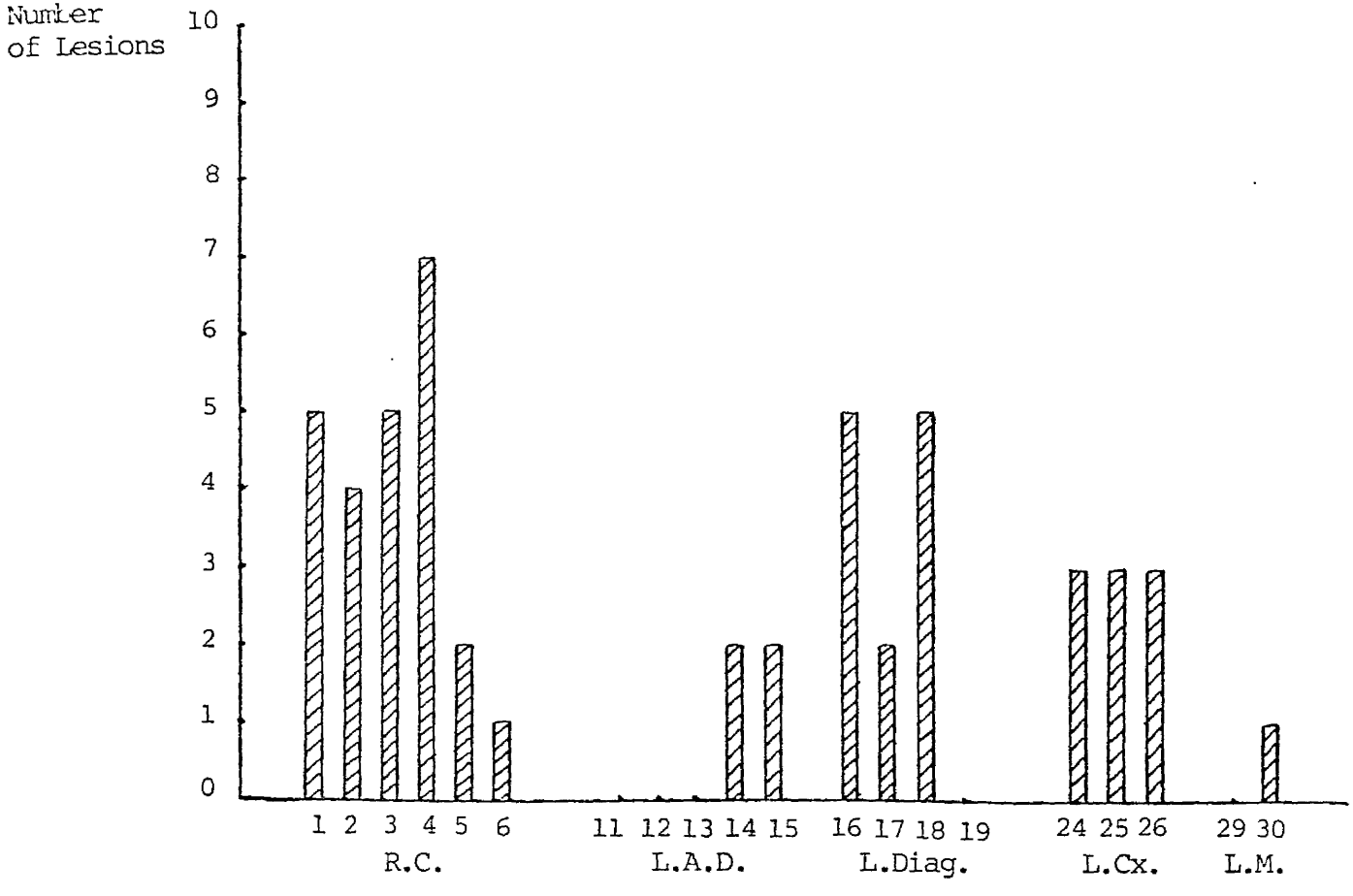


Figure 18 Incidence of Recanalisation (Old Lesions) at Segments of Coronary Tree in 27 Cases.

The relation between activity at the time of death and the different acute pathological lesions is shown in Table 13. Sixty-nine per cent of cases who were at rest at time of death had thrombosis. Thrombus was found in 60% of cases who were in moderate activity and in 63% of cases of maximal activity at time of death. Ruptured plaque, with mural thrombosis or intimal haemorrhage, was found in 21% of the resting group, 20% of cases of moderate activity, and 25% of cases of maximal activity.

Figure 19 and Table 14 show the average stenosis in each segment of the coronary tree for all test cases (92 cases). The second 2 cm. (segment 2) of the right coronary, the third and fourth 1.5 cm. of the left anterior descending branch (segments 13 and 14), the proximal part of the left diagonal branch (segment 16), and the proximal part of the left circumflex artery (segment 24), showed the highest average stenosis among all the segments. In general, the proximal parts of all the branches, excluding the main left stem, had higher grades of stenosis than those of the distal parts. The figures for the largest age group of men aged between 55 and 69 years (39 cases), showed similar results, with the same segments having the highest degrees of stenosis, and the proximal parts being more severely affected by the disease (Figure 20 and Table 15).

Figures 20 to 24 show the average stenosis for all age groups. The first three segments of the right

TABLE 13

	Luminal Thrombosis	Rupture plaque with Mural Thrombus or Haemorrhage	No Acute Lesion
Resting (61 cases)	42 (69%)	13 (21%)	6 (10%)
Moderate Activity (15 cases)	9 (60%)	3 (20%)	3 (20%)
Maximal Activity (16 cases)	10 (63%)	4 (25%)	2 (12%)

Relation of Activity at Time of Death with Presence of Acute Lesion (Total number 92 cases)

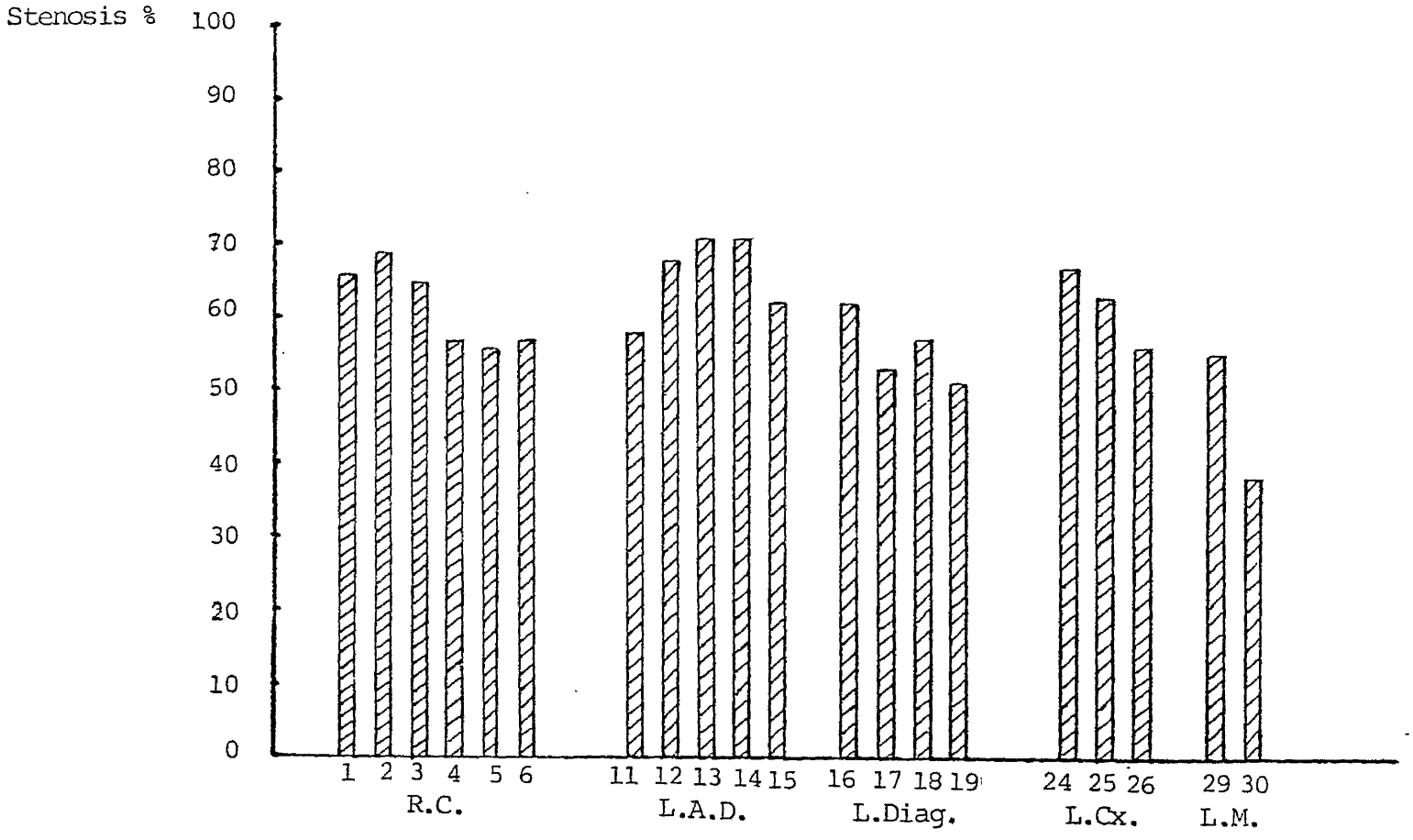


Figure 19 Average Stenosis of Segments of Coronary Tree in 92 Cases of Sudden Cardiac Ischaemic Death.

TABLE 14

Degree of Stenosis in Segments of Coronary Tree in 93 Cases of Sudden Cardiac Ischaemic Death

Artery Segment	Mean	Standard Deviation	Geometric Mean	Geometric Std. Dev.	Range
1	66	20	62	1.49	13-100
2	69	22	64	1.54	11-99
3	65	24	59	1.67	7-100
4	57	26	48	1.93	3-100
5	56	27	47	1.95	6-100
6	57	27	47	2.0	7-100
11	58	20	54	1.51	16-89
12	68	16	65	1.37	9-98
13	71	14	69	1.24	31-100
14	71	18	68	1.37	19-100
15	62	23	56	1.68	7-100
16	62	23	56	1.58	14-100
17	53	26	45	1.89	7-99
18	57	24	51	1.79	10-98
19	51	28	41	2.19	7-95
24	67	19	64	1.39	25-100
25	63	24	57	1.67	10-100
26	56	25	49	1.77	9-100
29	55	26	47	1.88	10-98
30	38	26	29	2.12	6-100

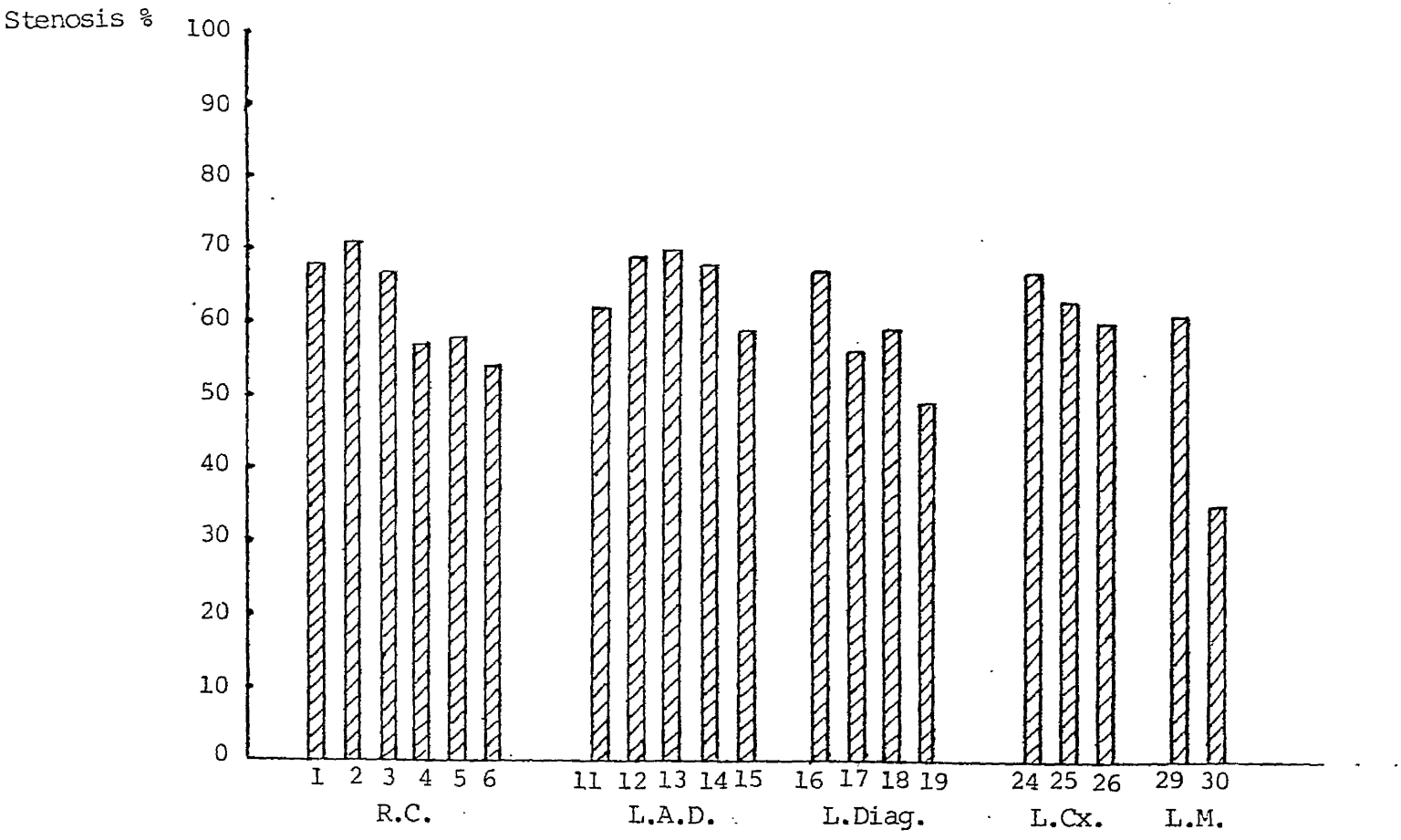


Figure 20 Average Stenosis of Segments of Coronary Tree in Men aged 55 - 69 (39 Cases)

TABLE 15

Degree of Stenosis in Segments of Coronary Tree in Men aged 55-69 (39 Cases)

Artery Segment	Mean	Standard Deviation	Geometric Mean	Geometric Std. Dev.	Range
1	68	20	65	1.41	17-100
2	71	20	67	1.42	18-99
3	67	21	63	1.46	19-100
4	57	25	51	1.73	9-100
5	58	28	49	1.95	8-100
6	54	26	45	2.05	8-100
11	62	20	58	1.52	16-89
12	69	15	67	1.28	28-92
13	70	14	68	1.25	13-95
14	68	19	65	1.38	24-98
15	59	24	52	1.73	7-98
16	67	21	63	1.46	17-99
17	56	26	49	1.73	15-99
18	59	20	56	1.44	26-92
19	49	21	43	1.8	15-67
24	67	21	63	1.44	25-100
25	63	26	55	1.75	10-100
26	60	27	52	1.81	9-97
29	61	28	51	2.02	11-98
30	35	21	29	1.88	13-69

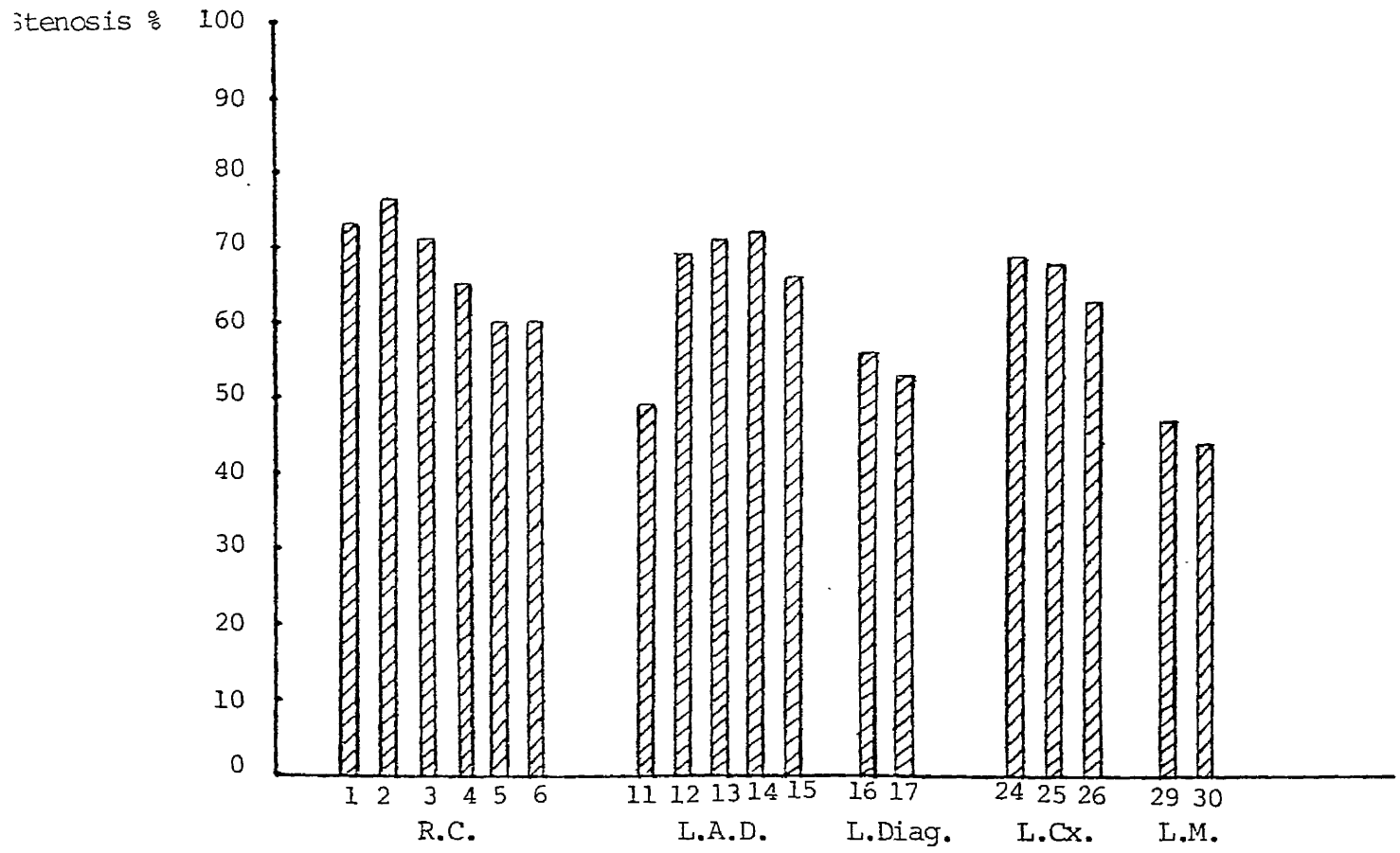


Figure 21 Average Stenosis of Segments of Coronary Tree in Women Aged 55 - 69 (20 Cases)

