Ciba Foundation Symposium

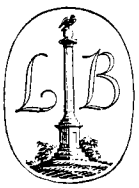
CARDIO-MYOPATHIES

Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., F.R.C.P.

and

MAEVE O'CONNOR, B.A.

With 136 illustrations



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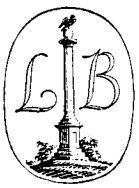

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The Ciba Foundation

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41 PORTLAND PLACE, LONDON, W.1

Preface

THE Director of the Ciba Foundation was looking for a suitable subject for a one-day meeting on cardiology when he received from Professor John Goodwin the proposal for the meeting recorded here. This proposal was accepted without hesitation and was worked out with the help of Professor Goodwin, Mr. W. P. Cleland and Mr. H. H. Bentall, under the most welcome supervision of Professor J. McMichael. It was soon apparent, however, that one day would not do justice to the subject, and the meeting was extended to cover three days.

The symposium was first planned under the title of "Disorders of Heart Muscle", later as "Primary Disorders of Heart Muscle", and then much consideration was given to various descriptions of hypertrophic and obstructive conditions. This was symptomatic of the doubts and misunderstandings, more particularly between the two sides of the Atlantic, concerning the interpretation of both symptoms and pathology as reported from various centres. By the time the conference was held, under the title of "Cardiomyopathies" (for simplicity), belief and interest in the problems here discussed had increased so rapidly and extensively that we were obliged to exclude more would-be participants than for any of the eighty-odd previous symposia. Limitation on membership is imposed mainly in the interests of thorough discussion, well exemplified on this occasion. But it is greatly hoped that the proceedings presented here will give a sense of vicarious participation to all readers, and that the book, studied at leisure, will help towards an early and fuller understanding and prevention of the conditions which, in various forms in all parts of the world, may be the cause of sudden death or of lingering incapacity.

On behalf of the Ciba Foundation, the editors gratefully

acknowledge the invaluable help of those already mentioned above, especially Professor Goodwin. The enthusiastic but down-to-earth leadership of Professor McMichael, the wholehearted manner in which all members participated in the symposium, and the care which they took in the special preparation of material for the papers and discussions, all contributed to the success of the meeting, a success which we hope will be reflected in this publication.

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Membership

Symposium on Cardiomyopathies held 15th–17th April, 1964

H. H. Bentall	Dept. of Surgery, Postgraduate Medical School, London
Monica B. Bishop	Dept. of Pathology, The Albany Medical College of Union University, Albany, New York
V. O. Björk	Dept. of Thoracic and Cardiovascular Surgery, University Hospital, Uppsala
E. Braunwald	Cardiology Branch, National Heart Institute, Bethesda, Maryland
W. Brigden	Institute of Cardiology, National Heart Hospital, and The London Hospital, London
Sir Russell Brock	Guy's Hospital, London
G. E. Burch	Dept. of Medicine, Tulane University School of Medicine, New Orleans, Louisiana
H. B. Burchell	Clinical Section, Mayo Clinic, Rochester, Minnesota
W. P. Cleland	Postgraduate Medical School, and Brompton Hospital, London
J. Cohen	Dept. of Medicine, Strong Memorial Hospital, University of Rochester, Rochester, New York
J. N. P. Davies	Dept of Pathology, The Albany Medical College of Union University, Albany, New York
R. L. Frye	Clinical Section, Mayo Clinic, Rochester, Minnesota
J. F. Goodwin	Dept. of Medicine, Postgraduate Medical School, London
R. Gorlin	Peter Bent Brigham Hospital, Boston, Massachusetts
G. R. Graham	Dept. of Clinical Physiology, The Hospital for Sick Children, London
A. Hollman	University College Hospital, London
R. J. Linden	Dept. of Physiology, The School of Medicine, University of Leeds
J. McMichael	Dept. of Medicine, Postgraduate Medical School, London
A. G. Morrow	Clinic of Surgery, National Heart Institute, Bethesda, Maryland
B. Nordenström	Dept. of Thoracic Radiology, Karolinska Sjukhuset, Stockholm

