Declaration.

This thesis has been composed and the work therein undertaken by myself without the collaboration of other workers. I have been aided on a technical level by the technicians listed in the Acknowledgement Section in the thesis.

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November 23rd 1971.

MYOCARDIAL REVASCULARISATION BY ARTERIAL IMPLANTATION.

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MYOCARDIAL REVASCULARISATION

An experimental study of the blood flow through the internal mammary artery after implantation into the ischaemic and non-ischaemic canine myocardium and the nature and extent of the connections established with the coronary arterial circulation.

Thesis submitted for the degree of Doctor of Medicine in the University of Glasgow, November, 1971

CONTENTS

	Page
INTRODUCTION	1
THE OBJECTS OF THE STUDY	7
SECTION I - Procedures and Methods	10
SECTION II - Bloodflow through the Newly Implanted Mammary Artery	
Introduction	32
Results	38
Discussion	47
Summary	51
SECTION III - Bloodflow in the Long-term Implant	
Introduction	53
Results	63
Discussion	103
Summary	116

Page

SECTION IV - Microscopic Observations in the Implant and the Myocardium

Introduction 120

Methods 122

Results 125

Discussion 139

Summary 169

SECTION V - An Angiographic Study of the Implant and its Connections with the Coronary Circulation

Introduction 173

Materials and Methods 175

Results 180

Discussion 186

Summary 202

CONCLUSION 204

REFERENCES 209

ACKNOWLEDGMENTS 226

INTRODUCTION.

INTRODUCTION

Although great effort has been expended on the elucidation of the underlying cause of coronary artery disease, the basic mechanisms are still elusive. At present, treatment is aimed at the amelioration of symptoms and at the salvage of what remains of functional myocardium following complete or almost complet cessation of bloodflow in the affected coronary artery. Rational therapy should obviously be directed towards the prevention of obstructive lesions before irreversible damage to the myocardium occurs, but at the present stage of medical knowledge this is, of course, not possible. The reality of the situation is that by the time most patients are presented for evaluation, the myocardium is to a greater or lesser extent irreversibly damaged and that subsequent management depends very much on the expertise of the medical cardiologist and to a smaller degree on the skill of his surgical colleagues.

Historically the treatment of coronary arterial disease and its sequelae has been in the hands of the physician and therefore attitudes of treatment have customarily been of a medical rather than of a surgical nature. In recent years drug treatment has reached new levels of sophistication and effectiveness revolutionising the approach to the management of the patient with coronary arterial insufficiency. Complete evaluation of the long term effect of any recent medical treatment of coronary artery disease however, has not been carried out and despite optimistic reports a number of patients do have pain which is difficult to control by drugs, a percentage still die and a residual morbidity remains.

Over the past twenty-five years a number of surgical procedures have been designed to relieve pain of occlusive vascular disease of the heart or to improve cardiac efficiency. These operations fall into four categories:-

(a) interruption of nervous pathways to and from the heart;

(b) removal or bypassing a single discrete localised obstructive lesion within a coronary artery;

(c) the removal of redundant scar tissue from the ventricle to increase cardiac efficiency; and

(d) the introduction of a new blood supply to the myocardium.

Interruption of nervous pathways is effected by bilateral upper thoracic sympathectomy in which the attempt is made to remove the efferent sympathetic fibres which help 'drive' the heart and also to interrupt the afferent sensory fibres carrying pain sensibility from the heart. This relatively simple procedure was reserved for those with severe angina but fell into disfavour mainly because of the doubtful logic upon which it was based.

The development of selective coronary cine-angiography has greatly stimulated progress in the application of surgical techniques directed to the removal or to bypassing discrete localised lesions of the coronary arteries (Sones and Shirey, 1962). Each of these operations was a logical extension of the operative approach to peripheral vascular disease. Endarterectomy when performed alone was found to be effective in removing the obstructive lesion but produced a 'ploughshare' effect obstructing the orifices of small branches from the main artery. It is now customary to remove only the protruding portion of the obstructive lesion and to patch the artery with a piece of vein, thus avoiding stenosis of the vessel and obstruction of small efferent tributaries. This operation however is also going out of fashion having been largely replaced by the bypass vein graft. The bypass vein graft technique involves attaching the upper end of the reversed saphenous vein to the ascending aorta and the lower end to the coronary artery below the occluded segment, thus avoiding disturbance of the obstruction which might lead to new thrombus formation and re-occlusion. It has the great advantage of supplying immediately a new source of blood through an undamaged conduit and is therefore highly effective in bringing early post-operative relief of symptoms provided that the artery below the distal anastomosis is free from obstructive disease and can give an adequate 'run-off' from the graft. It should be emphasised however, that the obstruction must be solitary or localised to a short segment of artery or arteries. Recently, attempts have been made to use this technique to bypass lesions in two coronary arteries in the same patient (Johnson and Lepley, 1970). Obstructions of both main coronary arteries, and the two principal branches of the left, the anterior descending and the circumflex branches, have been relieved by this method.

Unfortunately, only about 20% of patients with coronary artery disease have solitary lesions or short obstructed segments involving one or two main arteries (Diethrich, Liddicoat, Kinard and De Bakey, 1969). The remaining 80% of patients have multifocal, diffuse disease in the right coronary artery and in the principal branches of the left coronary artery. These patients are at present beyond help with either endarterectomy or grafting techniques.

For the patient with a residual left ventricular aneurysm following myocardial infarction, there is evidence that removal of the aneurysm leads to greater cardiac efficiency and some abatement of symptoms (Lillehei, Levy, DeWall and Warden, 1962). Extending the logic of this therapy, attempts have also been made to remove infarcted (non-aneurysmal) areas of ventricular wall in the immediate post-infarction period with largely, poor results (Heimbecker, 1969).

For the vast majority of patients (over 80%) with multiple lesions which involve all main coronary arteries, the techniques of thrombo-endarterectomy and bypass grafting are for the main part not practicable. For these patients the only methods available at present for the surgical relief of severe ischaemia lie in the introduction of new blood vessels to the myocardium. These can be divided into two groups:-

(a) Indirect methods - in which adhesions are produced between the heart surface and another vascular structure (pectoral muscle, omentum, lingula), in the hope that new vessels will grow into the heart.

(b) Direct methods - in certain lower animals the myocardium receives its blood directly from the chambers of the heart by sucking blood into a sponge-like system of sinusoids. In higher animals this has been largely replaced by the coronary circulation, but the sponge myocardium of the lower animals is thought to be represented by a network of sinusoidal spaces lying between the muscle fibres in direct communication with the coronary circulation.

Making use of this knowledge, Vineberg, in 1946, implanted the distal cut end of the internal mammary artery into a tunnel made in the myocardium of the ischaemic left ventricle to increase its supply of blood. At first this operation was met with scepticism, but in the last few years more and more surgeons have been making use of this operation or variations of it, to help revascularise the myocardium of the patient with multifocal and diffuse coronary artery disease.

OBJECTS OF THE STUDY.

THE OBJECTS OF THIS STUDY

Despite a fairly extensive literature on the subject of revascularisation of the myocardium by means of internal mammary artery implantation, few critical studies have in fact been made into the measurement of bloodflow in these grafts, the evolving changes in the microscopic structure of the implant, and the nature and extent of the connections which develop with the coronary arterial circulation. This relative lack of basic information has led to many misunderstandings about the place of this operation in the surgical management of the patient with widespread coronary artery disease.

The procedure itself does not fit into the usual categories of surgical therapy, i.e. no attempt is made to remove obstructing material from the coronary vessels, to reconstruct conduits or to bypass lesions by surgical anastomosis with other arteries. The operation of implanting an artery into a tunnel in the myocardium without any attempt to surgically connect it to the coronary circulation has no direct surgical therapeutic precedent, and because of this it is difficult to understand how it could possibly work.

The first purpose of this study was in fact to satisfy a curiosity about whether an artery implanted into the myocardium could make useful connections with the coronary circulation. Confirmation of this phenomenon prompted a search of the literature to discover what amount of blood could be carried by these implants to an ischaemic myocardium and by what mechanism was the anastomosis between the implant and the intramyocardial vessels effected. A paucity of bloodflow data and the almost total lack of coherent description of the development of the new pathways between the systemic and coronary circulation, prompted this study. The objects of this study were:-

1. To find out whether there was a flow of blood in the internal mammary artery, immediately after implantation.

2. To measure bloodflow in long-term implants.

3. To discover whether the bloodflow in long-term implants could increase with time to the level of bloodflow present in the anterior descending branch of the left coronary artery.

4. To determine, by microscopy, the nature of the changes within the implant and of the connections between implant and the coronary circulation.

5. To visualise, by angiography, the extent of the connections between implant and the coronary vasculature.

SECTION I.

METHODS AND PROCEDURES.

EXPERIMENTAL METHODS AND PROCEDURES

In all the experiments described in this study, the same basic procedure was adopted for operative technique and measurements of bloodflow. A standard method for the production of high quality single film angiograms of the implants and coronary vessels was evolved.

Material

All operations and experiments were carried out on mongrel dogs weighing 15 to 20 Kg. The dogs were unselected except for the exclusion of unhealthy, aged or those of obvious nervous disposition.

Anaesthesia

Anaesthesia was induced with intravenous thiopentone (20 mg./Kg body weight). A cuffed endotracheal tube was inserted and connecte to the outflow pipe of a standard Starling respiratory pump set at twenty-four cycles per minute. A Boyle's anaesthetic apparatus was connected to the inflow pipe of the Starling pump. Throughout the operation a 4:1 mixture of nitrous oxide and oxygen, together with 0·5% halothane was administered to the dog. It was rarely found necessary to alter the anaesthetic regime during the operation, but if a temporary increase in depth of anaesthesia were required the halothane was increased to 1% for a few minutes until stability was achieved and then decreased to 0·5% again. During all bloodflow measurements, the halothane was kept at 0·5%, since doses above this level tended to depress blood pressure. At the end of each survival operation, the animal was disconnected from the anaesthetic gases and allowed to breathe spontaneously without assistance prior to extubation. Secretions were removed from the trachea and oro-pharynx by suction and the endotracheal tube removed. Small doses of pethidine (1mg. per Kg. body weight) were administered intramuscularly if required during the first twenty-four hours post-operatively. In addition each animal received at the end of each survival operation, 1 Mega unit of long-acting penicillin.

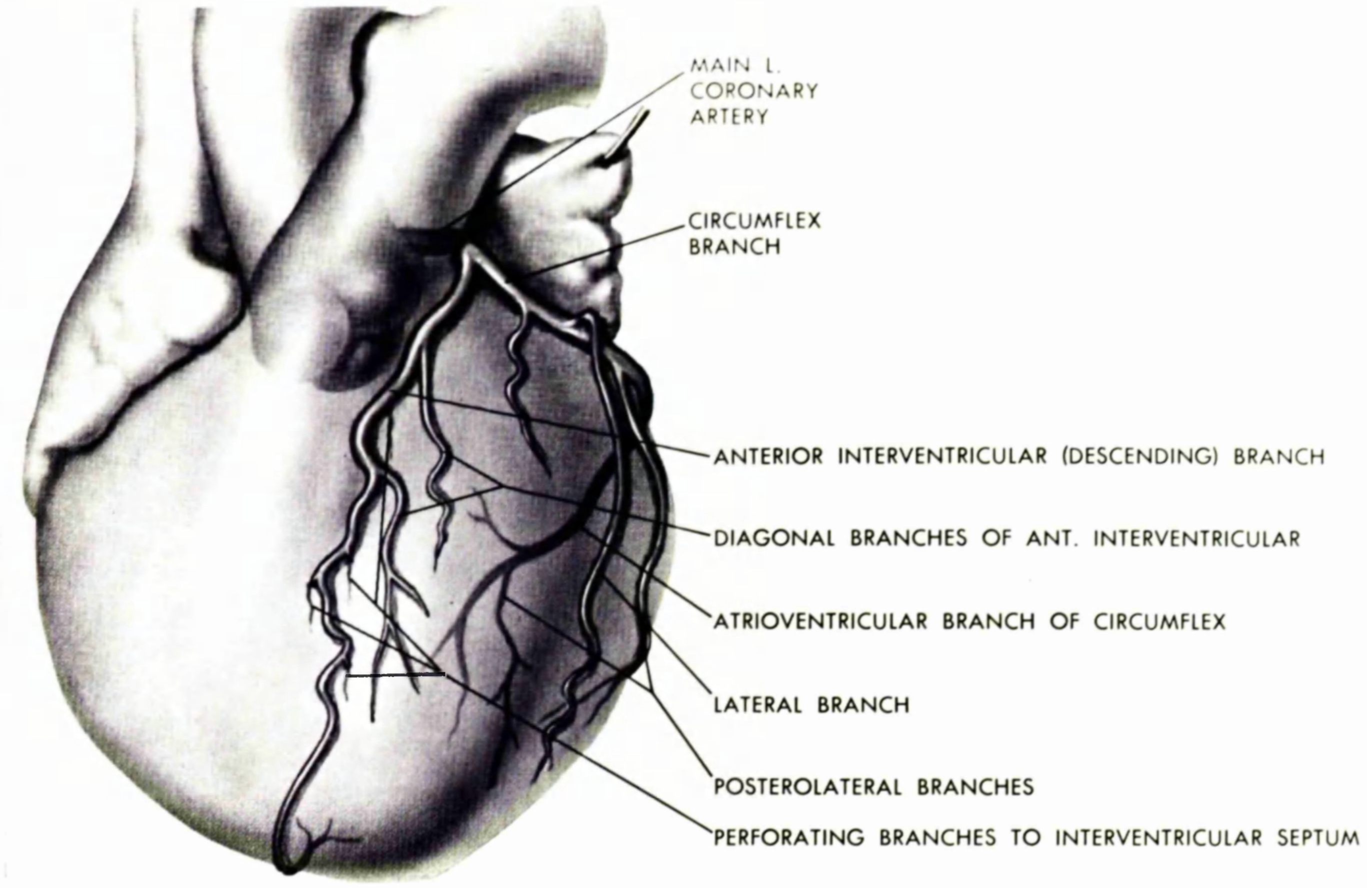
The Anatomy of the Internal Mammary Artery

This artery arises from the first part of the subclavian artery and inclines medially and then distally for a short distance beneath the posterior parietal pleura, before running anteriorly in a fold of pleura, lateral to the thymus gland, to the lateral edge of the sternum where it descends to the level of the seventh interspace and terminates in two or three vessels, one of which anastomoses with the superficial epigastric artery, the others with branches of the phrenic artery. Throughout its substernocostal course, the artery gives off branches on its antero-medial side at the level of each intercostal space. These side branches connect with the intercostal arteries and also send small branches through to the structures lying on the superficial aspect of the rib cage.