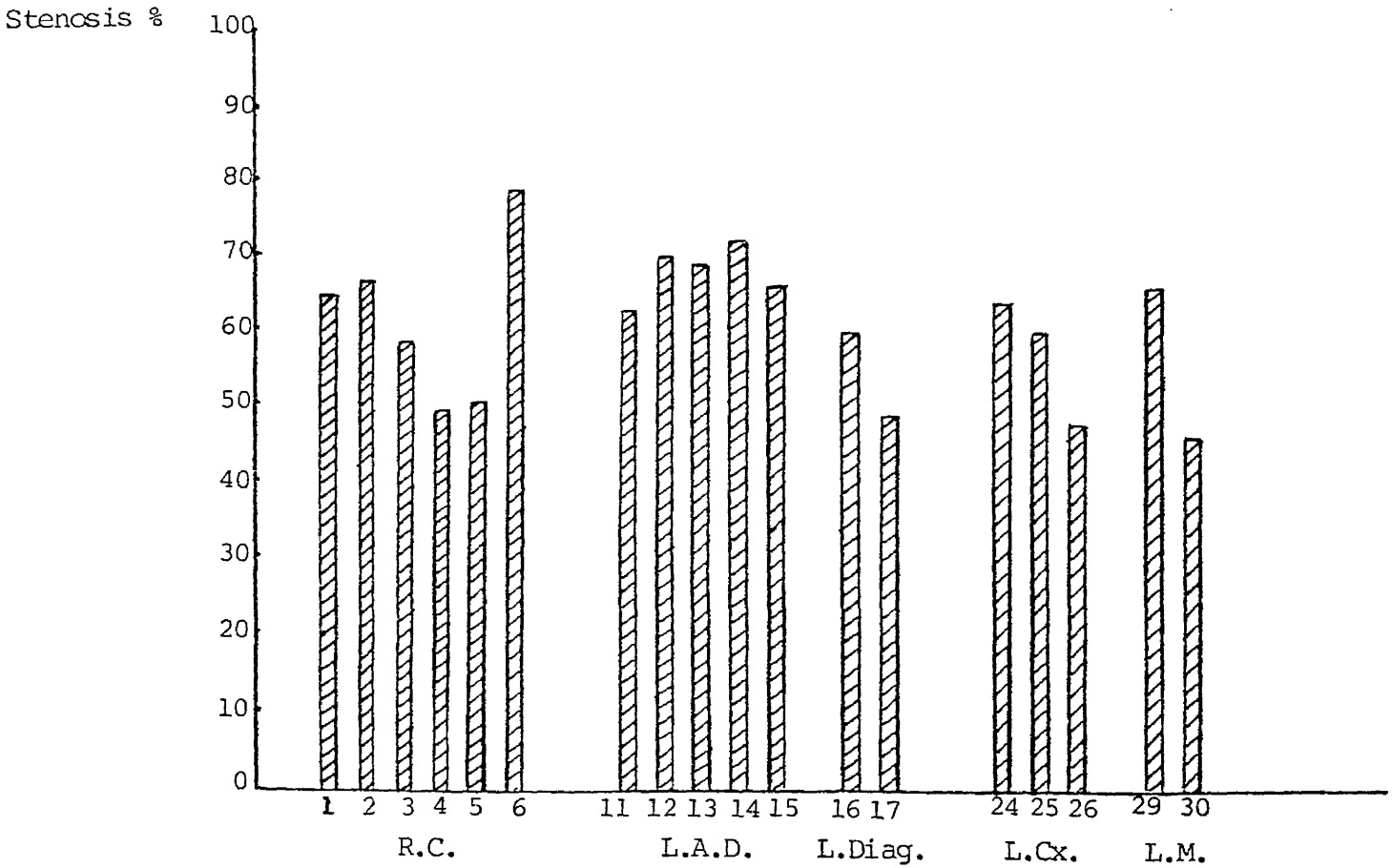


Figure 22 Average Stenosis of Segments of Coronary Tree in Men Aged 44 - 54 (20 Cases).

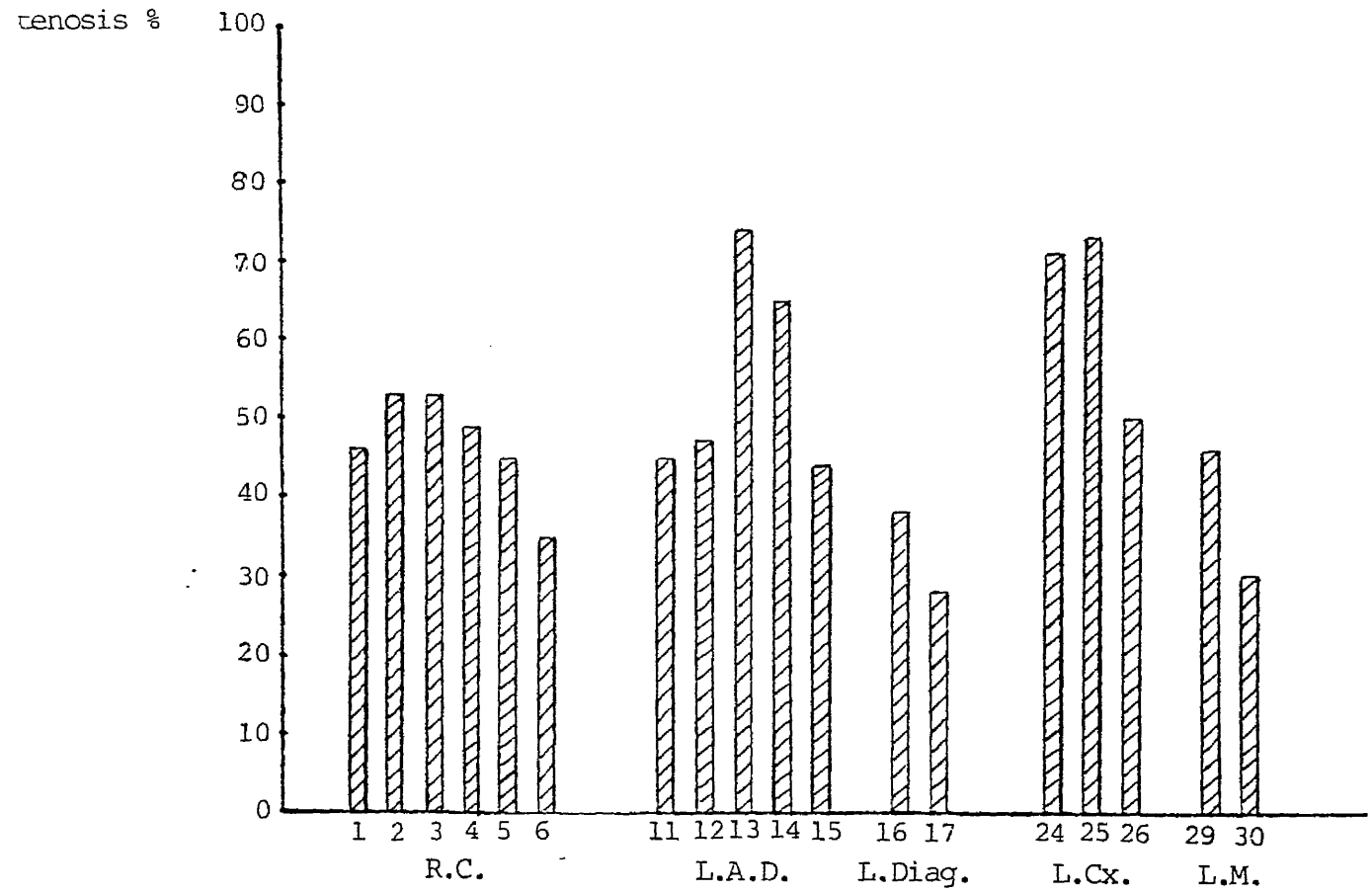


Figure 23 Average Stenosis of Segments of Coronary Tree in Women Aged 44 - 54 (5 Cases).

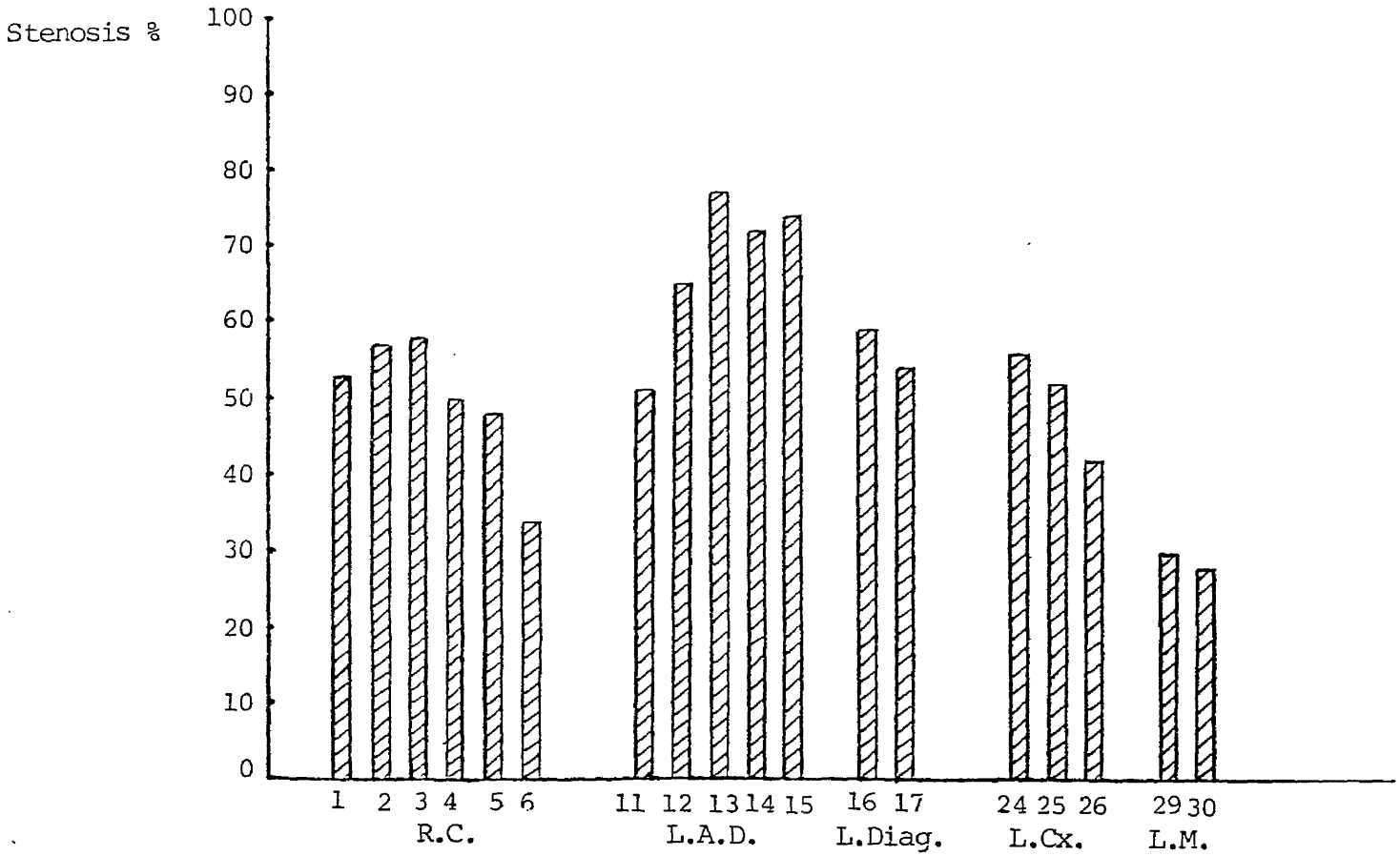


Figure 24 Average Stenosis of Segments and Coronary Tree in Cases Under the Age of 44 (8 Cases).

coronary (1, 2 and 3), the second, third and fourth segments of the left anterior descending branch (12, 13 and 14), as well as the first two segments of the left circumflex artery (24 and 25), had the highest stenosis averages in all age groups, except for cases under the age of 44 (8 cases), where the distal part of the left anterior descending branch (segment 15) showed greater stenosis than the proximal segment (12). At the same time, the proximal parts of both the first and second diagonal, as well as the proximal part of the left marginal branch, had higher averages of stenosis than the distal parts, in all groups.

The second 2 cm. of the right coronary (segment 2), had the highest average stenosis for the three largest age groups, whereas the third 2 cm. (segment 3) showed a slightly higher stenosis average for women aged between 44 and 54 years (5 cases). In the left anterior descending branch, the third 1.5 cm. (segment 13) showed the highest average stenosis for all age groups, with the exception of males aged between 44 and 54 years (20 cases), where the fourth 1.5 cm. had the highest stenosis average. At the same time, in the circumflex artery the proximal part (segment 24) had the highest averages of stenosis in all age groups.

However, in 17 of one hundred test cases, the distal parts were more severely affected by atheroma than the proximal parts. (Figure 25). In 12 of these cases, a

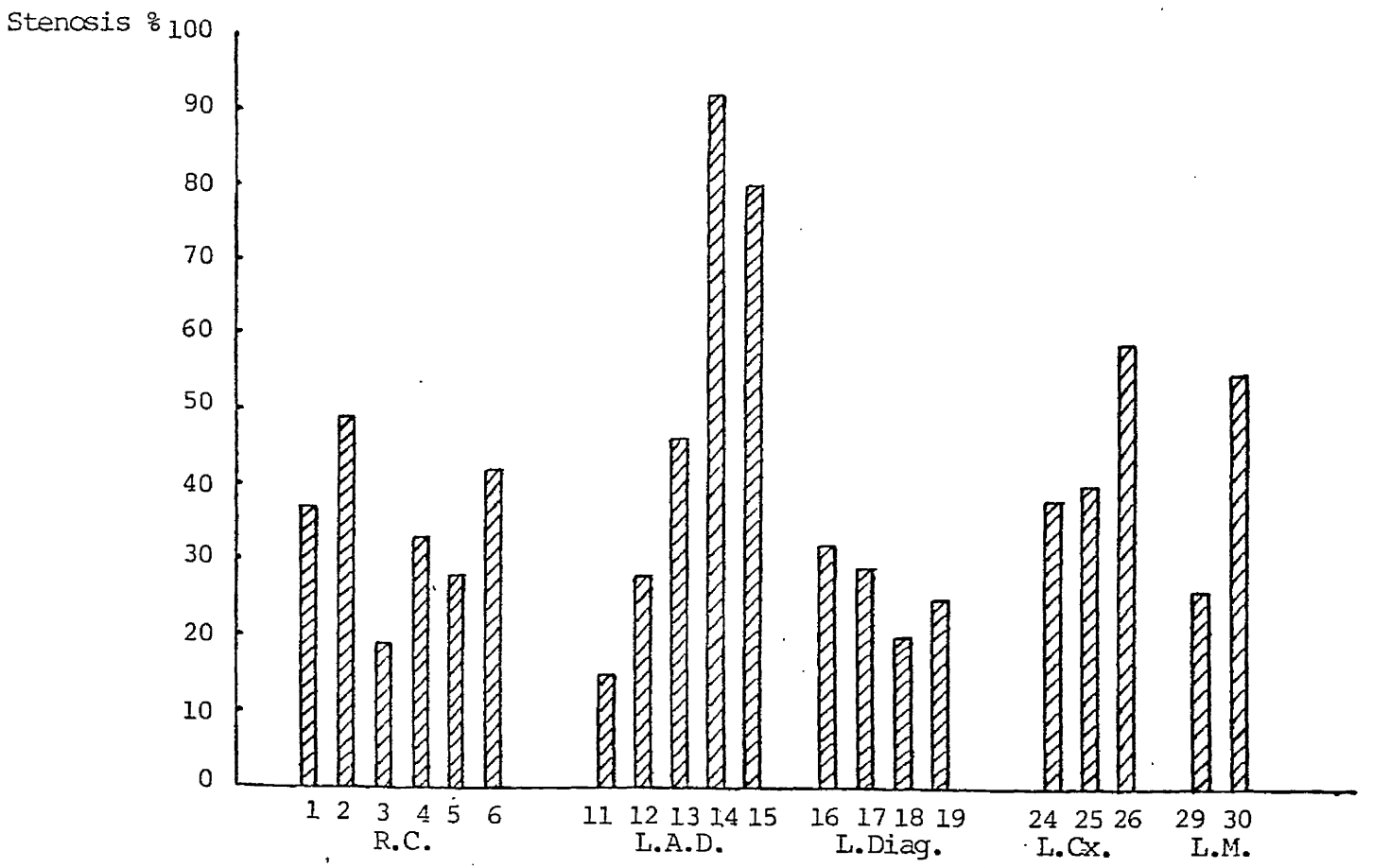


Figure 25 An Example of the Degree of Stenosis in Different Segments of Coronary Tree of a Case with Distal Lesions.

greater degree of stenosis was shown in one of the major vessels in the distal parts than in the proximal parts. In 4 cases, the distal parts of two arteries were more severely stenosed and in one case the three major arteries were more stenosed distally.

The distribution of the stenosis figures throughout the segments of the right coronary in all cases and the largest age group (Tables 16 and 17), shows that more cases had higher grades of stenosis, between 70 and 100%, in the first three segments than in the three distal segments. At the same time, more cases had stenosis of less than 50% in the distal parts than in the proximal parts.

Tables 18 and 19 show the stenosis figures for each segment of the left anterior descending branch in all cases and the largest age group. The figures indicate that the main left stem was much less affected with atheroma compared with the other parts of coronary vessels. Indeed the main left stem was the only segment of the coronary tree where not one single case had stenosis of more than 90%. The figures also show that in the first three segments of the artery (11, 12 and 13), the number of cases having stenosis greater than 95% was much less compared with the other distal segments (14 and 15) and the left diagonal branch (segments 16 and 17). At the same time, the number of cases having higher stenosis grades was greater in the proximal than in the distal parts of the vessel.