Celia M. Oakley	Dept. of Medicine, Postgraduate Medical School, London
E. H. O. Parry	Dept. of Medicine, Postgraduate Medical School, London
A. G. Everson Pearse	Dept. of Pathology, Postgraduate Medical School, London
P. M. Shah	The Hospital for Sick Children, Toronto; and Bombay
H. A. Snellen	Dept. of Cardiology, State University of Leiden, Leiden
R. E. Steiner	Radiodiagnostic Dept., Postgraduate Medical School, London
R. D. Teare	Dept. of Forensic Medicine, St. George's Hospital Medical School, London
E. D. Wigle	Dept. of Medicine, University of Toronto, Toronto
Eleanor Zaimis	Dept. of Pharmacology, Royal Free Hospital School of Medicine, London

CHAIRMAN'S INTRODUCTION

PROFESSOR J. MCMICHAEL

"OF all the ailments which may blow out life's little candle, heart disease is the chief." (William Boyd).

Knowledge of the natural history of heart conditions clarifies the majority—congenital malformations, rheumatic, hypertensive, valvular, ischaemic, pulmonary, etc. But there has always remained an inexplicable residue of instances in which the cause has not been understood. When I was a medical student my Professor of Pathology, James Lorrain-Smith, said "Never forget those causes of cardiac hypertrophy that we don't explain—call them idiopathic and *write it down*". Unfortunately this advice was not always taken. I can remember 30 years ago such patients being described as having "occult syphilis" and even later they were being pushed by pathologists into pigeon-holes labelled "burnt-out hypertension". But if hypertension had been the cause and hypertension disappeared why didn't these patients get better? I well remember pleading with my colleagues to adopt the Lorrain-Smith rule and call these instances "idiopathic" or "unexplained" heart disease, for at least the appreciation of ignorance could be the beginning of knowledge. I was particularly pleased when Wallace Brigden, who succeeded Paul Wood on our staff, picked up the threads of this story and indeed introduced the term "cardiomyopathy" in his St. Cyres lecture (Brigden, 1957); Brigden's successor, John Goodwin, then pursued the trail and as you will see the subject is full of interest.

The conditions under study in this symposium are probably not uniform. They vary in their clinical course, from protracted heart failure to sudden death, and indeed it was in the latter group that

Dr. Teare first defined the pathology of one of the most interesting forms. There are also varieties resulting from excessive consumption of alcohol, and other very important varieties with special dominance in Africans, whether on their own continent or in the West Indies. A great deal of interest was roused by Brock's recognition of a form of this disorder in which there seems to be muscular obstruction to outflow from the left ventricle. This observation was a natural consequence of the advance of surgery of the aortic valve, as such instances could well be mistaken, on older methods of diagnosis, for aortic stenosis. This, together with Brock's earlier work on subvalvular muscular obstruction in pulmonary stenosis, established fully the remarkable phenomenon that hypertrophy of the heart, even when "compensatory", could obstruct its own outflow.

The following list indicates the various names which have been used to describe this disorder and it may be part of our exercise in this discussion to clarify terminology.

Functional obstruction of the left ventricle	Brock, 1957
Pseudo aortic stenosis	Bercu and co-workers, 1958
"Une cause d'erreur etc."	Soulié and co-workers, 1959
Functional aortic stenosis	Morrow and Braunwald, 1959
Functional subaortic stenosis	Brachfeld and Gorlin, 1959
Obstructive cardiomyopathy	Goodwin and co-workers, 1960
Muscular subaortic stenosis	Brent and co-workers, 1960
Familial hypertrophic subaortic stenosis	Brockenbrough, Braunwald and Morrow, 1961
	Boiteau and Allenstein, 1961
	Whalen and co-workers, 1963
Diffuse subvalvular aortic stenosis	Kirklin and Ellis, 1961
Muscular subvalvular aortic stenosis	Menges, Brandenburg and Brown, 1961
Muscular subaortic stenosis	Wigle, Heimbecker and Gunton, 1962
	Wigle, 1963
Hypertrophic obstructive cardiomyopathy	Cohen and co-workers, 1964

I have never before taken part in a discussion in which we start with so few fixed or preconceived ideas. We are in fact launching

into poorly charted seas and perhaps we shall end the discussions with a slightly better map.