The Anatomy of the Anterior Descending Branch of the Left Coronary Artery

The left coronary artery in the dog divides after about 1 to 2 cm into the circumflex branch and the anterior descending branch. This latter branch supplies almost the whole of the anterior wall as well as most of the inferior surface of the left ventricle, (Fig. 1 In 48% of dogs the anterior septal artery has its origin from the anterior descending branch (Miller, Christensen and Evans, 1964). Therefore in these dogs the anterior descending branch of the left coronary artery supplies 75% of the interventricular septum of the dog heart.

The anterior descending branch marks the position externally of the inter-ventricular septum, separating the surface of the left ventricle from that of the right ventricle. The artery is characterised in the dog heart by the numerous branches which spring from it on its left side and run down diagonally across the surface of the anterior wall of the left ventricle. The terminal branches fan out and arborise freely at the apex of the left ventricle with the terminal branches of the circumflex branch of the left coronary artery. In some dogs the anterior descending branch ends high up on the ventricular surface about 1 cm. from its origin,



<u>Figure 1</u>

The distribution of the large branches of the left coronary artery.

terminating in numerous long branches which fan out over the anterior surface of the left ventricle, the phrase 'horse's tail' has been used to describe this arrangement.

The Optimal Level for Ligation of the Anterior Descending Branch of the Left Coronary Artery to produce Ischaemia of the Anterior Wall of the Left Ventricle without Heart-Block

In this study the anatomy of the anterior descending branch of the left coronary artery is important in two respects, from its relationship to the position of the intramyocardial tunnel to be described later, and also from the optimal place to ligate the artery in order to produce an ischaemic lesion of the anterior surfac of the left ventricle without causing ischaemia (and therefore heart-block) of the interventricular septum.

From a detailed study of the anterior descending artery and its branches it was found that if the artery were ligated 2 cm. from its origin, then this produced the required ischaemic lesion of the anterior wall but did not cause heart-block. Using this 'rule of thumb', heart-block never occurred in any of the dogs operated upon, and no ischaemic lesions were observed in the interventricular septum in any heart at post-mortem examination. It is thus inferred that the anterior septal artery has its origin (if at all) from the proximal 2 cm. of the anterior descending artery in the dog.

Operative Procedure

In the survival experiments, sterile precautions were strictly adhered to, the operations carried out in a clean theatre, with sterile instruments, gowns and gloves. Immediately after anaesthesia was commenced, the dog's chest was shaved and prepared with a pHisohex wash, followed by an application of surgical spirit and finally of tincture of iodine. Sterile towels were draped over the animal except for the chest area.

The chest was opened through the fifth left intercostal space, from the left sternal edge to the anterior axillary fold. The skin incision was never more than four inches long even in the largest dogs. This provided an excellent exposure of the pericardium and the left pleural cavity. Bleeding was minimal in all animals and was easily controlled with electrocoagulation. The ribs were spread with a Price-Thomas retractor which gave full visualisation of the left subclavian artery and its internal mammary artery branch. The artery was then mobilised from the subclavian artery to its terminal division at the level of the seventh intercostal space. All side branches were coagulated well away from the parent artery to avoid thrombosis in the latter. The artery was left undivided at the distal end at this stage and checked at regular intervals for pulsation. The pericardium was opened, 0·5 cm. anterior to the left phrenic nerve from the left superior pulmonary vein to the apex of the left ventricle and the heart lifted forward out of the sac.

Production of an Ischaemic Lesion of the Left Ventricle

In those animals which were to receive a concomitant ischaemic lesion of the left ventricle, this was accomplished by ligation of the anterior descending branch of the left coronary artery, 2 cm. from its origin. The anatomy of this artery and the reasons for choosing this particular site for ligation are discussed above.

The anterior descending artery was dissected free from the overlying epicardium and fat and separated from the vein running alongside, over a distance of about 0·5 cm., centred on the site chosen for ligation. A 3-0 Mersilene suture was placed round the artery at this point and tied securely. In every dog in which this procedure was carried out, an ischaemic area appeared immediately on the anterior surface of the left ventricle. This area first showed as a bluish area which then quickly blanched.

The absolute dimensions of the ischaemic patch varied of course with the size of the heart but in comparable hearts, the ischaemic lesions were of similar extent. Each lesion began immediately distal to the site of the ligation and extended down to just above the apex of the left ventricle which itself was rarely found to be infarcted, probably because of its supply from the circumflex branch of the left coronary artery. The medial boundary of the devitalised area was at the junction of the anterior walls of the two ventricles; the right ventricular wall was never observed to be involved in the lesion. Laterally, the ischaemic area extended to include most of the anterior wall of the left ventricle. After about fifteen minutes, the original ischaemic area seemed to shrink a little in size, probably due to collateral vessels from the other coronary arteries opening up. Thus using this simple technique, an ischaemic lesion was produced, severe enough to show a histological picture observed weeks or months later of infarction of ventricular muscle, yet which did not result in a single incident of heart-block or intra-operative death.

Implantation of the Internal Mammary Artery within the Left Ventricular Myocardium

The internal mammary artery was transected at the level of the

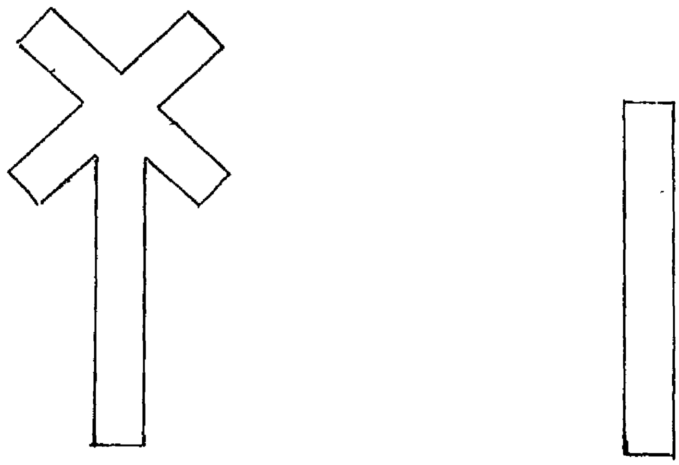


Figure 2

The two types of tunnel constructed within the myocardium in this study.

seventh intercostal space and a small rubber-shod bulldog clamp applied to it. A long 3-0 Mersilene suture was passed through a lip of the cut distal end of the artery and left untied.

A tunnel was then fashioned within the myocardium of the anterior wall of the left ventricle. This is shown diagramatically in Figure 2. The epicardium was incised transversely to a length of 0·5 cm., 2 cm. from the apex of the left ventricle and 1 cm. from the interventricular groove. A second similar epicardial incision was made 3-4 cm. (depending on the size of the heart) proximally on the left ventricle, again 1 cm. from the interventricular groove. The apex of the heart was tipped forward and a pair of straight mosquito forceps introduced through the distal incision into the mid-thickness of the anterior wall of the left ventricle and passed proximally to emerge through the upper incision. The forceps were now opened and the long ends of the Mersilene suture attached to the internal mammary artery grasped, pulled through the tunnel and out of the distal end.

The bulldog clamp on the artery was then released to ensure that blood was flowing freely and at pressure from its distal cut end. If there were any obstruction to flow at the end of the artery due to the adventitia having been pulled into the opening, this was dissected free. The artery was now gently pulled into the tunnel by the thread protruding from the distal end, until 2·5 cm. of its length (3·5 cm. in the larger hearts) were within. During the implantation procedure, the artery was left bleeding from its lower end, so that once it was within the myocardium, blood issued from the distal end of the tunnel. If this did not occur, the artery was withdrawn to ensure continuing patency. The distal end of the tunnel was closed with two fine sutures, one of which was also tied securely to the protruding thread, to anchor the implant within the tunnel. This was usually enough to haemostatically seal this distal end. Attention was now paid to the proximal end of the tunnel which occasionally required a single fine stitch placed laterally to effect haemostasis, great care being taken not to prejudice the artery as it passed into the mouth of the tunnel. At the end of this procedure the implant passed directly down from the left subclavian artery to the heart without tension, and without being tethered in any way to surrounding structures (Figure 4).

The tunnel itself was seen to lie within the area of ischaemia and the implant palpated to ensure a strong and continuing pulse. Inspection of the surface of the left ventricle did not reveal the presence of bruising in any of the animals. Haemostasis was

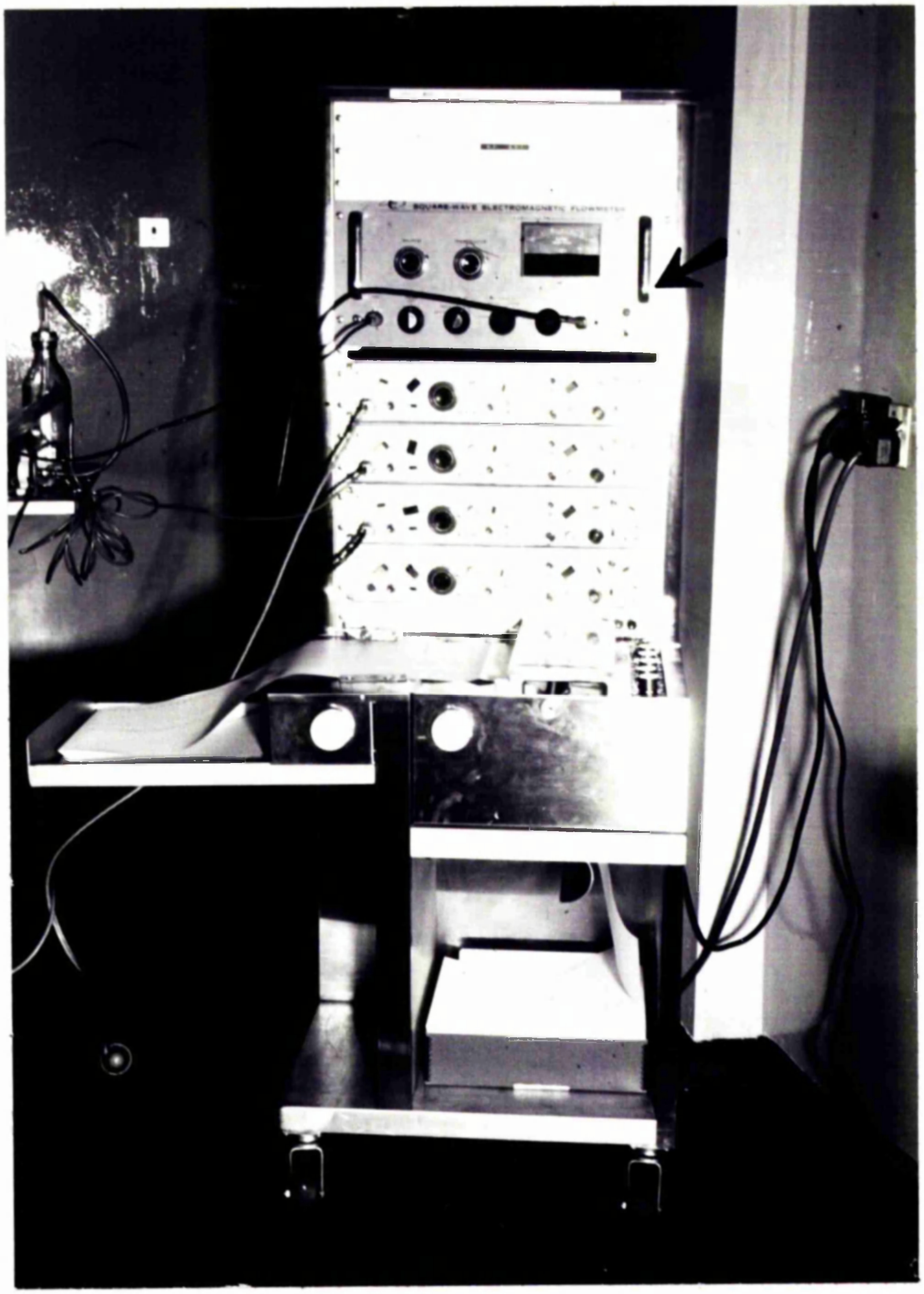


Figure 3

The electromagnetic flowmeter (arrowed) connected to the Grass recorder assembly.