TABLE 16

Stenosis%	1-25	26-50	51-69	70-85	86-95	95
Segments						
1	1	7	10	13	3	5
2	1	6	11	10	6	5
3	2	6	12	9	7	3
4	4	14	4	10	4	3
5	7	8	10	6	5	3
6*	6	7	8	2	3	1

Distribution of Stenosis in the Segments of the Right Coronary in Males 55-69 years (39 Cases)

*Number of cases for segment 6 (30 Cases)

TABLE 17

Stenosis%	1-25	26-50	51-69	70-85	86-95	95
Segments						
1	6	12	27	30	10	7
2	5	13	23	26	15	10
3	8	14	28	18	18	6
4	15	25	14	22	11	5
5	16	23	22	16	11	4
6*	15	11	19	9	8	2

Distribution of Stenosis in the Segments of the Right Coronary in all Test Cases (92 Cases)

*Number of cases for segment 6 (69 Cases)

TABLE 18

Stenosis%	1-25	26-50	51-69	70-85	86-95	95
Segments						
11*	0	6	5	8	1	0
12	0	5	17	14	3	0
13	0	6	13	16	4	0
14	1	7	9	14	6	2
15	3	12	9	9	5	1
16	1	9	10	10	6	3
17	7	13	7	5	5	2

Distribution of Stenosis in the Segments of the Left Anterior Descending branch in Males 55-69 (39 Cases)

*Number of Cases for segment 11 (24 Cases)

TABLE 19

Stenosis%	1-25	26-50	51-69	70-85	86-95	95
Segments						
11*	3	16	13	14	3	0
12	1	13	37	29	11	1
13	0	10	28	41	10	3
14	3	9	23	38	13	6
15	8	19	28	20	12	5
16	7	25	23	22	10	5
17	21	28	18	13	7	5

Distribution of Stenosis in the Segments of the Left Anterior Descending branch in All cases (92 Cases)

*Number of cases for segment 11 (54 Cases)

The distribution of the figures for the left circumflex artery (Table 20 and 21), shows the same findings as the other two vessels, with more cases having greater stenosis in the proximal part (segments 24 and 25) than in the distal part (segment 26).

The results show that in 49 cases, the three major vessels were stenosed to more than 70% of the lumen, 25 cases of these had stenosis of more than 80% in three vessels and in 4 cases the stenosis was more than 90%. On the other hand, in five of the ninety-two cases, a stenosis of more than 75% was confined to only one of the segments of one artery, with the rest of the vessels being relatively free of the disease. (Figure 26). In another five cases, two segments of the same artery were narrowed to more than 75%, and in four cases, two of the major arteries had only one segment stenosed to more than 75%, with the rest of the coronary tree relatively free.

Figures 27 to 29 show the average stenosis in the different segments of each of the two major vessels, when the third was severely narrowed to more than 90% in one or more segments. When the right coronary was stenosed to greater than 90% the stenosis figures of some of the segments of the left anterior descending branch were slightly higher than the average, whereas the figures of the left circumflex artery remained around the average percentages. On the other hand, in cases where either the left anterior descending or the left circumflex

TABLE 20

Stenosis%	1-25	26-50	51-69	70-85	86-95	95
Segments						
24	1	10	8	12	4	4
25	3	10	7	12	2	5
26	6	9	8	7	7	2

Distribution of Stenosis in the Segments of the Left Circumflex artery in Males 55-69 years (39 Cases)

TABLE 21

Stenosis%	1-25	26-50	51-69	70-85	86-95	95
Segments						
24	1	19	27	31	8	6
25	9	16	21	30	10	6
26	14	28	20	15	11	11

Distribution of Stenosis in the Segments of the Left Circumflex artery in All Test Cases (92 Cases)

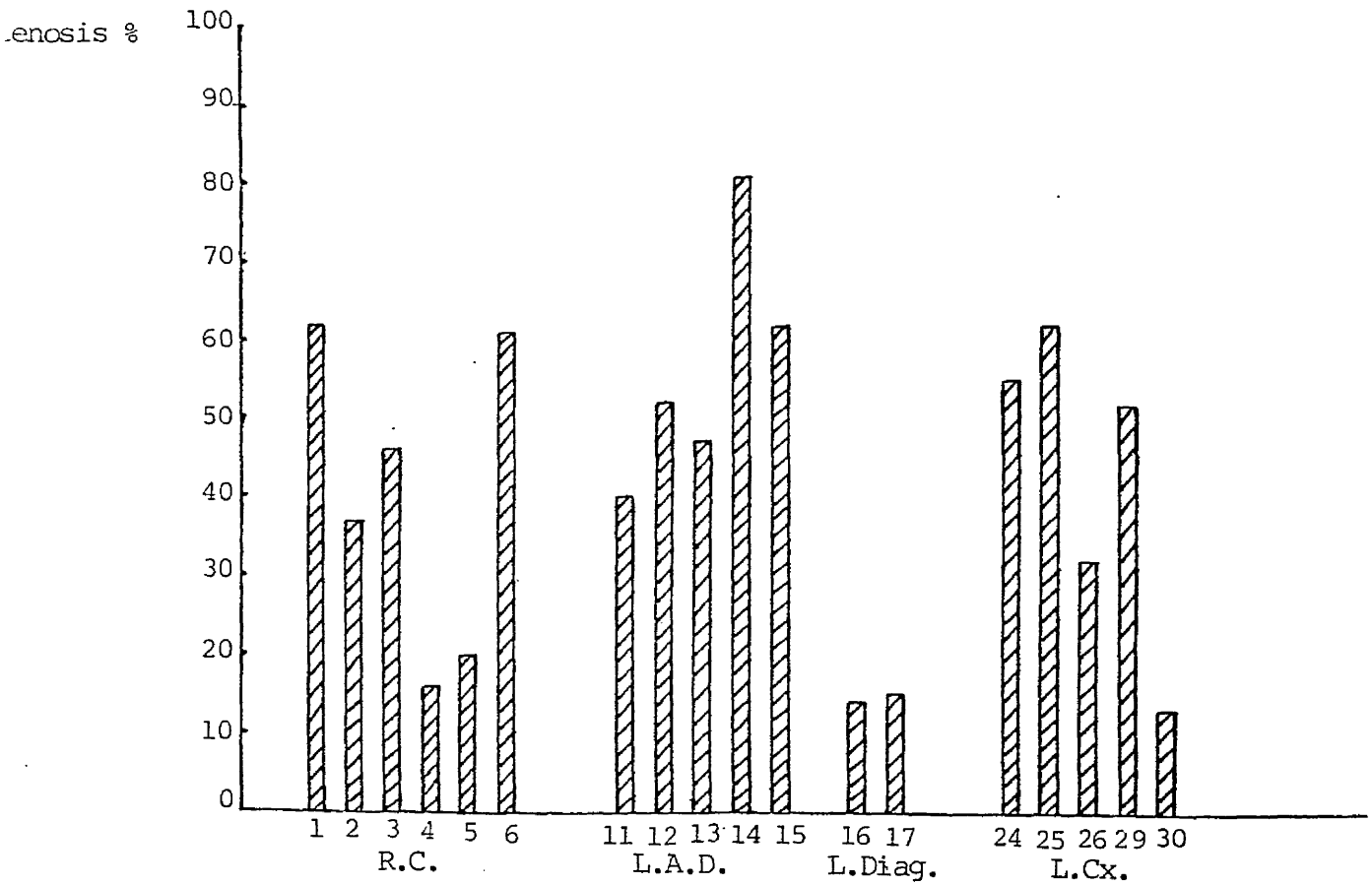


Figure 26 An Example of the Degree of Stenosis in Different Segments of Coronary Tree of a Case with a Single Segment Lesion.

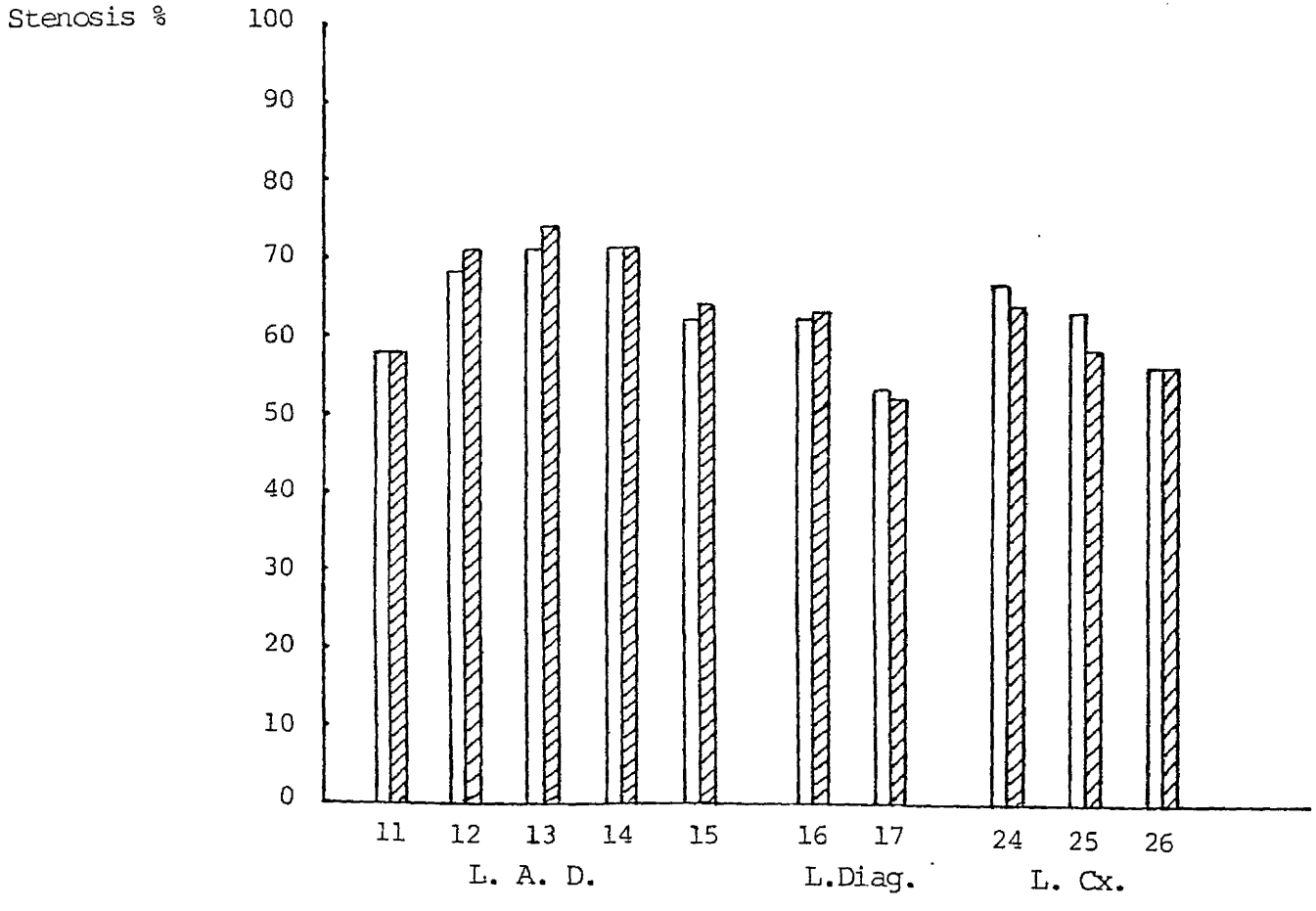


Figure 27 Average Stenosis in Segments of the Left Anterior Descending and Left Circumflex Branches in Cases where the Right Coronary was narrowed to more than 90% Compared with the Average SLenosis in 92 Cases.

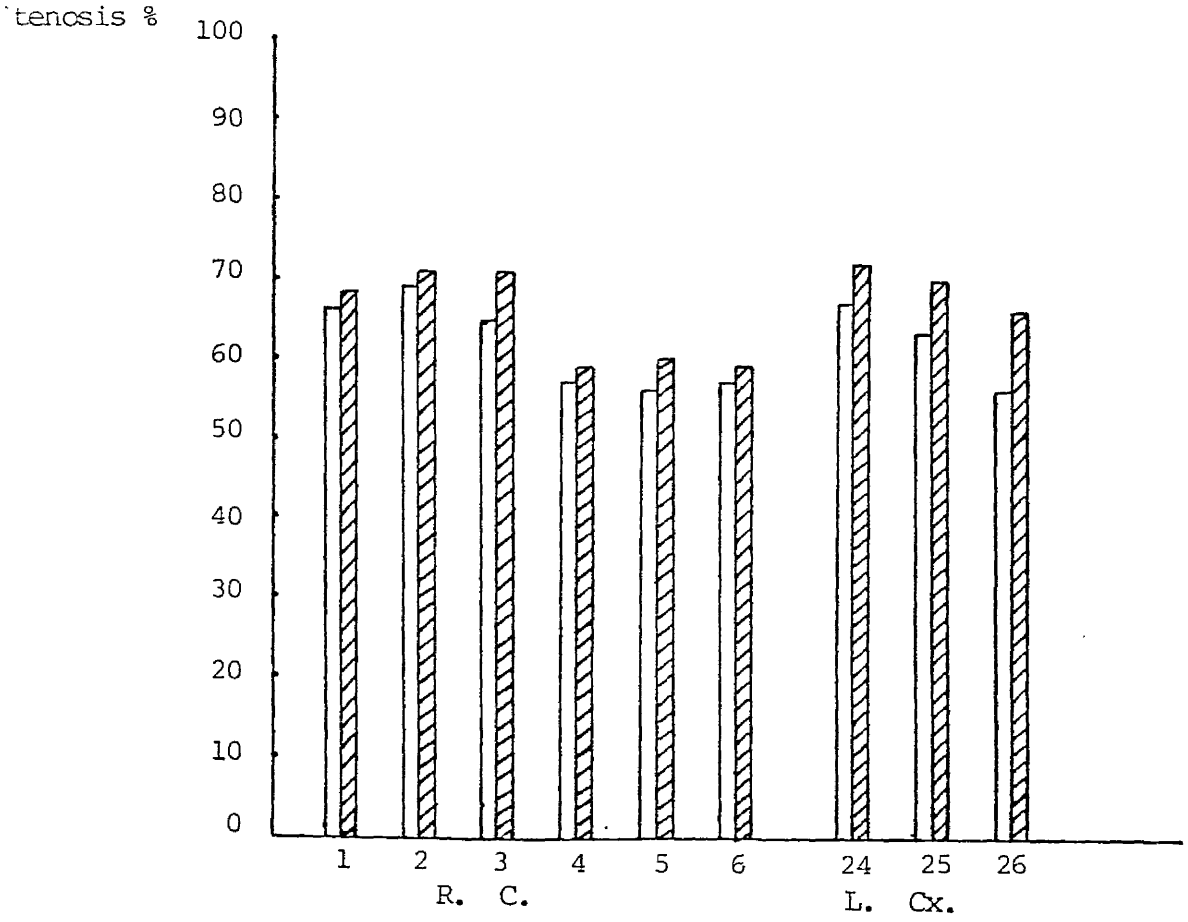


Figure 28 Average Stenosis in Segments of the Right and Left Circumflex Branches in Cases where the Left Anterior Descending was Narrowed to more than 90% Compared with the Average Stenosis in 92 Cases.

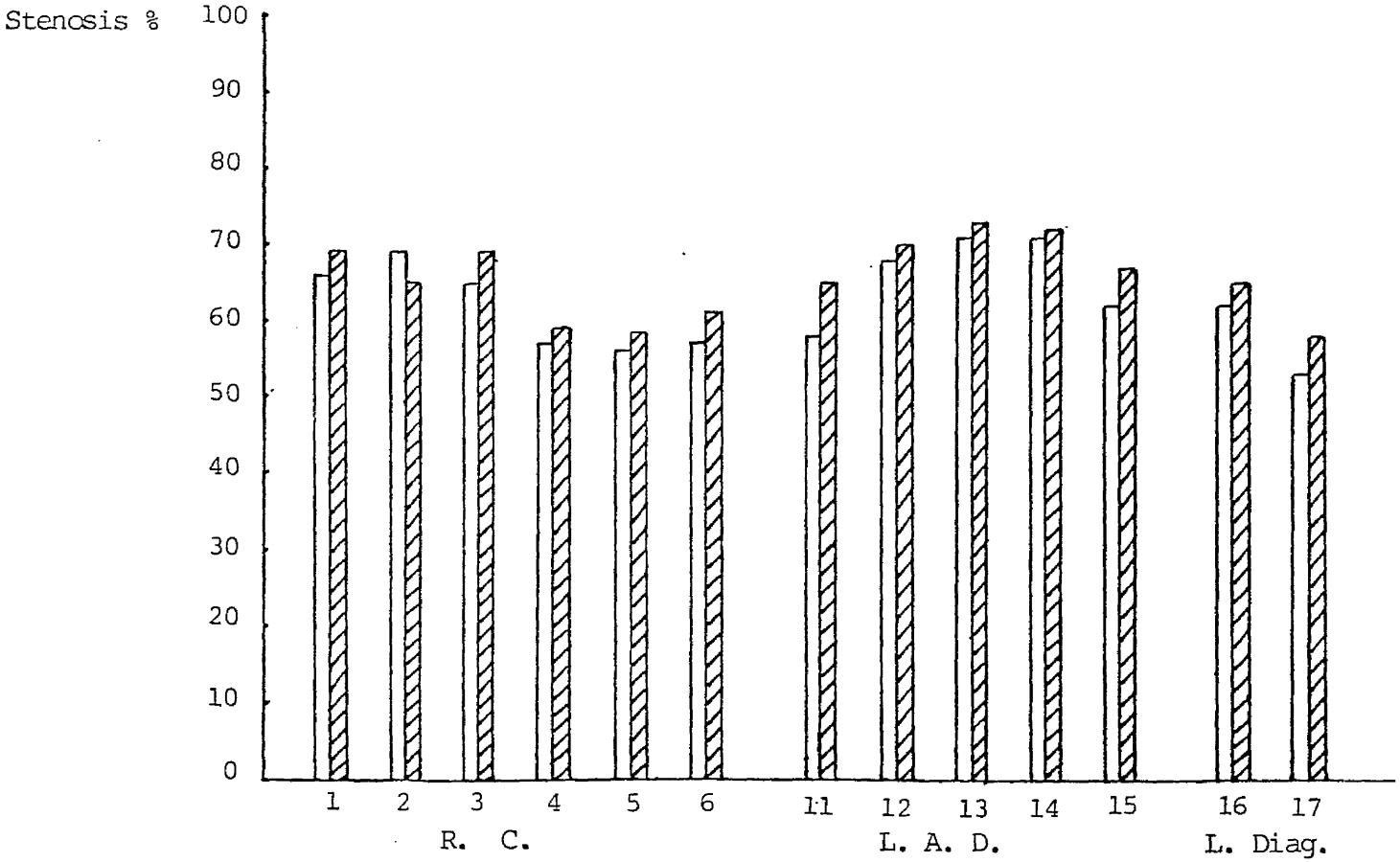


Figure 29 Average Stenosis in Segments of the Right and Left Anterior Descending Branches in Cases where the Left Circumflex was Narrowed to more than 90% Compared with the average Stenosis in 92 Cases.