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HYPERTROPHIC OBSTRUCTION OF THE LEFT VENTRICULAR OUTFLOW: CLINICAL RECOGNITION OF THE CONDITION

SIR RUSSELL BROCK

Guy's Hospital, London

I AM grateful for being accorded the honour of opening the clinical presentation of this remarkable condition of hypertrophic obstruction of the left ventricular outflow, which is not only a new disease recognized quite recently but also one that serves to indicate to us that ventricular action is not the simple mechanism it was long thought to be.

I had imagined from my student days, and certainly no one of my teachers had taught me otherwise, that the ventricular muscle masses were essentially quite simple and in fact rather crude structures that just filled with blood in diastole and discharged their contents in systole by a straightforward contraction that gave rise to a squeezing process much as is achieved by a small boy squeezing a ball filled with water. I understood that a complex nervous and vascular control mechanism existed that affected the rate, tonus, power and efficiency of the ventricular output: in fact this was a mechanism long studied, brilliantly elucidated, highly efficient, of great practical importance and carefully taught. But with all these superb controlling influences the final ejection phase was still only a crude mechanism. This exception applied especially to the action of the left ventricle. It is indeed rather noteworthy that so little was known about the left ventricle until quite recently. This was doubtless due to the fact that it was difficult to examine its action directly. The results of clinical and simple radiological

assessment were very meagre in the information they supplied. Post-mortem studies contributed little beyond the demonstration of gross organic disease. Experimental observations were made on the ventricles of animals, but few or no direct observations were made in man. Thus, although few realized it, the ventricles, and especially the left ventricle, although so familiar to us and so essential to life, remained one of the last territories within the body to be submitted to closer scrutiny and study.

In fact a little philosophic thought could have led to the deduction that an organ activated and controlled by such complex mechanisms as had clearly been demonstrated to exist, must itself be more complex, intricate or subtle than had been supposed.

It fell to the white light of surgery to illuminate this dark patch. This has often been so and I say it without fear even though I address an audience largely non-surgical. We meet on the common ground of Medicine (with a capital M) and it is desirable that surgery should at times be accorded recognition of the contribution it can make towards a better understanding, a more scientific understanding, of the normal and disturbed bodily processes in which we are all interested. It was the progress of heart surgery that gave the opportunity for more direct methods of study of the actual living heart. The availability of cardiac catheterization techniques, so notably and so worthily developed in this country by Professor McMichael, permitted precise pressure measurements to be made, but without the special experimental conditions provided by operations upon the heart the information obtained would have been less fruitful. We recognize once more the interdependence of medical and surgical techniques and how by their intelligent use together much more information is provided than if they are used alone.

I have mentioned that the existence of a somewhat complex mechanism of ventricular contraction could have been deduced from first principles. This complexity was first revealed in the case

of the right ventricle, doubtless because this structure was the first surgical target.

In 1955 I first wrote about control mechanisms in the outflow tract of the right ventricle. The clue was the observation of residual hypertension in the right ventricle after complete relief of pulmonary valve obstruction. It was clearly shown that this hypertension is due to hypertrophic changes in the outflow tract or infundibulum of the right ventricle which result from long-standing obstruction to emptying, and that these changes lead to a systolic shut-down, preventing proper emptying of the ventricle just at the phase when ejection should be most significant. I assume that no further amplification of this process is needed here.

Reflection on the developmental history of this part of the right ventricle provided significant clues. Keith (1904*a*) had long ago shown quite clearly the significance of the inclusion within the infundibulum of the musculature of the bulbus cordis and that it was reasonable to postulate that the control of the pulmonary outflow by the bulbar muscle in gill-breathing vertebrates persisted as a function in the infundibulum of lung-breathing vertebrates. He suggested that the contraction of the ventricular musculature was not synchronous but was progressive, almost of a peristaltic nature, and that the fibres of the infundibulum were not truly discharging but regulating fibres that maintain tonicity when the discharging fibres of the ventricle have passed or are passing into a state of diastole. He suggested that when the right heart is distended the circular fibres around the base of the pulmonary artery form a functional stricture at the commencement of ventricular systole. It is exactly 60 years since he lamented the failure of clinicians to pay any attention at all to the facts put before them by the anatomist and morphologist (Keith, 1904*b*).

The tonic or phasic nature of infundibular contraction received further support and amplification from recognition of the part it plays in determining variations in cyanosis and disability in Fallot's

tetralogy (Brock, 1957*a*). The final verification of the importance of secondary changes in the outflow tract of the right ventricle came from demonstration of the spontaneous correction of residual right ventricular hypertension after pulmonary valvotomy over a period of 12–18 months.