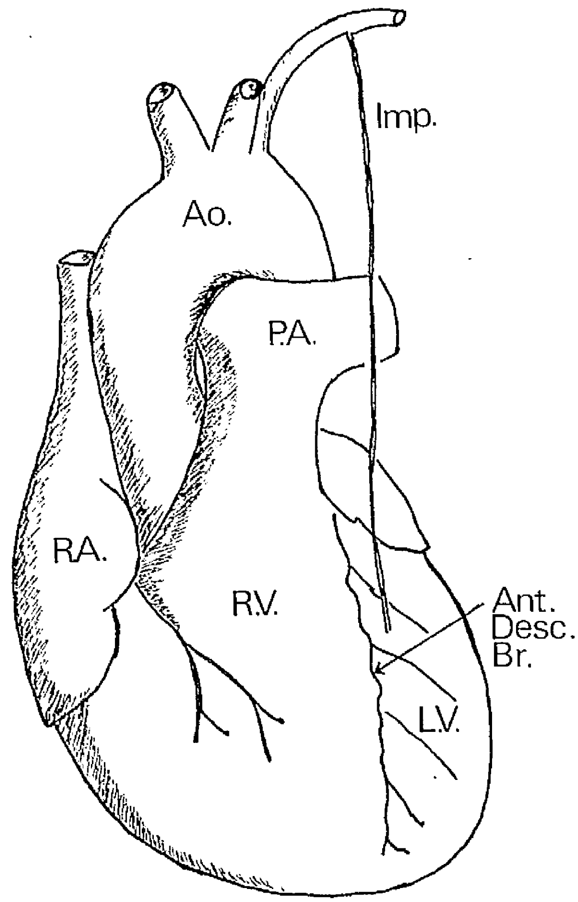


Figure 4

A drawing showing the position of the internal mammary artery in relation to the anterior descending branch of the left coronary artery as the former vessel passes down to the intramyocardial tunnel.

secured and measurements of bloodflow made on the implant and pulmonary artery as described below. The heart was replaced within the pericardial sac, the edges of which were now lightly approximate with interrupted sutures. Prior to closing the chest, the lungs were inflated and attention paid to the position of the upper lobe in relation to the implant which had been placed anterior to th lobe. All air was expelled from the chest cavity by full forced inspiration and the chest closed in layers without drainage. Only one dog in the entire series developed a loculated pleural effusion which had to be aspirated. Sutures were removed after two weeks. One dog developed a wound infection which healed after wound toilet was carried out and antibiotics given. All dogs in the entire series were ambulant and drinking within twenty-four hours of the operation.

Construction of Intramyocardial Tunnel with Side Branches

The main tunnel was fashioned as described above for the single tunnel implantation, but in addition the forceps were re-introduced into the myocardium at the distal end of the tunnel pointing towards the apex of the heart. The instrument was then angled at 45° to the main direction of the tunnel, first to the lateral side, and in the mid-thickness of the myocardium, a tunnel was made 2 cm. long, with a blind ending. This was repeated on the medial side of the main channel so that the tunnel system at this stage resembled the letter 'Y' (Figure 2). Two further blind ended tunnels each 2 cm. long were constructed from the main tunnel, but in the opposite directions, so that the system finally resembled a cross with a long centre stem (Figure 2).

The internal mammary artery was then introduced into the 'stem' of the system in the manner described above and secured. Blood from the implanted artery would theoretically not only flow into the distal part of the main tunnel but also into the four side arms.

Electrocardiographic Recording

The electrocardiograph was obtained by using very small needles as electrodes. Sterile needles were chosen and placed subcutaneously in each of the fore limbs and the right hind limb, the E.C.G. wires were then plugged into the ends of the needles. The leads were connected to the E.C.G. preamplifier in the Grass recorder (Figure 3). The electrocardiograph was continuously displayed on paper during the whole procedure.

Measurement of Blood Pressure

A small purse string suture was placed on the anterior surface of the thoracic aorta and a thin polythene catheter introduced through a small stab-wound in the middle of the suture and pushed up to the aortic arch. The catheter was connected via a two feet polythene manometer line to a Statham transducer. The system was intermittently perfused with heparinised-saline (0·9%) from a reservoir connected to the manometry line through a three-way tap. The transducer was calibrated from a mercury sphygmomanometer and connected to the multichannel Grass recorder for continuous display. At the end of the procedure, the catheter was removed and the purse string suture tightened to effect haemostasis.

Measurement of Bloodflow by the Electromagnetic Flowmeter Technique

The principle of the electromagnetic flowmeter technique for measuring the flow of blood within vessels is based on Faraday's law of electromagnetic induction. Faraday demonstrated electromagnetic induction in both solid and liquid conductors. Young in 1920, detected an induced electromotive force in a river due to the motion of the water through the earth's magnetic field. The first electromagnetic measurements of velocity however were made by Williams in 1930 in solutions of copper sulphate, but he did not include the measurement of flow in his experiments.

The application of the electromagnetic induction phenomenon to the study of bloodflow was first mooted by Fabre in 1932 but was in fact carried out by Kolin (1936). Kolin's work represents the real beginning of the era of measurement of bloodflow by the electromagneti induction method. The same method was described independently by Wetterer in 1937. Initially the procedure was to produce a constant magnetic field within the vessel using either an electromagnet or a permanent magnet. The magnet can be constructed so that it fits the outside of the vessel wall snugly and at the same time generates a uniform magnetic field of high strength across the whole artery.

Signals of severe millivolts can be obtained from the aorta and pulmonary artery using the method. Since the diameter of the vessel is known by choosing the electromagnetic probe (the magnet) which will just fit without producing distortion, the velocity measurement can be translated to a flow rate by application of relationship

$$\text{Instantaneous Flow} = \text{Velocity} \times \pi r^2$$

The main drawback to the use of direct current to energise the electromagnetic field lies in its ability to disadvantageously cause electrode polarization. To circumvent this, alternating current was used to produce an alternating electromagnetic field and this problem receded. (Einhorn, 1940, Thurlemann, 1941). Different shapes of alternating waves have been used including the sine wave, square wave, and trapesoid wave, but only the first two mentioned have been used extensively.

The use of the alternating current to produce an alternating magnetic field within the vessel means that the flow signal picked up by the probe is an a-c voltage in phase with the a-c magnetic field strength. The amplitude of this signal voltage can be shown mathematically to be proportional to the average instantaneous flow velocity and thus to flow rate. Since a signal is delivered which is amplitude modulated it can be used to great advantage with the use of a-c amplifiers which allow greater gain and are much more stable than d-c amplifiers. One great advantage of this is that very low flow signals can be recorded and so with appropriately designed probes, flow rates can be measured in very small blood vessels.

The main disadvantage with the sine-wave method is that a specious voltage is induced by the alternating magnetic field which forms a 'transformer loop' between the electrodes, the electrode leads and the blood vessel. This transformer E.M.F. unless cancelled, augments the signal from the induced voltage and gives exaggerated estimates of velocity and flow. The spurious signal can be cancelled electronically but only with difficulty and with extra equipment built into the flowmeter. For this and other less important reasons the a-c sine-wave electromagnetic system has been largely abandoned for the present, although some models are still available commercially.

The Square Wave Electromagnetic Flowmeter

This type of flowmeter was introduced by Denison, Spencer and Green (1955) and further developed by the first two authors (1960). The square wave alternating current has the great advantage that during the 'horizontal' components of the wave form, the field strength is constant and thus no transformer loop is formed with resulting spurious signal. Thus the a-c square wave system behaves in its horizontal phases like a direct current flowmeter but also functions as an alternating current flowmeter with the advantages, mentioned above, of that type.

During each cycle therefore, two signals of opposite polarity are picked up from the blood stream by the probe surrounding the vessel, amplified and passed through a discriminating demodulator. The problem of eliminating electrocardiograph interference from the flow signal is overcome by using a high carrier frequency. During the short phase of reversal of the magnetic field, there is a tendency as in a-c sine wave systems for a transformer E.M.F. to develop, but this can be eliminated by switching off the amplifier during this short period. The signal from the flowmeter can be easily recorded by a direct writing device. The apparatus used in this study was the Carolina Square-wave Electromagnetic Flowmeter connected to the Grass Multichannel Recorder (Figure 3).

Calibration of the Flowmeter and Probes

The electromagnetic flowmeter no matter which principle is used, constant or alternating magnetic fields, delivers linear calibration curves and equal sensitivities with opposite signal

<u>Figure 5</u>

The electromagnetic flow probes.

directions both to forward and reverse flow. Using flow models many groups of workers have shown this linear relationship between bloodflow and the electrical signal as well as the high reproducibility of the results (Kolin, 1936; Wetterer, 1937 and 1943; Westersten, Herrold and Assali, 1960; Thuran and Cohen, 1963; Scher, Weigert and Young, 1953; Engell and Lauridsen, 1966; Cappelen and Hall, 1967).

The flow probes used in this study (Figure 5) were calibrated by the manufacturer (Carolina Medical Electronics) but it was recognised that the use of such standard calibration factors might lead to inaccuracies of measurement. Each probe used was therefore again calibrated in the laboratory using excised arteries of the appropriate diameter interposed between two lengths of rubber tubing of similar diameter and connected to a pump of known flow rates. Each probe in turn, was placed on the middle of the arterial segment and connected to the flowmeter. Blood was pumped through the system at different flow rates and a calibration factor calculated for each probe. The flow rate was checked by measuring the quantity of effluent blood from the system. The Carolina flowmeter, itself, has a calibration accuracy of ± 5%, claimed by the manufacturers.

Measurement of Bloodflow

To measure bloodflow through a vessel, a flow probe was chosen which fitted snugly around it. For pulsatile flow the lumen circumference of the probe should be a little less than the circumference of the blood vessel, but no more than 20% less. The probe was applied to the vessel and connected to the flowmeter. For good electrical conductivity the vessel wall was kept wet with frequent applications of physiological saline. The flowmeter which had been previously balanced (and the recorder sensitivity adjusted to obtain a convenient deflection) was then 'zeroed'. In establishing zero flow in the implant and coronary artery, these vessels were temporarily occluded above and below the probe. In the case of large vessels such as the pulmonary artery this method was not physiologically practicable, and for these, zero flow was achieved by placing the large probe in a beaker filled with saline, turning the electromagnet off and resetting the output control to zero. Frequent zero readings were obtained during each experiment. It was found on checking the apparatus that zero drift was not a major problem, the amount of drift was found to be 1 mm. every ten minutes when the recorder sensitivity was 50 mm. per volt (i.e.2%). Since recordings were made in most cases for only one minute at a time, this source of error which can be difficult to deal with in many electromagnetic flowmeter systems was minimal with the apparatus used.

The bloodflow in mls per minute could be read off directly from a meter on the equipment used in this study. In addition, however, the bloodflow during a single flow pulse in either the implant, coronary artery or in the pulmonary artery could be measured from the flow patterns made by the Grass recorder. In the experiments involving the calculation of resistance to flow during the diastolic period of the cardiac cycle, the mean flow and the mean aortic pressure during diastole were measured. Since flow in diastole could not be measured directly by the flowmeter and the mean pressure during diastole varied a little at successive pulses, the only way in which the most accurate assessment of resistance to flow could be made, was to measure mean bloodflow in diastole during a single cardiac cycle, and the mean blood pressure during diastole in the same cardiac cycle. Mean diastolic flow was therefore measured from its recorded height above the base-line, with the recorder calibrated to a given mean flow per centimetre deflection of the pen.

Calculation of Volume Bloodflow from a Single Flow Pulse Wave

To calculate how much blood has passed the flow probe during a given single cardiac cycle and express it in terms of mls per minute, an equation has been formulated by the manufacturers of the flowmeter. By the use of this method, a rough check could be made from the recorded patterns of flow, during periods of stable flow conditions, on whether the flowmeter was giving accurate integration readings. The method could also be used to calculate flow during any cardiac cycle if this volume flow had to be related to some other parameter during the same period of time. The volume flow during a single cardiac cycle is given by the formula:-

$$V = \frac{F \times A \times M \times Fa}{0{\cdot}1 \times S \times G}$$

(Where V = volume flow; F = actual probe factor; A = area under the recorded flow curve in square mm.; M = multiplier control setting Fa = arbitrary setting of probe factor control on flowmeter; S = paper speed in mm. per minute; G = recorder sensitivity in mm. per volt).

To convert this to a flow per minute it is multiplied by the heart rate per minute or in other words the paper speed per minute divided by the R-R interval (from E.C.G.) in mm.

Substituting into the first equation, the final equation reads:-

$$\text{Volume flow per minute} = \frac{10 \times F \times A \times M \times Fa}{G \times (R\text{-}R)}$$

Example:-

If F = 120

A = 200 sq. mm.

M = 1

Fa = 1

G = 25 mm. per volt

R-R interval = 10 mm.

$$\text{Then volume flow per minute} = \frac{10 \times 125 \times 200 \times 1 \times 1}{25 \times 10}$$

$$= 1{,}000 \text{ ml.}$$

SECTION II.

BLOODFLOW THROUGH THE NEWLY IMPLANTED INTERNAL MAMMARY ARTERY.

INTRODUCTION

The concept that blood can flow immediately through a vessel whose cut distal end has been implanted within the myocardium without any attempt to anastomose it to the coronary circulation, is a difficult one. It is contrary, it seems, to normal surgical experience and indeed to commonsense. And yet, that this could occur was seriously put forward by Vineberg (1958) who proposed that immediate bloodflow through internal mammary implants was achieved because of the sinusoidal structure of the myocardium. This network of endothelium-lined spaces between the muscle fibres in the heart was first discussed by Wearn, Mettier, Klumpp and Zschiessche (1933) and is crucial to the hypothesis that blood can flow through the graft and myocardium from the moment of implantation.