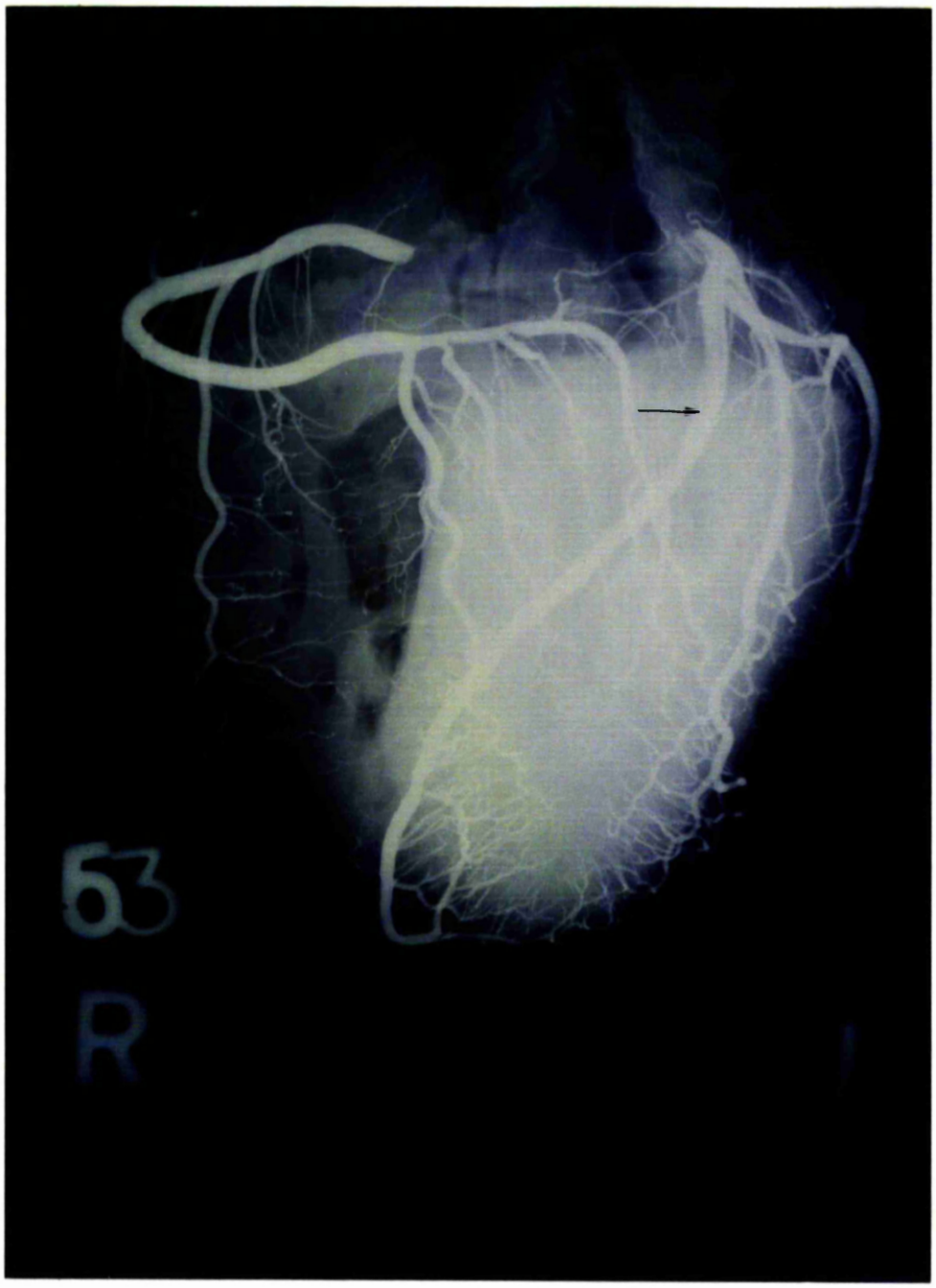
arteries were severely stenosed to more than 90% the stenosis figures of the other two vessels were higher than the average.

When the angiographic results compared to the histologic measurements of the arteries, it was found that the angiograms did not correlate well with actual measurements in 41 cases. In 33 cases, the stenosis shown by the angiography was less than what was estimated by measurements, (Figure 30) whereas in eight cases the angiograms have overestimated the degree of narrowing (Figure 31).

Thirty-eight (42%) cases had recent myocardial infarction (Figure 32). In 27 of these, one or more luminal thrombus was found in the coronary arteries. Mural thrombus was found in association with plaque fissuring in 3 cases. In 4 cases, the only acute lesion found in the coronary arteries was plaque fissuring with intimal haemorrhage. In another 4 cases (10%), no recent pathological event in the coronary arteries was found. Two of these cases had old occlusion (recanalisation) in one of the arteries. In 14 cases, an acute pathological lesion was found in more than one artery. In 2 cases, a thrombus was found in an unexpected coronary artery.

Sixteen of the 38 infarcts were only recognised by using the enzyme test (42%). In the other 22 recent infarcts, the diagnosis was confirmed by histologic examination. (Figure 33). In 24 cases, healed myocardial

Figure 30



An example of underestimation of coronary stenosis by angiography. In the left anterior descending branch (arrow), the stenosis was shown by planimetry to be 81%

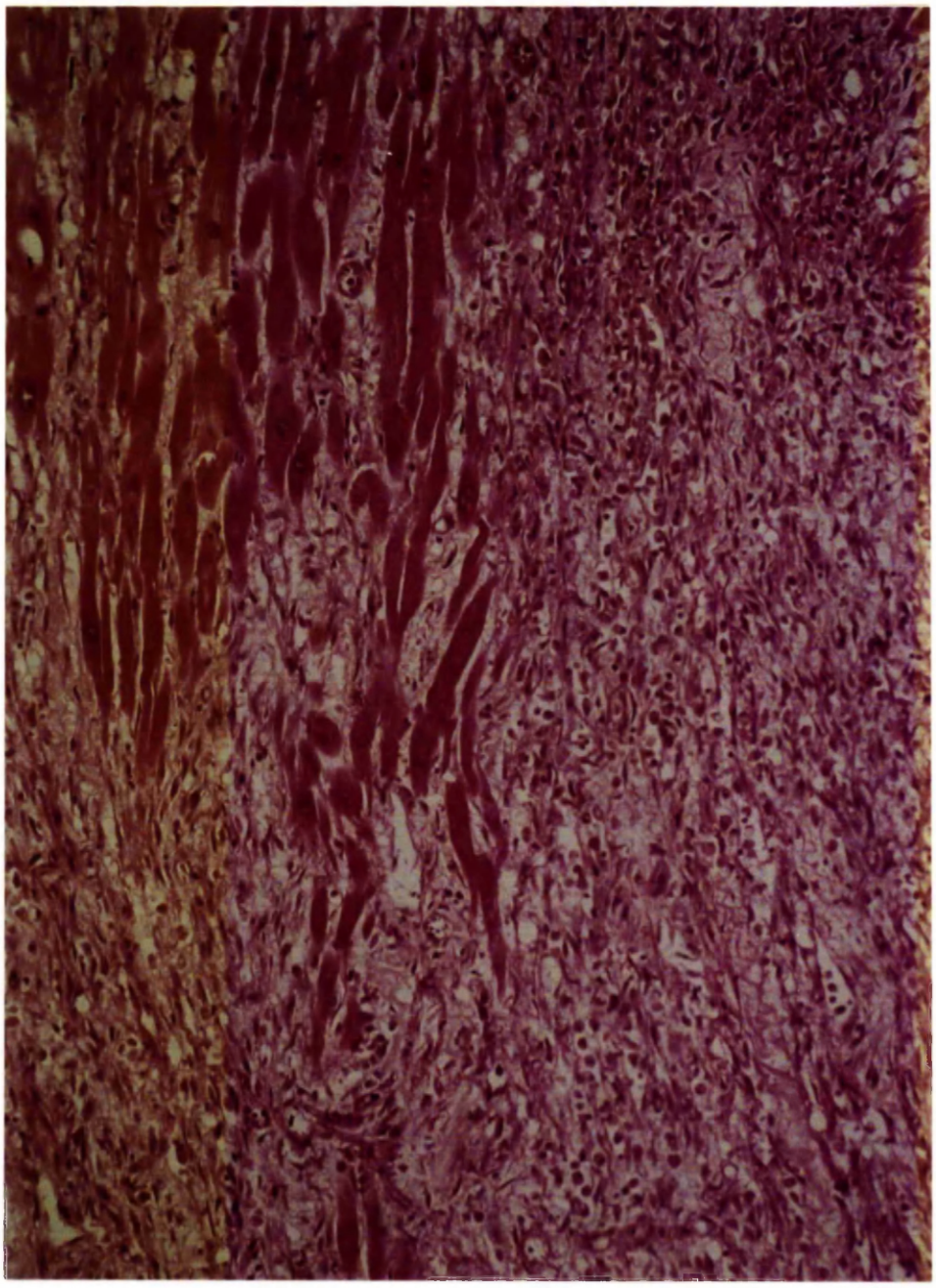
Figure 31

An example of overestimating the narrowing by angiography. By planimetry, the stenosis in the left circumflex branch (arrow) was only 53%.

Figure 32

Combined circumferential and regional postero-lateral infarction with rupture of the posterior wall (arrow).

Figure 33



Section of the heart showing recent organising myocardial infarction.

infarcts were found in association with the recent infarctions. (Figure 3).

Of the 38 recent infarcts, there were 9 anterior infarcts, 3 lateral, 16 posterior, 8 circumferential, (Figure 34) and 2 purely septal infarcts (Table 22).

In 8 of the 9 cases with anterior infarction, there was an acute lesion in the left anterior descending branch. In 6 of these, another acute lesion was found in an accompanying vessel. An acute lesion was found in the right coronary in 10 of the 16 cases with posterior infarction. In 7 cases of these, there was more than one artery involved. Table 22 shows the different pathological findings in the 38 cases with recent myocardial infarcts.

Forty-six cases (51%), had old myocardial infarction. (Figures 35 and 36). Twenty-four of these cases had old lesions (recanalisation) in one or more of the coronary arteries.

In the non-ischaemic cases (30 cases), no luminal thrombi were found. Plaque rupture with intimal haemorrhage was found in one control case, where death proved to be due to a drug overdose. Recent myocardial infarction, of the circumferential type, was found in 2 control cases. In four cases, the degree of stenosis was greater than 75% of the lumen, in 2 cases of these the stenosis was more than 85%.

Figure 34

Recent circumferential myocardial infarction demonstrated by the nitro-blue tetrazolium test.

TABLE 22

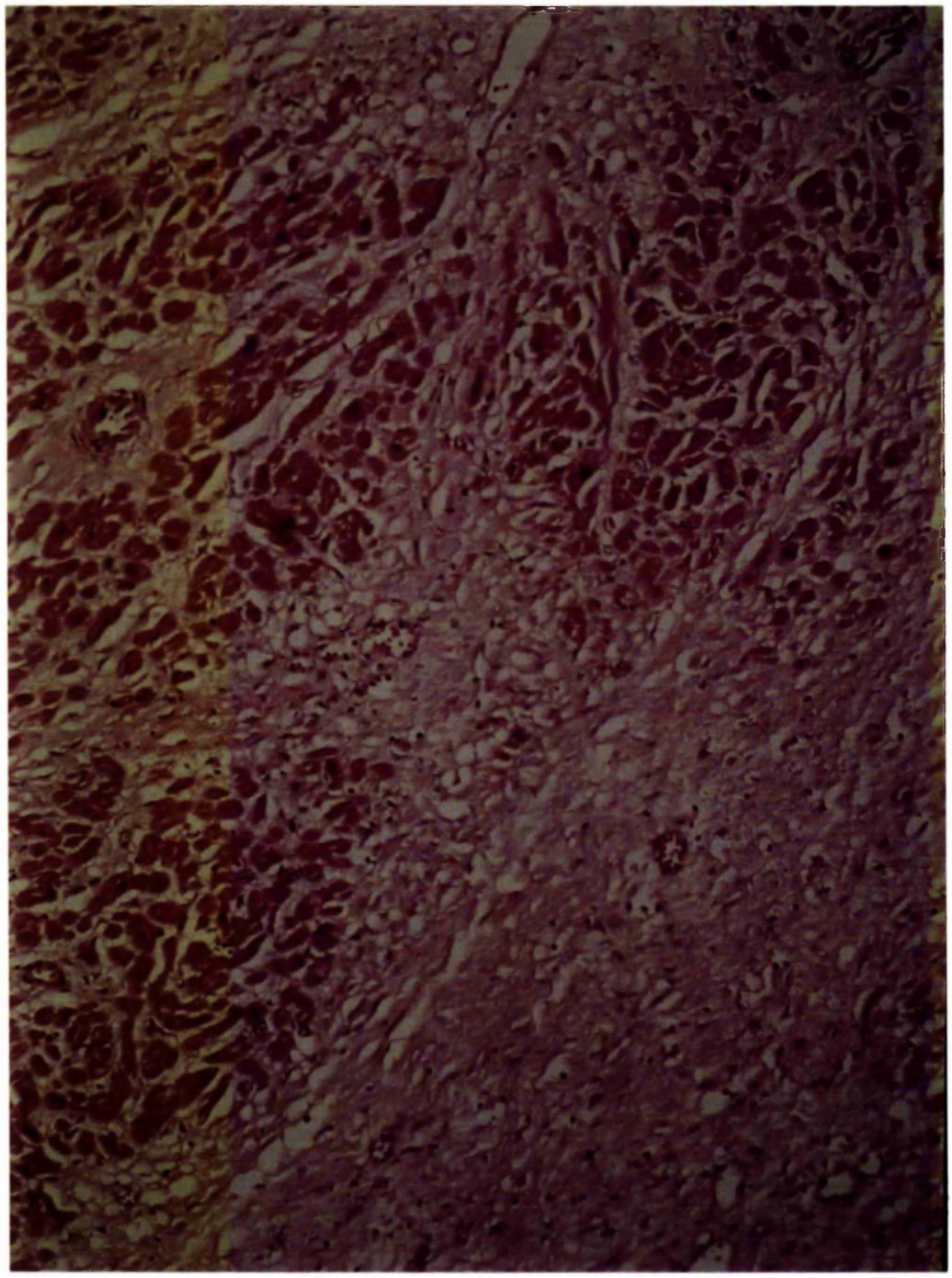
Location of Infarction	Number of Infarcts	Right Coronary	Left Anterior Anterior Descending	Left Circumflex	Recent event in more than one artery	Recent Event in unexpected artery	No Recen Event
Anterior	9	5	8	1	5	0	1
Lateral	3	1	0	2	0	0	0
Posterior	16	10	3	7	6	2	3
Circumferential	8	4	6	0	2	0	0
Septal	2	1	2	0	1	0	0

Different Pathological Findings in 38 Cases with Recent Myocardial Infarction.

Figure 35

Old myocardial infarct at the posterior part of the septum with involvement of parts of the posterior wall and the papillary muscles.

Figure 36



Section of the myocardium showing an old infarct with fibrosis.

Summary of Results

In 92 sudden ischaemic deaths, 81 cases had acute coronary lesions. Fifty-nine cases (64%) showed plaque rupture; in 39 cases the rupture was associated with luminal thrombosis, in 6 cases with mural thrombosis and in 11 cases with intimal haemorrhage. Intraluminal thrombi were found in 61 cases (66%), in 22 cases of these no plaque fissuring could be identified.

The recent coronary lesions were found to occur mostly in the proximal parts of the coronary tree, whereas the non-fatal old lesions were identified more frequently in the distal segments. No obvious relationship could be shown between the incidence of the acute coronary lesions and either the survival duration after the onset of symptoms or the activity at the time of death.

Recent myocardial infarction was demonstrated in 38 cases (42%), 34 of these (90%) had acute coronary lesions. Forty-six cases had old infarcts, 24 of these (42%) exhibited old coronary occlusions.

In general, the majority of cases showed severe atheroma in the three or at least two main branches, with the proximal segments being more affected by the disease.

CHAPTER V
UNCOMMON CAUSES OF SUDDEN CARDIAC DEATH

1 - CORONARY ARTERY DISEASE ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Although cardiac involvement of various types in systemic lupus erythematosus (SLE) is common, and is reported in more than 50% of patients at some time during their illness (Brigden et al, 1960), only rarely does the heart play a major role in determining the patients' prognosis. All layers of the heart are susceptible to involvement; pericarditis has been reported in 75% of cases, myocarditis in 20%, and Libman Sachs endocarditis in 20-50% (Taubenhaus et al, 1955; Shearn, 1959; Homcy et al, 1982).

Coronary arterial manifestations are, however, less common, and when present usually take the form of a vasculitis of the small branches. Disease of the major coronary arteries has been reported only rarely. When present, it is usually of inflammatory nature, and SLE is not generally considered as a predisposing cause of atherosclerosis. Although some of the recent reporters (Halder and Robert, 1981) have shown an increased frequency of coronary artery disease in patients of SLE, the published data suggest that clinically significant coronary disease in such cases is still rare (Homcy et al, 1982).

CASE REPORT

This 22 year old woman was known to suffer from SLE. The condition was first discovered at the age of six, and since then the patient was under corticosteroid therapy. She was also known to suffer from epilepsy, high blood pressure, and duodenal ulcer, and was receiving treatment for these conditions. In recent years, the patient complained of chest pains, these were diagnosed as manifestations of ischaemic heart disease, secondary to the underlying condition. Six months before death, the patient developed myocardial infarction, and was admitted to hospital for a few weeks.

A few minutes before death the patient complained of feeling unwell, and was given a trinitrin tablet, but soon she began to develop convulsions and collapsed. On arrival of the ambulance, she was found to be dead.

Pathological findings: The body was that of a slimly built young adult female. Examination of the head and neck revealed no gross pathology in the brain. The lungs were somewhat congested. The heart was of normal size and weighed 300 gm. The epicardium had a granular appearance. Sections through the heart showed vegetations on the anterior cusps of the mitral valve and in addition the myocardium had a mottled appearance, particularly marked on the lateral wall of the left ventricle. All major coronary arteries were severely diseased, with evidence of previous thrombosis in both the

right and left anterior descending branch. The major arteries in the thorax and abdomen appeared normal.

The gastgrointestinal tract was not remarkable. The liver was congested. The gall-bladder, pancreas, and adrenal glands showed no gross abnormality. The spleen was somewhat enlarged and there was an unusual prominence of the lymphoid tissue. Both kidneys had a granular surface and an unusual mottled appearance.

Histologically, the coronary arterial lesions were characteristic of atherosclerosis. (Figure 37). No signs of arteritis, either active or healed, were encountered. The adventitial lymphocytic infiltration present was considered within the range of changes classically associated with coronary atherosclerosis. There was evidence of recent as well as organising intramural and intraluminal thrombosis in sections of both the right and left anterior descending branches. (Figure 38). In many of the coronary sections there was narrowing of the coronary lumen up to total occlusion. (Figure 39). Sections of the myocardium revealed signs of healed myocardial infarction, (Figure 40) but no evidence of recent damage.