By induction and by deduction it seemed probable that similar control mechanisms might exist in the left ventricular outflow. At the very least it seemed probable that the left ventricle, so fundamental to the support of life, was not devoid of a more refined mechanism than a crude once-and-for-all ejection action. It remained, therefore, to look for cases of residual left ventricular hypertension after aortic valvotomy comparable with those occurring in the right ventricle after pulmonary valvotomy. At that time I was doing many closed aortic operations and studies disclosed two definite cases in which this mechanism occurred (Brock, 1955), and one following open aortic valvotomy.

In 1956 I operated on a woman aged 58 with clinical features of severe aortic stenosis including angina and syncope. Pressure records at operation showed a gradient of 93 mm. Hg between the left ventricle and the aorta. A pressure withdrawal record showed that the level of obstruction was subvalvar. This information caused great anxiety because her state was critical and whereas a rapid valvotomy might have been tolerated, it seemed unlikely that she would stand the more severe manipulation needed to relieve a subvalvar stenosis. Ventricular fibrillation occurred and resuscitation failed. At autopsy the valve cusps were normal, there was no fibrous subvalvar stenosis but only gross muscular hypertrophy where the aortic vestibule joined the ventricle proper. It seemed as if the muscular hypertrophy had assumed malignant proportions.

One swallow does not make a summer and even if I had been percipient enough to understand this case, any deductions from it of a new disease process would have been unjustified. However, it did serve as a conditioning experience and nagged away in the back

of my mind until the following year, 1957, when a crucial case was encountered.

This was a woman aged 63, who was referred to me for aortic valvotomy for severe aortic stenosis. The clinical picture was peculiar and unusual. She had been known to be hypertensive since 1936, i.e. for 21 years, and for the previous five years had been given tablets for reduction of the blood pressure; her chief symptom had been headache. Four years earlier she had begun to have dyspnoea which steadily increased so that latterly she could not even walk about the house in comfort. Two years earlier she had begun to have angina of effort; paroxysmal nocturnal dyspnoea followed.

During the hypertensive phase her blood pressure had been as high as 210/110 mm. Hg. By the time I was asked to perform a valvotomy her blood pressure was 110/70. Left heart catheterization showed that the pressure in the left ventricle was 270/20, while that in the brachial artery was 110/70, a peak systolic gradient of 160 mm. Hg.

I was unconvinced that the aortic valve was calcified and this fact alerted me to the possibility of the stenosis being subvalvar in position, and not fibrous but muscular in nature. This conclusion was reached by analogy from knowledge of changes freely demonstrated as occurring in the right ventricle, from similar changes observed in the left ventricle in association with valve stenosis, from the experience of the mysterious case of the year before, and from the undoubted history of a pre-existing cause of severe left ventricular hypertrophy, namely long-continued systemic hypertension. I was alarmed because I felt that operation might reveal an inoperable state.

Some calcification was detectable near the aortic valve, and after further careful radiography it was reported that this might be aortic in site. Operation was therefore accepted.

At thoracotomy, however, no calcification could be felt in the aortic valve and a pressure withdrawal record showed that the site

of obstruction was subvalvar. Dilating instruments encountered no resistance and it was clear that no organic stenosis existed. Death occurred two hours after operation.

Autopsy confirmed that the aortic cusps were normal. The calcium observed radiographically was in the mitral valve. The left ventricle was grossly concentrically hypertrophied, and there was no fibrous stricture.

The whole case made a great impression on me, but I was even more impressed by the significant comment of the pathologist who examined the heart at autopsy. In the way pathologists have, he slit the left ventricle open longitudinally, took one look at its meaty interior and said, "Well, there's nothing wrong there."

I was impressed because we had had the opportunity of studying this left ventricle critically during life and at operation. We had observed gross clinical disease and had confirmed gross mechanical derangement at operation. These observations were made during life, on the living ventricle. The pathologist did not have this advantage. He was looking at the heart in death and I realized even more fully the disadvantages of attempting to study and assess in death such an important thing as left ventricular function.