Doubts have been cast on the presence of immediate flow in these implants by several studies in recent years. Using a right-heart preparation, Alshamma, Criollos and Roe (1968) failed to establish the presence of flow in internal mammary grafts immediately after implantation. Myocardial clearance of Kr^{85} and Xe^{133} was used by Seeman (1968) who showed that immediately following implantation, the bloodflow recorded in the surrounding area, while the arterial graft was open, did not differ significantly from the value obtained during clamping of the vessel. Several angiographic studies have been made on the newly implanted vessel (Bellman and Frank, 1958; Pearl, Goseph, Citret and Kallemeyn, 1959; Maruyama, Warren, McCombs, Vickery and Brener, 1966). All of these workers failed to demonstrate filling of the intramyocardial part of the vessel immediately after implantation.

Despite this mass of evidence for immediate cessation of flow in the implant, other careful studies have indicated that flow continues, but at a reduced level, following implantation. A small mean forward flow was observed by Provan, Hammond and Austen (1966), using a non-cannulating electromagnetic flowmeter. Aranow, Covelli and Norman (1967) found a significant increase in myocardial blood immediately after implantation using the radioactive gas clearance method. Direct measurement of the coronary sinus return was made by Suma, Hammond, Buckley and Austen (1969) who also confirmed an increase in myocardial bloodflow occurring immediately after implantation of the internal mammary artery.

As has been discussed, great care must be taken to ensure that the internal mammary artery does not become occluded by thrombus, following prolonged clamping prior to implantation; or that the adventitial covering does not block the distal cut end of the vessel. If one of these events should occur then, of course, there will be no flow after implantation. In all the papers discussed above, no mention was made of whether the vessel was definitely patent throughout its length. Small differences in surgical technique at this initial stage can make all the difference to the subsequent findings, no matter what method of bloodflow measurement is used. It is possible that some of the workers reporting no flow in the grafts obtained these results because of lack of sufficient attention to surgical detail.

The purpose of the investigations described in this section was to attempt to clarify the picture presented by this contradictory evidence on whether or not blood flows in these grafts immediately following implantation.

In addition, a further study was undertaken in which four side channels connected with the main intramyocardial tunnel were fashioned. This was done on the assumption that the 'run-off' of blood from the implant through the myocardium would be augmented by providing access to a greater number of sinusoids.

Methods

A full description of the anaesthetic principles employed, plus the technique of implantation of the internal mammary artery into the myocardium together with the method of producing acute myocardial ischaemia by ligation of the anterior descending branch of the left coronary artery, is given in the Procedures and Methods section. A total of twenty-four dogs were studied, and divided into two groups of twelve each. In the first group, each dog received an internal mammary implant into the anterior wall of the left ventricle utilising a single intramyocardial tunnel in the myocardium, together with ligation of the anterior descending coronary artery. In the second group, the implant was introduced into a main tunnel from which four short extensions were made (Figure 2). Coronary artery ligation was carried out as in the first group.

The bloodflow through the implanted mammary artery was measured in both groups with the electromagnetic flowmeter technique as previously described. A snugly fitting probe was placed on the

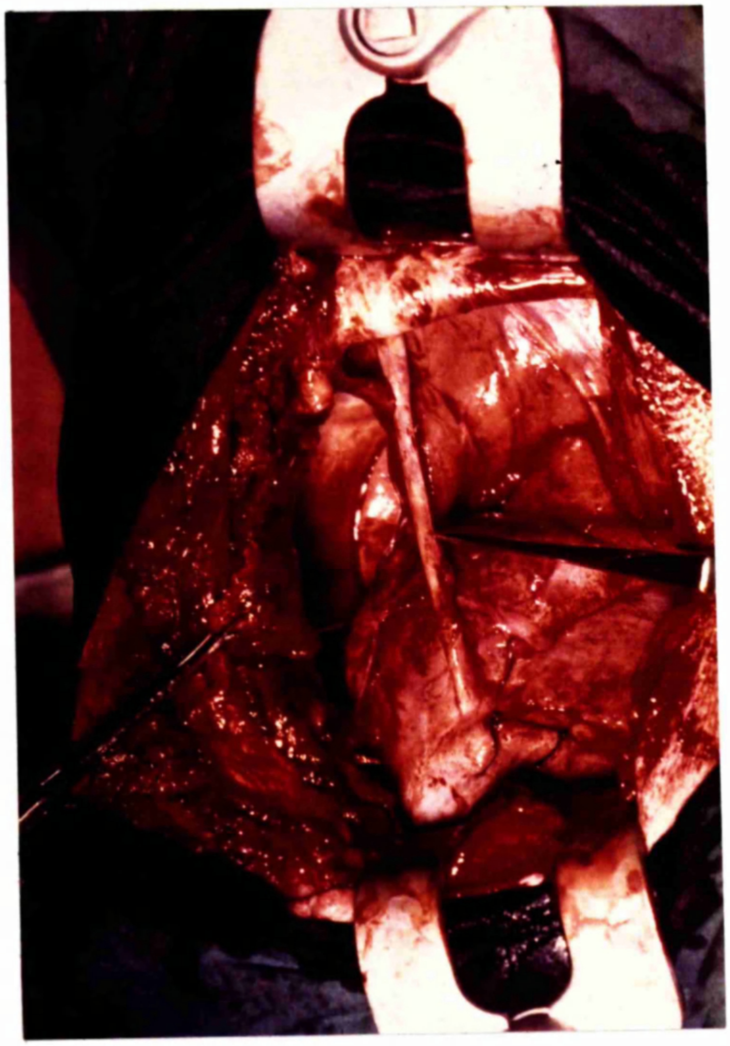


Figure 6

The internal mammary implant passing down to the left ventricle.

artery 5 cm. from the point of implantation (Figure 5). Repeated volume flow and mean flow measurements were then made with frequent zero readings. Cardiac output measurements were obtained with the electromagnetic flowmeter in both groups of dogs by placing a suitably sized probe round the pulmonary artery close to the pulmonary valve (Figure 6). Pulmonary artery bloodflow (Figure 7) was measured in preference to aortic bloodflow for two reasons. First, since coronary artery flow removes approximately five per cent of the bloodflow from the aorta during diastole, aortic flow is not a true indication of cardiac output. Secondly, the pulmonary artery is much more accessible and requires less dissection posteriorly for the accurate positioning of the flow probe, than the aorta. Details of establishing true baselines during measurement are discussed in Section I. Since the flowmeter apparatus allowed measurement of only one flow at any given time (single channel) it was not possible to achieve simultaneous bloodflow in both the implant and in the pulmonary artery. The practice adopted was to position the probes round the implant and pulmonary artery and leave these in place attached to their respective extension cables. When the implant flow had been measured the extension cable from that probe was disconnected from the flowmeter and the other cable immediately plugged in place. In this way the cardiac output could

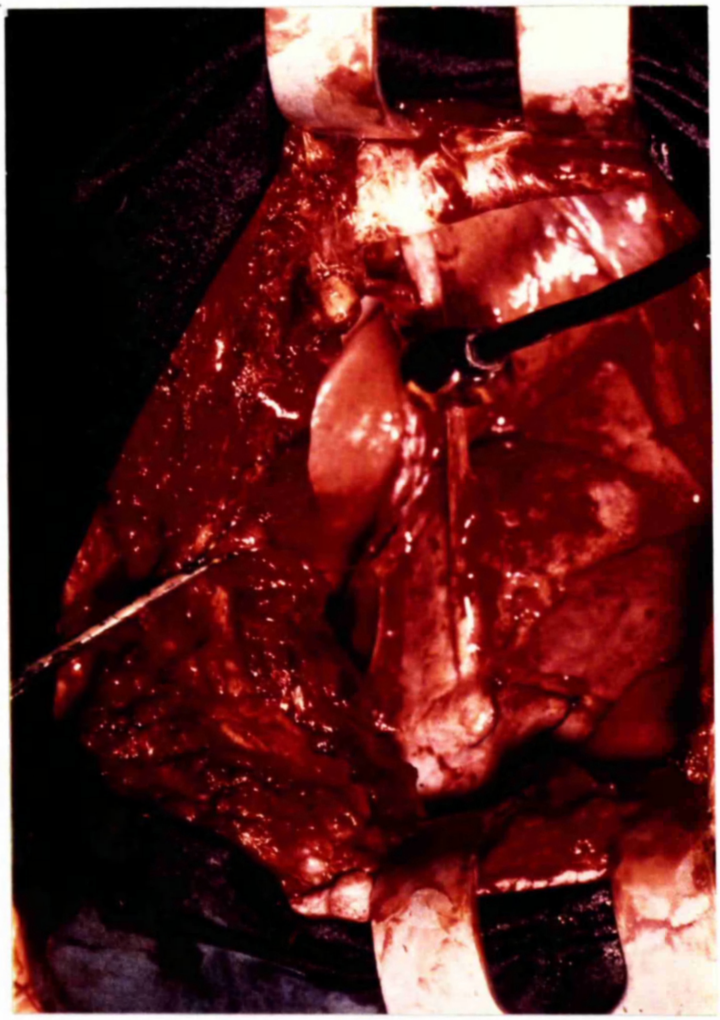


Figure 7a

Flow probe on the internal mammary artery.

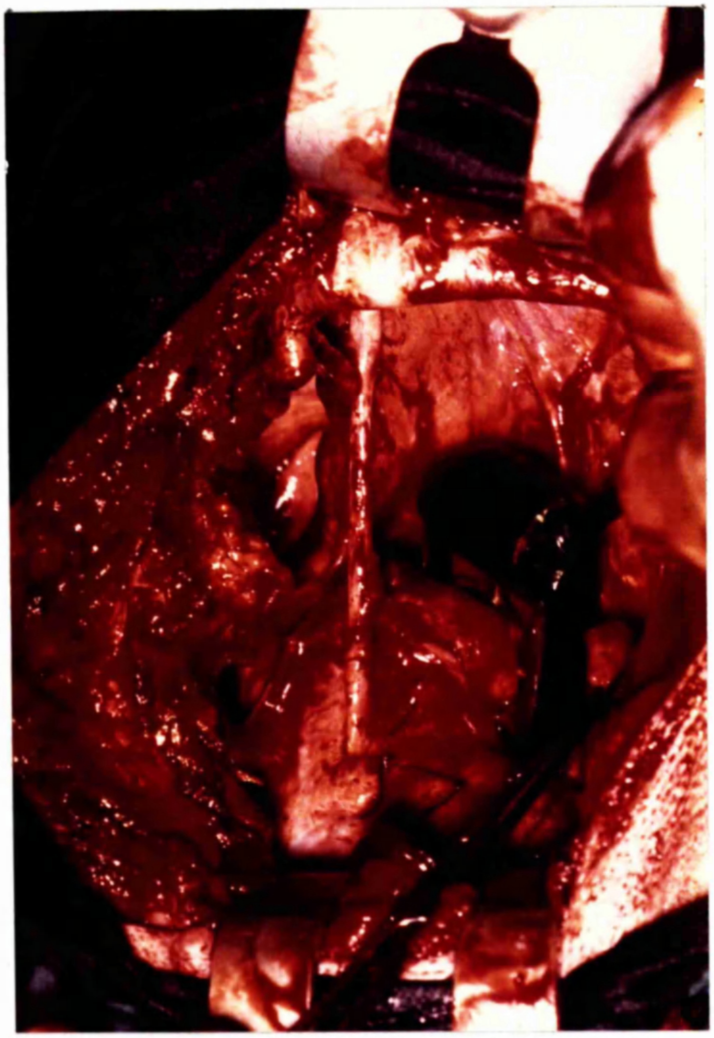


Figure 7b

Flow probe on the pulmonary artery.

be measured without delay.

During all flow experiments the electrocardiograph and blood pressure were monitored continuously. Pulsatile and mean bloodflow in both the implant and pulmonary artery together with blood pressure and the electrocardiograph, were recorded on the Grass Polygraph Multichannel Recorder (Figure 3). Blood pressure was monitored by introducing one end of a length of fine polythene tubing into the arch of the aorta and attaching the other end to a Statham strain-gauge transducer; the tubing was flushed at regular intervals with heparinised physiological saline solution from a gravity reservoir. The electrocardiograph was recorded from needle electrodes placed subcutaneously in the limbs. In addition, measurements of arterial pH, pO_2 and pCO_2 were carried out at intervals to ensure metabolic and respiratory stability.

Results

Flow Patterns in the Newly Implanted Internal Mammary Artery

The flow curves obtained from the new implant are shown in Figure 8. The observed pattern was pulsatile in all experiments. In all twenty-four implants the main component was a forward one. In several dogs there was also a small but definite reverse flow wave.