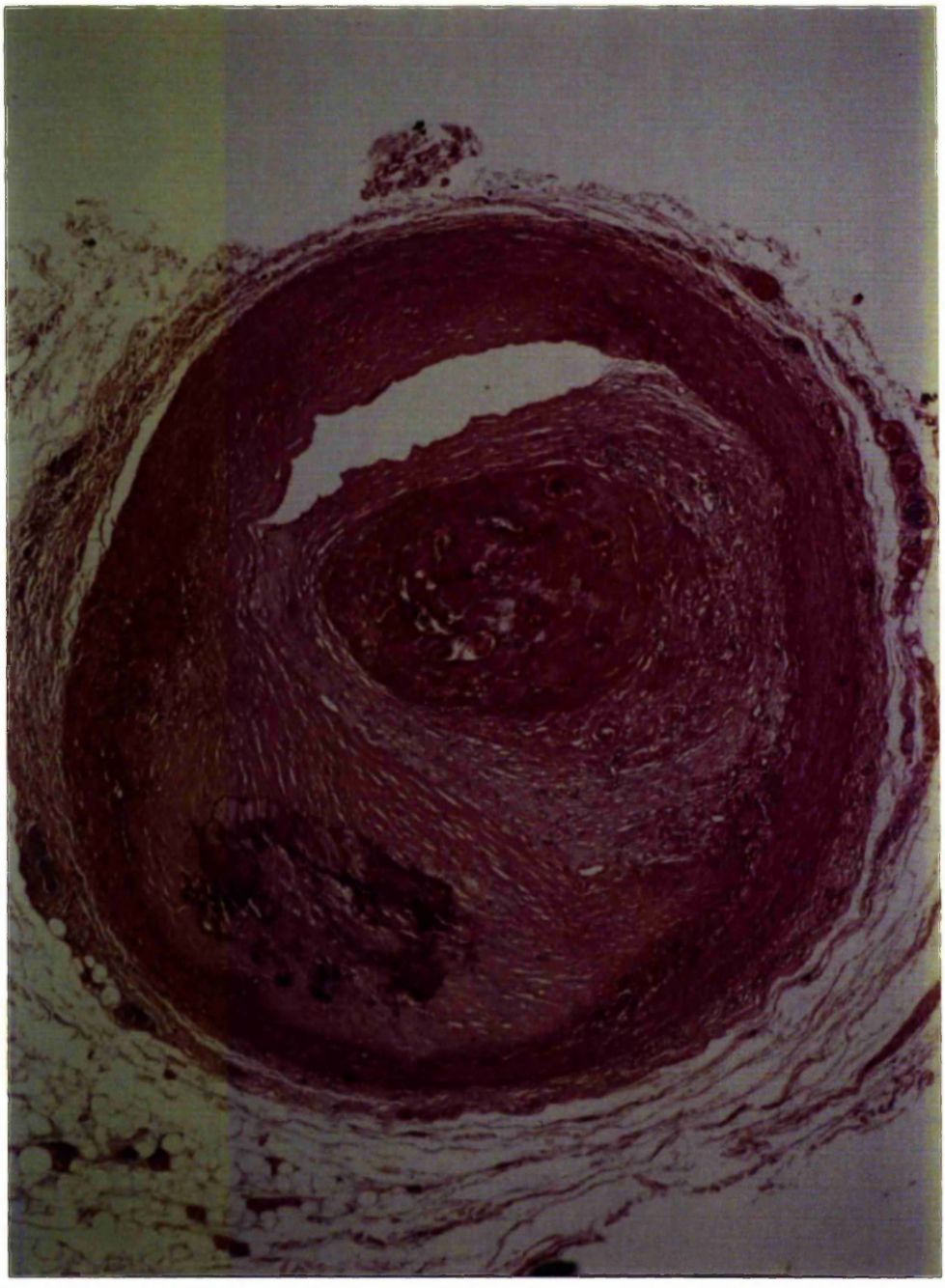
Comment

The cause of death in SLE is usually related to renal insufficiency and infection, although very rarely ischaemic heart disease has been reported as a major complication (Homcy et al, 1982). However, it has been

Figure 37

Characteristic morphology of atherosclerosis with an organised thrombus (arrows) building up the atheromatous growth. This person was suffering from systemic lupus erythematosus.

Figure 38

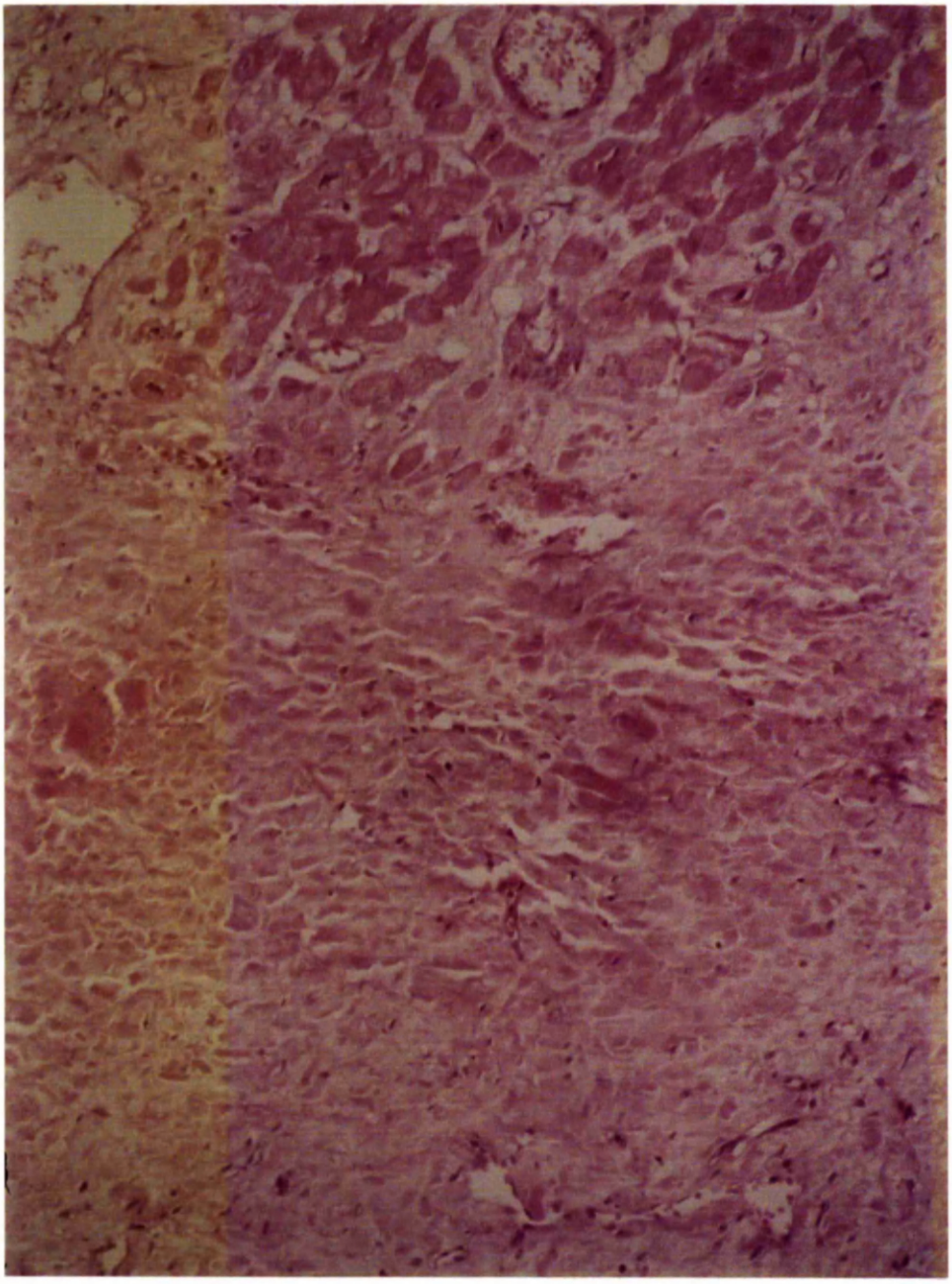


Total occlusion of the coronary artery by an organising thrombus in a patient with systemic lupus erythematosus.

Figure 39

The coronary artery of the same case of systemic lupus erythematosus with complete occlusion by atheroma.

Figure 40



Section of the myocardium of the same case showing healed infarction.

claimed that there is no proof for the pathologic changes associated with the disease to have ever resulted in occlusion of a major coronary artery, and although coronary atherosclerosis was found in patients dying from SLE in several reports, it was suggested that there is no relationship between the two conditions (Shearn, 1959).

In some cases, there is pathologic evidence of vasculitis as the basis of the ischaemic process, and healed arteritis was suggested as the atherogenic factor (Tsakraklides et al, 1974). Severe atherosclerosis was suggested to develop in the early life of the lupus patients as a result of nephrotic syndrome and the persistent hyperlipidaemia (Simon et al, 1973). Another explanation for the two conditions is an autoimmune reaction, which might predispose arteritis into atherosclerosis (Tsakraklides et al, 1974). On the other hand, experimental studies showed that actual reduction of blood flow through sites of inflammatory tissues could follow administration of corticosteroids (Taubenhaus et al, 1955).

While the literature on the subject of coronary atherosclerosis in association with SLE has some confusing elements, one certain factor is there are few cases, such as the case reported in this study, in which the coronary lesions are typically atherosclerotic where none of the commonly recognised causes of coronary atherosclerosis in young patients are present. Since these lesions occur in

children and young adults, it is suggested that they are related to the underlying lupus process than to primary coronary disease. Such lesions were described by several reporters (Kong et al, 1962; Tsakraklides et al, 1974; Homcy et al, 1982), as well as in this case. SLE is one of the very rare causes of sudden ischaemic death, particularly in young patients where the atheromatous lesions could be identical to those seen in classic coronary atherosclerosis.

Summary

In a 22 year old woman with long history of systemic lupus erythematosus, sudden death was the result of coronary thrombosis and extensive atherosclerosis. The lesions were similar to typical coronary atherosclerosis. Old myocardial infarction was identified clinically six months prior to death.and was confirmed at autopsy. An association between SLE and coronary atherosclerosis has previously been reported in a limited number of cases.

2 - HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

Hypertrophic obstructive cardiomyopathy seems to be underdiagnosed by pathologists (Davies, 1975); those who regularly carry out autopsies on sudden death should meet this condition. Although the disease has received great attention since the original clinical observation in 1957, and the pathological observation in 1958 (Teare, 1958), cases have been described by Liouville almost 90 years before this, and a case was clearly described by Schmincke in 1907 (Cited by Olsen, 1979).

Cardiomyopathy, in general, is a convenient term for the classification of a heterogenous group of chronic myocardial disorders which are not due to congenital abnormality, ischaemia, hypertension, valve disease, or coronary artery disease; and appear to be non-inflammatory (Anderson, 1980). The most easily recognised picture of hypertrophic obstructive cardiomyopathy is of disproportionate and asymmetrical left ventricular hypertrophy, with small ventricular cavity (Davies et al, 1974). Cardiac function is affected by the undue rigidity of the left ventricle, which interferes with diastolic filling and in many cases the bulging hypertrophied septum obstructs the outflow of the left, and less commonly, the right ventricle (Goodwin, 1970). The disease presents from early childhood to old

age. Some cases progress through life and others remain static. In a study of 47 cases of hypertrophic obstructive cardiomyopathy by Davies and his colleagues (1974), ages ranged from 13 to 87 years, and 37 of patients were men, with sudden death being the commonest presentation in the younger cases. In 20 to 30 per cent of cases, there is family history, but no racial or geographic incidence is known (Braunwald et al, 1964). The disease may present by heart failure or atypical angina, but it also causes sudden death (Davies, 1975).

The clinical and pathological characteristics of hypertrophic obstructive cardiomyopathy are well known (Teare, 1958; Goodwin, 1970; Davies et al, 1974, Olsen, 1979). Though hypertrophy of all chambers is present, hypertrophy of the interventricular septum is striking. Ventricular hypertrophy may affect a localised area, the asymmetric form, but symmetrical hypertrophy is not uncommon. The typical asymmetric form shows a localised septal hypertrophy, which may extend to the anterior wall or rarely to the posterior wall. Involvement of the right ventricle is not unusual and may be due to septal thickening, or to involvement of the free wall of the right ventricle. A distinctive band of fibrous thickening below the aortic valve is sometime present. Papillary muscle involvement leads to a bullet-like shape. The ventricular cavity is often small in relation to the ventricular mass, even in patients dying from

congestive heart failure. Increased total heart weight is common, but the consistent feature is the disproportionate increase in the left ventricular weight.

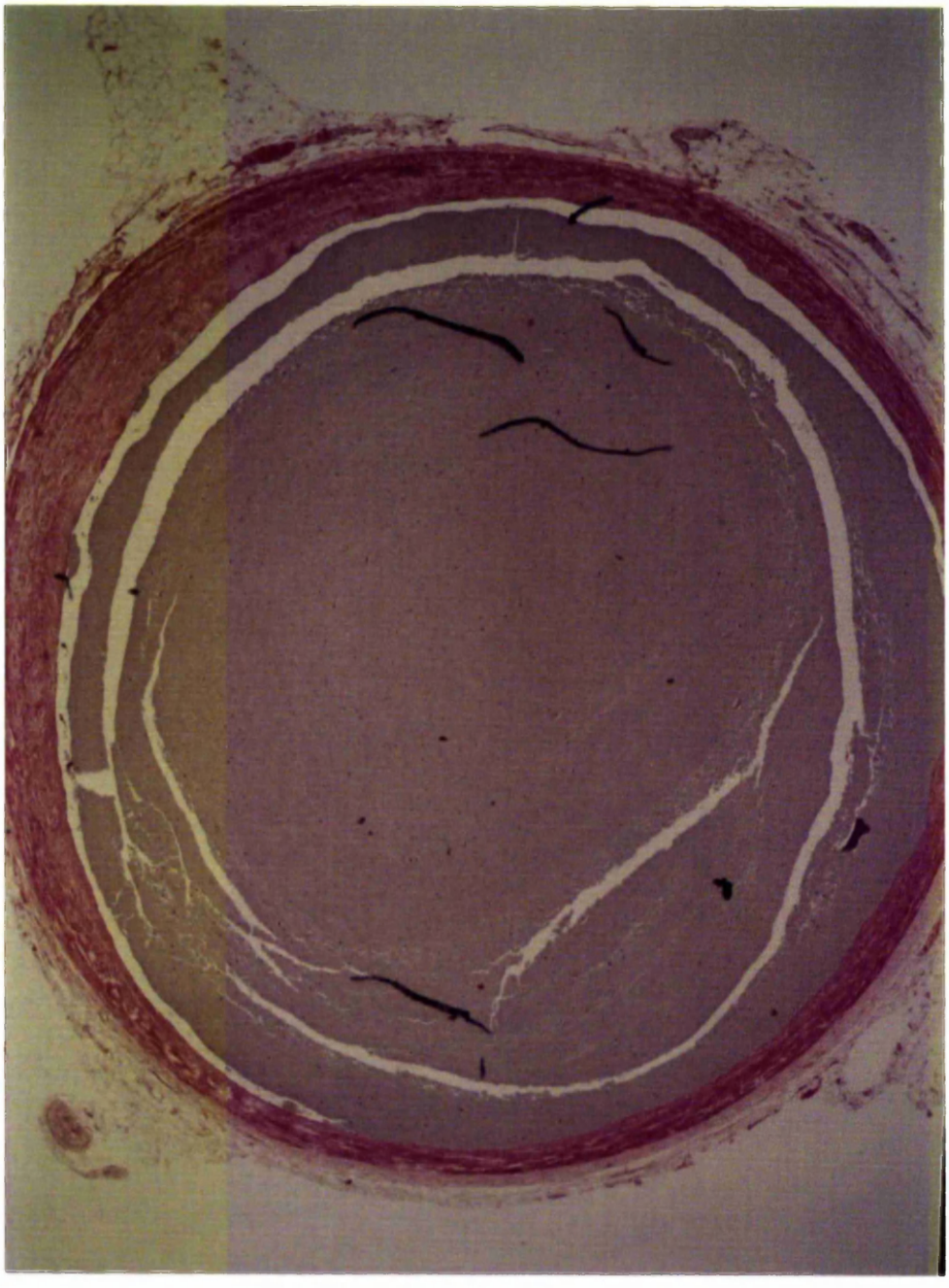
The histologic features consist of short runs of severely hypertrophied muscle fibres, interrupted by connective tissue, large bizzare nuclei with clear perinuclear area, interstitial fibrosis, and disordered whorled arrangement (Davies et al, 1974; Olsen, 1979).

Case Report

This 36 year old man died suddenly and unexpectedly while staying at his home. His medical records showed that he had no serious illness during his life, apart from suffering from "spasmodic torticollis" which proved to be not due to any gross abnormality.

Significant autopsy findings included slight congestion of the lungs, an increase in the total heart weight, being of 600 grammes, with marked hypertrophy of both the left and right ventricles. Sections through the heart revealed marked increase in the thickness of the interventricular septum with whorling of the muscle fibres. The left ventricular cavity was smaller in proportion to the left ventricular wall. Post-mortem coronary angiogrpahy and sections through the coronary arteries showed normal vessels (Figure 41). The aorta and major vessels showed no gross abnormality. Examination of the other organs revealed no significant pathology.

Figure 41



Section of the coronary artery in a case of hypertrophic obstructive cardiomyopathy showing a vessel almost completely free from atheroma.