I pictured the condition as a functional obstruction and in my first description of it gave it this name. Quite correctly this has been criticised and a better term, "hypertrophic obstruction", has been suggested. At the time of my original description, however (Brock, 1957*b*), I committed an even more serious offence. Being impressed by the preceding history of systemic hypertension, I postulated that this could be the prime cause of the condition. For this I was sharply assailed. Indeed I was told that if I had taken advice I would have learned it would have been wiser not to have written about the condition at all but to have kept quiet about what was clearly an incomprehensible, doubtful, and probably spurious condition.

I feel I really need make no apology for having in this initial case, and in view of the circumstances, attributed so much importance

to muscular hypertrophy secondary to systemic hypertension. At that time we did not know that such a preceding history was rare and that more cases would be encountered in which no preceding hypertension existed, or indeed any acceptable explanation except our old friend "cardiomyopathy". Although this term sounds scientific and explanatory, it may indeed not be so but may only cloak our continuing ignorance of the true nature of this disease. The elucidation of the possible nature of the underlying process is, however, one of the reasons for this symposium and is beyond my terms of reference.

I only wish to add that if we go back to first principles and consider or meditate upon the probable existence of a more complex system of left ventricular activation and control of contraction than a simple total squeeze effect, then the cause of this condition may lie in some dysfunction or disorder of this mechanism of delicately controlled and possibly sequential ventricular contraction. In the later discussion I hope to be able to present some strong evidence that this may be so.

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THE PATHOLOGICAL RECOGNITION OF OBSTRUCTIVE CARDIOMYOPATHY

R. D. TEARE

Department of Forensic Medicine, St. George's Hospital Medical School, London

ANY classification of the cardiomyopathies from a pathological point of view is a difficult problem, but it has been attempted by Goodwin and co-workers (1961). In practice, three categories are probably sufficient:

(1) Cardiomyopathies associated with general disease, e.g. carcinomatosis or polyarteritis.

(2) Cardiomyopathies which have been thoroughly investigated and in which no concrete diagnosis has been made, and which are variously labelled as alcoholic or post-infective, etc. Post-mortem examination rarely elucidates the aetiology of such cases.

(3) The third group of cardiomyopathies has achieved a multitude of nomenclatures but pathologically is, I think, still best described as an asymmetrical hypertrophy of the heart.

This hypertrophy certainly is the most important point in the pathological recognition of the disease, and can be defined as a localized muscular enlargement of the interventricular septum and the adjacent anterior wall of the heart. Between one-third and one half of the total circumference of the left ventricle is involved, and the change from normal thickness to hypertrophy is gradual rather than abrupt. It is this group which has produced the obstructive lesion clinically—a lesion which, as other speakers will describe, may be amenable to treatment.

So far as forensic pathology is concerned, these cases have largely presented as examples of sudden and unexpected death in healthy

young adults. A pathologist is naturally alerted to the probability of some unusual cardiac lesion when presented with sudden death in early adult life; particularly is this true when there is no history of indigestion or any other symptom which could mimic coronary pain.

The possible familial incidence of the condition is not often obvious at the time of autopsy, and I was fortunate in seeing two cases in brother and sister with a rather unusual family name within a short period of time.

It was with some trepidation that in 1957 I reported eight cases of this condition (Teare, 1958), thinking that it was an extreme rarity. In fact this is not so, as can be seen by a study of the literature. Braunwald, Brockenbrough and Morrow (1962) have described 27 similar cases. Paré and co-workers (1961) described a family of 77 amongst whom 20 members have shown signs and symptoms of a condition which the authors call "hereditary cardiovascular dysplasia", while another ten have died of this condition, which if not identical with is very similar to the condition under review. Bevegård, Jonsson and Karlöf (1962) have reported eight cases, two of which were in a brother and sister, while two occurred in families where several members had died of heart disease of unknown causes.

Menges, Brandenburg and Brown (1961), describing eight cases, drew attention to the finding that the ratio of the thickness of the septum to that of the left ventricle in three cases was 1·55, 1·76, and 1·55, as against a ratio of 0·95 in controls.

Wigle, Heimbecker and Gunton (1962) reported ten cases, including three deaths, all of which showed localized enlargement of the interventricular septum, i.e. they were proved pathologically.

Shabetai and McGuire (1963) described two cases, one of which had a history suggestive of an affected family, but the father had an ECG which revealed the presence of the Wolff-Parkinson-White syndrome.