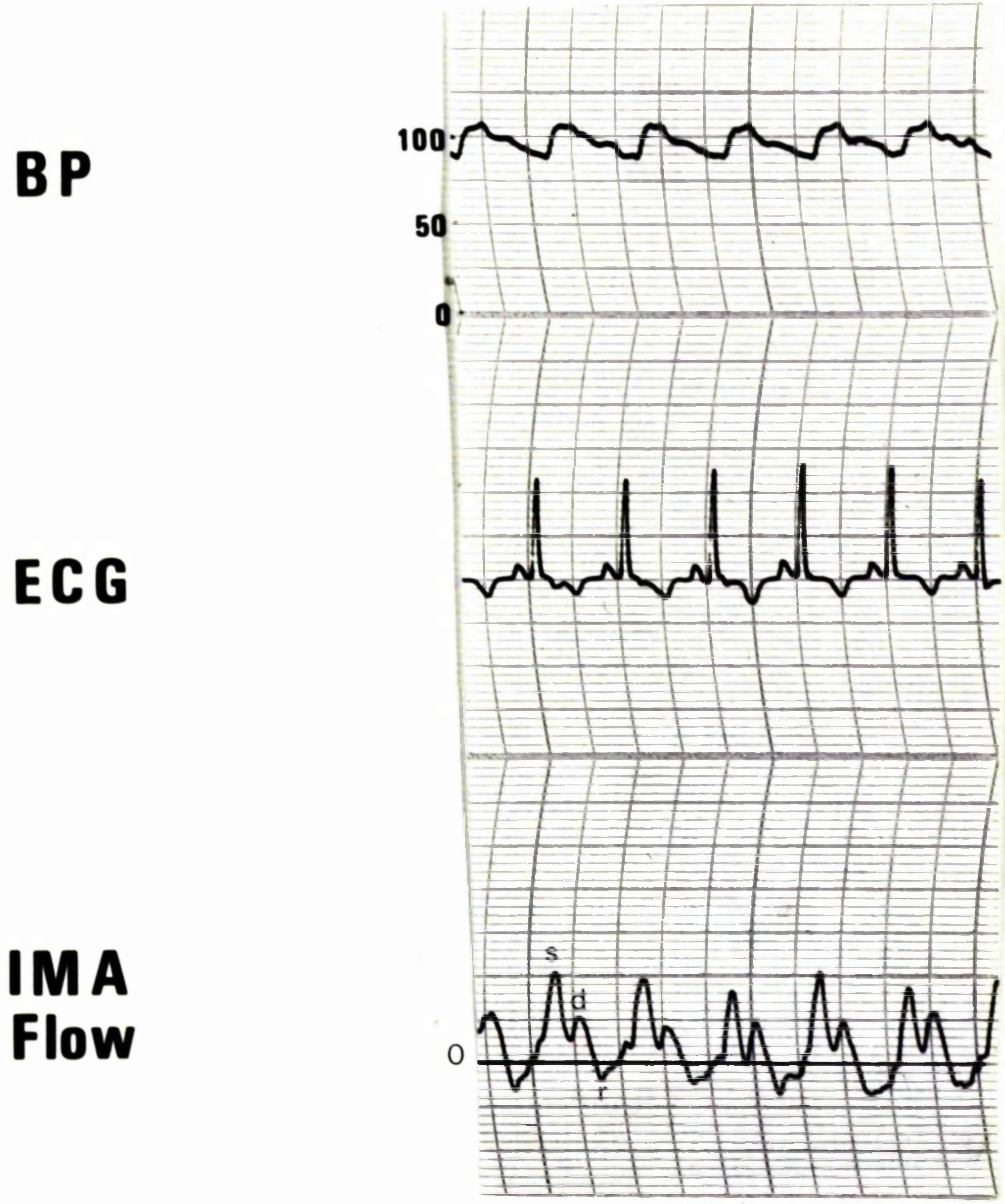


Figure 8

The flow pattern from the internal mammary artery immediately after implantation, showing the systolic (s) and diastolic (d) components of forward flow with a reverse flow wave (r).

Systolic and diastolic components could be distinguished in the forward wave; these corresponded to the onset and duration of these two phases of the electrocardiograph. These two parts of forward flow in the implant were close together and indeed were often conjoined (Figure 9). This contrasted with the flow pattern in the intact internal mammary artery before dissection from the chest wall, in which the systolic and diastolic components were always distinct and separate (Figure 10). In the first group of twelve dogs (the single-tunnel group) in addition to the total forward and reverse flows which will be discussed later (Table 1) the volume flow in systole and diastole were each calculated separately from the flow recordings. Table 2 shows the results obtained for each of these two phases of the cardiac cycle in mls per minute and also as a percentage of total forward volume flow. In five implants, the systolic flow was less than 40% of the total forward volume flow, in three others it was between 40 and 60% whilst in the remaining four it was greater than 60%. The average figures for systole and diastole were 47·3 and 52·7% respectively. Thus, taking the twelve implants in this group as a whole, the two components of flow were of about equal volumes.

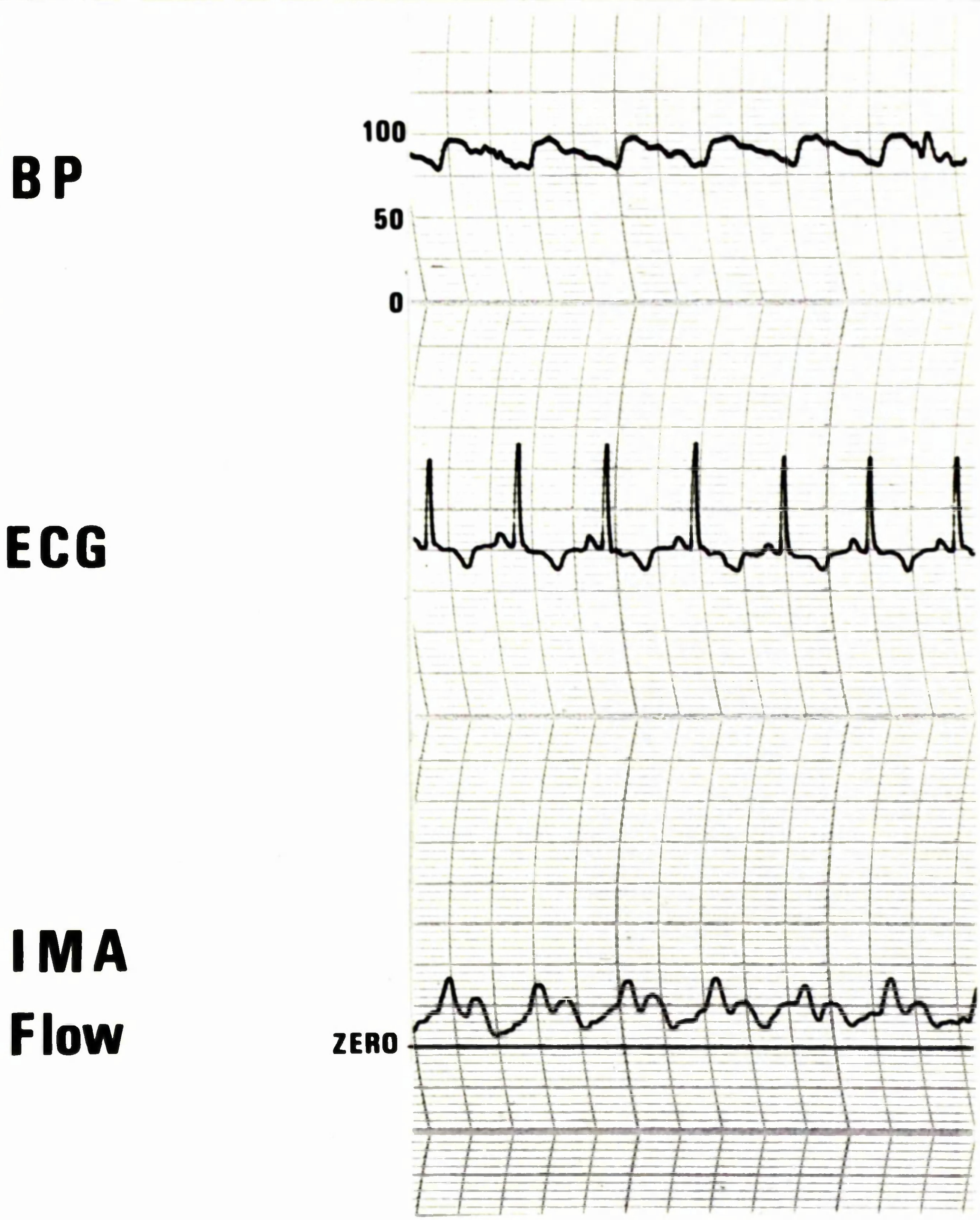


Figure 9

Flow pattern from the internal mammary artery immediately after implantation showing the systolic and diastolic flow components less clearly separated with no reverse flow phase.

Figure 10

Flow pattern from the internal mammary artery before its dissection from the chest wall. The systolic and diastolic components of forward flow are well separated and distinct.

Figure 11

Pulsatile flow pattern from the internal mammary artery 14 weeks after implantation.

Flow Measurements in the Single-Tunnel Group

Forward Volume Flow

All grafts in this group had a measurable flow of blood from the moment of implantation which varied in the twelve dogs from 3·10 to 18·71 ml. per minute with an average of 9·47 ml. per minute (Table 1). Three implants had a forward flow of less than 5 ml. per minute, three were between 5 and 10 ml. per minute, four between 10 and 15 ml. per minute, whilst the remaining two were above 15 ml. per minute.

Reverse Volume Flow

A reverse flow was also observed in five of the twelve implants. This varied from 0·21 to 2·30 mls per minute. Expressed as percentages of forward volume flow, the reversed flow ranged from 1·6 to 74·2% in the five implants with an average of 32·9%. In the twelve dogs, the average reverse flow was 0·5 ml. per minute, which was 5% of the average forward volume flow.

The Proportion of the Cardiac Output carried forward through the Newly Implanted Internal Mammary Artery to the Myocardium

The cardiac output was measured in all twelve dogs in this first group, but three of these values had to be eliminated because of an artefact which was evident on the flow tracings from these

Dog	Forward volume flow (mls per minute)	Reverse volume flow (mls per minute)
1	5·45	0·00
2	10·13	0·00
3	7·24	0·00
4	3·10	2·30
5	3·33	1·36
6	18·71	0·00
7	6·50	1·33
8	16·60	0·00
9	10·89	0·00
10	14·60	0·00
11	12·80	0·21
12	4·23	0·85
Means	9·47	0·50

Table 1

Bloodflow in the internal mammary artery immediately following implantation into the ischaemic myocardium in twelve dogs.

Dog	Forward volume flow mls per minute	Forward flow (mls per minute)		Percentage of forward flow	
		Systole	Diastole	Systole	Diastole
1	5·45	4·32	1·13	79·2	20·8
2	10·13	3·43	6·70	33·8	66·2
3	7·24	4·10	3·14	56·6	43·4
4	3·10	0·74	2·36	23·5	76·5
5	3·33	2·17	1·16	65·1	34·9
6	18·71	5·05	13·66	27·0	73·0
7	6·50	1·62	4·88	33·2	66·8
8	16·60	8·01	8·59	48·2	51·8
9	10·89	6·62	4·27	60·8	39·2
10	14·60	9·60	5·00	65·8	34·2
11	12·80	4·00	8·80	31·2	68·8
12	4·23	1·84	2·39	43·5	56·5

Table 2

The systolic and diastolic components of forward volume flow in the newly implanted internal mammary artery in twelve dogs.

dogs, due to a faulty pulmonary artery flow probe. In the remaining nine dogs the cardiac output varied from 957 to 2,800 mls per minute. When the proportion of the cardiac output flowing through the implant was expressed as mls per minute per litre of cardiac output, the values varied from 1·2 to 15·6 (Table 3) with an average of 6·2 mls per minute per litre cardiac output.

Dog	Forward volume flow mls per minute	Cardiac output mls per minute	Proportion of cardiac output through implant mls per minute per litre cardiac output
1	5·45	1,886	2·9
2	10.13	2,126	4·8
3	7·24	2,026	3·6
4	3·10	1,340	2·3
5	3·33	2 800	1·2
6	18·71	1,200	15·6
10	14·60	1,751	8.3
11	12·80	957	13·4
12	4·23	1,318	3·3

Table 3

The proportion of the cardiac output carried by the newly implanted internal mammary artery to the ischaemic myocardium in nine dogs.

Initial Flow Measurements in the Multi-Tunnel Group

Forward Flow

The twelve grafts had a measurable blood forward volume flow immediately after implantation. This varied from 4·45 to 21·85 mls per minute with an average value of 12·23 mls per minute (Table 4). This was an increase of 2·76 mls per minute (29·1%) over the average immediate flow in the single-tunnel group. The average implant flow in this group per litre of cardiac output was 8·5 mls per minute, an increase of 37·1% over that of the single-tunnel group. The increase in forward volume flow in the multi-tunnel group over those in the single-tunnel group did not reach statistical significance. Nor was there any significant difference between the proportion of the cardiac output carried by the implant in the single and multiple tunnel groups of dogs.

Dog	Forward volume flow (mls per minute)	Cardiac output (mls per minute)	Proportion of cardiac output carried in implant (mls per minute per litre cardiac output)
55	21·85	1,604	13·6
56	14·05	1,424	9·8
57	15·38	2,041	7·5
58	19·49	1,095	17·8
59	7·68	1,119	6·9
60	13·56	1,415	9·6
61	7·00	1,749	4·0
63	5·40	1,610	3·3
64	11·37	1,284	8·9
65	11·45	1,615	7·1
66	4·45	1,904	2·3
67	15·10	1,400	10·8
Means	12·23	1,522	8·5

Table 4

Forward bloodflow and the proportion of the cardiac output carried by the newly implanted internal mammary artery in twelve dogs with ischaemia of the myocardium and extra side branches from the main intramyocardial tunnel.

Discussion

This study demonstrated that blood does flow through the newly implanted internal mammary artery into the myocardium and that it continued for at least one hour following implantation. With careful calibration of the flowmeter and frequent zero readings taken during the experiments, the possibility that these values were due to artefact was indeed remote. The flow wave patterns were smooth and reproducible, and did not have the contour of any known artefact. The mean value obtained for forward volume flow in the single-tunnel group of 9·47 mls per minute (for twelve implants) was higher than that of Provan, Hammond and Austen (1966) who observed an average mean flow of 5·2 mls per minute (range 1 to 15 mls per minute) in their ten dogs using a similar electromagnetic flow probe method, and the 2·0 mls per minute mean flow found by Di Giglia, Lazzara and Oschner (1969).