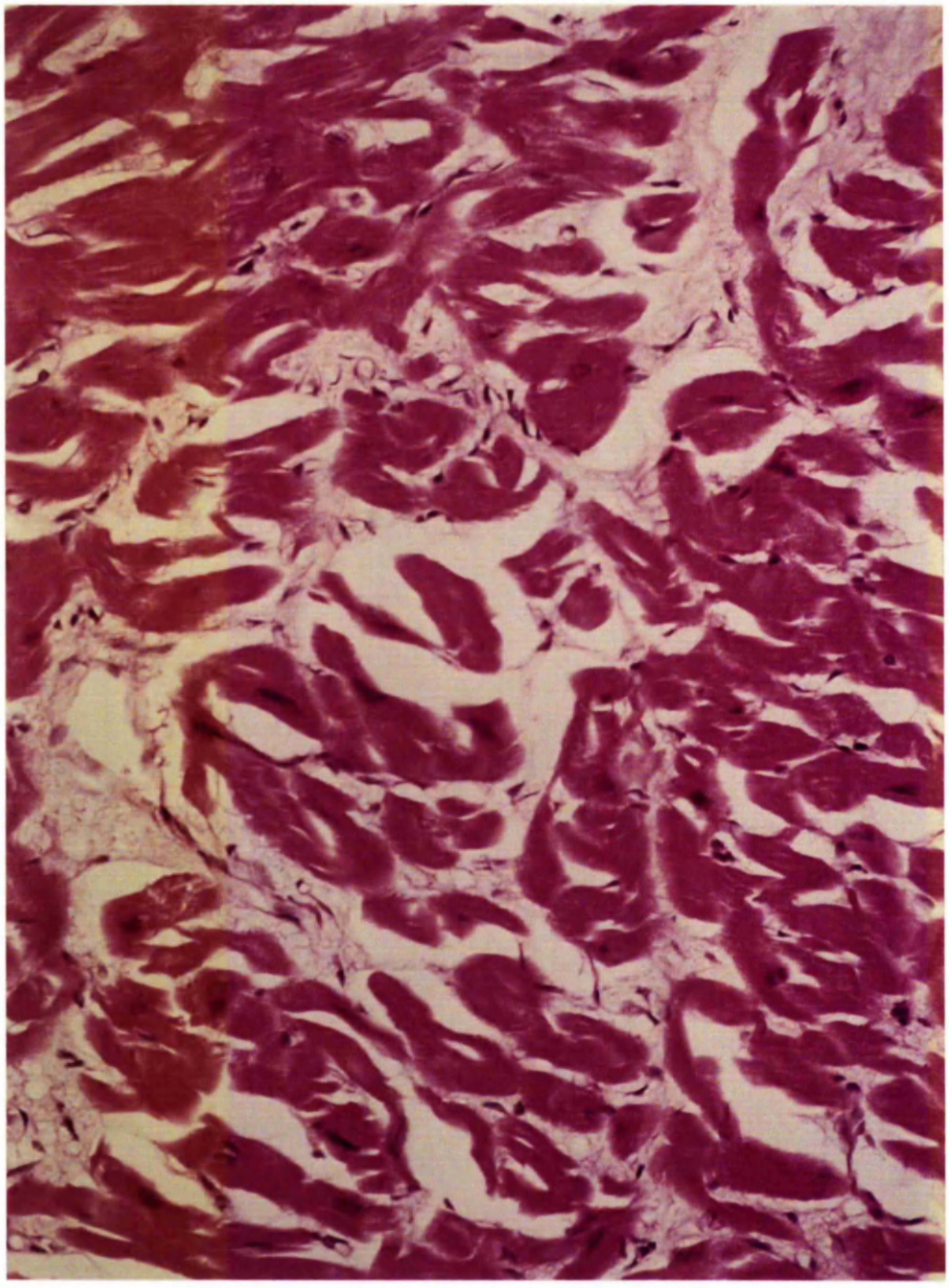
Blood, urine and liver samples were taken from the case. The samples were analysed for alcohol, barbiturates, paracetamol and basic drugs. However, all the toxicological analyses gave negative results.

Histologically, sections of the heart showed an obvious disarrangement of the muscle fibres, with increased interstitial fibrosis. This feature was most characteristic of sections of the interventricular septum. (Figure 42). However, the cardiac muscle fibres were not markedly hypertrophied and showed normal-shaped nuclei.

Comment

The morphological characteristics of hypertrophic obstructive cardiomyopathy are well known, and many pathologists are familiar with the disease, especially the easily recognised asymmetric septal form, seen in the young and early middle-aged subjects. However, the reliability of the macroscopic, histologic, as well as the electronmicroscopic features of the disease have been questioned (Olsen, 1979), and it seems that none of these criteria are absolute. Thus asymmetric hypertrophy alone, particularly when associated with another disease should be viewed with caution, and it is the combination of changes that permits a diagnosis, rather than an isolated feature. In the reported cases, some of the disease's gross features, as well as other histologic criteria were absent. The fibrous band below the aortic valve (Davies et al, 1974) was not present and the muscle

Figure 42



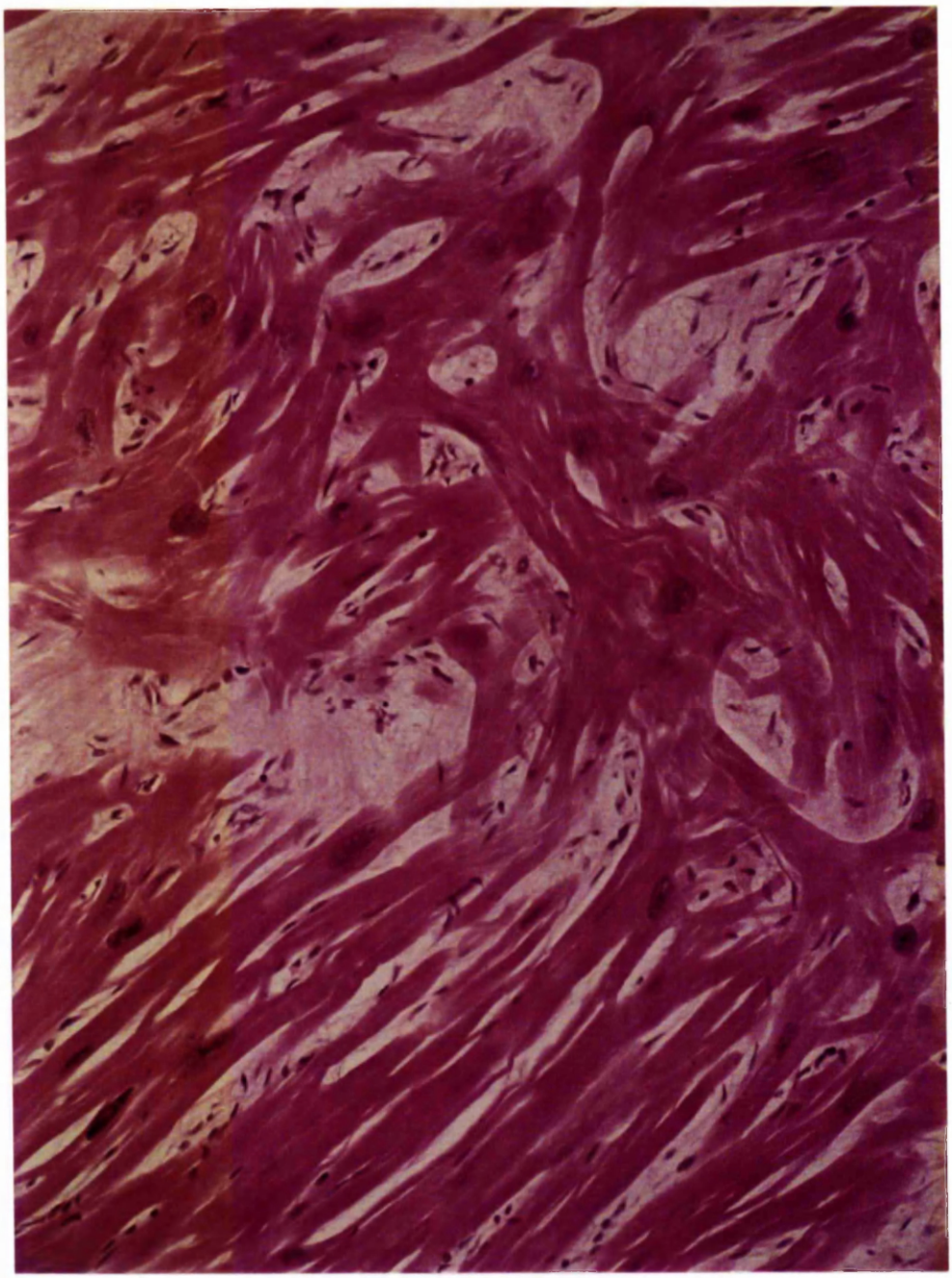
Section of the interventricular septum of the same case showing the characteristic disarray of the muscle fibres.

fibre nuclei were not so-called bizzare-looking. However, other pathological features were prominent (Figure 43) and allowed the diagnosis of the condition.

Summary

This 36 year old man died suddenly and unexpectedly. He had no significant medical history, but post-mortem examination showed that he suffered from hypertrophic obstructive cardiomyopathy. Most of the pathological features of the disease were identified, and toxicological tests were negative. Sudden death is the commonest presentation in the younger patients with hypertrophic obstructive cardiomyopathy.

Figure 43



The characteristic "whorled" appearance (arrows) of the cardiac muscle in the same case.

CHAPTER VI

DISCUSSION

In spite of the fact that ischaemic heart disease is the commonest cause of natural death in the western countries, the exact mechanism responsible for the sudden ischaemic death is poorly understood. Atherosclerosis, which is the underlying cause of ischaemic heart disease, seems to be one of the topics fated to evoke sterile controversy, and our knowledge of the exact processes involved in the progression of atherosclerotic lesions is still limited.

Part of the problem is that the disease progresses for many years before any clinical symptom develops. On the other hand, the legal system, particularly in Scotland, aims to exclude unnatural deaths and not to derive pathological data about the natural diseases. Although cases of "sudden ischaemic death" come to autopsy by thousands every year, very little morphological data emerges due to the enormous amount of work imposed on the pathologists, particularly when the Procurator Fiscal or Coroner is anxious to get the death certificate issued.

It must be said that in certain cases the pathologist is satisfied to issue "ischaemic heart disease" as the cause of death when the only pathological finding is a little atheroma obstructing 10 to 30 per cent of the coronary lumen. Yet that is the sort of lesion which most of pathologists would be inclined to ignore if another significant pathological finding was present.

There is no doubt that designating such cases with very little atheroma and no acute lesion as "ischaemic cardiac death" must have led to some confusion in understanding the disease and in particular among epidemiologists investigating the various risk factors.

The present study was an attempt to understand why persons, with coronary arteries severely narrowed for years, die suddenly and in many occasions without a single warning symptom or sign. The simple explanation might be that these people had developed a recent pathological lesion in their coronary arteries. From the previous pathological and clinical studies of cases of sudden ischaemic death, one clear fact emerges that no general agreement exists on whether an acute coronary event is responsible for the triggering mechanism of the sudden death. Most of the previous studies have suggested that incidence of coronary thrombi is very low (Schwartz and Gerrity, 1975 and Baroldi et al, 1979) and to the conclusion that there is no causal link between thrombi and sudden cardiac death. It had also been suggested that the myocardium of patients living in soft water areas is more susceptible to ischaemic damage than in patients of hard water areas (Crawford and Crawford, 1967). In addition it has been claimed that there is more atheroma in patients living in Glasgow (soft water area) and aged 30-44 years than in patients of the same age group living in London (hard water area).

In this study, the coronary arteries were examined carefully and in detail, using a quantitative microscope for assessing accurately the degree of luminal stenosis of every three millilitre cross-section segment of the whole epicardial coronary artery tree. At the same time, the incidence of the different recent events in the coronary arteries in this study, was compared with an identical study of a similar group of patients in the London area. Comparison of the extent and distribution of the coronary stenosis between the two areas is not available at the present stage of this study, but it is hoped that this can be accomplished in the near future.

Acute coronary lesions in sudden ischaemic death

The present study shows that in 88% of cases, where death occured suddenly from ischaemic heart disease, a recent pathological event was present in one or more of the coronary arteries. In the London study (Davies and Thomas, 1984), the incidence was similar (95%). Both studies confirm that when a careful and detailed examination of the whole coronary tree is used, a high incidence of acute lesions in the atheromatous plaques is uncovered. This study proves that, in the vast majority of cases of sudden cardiac death, there is a recent pathological event which is responsible for the sudden nature of death.

However, another group of cases (12%) with high grades of stenosis, had no demonstrable recent coronary event, although it should not be assumed that the acute lesions were totally absent. It could be that some of these cases had plaque rupture or tiny mural thromboses that were missed during the histological preparation. Alternatively a thrombus might have been lysed or dislodged in the hours before death. That does not mean, however, that all these patients did not die from alternative mechanism.

The existence of a second group among cases of sudden ischaemic death, where no recent events can be found, must be accepted. On the other hand, the mechanism by which these patients die remains a mystery and it is almost impossible to decide if any other ischaemic mechanism could be responsible for the death or if a recent event in the coronary arteries was missed by the pathologist, especially in cases with a single lesion occupying only one or two millimetres of the coronary tree, or even if these people had died from some other cause, cardiac or non-cardiac. However, it is obvious that the number of cases forming this second group, depends to a great extent on the pathological technique employed in the study.

Eight of the one hundred test cases who died suddenly and unexpectedly constituted a third group in whom the only pathological finding was atherosclerotic lesions occupying between 20 to 70 per cent of the coronary lumen. In such cases other causes of death had been excluded at autopsy, including the possibility of a drug overdose. The question of how exactly these persons died suddenly seems to be unanswerable and as it has been suggested in the previous group the probability of a missed acute coronary lesion, or another cardiac ischaemic mechanism cannot be ruled out, particularly in cases with higher stenosis grades. However, in other cases with very little atheroma it is unlikely that cardiac ischaemic mechanism contributed in the sudden death.

Plaque Rupture

Plaque rupture or fissuring has been known to pathologists for many years (Leary, 1934 a and b, Constantinides, 1966). Yet, only a few are aware that rupture of the soft lipid-rich plaques is a major life-endangering event in sudden ischaemic death. Atheromatous plaques vary to a great extent in their structure. The extremely solid fibrous lesions do not seem to be life-threatening. On the other hand, the present study shows that the soft plaque containing a large pool of lipids and separated from the lumen by a thin fibrous cap, is the dangerous lesion because it is

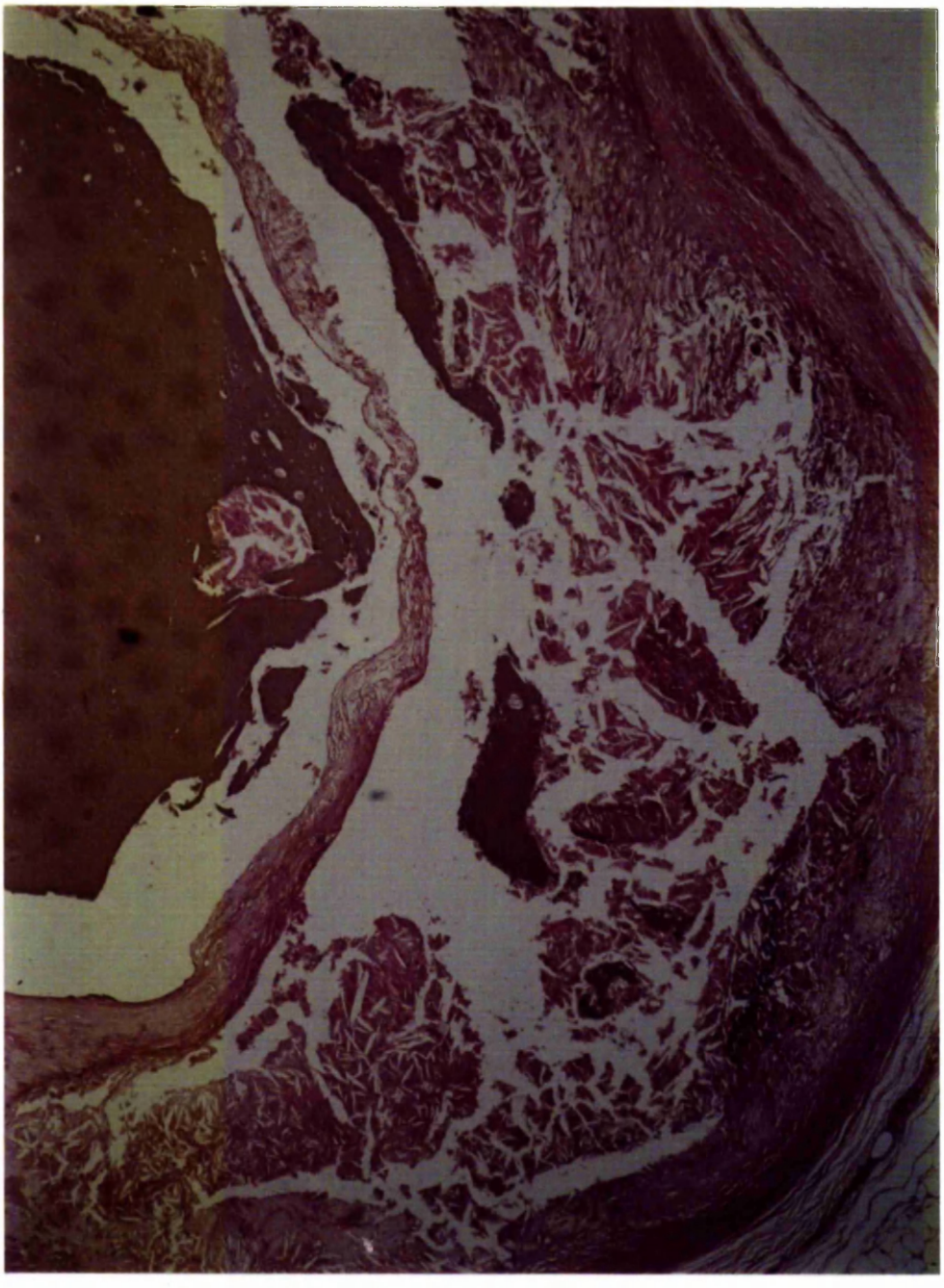
prone to rupture, fissuring or cracking. (Figure 44).

In this study plaque fissuring was found in 64% of the cases. In the London study the incidence was higher (95%). In some cases a rupture happened in more than one segment of the coronary tree, whereas in other cases, a rupture occurred in a single plaque located between two relatively normal segments of the artery, making it rather difficult to recognise unless serial sections were taken.

When the soft lipid-rich plaque undergoes rupture with cracking of the fibrous cap the result is direct contact between the flowing blood and the atheromatous content. This crack may reseal leaving only little intimal haemorrhage, with or without a tiny mural thrombus. (Figure 45). At the other extreme, blood can dissect into the plaque, forming an intramural thrombus. Alternatively, the atheromatous contents may extrude into the lumen, leading to an occlusive luminal thrombosis.