The cases of Brent and co-workers (1960) showed uniform

hypertrophy of the left ventricle, while among those of Taylor, Bernstein and Jose (1964) three were certainly asymmetrical and there was no family association.

In addition I have had many personal communications reporting isolated examples of this condition.

The material of which I have personal experience now consists of 18 cases, 15 in men and three in women. Ages ranged between 19 and 54 in men and 21 and 45 in women. Seven cases had had symptoms of heart disease, while another three had been found to have cardiac abnormalities on routine medical examination. Two pairs of brother and sister are included in the cases, while another two cases had family histories of sudden deaths at an early age in siblings. One man was a Jamaican. Eight cases died suddenly and under no exertion, seven were taking mild exercise at the time, e.g. cycling or running for a bus, and three died postoperatively.

In recent years, in obscure cardiac deaths we have thought it advisable to inject the coronary arteries with a radio-opaque medium before dissecting the heart. In obstructive cardiomyopathy we have noted the small number of branches in the left anterior descending coronary artery on more than one occasion. Whether this is an artifact or whether it explains the ischaemia is difficult to tell. We have also taken X-rays of the heart in this condition with the left ventricle filled with medium, and it has been gratifying to find how closely this picture resembles the ordinary vertical section of the heart in obstructive cardiomyopathy and also the angiocardiogram taken in a proved case. Morrow and Braunwald (1959) had noted the slit-like left ventricular cavity in their earlier observations of this condition.

The microscopic picture is not illuminating. A bizarre and disorderly arrangement of bundles of muscle fibres runs in divers directions, separated by connective tissue and clefts. The connective tissue tends to break up and interrupt the muscle bundles, giving the impression of inefficiency in muscular contraction of the tumour as a whole, while the clefts are lined with endothelium

covering sparse elastic tissue which is similar to the structure of the normal endocardium. The individual muscle fibres appear to be mature and there is no suggestion of malignancy. They vary considerably in thickness, and show sufficient nuclei to indicate that the fibres have been cut centrally and that the appearance of variation in thickness is not due to a chance tangential section. A considerable amount of fibrosis is seen. It is mainly found in the centre of the muscle bundles and is thought to be ischaemic in origin.

It must be admitted, however, that some cases which macroscopically appear to be identical with asymmetrical hypertrophy appear to consist of normal muscle.

Morgan (1964, personal communication) has drawn attention to the hyperplasia of elastic and muscular tissue in the intima and media of coronary artery twigs in one case of obstructive cardiomyopathy.

James (1964, personal communication) believes that many obscure cardiac abnormalities may be primarily arterial rather than muscular in origin. So far genetic investigation of these cases has been fruitless.

Two main problems relating to the pathological recognition of this disease still remain:—

(1) Why is it not more readily recognized by colleagues who do the same type and volume of work? Is this due to over-diagnosis on my part or to some difference in nomenclature between my colleagues and myself?

(2) Is this condition responsible for any of the obscure cot or crib deaths which are so frequently met with in forensic practice?

This may be one of the more fruitful side avenues of research which this symposium has prompted.

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DISCUSSION

Gorlin: Dr. Teare, you implied that hypertrophy is a factor in ischaemia and so forth. Could you also comment on the relationship of the capillary to the muscle fibre? Is it one to one as in the normal? Do you believe that there is an increased distance between a given capillary and the centre of the fibre?

Teare: We feel that the centre of these muscle bundles has not been getting an adequate blood supply and that is why they have fibrosed. Whether this is due to the fact that the coronary supply has not increased in a fashion commensurate with the muscular enlargement, or whether it is due to actual changes in the smaller coronary twigs, I don't know. As I said, one or two other observers think that it is due to hypertrophy of muscle and elastic tissue within the coronary twigs themselves. I haven't seen any change at the capillary level. We have been looking at vessels about 200 μ in diameter, as against the capillary level of 30 μ.

Steiner: The impression I had from the injected specimen of your first case [not illustrated] was that the main arteries were, if anything, dilated. This is also the impression we get from *in vivo* studies. There is a curious discrepancy in size between these very large main arteries and the smaller twigs, which nevertheless look pretty good to us, radiologically. Could this be an artifact?

Teare: I don't think so, because on ordinary section of the asymmetrical heart, the anterior descending coronary can always be seen by