The flow pattern found in the internal mammary arteries immediately after implantation was pulsatile, confirming the observation of Provan, Hammond and Austen (1966). These workers also stated that their impression was (although they did not make actual measurements) that the diastolic component of forward flow was larger than the systolic component. This was not borne out when these were individually measured in this study; five of the twelve implants had a dominant diastolic component, four a dominant systolic component, whilst in the remaining three implants, the two components were about equal. A larger forward flow is expected during diastole since it is during the relaxed phase that blood moves through the coronary arteries into the heart, but in systole, forward bloodflow through the coronary arteries ceases because of the extremely high extravascular pressure and may in fact reverse temporarily. It is surprising therefore, that in some newly implanted arteries, the systolic component is the larger. This may occur because blood during systole flows into the space around the implant, which might not be completely compressed by surrounding traumatised myocardium. During systole in these dogs, blood may accumulate in a small pool within the myocardium and move into the spaces between the columns of muscle cells during diastole.

The drainage pathway of blood from the newly implanted internal mammary artery could not be expected to be from the implant directly to the coronary arterial system, at least not until vascular channels are formed between them. Since these vascular connections make their appearance only after several weeks have elapsed since implantation (see Section IV), another pathway must be postulated for blood entering the myocardium from the early implant. There seems to be no alternative at present, to the view that blood from the implant enters the endothelium-lined spaces between the columns of myocardial cells and hence to the venous system. This view is held by many workers in the field (Vineberg, 1967; Smith, Mobin-Uddin, Lombardo and Jude, 1967; Suma, Hammond, Buckley and Austen, 1969), and is supported by observations made in this study (Section IV). Since this initial flow of blood into the myocardium most probably enters the venous system without traversing the arterial circulation, it is doubtful whether it can be of any real value in terms of gaseous transport and nutrition to myocardial cells.

The mean volume implant flow of 9·4 mls per minute observed in the present study immediately after implantation was close to the mean value of 10·1 mls per minute found during the first ten weeks after implantation. During this ten week period there must be a gradual change-over from a passive circulation from implant through the myocardium to a more active circulation as anastomoses develop between the implant and the branches of the coronary arteries. Histological and angiographic evidence will be presented later in support of the view that the period before ten weeks is a most active one in the development of vascular channels between implant and the coronary arterial circulation (Sections IV and V). How long the 'passive' component of the circulation through the myocardium remains is not known, but presumably it decreases with time.

The addition of a number of side channels to the main intramyocardial tunnel did not significantly increase the flow in the newly implanted artery or the proportion of cardiac output carried by the implant. There was therefore no advantage in constructing additional tunnels connected to the main one.

Summary of Section II

The principle aim of Section II was to study bloodflow through the internal mammary artery into the ischaemic left ventricular myocardium, when implanted into a single conventional tunnel and also into a tunnel with four side branches. The following conclusions were reached:-

1. There was an immediate forward flow in all grafts in both groups (total of twenty-four dogs), which averaged 9·47 mls per minute in the single-tunnel group and 12·23 mls per minute in the multi-tunnel group. Flow was present in all implants throughout the operation.

2. The proportion of cardiac output carried through the newly implanted artery to the myocardium averaged 6·2 mls per minute per litre of cardiac output in the single-tunnel group and 8·5 mls per minute per litre of cardiac output in the multi-tunnel group.

3. There was no evidence of a statistical difference between the mean forward flow and also the proportion of cardiac output carried through the implants in the two groups. The construction of extra tunnels within the ischaemic myocardium therefore did not increase 'run-off' significantly.

4. An analysis of the flow patterns obtained from newly implanted arteries, showed that the flow was pulsatile, there was a dominant forward flow wave followed in some cases by a small reverse flow wave. The forward wave had two components, systolic and diastolic which were close together and often conjoined. The pattern of forward flow therefore differed from that seen in the internal mammary artery before its dissection from the chest wall. Measurement of flow in each of the two components of the forward wave did not reveal a consistently dominant diastolic flow phase.

Possible reasons for these observations are discussed and comparisons made with the findings of other workers.

SECTION III.

BLOODFLOW IN THE LONG-TERM IMPLANT, THE PROPORTION OF CARDIAC OUTPUT CARRIED, THE PERFUSION OF THE MYOCARDIUM, THE RESISTANCE TO FLOW WITHIN THE IMPLANT, AND THEIR COMPARISON WITH THE VALUES OBTAINED IN THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY.

INTRODUCTION

It has been amply demonstrated that when an internal mammary artery has been implanted into a tunnel in the ischaemic myocardium, connections develop between it and the adjacent intramyocardial branches of coronary arteries. This concept was first introduced by Vineberg in 1946 who suggested that this operation might bring relief of symptoms of occlusive arterial disease of the heart. Although anastomoses between the implant and coronary arterial system can be clearly demonstrated by selective internal mammary artery angiography (Effler, Sones, Groves and Suarez, 1965), their functional effectiveness in restoring an adequate blood supply to the ischaemic area remained open to doubt. Radiographic appearance, however, has not been shown to be a good index of the bloodflow through the implant (Dart, Kato, Scott, Fish, Nelson and Takaro, 1970). Despite the lack of evidence of effective flow through these implants, large numbers of such procedures have been carried out in human patients with extensive multifocal occlusive disease of the coronary arterial circulation, (Favaloro, Effler, Groves, Sones and Fergusson, 1967). In many centres it has been thought that a single implant would not adequately revascularise the whole of the left ventricle, and so both internal mammary arteries have been implanted in many patients (Favaloro, 1967). Again variations on the theme have been performed using a whole spectrum of other implants such as a pedicle containing internal mammary artery, vein and surrounding muscle and fascia (Sewell, 1966), intercostal artery (Pearce, Hyman, Brewer, Smith and Creech, 1966), saphenous vein (Ferlic, Quattlebaum and Lillehei, 1966).

The demonstration that many patients whose implants were shown radiologically to be occluded but were, in spite of this, symptomatically improved has led to the now widely held belief that the improvement in these patients was due mainly (if not all) to the placebo effect of surgery. In the minds of many people, especially in this country, arterial implantation into the myocardium was relegated to the ranks of other dubious revascularisation procedures such as internal mammary artery ligation, pericardial abrasion and talc dissemination. In the face of this criticism, the operation of internal mammary artery implantation has been persisted with in many centres with stricter control in the selection of patients, the methodology of operation and the assessment of results. It has become recognised that no patient should be subjected to any type of revascularisation procedure unless a full angiographic assessment has been made of the severity and extent of his coronary artery disease, and where possible at some interval after operation, a similar procedure be carried out together with a full measurement of cardiac performance.

Direct coronary artery surgery at the present time can be offered only to those patients with discrete single lesions of main coronary vessels. Such patients form only a small proportion of the total population of people with this disease, probably amounting to about 10 to 20% of the entire number. The operations offered to these people include local endarterectomy, with or without concomitant vein patch (Bailey, May and Lemmon, 1957) and bypass vein graft procedures. Bypass vein graft procedures have been carried out from the aorta to coronary artery branches down to 2 mm. in diameter thus increasing the number of patients who might benefit from this direct approach (Johnson and Lepley, 1970). The great majority of sufferers from ischaemic heart disease (about 80%) are still, however, beyond the scope of direct coronary artery reconstruction, and therefore at present, the only surgical therapy which can be used in this type of patient with diffuse multifocal disease of the coronary arteries is the implantation procedure. The two main problems in connection with this operation are first, the amelioration of symptoms in a small percentage of patients with radiological evidence of graft occlusion, and second, whether a patent graft is capable of delivering a sufficient quantity of blood to the myocardium to make up for the loss of perfusion through the occluded coronary artery. The first of these problems is discussed in Section V where some evidence is presented which suggests that there might be an alternative explanation to that of the so called placebo effect. The second question is dealt with in this section and involves direct measurement of the flow of blood through the implants to the myocardium by means of the electromagnetic flowmeter technique.

Using this method of bloodflow measurement, Provan, Hammond and Austen (1966) demonstrated in implants inserted into the dog myocardium which was gradually made ischaemic by arterial constrictors placed round the origin of the anterior descending artery, (Vineberg, Mahanti and Litvak, 1960), that one to six weeks later the average mean flow was 5·2 mls per minute but at thirty weeks, the average mean flow reached a maximum of 28 mls per minute. In addition, they found that all implants studied were patent. Internal mammary implant bloodflow to the ischaemic myocardium (using arterial constrictors) has also been studied indirectly by measurement of coronary sinus blood by Alshamma, Criollos and Roe (1968), following the removal of the coronary arterial contribution by clamping in the isolated heart preparation. These workers found that flow from the implant averaged 4·2 ml. per 100 gm. of whole heart per minute at five weeks and increased gradually to 12·0 ml. per 100 gm. of whole heart per minute at six months. Clearance of implant blood from the myocardium has been estimated by Seeman (1968) using radio-isotopes (Krypton - 83 and Xenon - 133) injected into the implant and measuring radio-activity over the left ventricle. He found that the implant contribution to the myocardium made ischaemic by ligation of the anterior descending coronary artery was 5·2 mls per minute per 100 gm. of left ventricular weight at three weeks after implantation. This represented an increase of 36% in bloodflow to the ischaemic myocardium. Three weeks later this increase in bloodflow had risen through the myocardium by 250%. There is therefore much experimental evidence to show that blood does flow through the internal mammary implant into the ischaemic myocardium, this flow is small initially but increases significantly after six weeks to reach a peak at about twenty-four weeks. It has also been shown by Vineberg (1946 and 1962) that ischaemia of the myocardium increases the likelihood of graft patency from 20 to 80%. Gorlin and Taylor (1966) have demonstrated in the human ischaemic myocardium a conversion from an anaerobic to an aerobic metabolism following implantation of the internal mammary artery.

The three studies mentioned above on measurement of blood flow in long-term implants using different preparations and techniques of measurement, produced data which could not be compared with each other. In the first study, Provan, Hammond and Austen (1966) gave absolute mean flow values obtained per minute. Alshamma, Criollos and Roe (1968) expressed the coronary sinus effluent (with the coronary arteries clamped) per 100 gm. of <u>whole</u> heart, whilst Seeman, using the radio-isotope clearance method, gave his values per 100 gm. of <u>left ventricle</u>. These workers all agreed however, that there was a measurable blood flow in the internal mammary implants at six weeks and that this flow increased with time.

In the studies mentioned above of Provan, Hammond and Austen (1966) and of Alshamma et al. (loc. cit.) the method used to effect ischaemia of the left ventricle was to place an Ameroid constrictor round the anterior descending branch of the left coronary artery and then at the same operation, implant the internal mammary artery into the left ventricular myocardium. The main reason for employing this method of producing ischaemia was to cause a gradual diminution in the blood supply to the left ventricle. But using this method it was impossible to demonstrate at the time of the operation what area of the ventricle would become ischaemic, since the anatomy of the coronary arterial supply to the ventricles is so variable. Furthermore, there was no way of determining exactly when the ischaemia occurred. It therefore follows that in the two studies in question, the mammary vessels were placed in areas which may or may not have been ischaemic and also that the vessels were implanted before ischaemia actually occurred.

In the studies described in this section, ischaemia was produced by acute ligation of the anterior descending branch of the left coronary artery. The same part of the left ventricle (the anterior wall) was infarcted in each case. The internal mammary artery was then implanted into the edge of the ischaemic area nearest the inter-ventricular septum (Section I). In this way it was certain at the outset that the implant was positioned in an ischaemic area, the actual moment when ischaemia occurred was known, and finally that any effect of ischaemia on the subsequent development of the graft would be present from the beginning and not after some indeterminate period of time. In the sections which follow, the word 'ischaemic' is used to denote that an ischaemic lesion of the myocardium had been produced at the original operation.

In spite of the many publications in the field of myocardial revascularisation by implantation with the internal mammary artery, few studies have involved the actual measurement of bloodflow in the grafts, and none, as far as the author is aware, carried out in human subjects. This reluctance to assess bloodflow in implants in the clinical field is probably a reflection of the difficulties involved in the techniques of measuring bloodflow in this situation. It will be obvious from the survey of the most important contributions in this area, as discussed earlier, that present knowledge in the experimental field is limited to flow patterns in the implants, that bloodflow through long-term implants lies within the range 5 to 28 mls per minute, and that flow in the implants may increase with time. No real details have been given in any of the previous studies on implant flow - merely ranges of flow and mean figures, without statistical support.

In this present study, four main aspects of implant flow have been studies: forward volume flow, the proportion of the cardiac output carried through the implant, the perfusion of a given weight of left ventricle by the implant and the resistance to bloodflow in the implant. These same aspects of bloodflow have also been studied in the anterior descending branch of the left coronary artery at the point of its subsequent ligation. Statistical analysis has been carried out on the degree of relationship between each of those four aspects of flow in the internal mammary artery and the duration of implantation, by measurement of the coefficient of correlation between the values, and calculation of the regression equations. In view of the histological evidence (Section IV) of an increase in the number and the degree of maturity of blood vessels in the immediate vicinity of the implant within the myocardium at about ten weeks, plus the observation that all arteries (except those radiologically occluded) implanted for ten weeks or more exhibited full anastomosis with both branches of the left coronary artery on angiographic examination (Section V), a statistical comparison was made of forward volume flow, the 'proportional' flow, myocardial perfusion and resistance to flow, before and after ten weeks following implantation to ascertain whether a change had occurred at this time. In addition, the values obtained in each of those periods were compared with those of the anterior descending branch of the left coronary artery. These statistical analyses were made first by the Variance Ratio test (Snedecor, 1946) to ensure that the samples were from populations identical in variance, and then by Student's t-test to compare the difference between the means in the groups. In view of the small numbers in each sample, Bessel's correction was applied, to take account of the bias inherent in such situations.