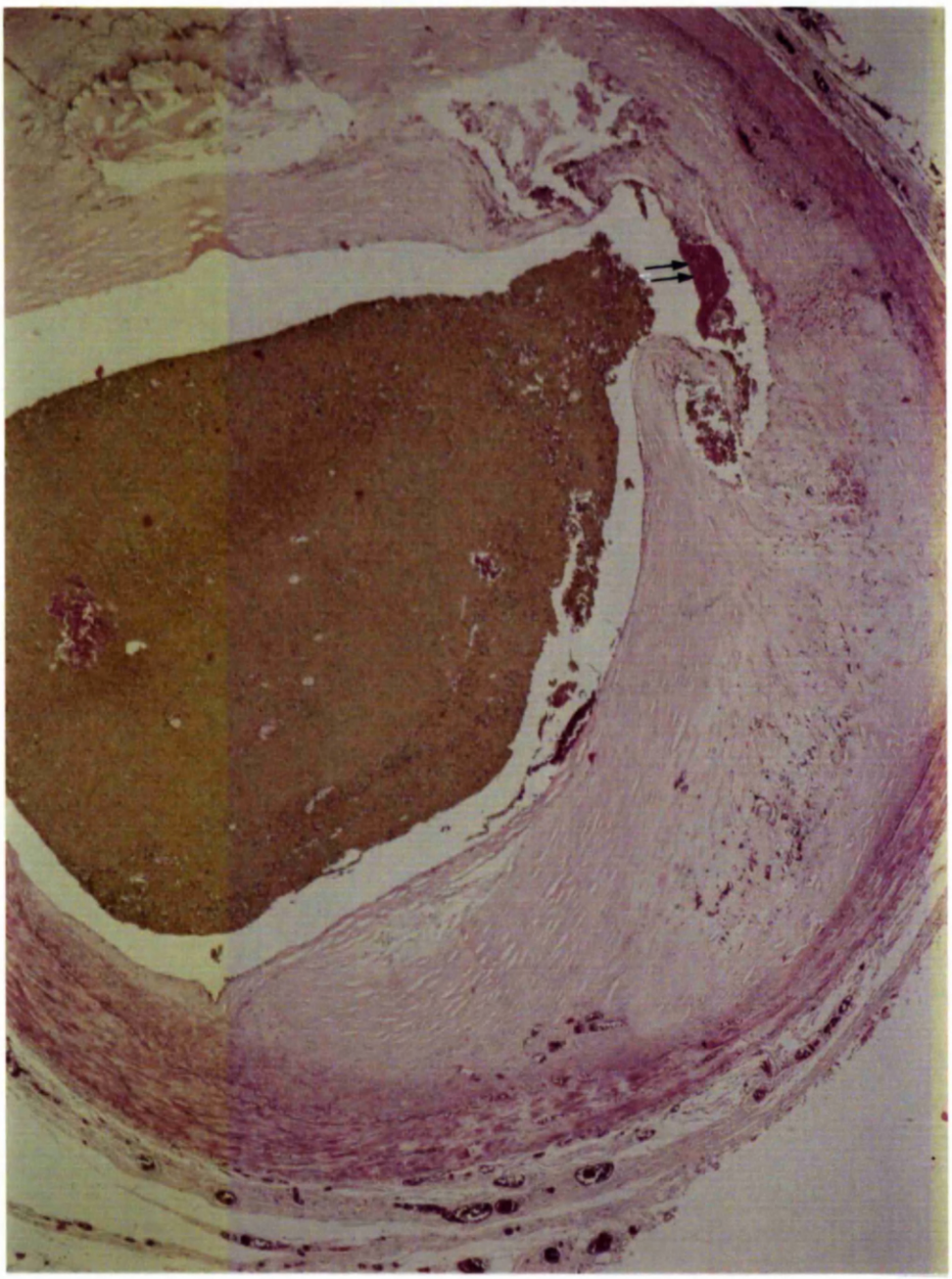
It seems that the degree of the pre-existing stenosis plays a decisive role in the fate of plaque fissuring. When the stenosis is less than 75%, the rupture tends to cause intimal haemorrhage without luminal thrombosis but with stenosis greater than 75%, thrombus formation occurred with increasing frequency, confirming the work of Falk, 1983. In 39 cases (42% of cases of sudden ischaemic death), the rupture resulted in luminal thrombosis, in 6 cases (7%) mural thrombi were found accompanying the rupture, and in 15 cases (16%) the rupture was associated with intimal haemorrhage.

Figurer 44



A lipid-rich necrotic plaque with the injection medium clearly demonstrated inside the atheromatous plaque. Fissuring was noted in an adjacent section.

Figure 45



Fissuring of an atheromatous plaque with a tiny mural thrombus (arrows) resealing the cracked site.

The distribution of plaque fissuring in the present study shows that it happened more frequently in certain segments of the coronary tree than in others. These parts were also the sites for the highest grades of stenosis as well as the highest incidence of thrombosis. This lends no support to the idea that certain parts of the coronary tree are more vulnerable to rupture, regardless of the extent of the pre-existing stenosis. Rather, recent plaque rupture seems to constitute a kind of common final pathway in the atherosclerotic process, its fate being determined to a great extent by the degree of the previous stenosis. Careful histological examination of the coronary artery indicates that plaque rupture commonly initiates thrombosis. This is clearly strong evidence against suggestion that thrombus is secondary to infarction (Chapman, 1965; Bouch and Montgomery, 1970).

There is no evidence shown by this study of an existing relationship between plaque fissuring and the survival duration between the onset of symptoms and the time of death. Moreover, the study does not confirm claims that plaque rupture is the underlying fatal event in older, rather than younger patients (Leary, 1934; Falk, 1983). The study failed to show a link between the activity at the time of death and plaque rupture. While this does not rule out the possibility that a sudden burst

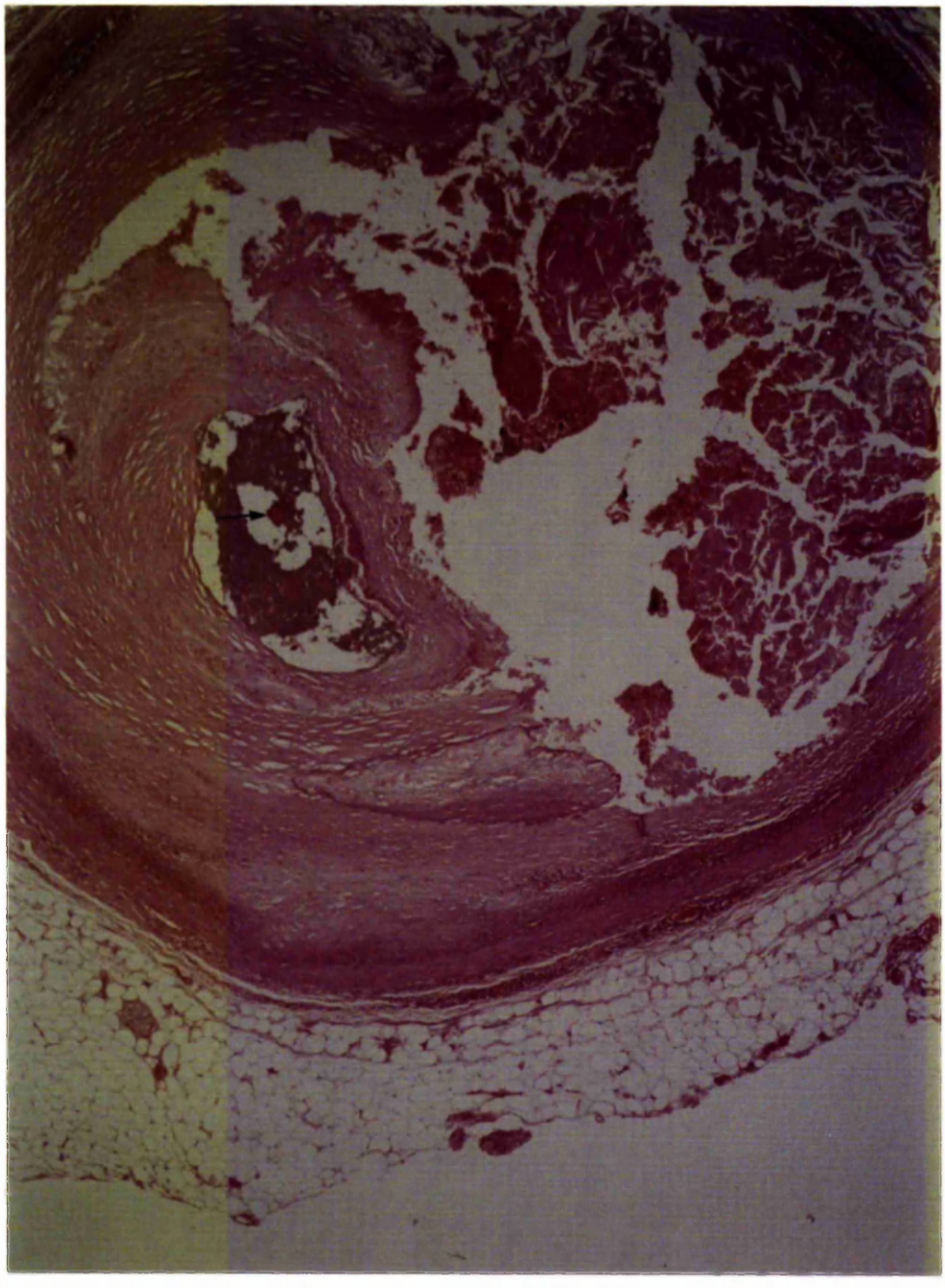
of activity, particulary unaccustomed activity, may precipitate sudden death, it is possible that the mechanism responsible for the sudden rupture of the thin fragile cap, may be no more than the normal haemodynamic stresses (Falk, 1983).

Intraluminal Thrombosis

The present study has shown that at least 66% of patients who die suddenly from ischaemic heart disease have recent luminal thrombi in the coronary arteries. In 38% of the cases, the thrombus was obstructing more than 50% of the lumen. An additional 28% of the cases had minor thrombi occluding less than 50% of the lumen. (Figure 46). These findings compare favourably with those of the London study where 44% of the cases had major thrombi and 30% minor thrombi. The mechanism of death in such cases with smaller thrombi, could have been the passage of platelet emboli carried into the small myocardial vessels (Davies and Thomas, 1984). Previous pathological studies concluded that coronary microthrombi appear to be the main pathologic process in a subgroup of patients of sudden cardiac death (El-Maraghi and Genton, 1980).

Seven per cent of the cases in this study had mural thrombi accompanying plaque rupture, whereas in 15% of the cases, the only demonstrable lesion was plaque fissuring

Figure 46



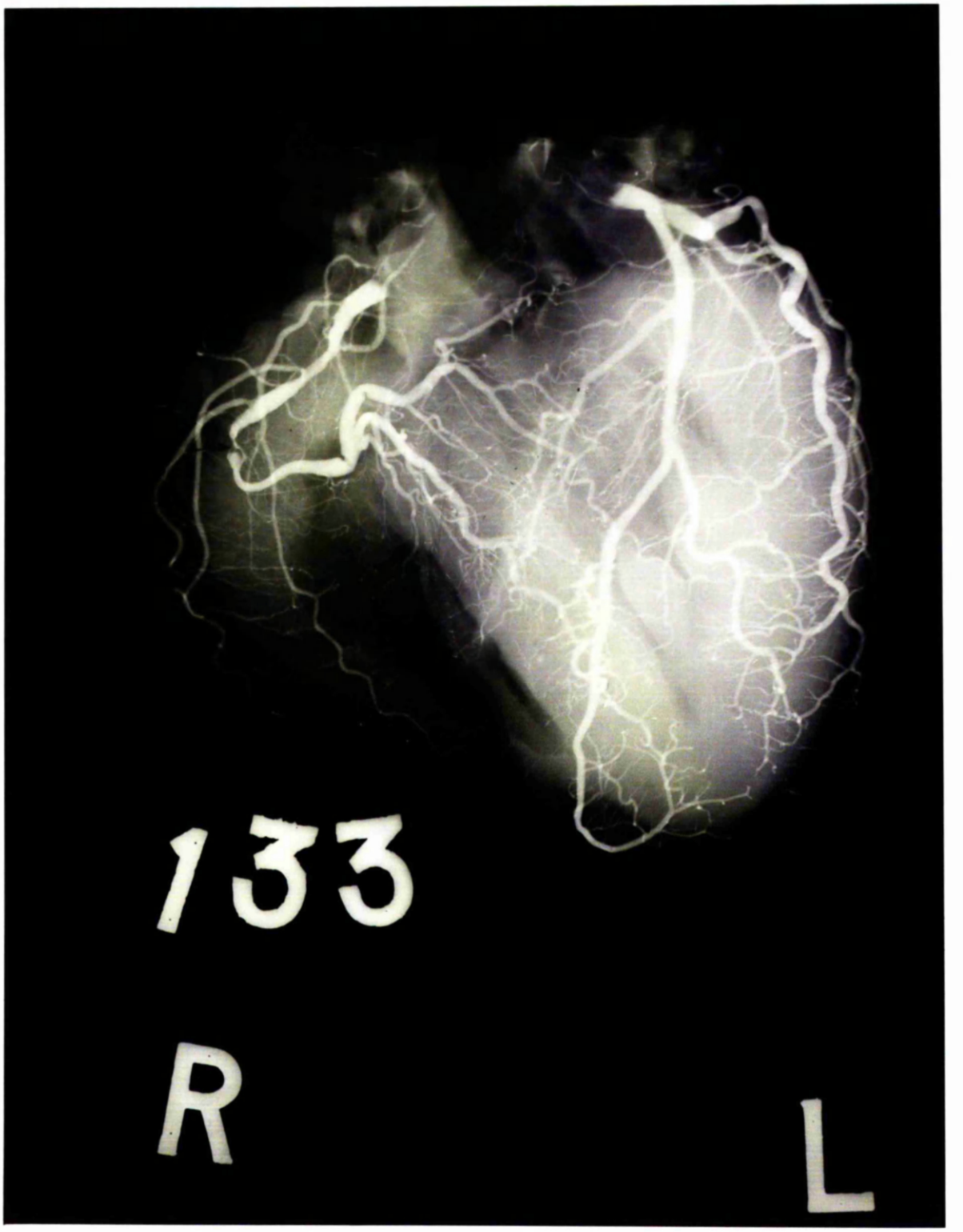
A minor thrombus (occupying less than 50% of the lumen) distal to a site of rupture (arrow). Another tiny organised thrombus is present at the right-hand side of the lumen.

associated with intimal haemorrhage. In such cases, where no luminal thrombus was found, a possible explanation for the mechanism of death could be a local vascular spasm, precipitated by plaque fissuring or a large mural thrombus might bulge into the lumen, causing as much obstruction as that of an occlusive luminal thrombus (Davies and Thomas, 1984). A furthur possibility is that the torn flap of intima has a valve-like effect, mechanically obstructing the lumen.

The present finding of acute luminal thrombosis without evident disruption of the intimal lining in 36% of cases with luminal thrombosis and in 24% of all cases of sudden ischaemic death, might suggest a possible prophylactic role for platelet-active substances such as aspirin (Liberthson et al, 1974). While it is possible that the present methodology of 3 millimetre sectioning of the epicardial coronary tree may miss occasional intimal disruptions, and therefore under-estimate the frequency of plaque fissuring, it seems unlikely that a large number of intimal ruptures have been missed.

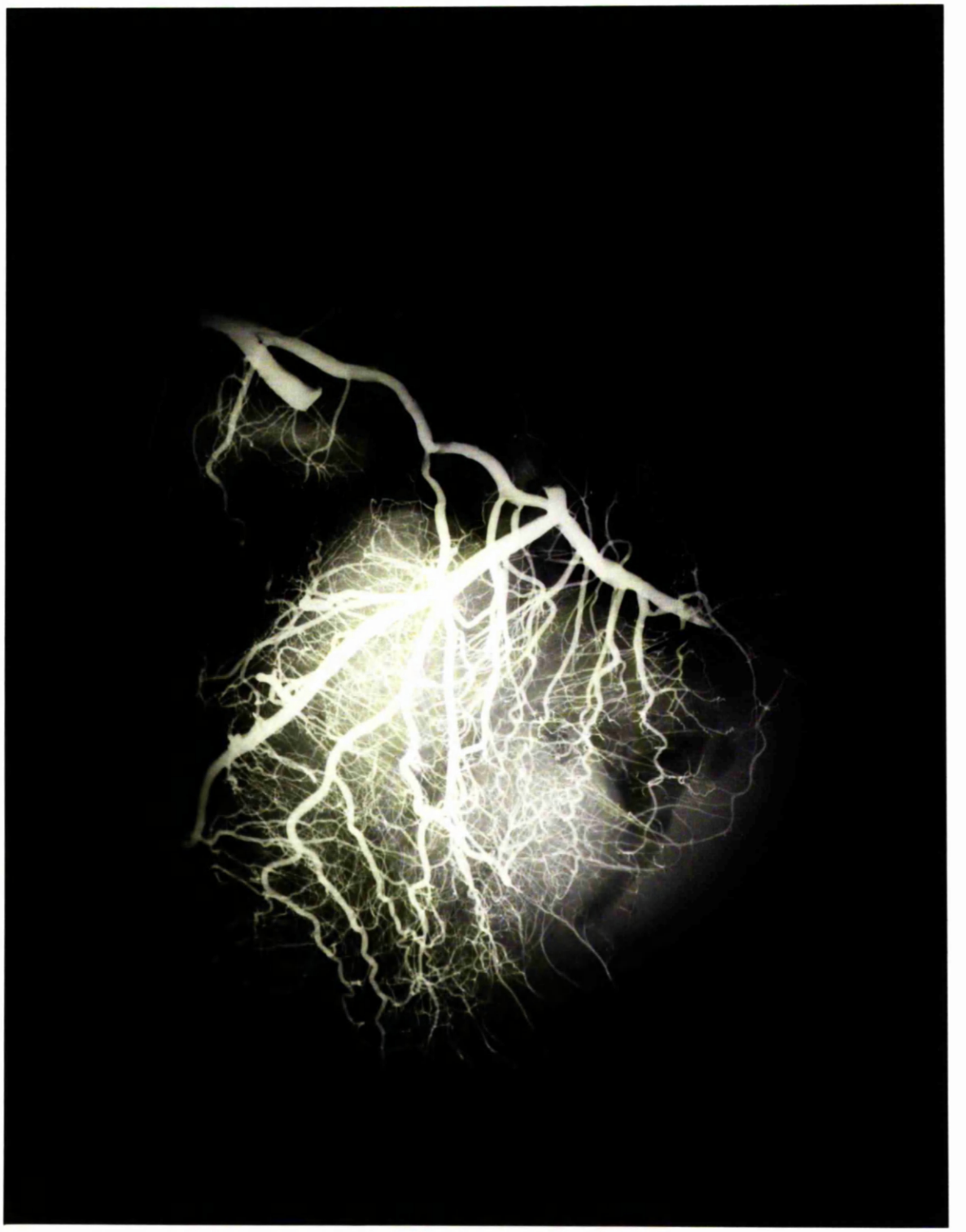
The frequency by which either plaque fissuring or luminal thrombosis was found in both the right coronary (Figure 47) and the left anterior descending branch was almost the same. However, many fewer acute atherosclerotic lesions were present in the left circumflex artery. (Figure 48). There was no evidence to support the notion that acute lesions in the artery that

Figure 47



Post-mortem coronary angiogram showing total occlusion of the right coronary artery (arrow).