RESULTS.

Implantation of the Internal Mammary Artery into the Non-Ischaemic Myocardium

Twelve dogs were studied after periods ranging from nine to thirty-two weeks (Table 5). All of the implants were patent in their extracardiac course but only three of the implants had a forward bloodflow (25%) and only one of these had a flow of any magnitude (23·2 mls per minute); the remaining two dogs had a minute flow of 1·0 and 2·0 per minute respectively (confirmed by direct measurement after the implant was cut across). There was no forward bloodflow in the other nine grafts. When the grafts were transected, the proximal end of each of the two grafts with the small forward flows was found to bleed not only from the lumen but also from the walls of the implants, that is the periarterial vessels seemed to be enlarged and contributed to the forward bloodflow.

All three of the implants with forward bloodflow had a reverse flow from the cut end of the implant still connected with the heart. In addition, three of the grafts with no detectable forward flow showed the same phenomenon. These six reverse flows which were very small, were measured over several minutes and varied from 0·5 to 1·0 mls per minute (Table 5). This back flow could only have come from the myocardial or epicardial vessels and was therefore

Dog	Weeks	Forward flow mls per minute	Back flow mls per minute
1	9	0·0	0·5
2	13	0·0	0·5
3	25	0·0	0·5
4	26	0·0	0·0
5	26	23·2	0·5
6	27	0·0	0·0
7	27	0·0	0·0
8	27	0·0	0·0
9	28	0·0	0·0
10	29	1·0	1·0
11	30	2·0	0·5
12	32	0·0	0·0

Table 5

Volume bloodflow in the internal mammary artery after nine to thirty-two weeks following implantation into the non-ischaemic myocardium in twelve dogs.

evidence of a connection between the graft and the coronary vessels even in the absence of ischaemia of the myocardium. This blood was then subjected to blood gas analysis and shown to have the same oxygen tension and carbon dioxide tension as blood from the thoracic aorta and was therefore arterial in origin.

Bloodflow through Grafts Implanted into the Ischaemic Myocardium

From a total of twenty long-term internal mammary implants introduced into the ischaemic myocardium, two were found to be occluded in the intramyocardial course. This represented a patency rate of 90%. One further dog had a patent graft with a small bloodflow (4·4 mls per minute) which was found to be closely adherent to the upper lobe of the left lung. Subsequent angiography showed the presence of vascular connections between the graft and this lobe of lung (Figure 12); data from this dog were therefore not included in the study.

The remaining seventeen dogs were studied up to twenty-seven weeks after the original operation. The average mean arterial blood pressure was found to be much lower in these animals during thoracotomy than in normal intact dogs. In the normal conscious intact dog the mean blood pressure is usually about 150 mm. Hg but in the animals in this study with severe ischaemic lesions of the left ventricle, the combination of anaesthesia plus thoracotomy with the inevitable dissection in the immediate environment of the heart the average mean pressure for all dogs was 97 mm. Hg.

The results are given in Tables 6 to 14. Although the mean arterial pressure varied in different dogs, in each dog it was

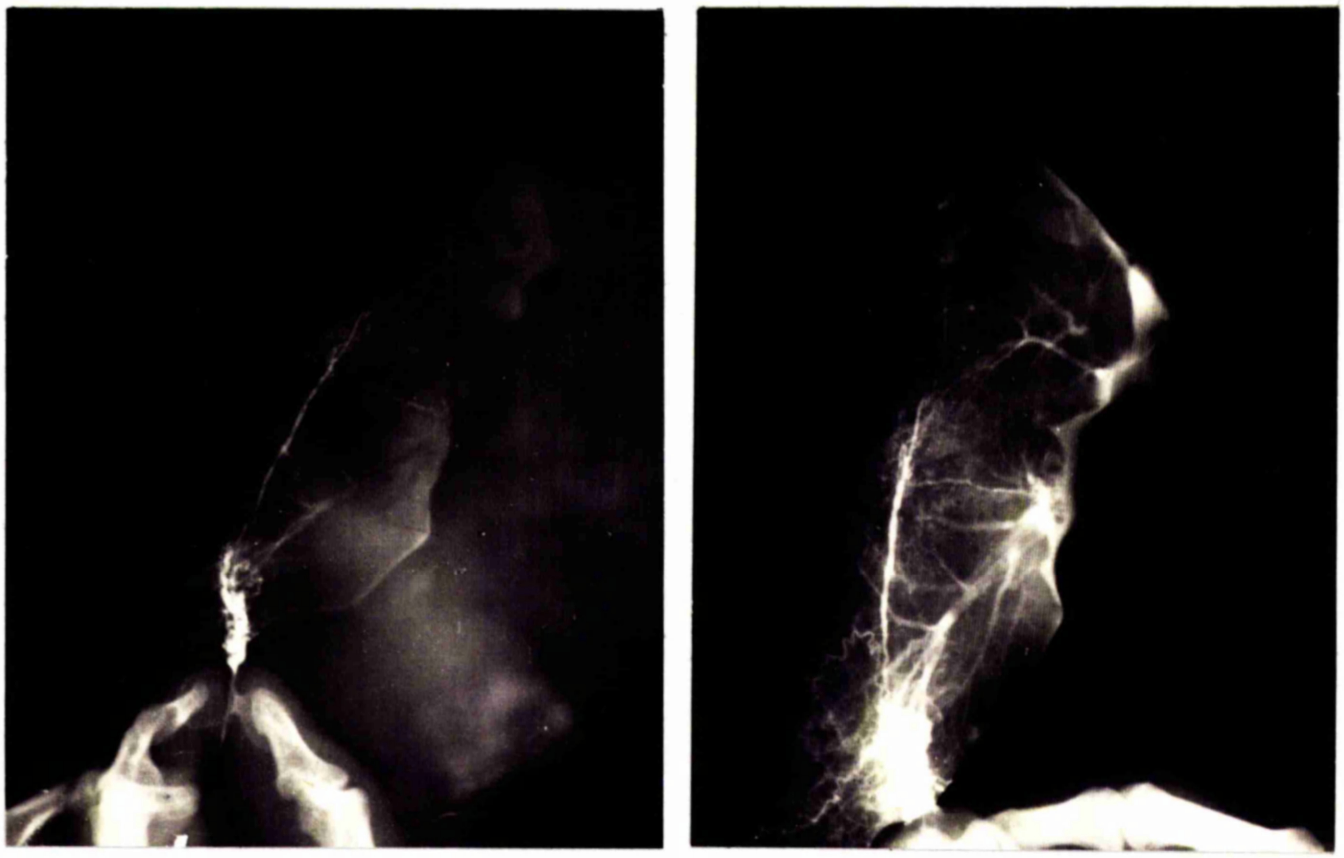


Figure 12

The blood vessels of the upper lobe of the left lung outlined after the injection of radio-opaque contrast into the internal mammary artery implanted into the myocardium of the left ventricle. The implant was adherent in its middle third to the surface of the lung.

fairly constant. The blood gases were kept within normal limits throughout all experiments by adjustment of the oxygen intake and the volume delivered by the ventilation pump. The pO_2 of arterial blood varied from 100 to 120 mm. Hg and the pCO_2 from 30 to 40 mm. Hg. The pH of arterial blood was fairly constant (7·3 to 7·5) during the flow measurements.

Dog	Weeks	Internal mammary artery Forward volume flow mls per minute	Internal mammary artery Reverse flow mls per minute	Mean blood pressure	Heart rate
45	2	7·7	0·0	85	150
44	4	5·7	0.6	85	107
25	5	17.3	0·0	129	200
40	5	10·8	0.0	108	174
41	5	13·2	1·7	112	115
34	8	5·9	0·0	93	130
31	10	14·8	0·0	81	130
32	10	16·3	0·0	91	125
30	11	10·1	0·0	82	115
26	14	7·5	0·2	128	150
28	14	33·8	0·0	98	125
23	14	20·3	0·0	98	150
24	14	18·2	0·0	60	136
18	16	32·4	0·0	136	120
51	25	12·0	0·0	124	150
48	26	19·0	0·0	64	100
47	27	12·7	0·0	75	110

Table 6

Forward and reverse volume flows in the internal mammary artery implanted into the ischaemic left ventricular myocardium from two to twenty-seven weeks previously in seventeen dogs.

Forward Bloodflow in Long-term Implants

The forward volume bloodflow varied in all seventeen implants from 5·7 to 33·8 mls per minute. The smallest flow was observed at four weeks and the largest at fourteen weeks. Since it was not possible to keep the mean arterial blood pressure at the same level in all dogs, comparisons between forward bloodflow values in different dogs was not expected to yield a meaningful correlation. The mean arterial pressure in the seventeen dogs was 97 mm. Hg with a range of 58 to 136 mm. Hg and yet in spite of this wide range in blood pressure, there was a correlation coefficient of 0·624 between forward flow and the number of weeks after implantation during the first sixteen weeks (fourteen out of the total seventeen values). This coefficient was significant at the 5% level (Snedecor, 1946). The equation for the curve representing these values was calculated at $y = 3 \cdot 946 + 1 \cdot 208x$. When however, the coefficient was calculated over the twenty-seven week period, it was not found to be significant ($r = 0 \cdot 301$). This would suggest that initially there was an increase in flow with duration of implantation, but after a time, a plateau was reached during which no further increases in flow occurred. When the values for forward flow were plotted against time, the slope suggested a curvilinear relationship with the plateau beginning nearer ten weeks than sixteen weeks (Figure 13a).

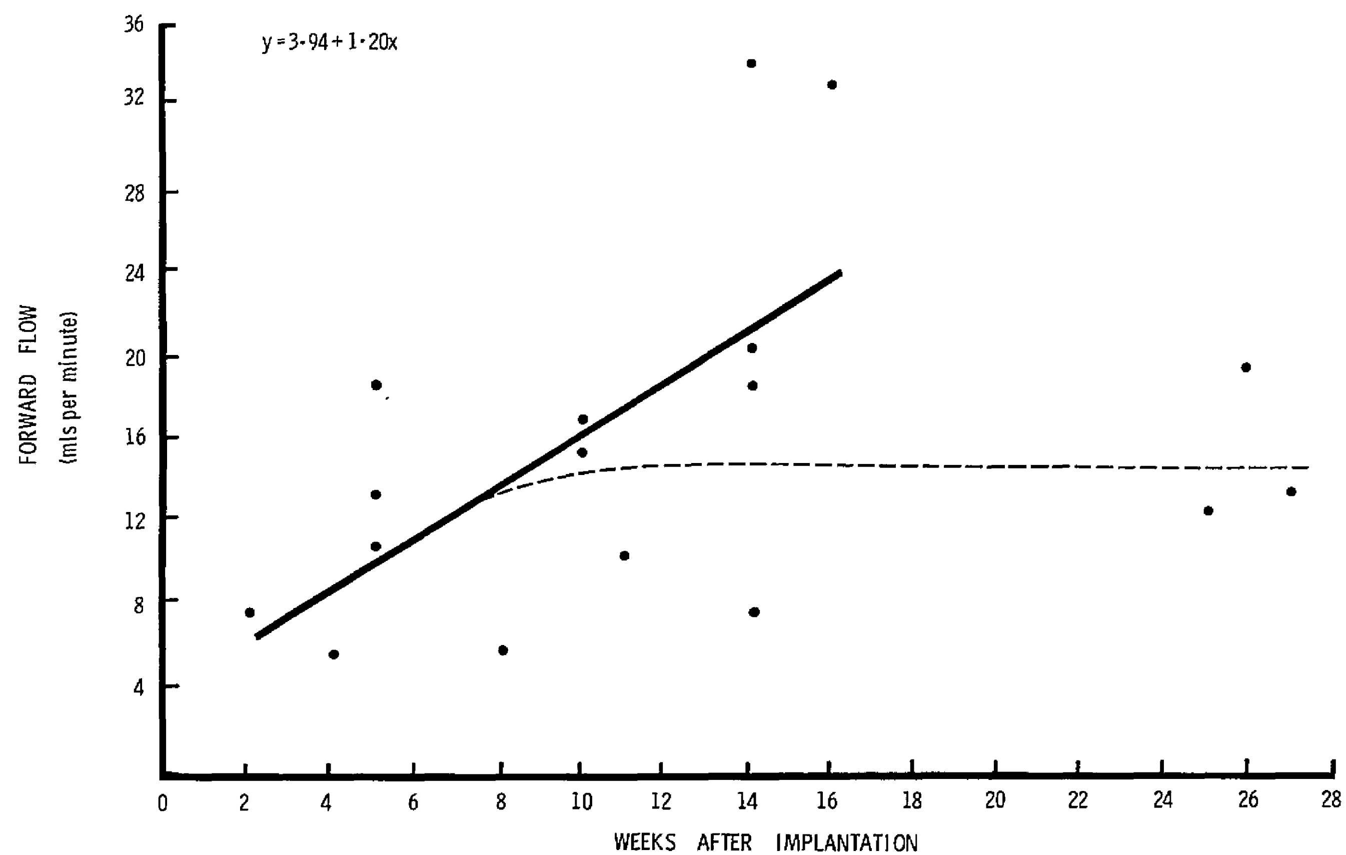


Figure 13a

The relationship of forward volume flow in the internal mammary artery to duration of implantation. The heavy line is the calculated linear regression slope to sixteen weeks, the interrupted line is the hand drawn 'best fit' for all values.