Figure 48



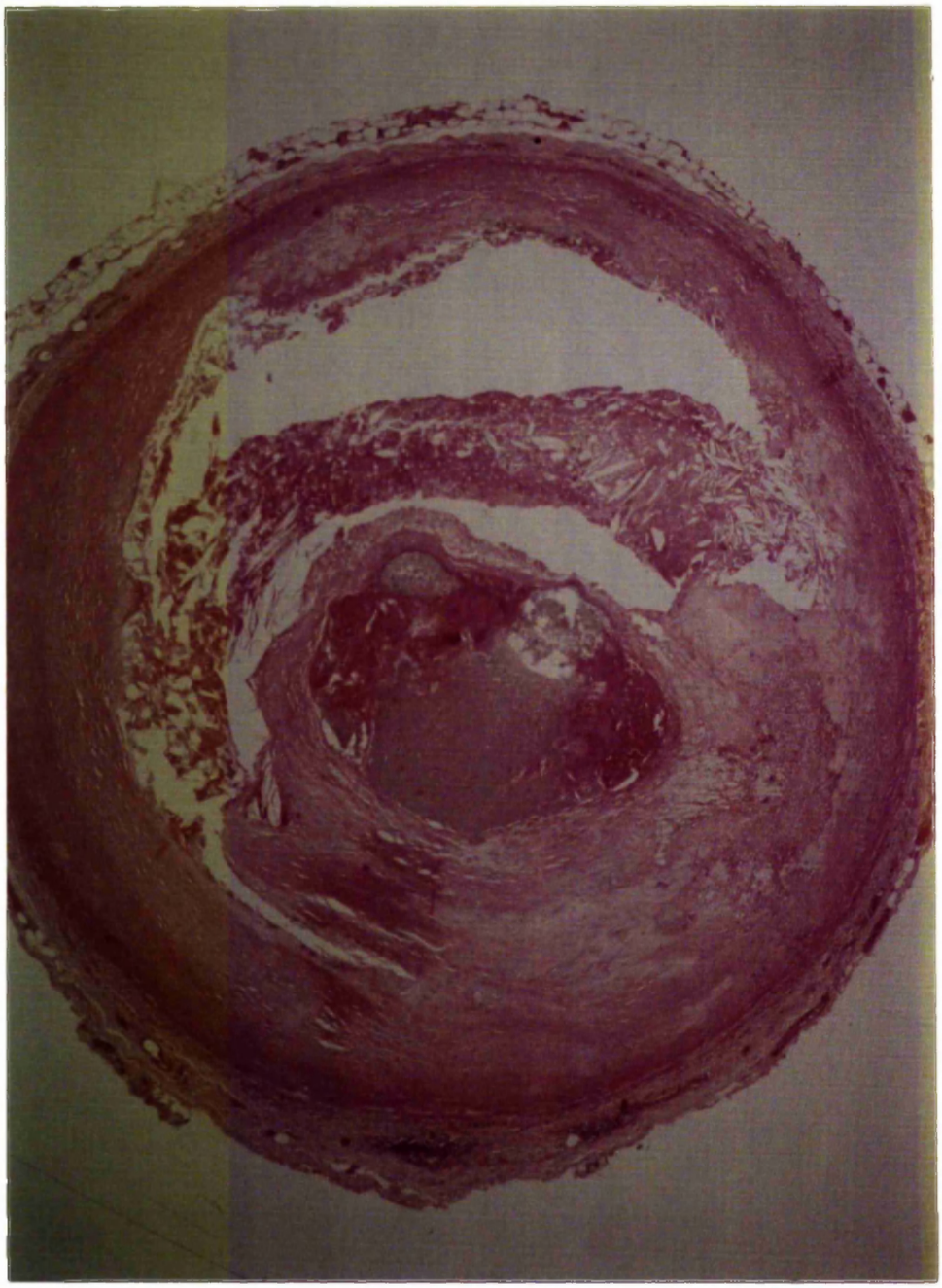
Total obstruction of the left circumflex branch (arrow) is shown by the post-mortem coronary angiogram.

usually supplies the conduction system are particularly life-threatening (James, 1969; Davies and Thomas, 1984).

The distribution of acute luminal thrombi in the different segments of the coronary tree shows great similarity to that of plaque fissuring. The majority of the recent coronary lesions, including thrombi whether major or minor, occurred at parts of the coronary tree where stenosis was most common. (Figure 49). This suggests that the degree of the pre-existing stenosis is the most important decisive factor in the fate of ischaemic heart disease. The nature of the atherosclerotic lesion plays another significant role in the history of the disease, as it is the lipid-rich plaques which are prone to rupture. The fate of the ruptured plaque depends on the size of the crack, as well as on the platelet response in the arterial lumen. The development of myocardial infarction depends on the establishment of the occluding thrombus, and the extent of the collateral circulation. Intra-coronary thrombolytic therapy may therefore be of great value in reducing the incidence of sudden cardiac death in cases of luminal thrombosis. Whether cases of mural thrombosis can be influenced by such therapy or not, is as yet unknown (Davies and Thomas, 1984; Ganz et al, 1981).

There has been controversy in the literature, concerning the frequency of coronary thrombosis as well as plaque rupture, in sudden ischaemic death, with various

Figure 49



Coronary thrombosis in an artery with a pre-existing stenosis of 85%.

groups reporting markedly different findings, varying from 10% to 60% (Liberthson et al, 1974; Lie and Titus, 1975; Baroldi et al, 1979). The data reported in the present study, in accordance with the London study, indicate that both plaque rupture and luminal thrombosis are present in the majority of cases of sudden ischaemic death.

This study does not show obvious difference in the incidence of thrombosis between cases who died instantaneously or within 24 hours from the onset of symptoms. Previous workers (Friedman et al, 1973; Spain and Bradess, 1970), have claimed that acute lesions are not found in cases dying instantaneously from coronary heart disease and the only findings in such cases are old coronary occlusions. It was also claimed that the longer the time interval between the onset of symptoms and death the more the acute lesions are present. In the present study, luminal thrombi were found in 60% of cases who died within 15 minutes, in 58% of cases who died between 15-60 minutes, in 66% of cases who died between 1-6 hours, in 73% of cases who died between 6-24 hours and in 56% of cases who were found dead but known to have been alive within the previous 24 hours. The results in both this study and the London study do not show an increase in the incidence of either plaque fissuring or luminal thrombosis with prolongation of the time between the onset of symptoms and death.

Old Occlusions

Old non-fatal occlusions represented by the presence of recanalisation, were shown to occur more frequently in the distal parts of the right coronary artery as well as the first and the second left diagonal branches. The distribution of recanalisation in the present study, compared to the pattern of distribution of both plaque fissuring and luminal thrombosis, suggests that there are certain parts of the coronary tree, where acute lesions tend to be non-fatal and to undergo organisation and recanalisation. On the other hand, it seems that in other parts, usually the proximal segments, the acute events are more likely to end fatally. This could be of some interest to the clinicians, as severe stenosis of proximal parts, which should be detected by angiography in life, may be an indication for grafting operations.

The distribution and severity of coronary atheroma

The present study shows that in the majority of the cases the proximal parts of the main coronary branches were more severely affected by atheroma, and had higher average stenosis than the distal parts. This finding was almost constant in all different age groups. Certain parts of the coronary tree, such as the second 2 cms. of the right coronary and the second and third 1.5 cms. of the left anterior descending branch, showed the highest

average stenosis in almost all age groups. Such findings may support the importance of the role of haemodynamic factors in plaque formation. Since the chemical composition of the flowing blood, as well as the arterial wall structure, are unlikely to be different from one segment of an artery to another, it does not seem unreasonable to attribute the location and, to some extent, the severity of the atherosclerotic lesions to the interaction between the blood flow dynamics and the reactivity of the arterial tissues, according to their situation along the coronary tree (Woolf, 1982).

However, in 17 of the cases, the distal parts of the major branches were the more severely stenosed than the proximal parts. That may give some indication that whatever the extent of the role played by the haemodynamic forces, it cannot be the only factor controlling the location of the atherosclerotic lesions. The presence of 18% of cases dying from ischaemic heart disease, with more significant atheroma in the distal parts of their coronaries, could be of some clinical importance as such lesions could be regarded as clincally insignificant by angiography during the patient's life.

This study shows that 53% of patients dying suddenly from ischaemic heart disease have three vessel disease with high grades of stenosis more than 70% of the lumen. In 27% of the cases, all the major vessels were narrowed to more than 80%, and in 4% the stenosis in the

three arteries was greater than 90%. On comparing the extent of stenosis in each of the two major vessels when the third was severely stenosed to more than 90%, the study showed an increase in the stenosis figures of most of the vessels to more than the average in such cases, indicating that in a considerable number of cases, the disease affects all the coronary vessels equally.

On the other hand, the results also showed that a smaller number of cases (15%), had a limited part of the coronary vessels affected by atheroma, while the rest was relatively free of the disease. However, these small parts were the only significant lesions in these cases, and were the sites of the acute events in 11 of the 14 cases.

Post-mortem coronary angiography

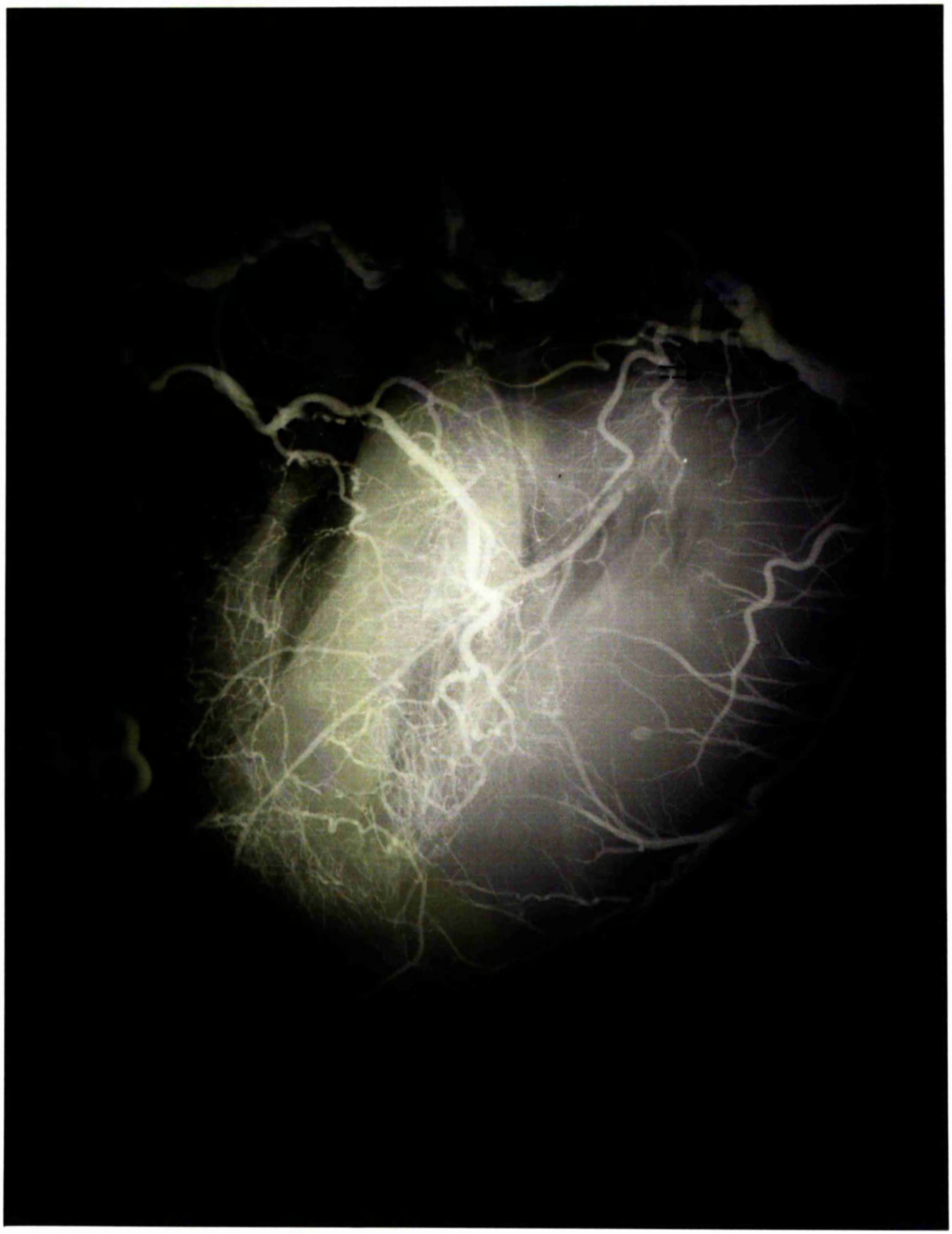
This study has shown that post-mortem coronary angiography does not seem to be a reliable diagnostic method for estimating the severity of coronary atherosclerosis. Comparing the angiographic results with the accurate histological measurements of the degree of luminal stenosis in 100 test cases, in 41% of the cases the angiograms did not correlate well with the measurements. It seems that the angiograms tend to under-estimate the degree of stenosis (33%). However, in a small group of cases (8%), the angiograms over-estimated the degree of narrowing. Although post-mortem coronary angiography has the great advantage of producing a fair

idea about the extent of atherosclerotic lesions and sites of coronary obstructions, as well as illustrating the anatomy of the coronary tree and the extent of collateral circulation, (Figure 50) while leaving the arteries and the heart undamaged for subsequent investigations, it cannot be recommended as an alternative method for routine diagnosis of cases of coronary artery disease. Histological examination of 2-3 millimetre cross section segments of the whole coronary tree is essential for ensuring reliable results in such cases.

Myocardial Infarction

The relatively low incidence of recent myocardial infarction in the present study (42%) reflects the importance of case selection in investigating cases dying from ischaemic heart disease. Had these patients survived longer after the ischaemic episode, a bigger number might have shown signs of infarction. On the other hand, it is predicted that some of the cases who did not show demonstrable ischaemic changes in the myocardium in this study, had early infarcts which were too early to be detected, either histologically or by the enzyme test. Indeed in 42% of the cases who had recent infarcts, the microscopical examination did not show recent ischaemic changes, which were diagnosed by the enzyme technique alone.

Figure 50



Post-mortem coronary angiogram showing total occlusion of the left anterior descending branch (arrows). New collaterals allowed filling of the artery distally via the right coronary artery.

In 90% of the cases with recent myocardial infarction, there was an acute lesion in one or more of the coronary arteries, and 71% of the cases had luminal thrombosis. In the majority of the cases, the acute lesion was in the artery supplying the area of infarction. Only in two cases (5%), a thrombus was found in an unexpected coronary artery. In all the cases with diffuse subendocardial infarction, there was severe stenosis (more than 70%) of the three major branches, and a recent lesion was present in one or more of the coronary arteries. The study also shows that in 52% of the cases who had healed myocardial infarction, the ischaemic damage was due to an old atherosclerotic lesion in the coronary arteries. That was suggested by the presence of recanalisation in the subtending coronary artery in 24 of the 46 cases with old infarcts.

The presence of acute coronary lesions in the majority of cases with recent myocardial infarction (90%), clearly indicates the importance of coronary thrombosis and plaque rupture in the pathogenesis of myocardial infarction. Since the findings are similar in both London and Glasgow it seems to rule out any difference in susceptibility to ischaemic damage in residents of these two populations. This contradicts the suggestion of Crawford and Crawford (1967) that the myocardium in people living in Glasgow is more susceptible to the effects of ischaemia than those living in London.

Control Cases

The findings in the non-ischaemic group (30 cases), although being of smaller number compared to the test cases, have demonstrated the significance of the severely stenosed vessels in the fate of the sudden coronary death. The importance of the acute lesions as the potential cause in the mechanism of sudden ischaemic death is well demonstrated by their absence in the majority of the control group (97%). Plaque rupture was found in one control case, whereas thrombosis was not present in any of the 30 controls. At the same time, the extent of atherosclerosis in the control group was much less than in any of the test groups. The presence of circumferential subendocardial infarction in two of the controls can be explained by the sudden drop in blood pressure, as one died from intracerebral haemorrhage, and the other from a drug overdose.

SUMMARY AND CONCLUSION

One hundred and thirty cases died suddenly and unexpectedly in the Glasgow areas have been studied in the present work which is an attempt to understand the pathogenesis of sudden ischaemic cardiac death. The study included post-mortem coronary angiography, enzyme and histologic diagnosis of myocardial infarction as well as morphologic observation and measurement of histologic blocks of 3 mm. cross-sectional segments of the whole epicardial coronary tree.

In 81 of the 92 cases who died suddenly from ischaemic heart disease, recent coronary events were identified in the form of plaque fissuring and/or coronary thrombosis. It has been shown that these lethal acute lesions occur mostly at parts of higher grades of stenosis, mainly the proximal segments. By contrast, the old non-fatal occlusions were found more frequently in the distal segments. It has also been shown that the nature of the atheromatous plaque plays an important role in the pathogenesis of sudden ischaemic death as the soft lipid-rich plaques are prone to rupture which seems to be the triggering mechanism responsible for the sudden death in the majority of cases. The study also shows that there is no difference between cases dying suddenly and those who develop infarction and admitted to hospital.

On the other hand, the present work shows the existence of other two smaller groups among those who

collapse and die suddenly in whom no acute coronary lesion could be identified. One group (11 cases) showed severe degrees of coronary narrowing whereas the second (8 cases) presented varying degrees of less atherosclerosis. In both groups the mechanism of death is obscure and open to speculation which, unfortunately, cannot be assessed adequately by pathologists.

The majority of cases in this study showed severe atherosclerosis in three or at least two of the major vessels. On the other hand, a fewer number of cases exhibited discrete areas of narrowing limited to one or two arteries. The atheroma usually affected the proximal parts of the vessels, though in 18% of cases the stenosis was confined to the distal rather than the proximal segments.

The incidence of myocardial infarction was understandably low (42%). Ninety per cent of these showed an acute coronary lesion, usually in the subtending artery. A finding which rules out both suggestions that infarction precedes thrombosis and that the myocardium of people living in Glasgow is more susceptible to ischaemic damage.

Whereas post-mortem coronary angiography has been proved to misinterpret the degree of coronary stenosis, the nitro-blue tetrazolium test seems to be a simple, reliable and fast method in the diagnosis of recent myocardial infarction for routine purposes.

It is concluded that sudden ischaemic death victims usually suffer from severe coronary atherosclerosis in more than one artery, particularly in the proximal segments. Recent events in the narrowed soft pultaceous plaques, usually in the form of fissuring, precipitate thrombosis and sudden death. It is the nature of these plaques varying greatly from the very soft necrotic to the hard fibrotic which needs more attention. A combined effort of pathologists, epidemiologists and biochemists is needed in order to uncover some of the unknown areas in this field.

More attention should be paid to patients with distal lesions, as it seems that they constitute a small number of ischaemic heart disease victims. These patients, as well as those with uniformly stenosed arteries for long segments, might be the sort of cases suitable for endarterectomy. Meanwhile, it is these patients with severely narrowed proximal parts, which should not be difficult to diagnose by angiography during life, who are the ones at big risk of developing acute coronary events and who may be in great need for a by-pass operation.

At the same time the completion of the comparative study between Glasgow and London with regard to the extent and distribution of the atherosclerotic lesions in the two populations and particularly in the younger subjects, should be of great interest.

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