Period	No. in Sample	Range (mls per minute)	Mean (mls per minute)	Standard Deviation	Standard Error of Difference	t	p-value	
Before 10 wks	6	5·7-17·3	10·1	4·18	3·72	2·09	$<0{\cdot}05$	Significant difference
After 10 wks	11	7·47-33·8	17·9	8·03				

Table 7

Comparison of forward flow in the internal mammary artery before and after ten weeks following implantation.

Comparison of forward volume flow values before ten weeks following implantation with those between ten and twenty weeks demonstrated a significant increase in the latter group ($t = 2 \cdot 01$, $p < 0 \cdot 05$). No difference could be shown between the ten to twenty weeks group and those implanted more than twenty weeks. When values before ten weeks following implantation were compared with all values over this period (up to twenty-seven weeks) there was an increase in the mean value from 10·1 to 17·9 mls per minute, representing an increment of 78%. This increase was statistically significant ($t = 2 \cdot 09$, $p < 0 \cdot 05$). These results are shown in Table 7.

The Proportion of the Total Body Flow carried by the Internal Mammary Artery Implants

The cardiac output was measured in all of the seventeen dogs in this group and varied from 845 to 2,984 mls per minute (Table 8). This variation mainly reflected the haemodynamic efficiency of the ischaemic heart during anaesthesia and thoracotomy but also of importance in this variation may have been heart size. Although the body weights of the dogs were between 15 and 20 Kg., the left ventricular weight ranged between 67 and 164 gm. This surprising range in left ventricular weight over such a small difference in body weight might be explained in terms of nutrition (the proportion of body fat) and the breed of dog (the 'running' dog probably has a greater heart/body mass ratio). The proportion of the cardiac output brought to the ischaemic left ventricular myocardium by the graft was calculated by expressing the graft flow in terms of mls per minute per litre of cardiac output.

This 'proportional' flow varied from 4·6 to 19·8 mls per minute per litre of cardiac output (Table 8). The smallest proportional flow was observed in two dogs at four and eight weeks respectively and the largest at twenty-six weeks after implantation. When the proportion of the cardiac output carried by the internal mammary artery was plotted against duration of implantation, there was a suggestion of a linear relationship throughout the range of values

Dog	Weeks	Internal mammary artery Forward volume flow (mls per minute)	Cardiac output (mls per minute)	Proportion of cardiac output carried by implant (mls per minute per litre cardiac output)
45	2	7·7	1,200	6·4
44	4	5·7	1,241	4·6
25	5	17·3	1,850	9·4
40	5	10·8	1,600	6·8
41	5	13·2	845	15·6
34	8	5·9	1,291	4·6
31	10	14·8	1,120	13·2
32	10	16·3	928	17·6
30	11	10·1	1,014	10·0
26	14	7·5	900	8·3
28	14	33·8	2,984	11·3
23	14	20·3	2,420	12·4
24	14	18·2	1,295	14·1
18	16	32·4	2,500	13·0
51	25	12·0	1,024	11·7
48	26	19·0	960	19·8
47	27	12·7	1,000	12·7

Table 8

The proportion of the cardiac output carried by the internal mammary artery implanted into the ischaemic left ventricular myocardium from two to twenty-seven weeks previously in seventeen dogs.

Period	No. in Sample	Range (mls per minute per litre cardiac output)	Mean (mls per minute per litre cardiac output)	Standard Deviation	Standard Error of Difference	t	p-value	
Before 10 wks	6	4·6-15·6	7·9	3·80				
					1·83	2·84	< 0·01	Significant differen
After 10 wks	11	8·3-19·8	13·1	3·08				

Table 9

Comparison between the proportion of the cardiac output carried in the internal mammary artery, before and after ten weeks following implantation.

(Figure 13b). The coefficient of correlation between these values was calculated at 0·531, which was significant at the 5% level (Snedecor, 1946). The regression line was represented by the equation $y = 7{\cdot}61 + 0{\cdot}296x$.

When the group implanted for less than ten weeks was compared with that implanted between ten and twenty weeks, there was a significant increase in the mean value of the latter group ($t = 2{\cdot}49$, $p < 0{\cdot}05$). No difference could be demonstrated between the mean values of the group between ten and twenty weeks and that over twenty weeks. Comparing values obtained before ten weeks with all values after that time (ten to twenty-seven weeks), it was found that the mean 'proportional' flow increased from 7·9 to 13·1 mls per minute per litre of cardiac output, representing an increment of 66%. Analysis (Table 9) showed this increase to be significant ($t = 2{\cdot}84$, $p < 0{\cdot}01$).

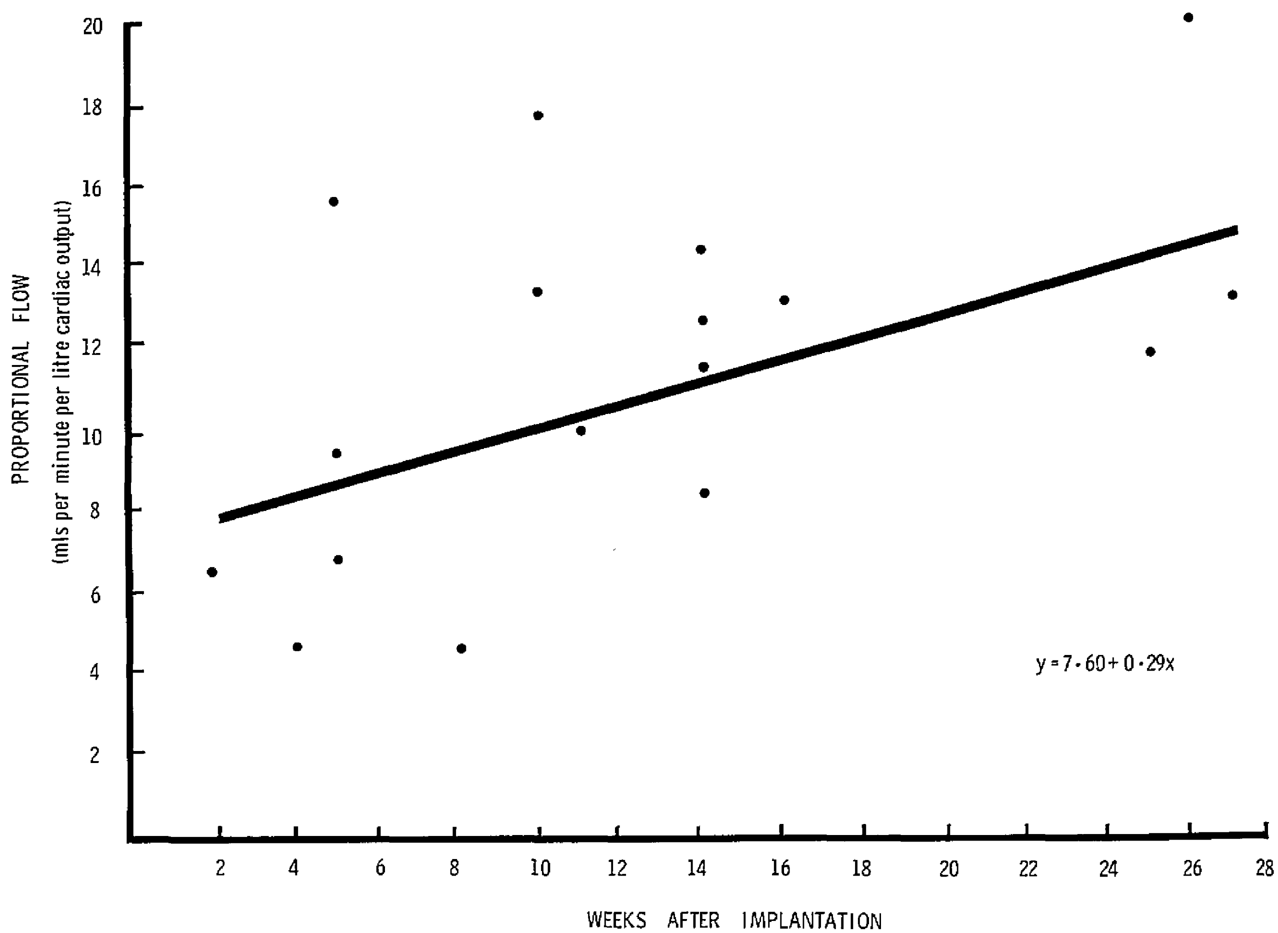


Figure 13b

The relationship of the proportion of the cardiac output carried by the internal mammary artery to the duration of implantation. The linear regression slope is drawn.

The Relationship of Forward Implant Flow to Cardiac Output

The values for absolute forward volume flow in the implants when plotted against their respective cardiac output measurements, irrespective of duration of implantation, showed what seemed to be a straight line relationship (Figure 13c). This linear relationship was confirmed by analysis ($r = 0{\cdot}772$, $p < 0{\cdot}001$). This highly significant correlation between forward implant flow and the cardiac output level showed that the value obtained for the latter was at least partly dependent on the cardiac output level, or on one or both of its two main determinants, left ventricular systolic pressure and peripheral vascular resistance. (Although the cardiac output in these studies was measured in the main pulmonary artery, it was assumed that the output from the left ventricle per minute would be identical to that of the right ventricle).

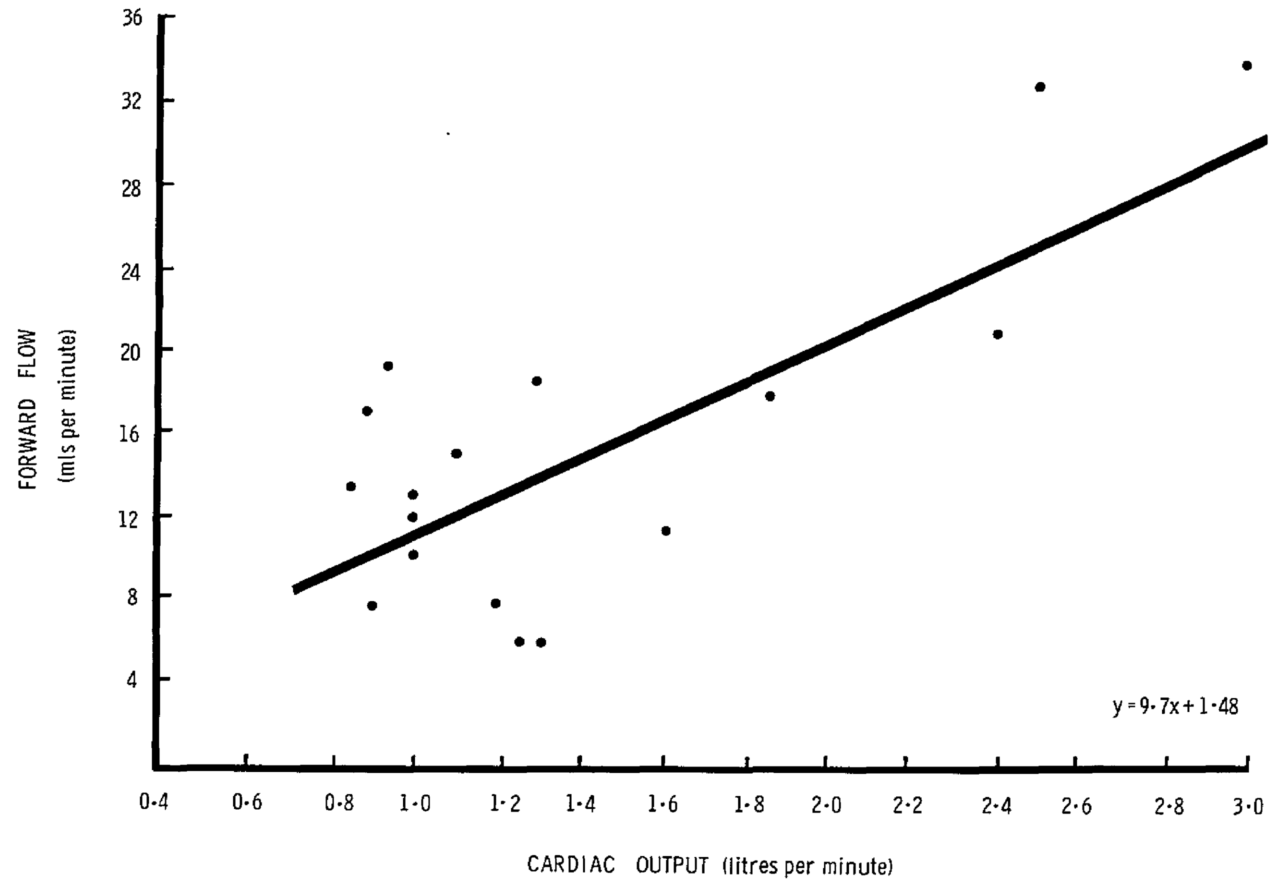


Figure 13c

The effect of the cardiac output level on the forward volume flow through the internal mammary artery from two to twenty-seven weeks after implantation. The regression line is drawn.

Measurement of the Additional Myocardial Bloodflow from the Implanted Internal Mammary Artery

The forward volume bloodflow was expressed per 100 gm. of left ventricular weight, thus giving a measure of the additional volume of blood perfusing the myocardium. This varied from 4·2 mls per minute per 100 gm. left ventricle at four weeks to the maximum figure of 25·7 mls per minute per 100 gm. left ventricle at sixteen weeks (Table 10). When these perfusion values were plotted against time (Figure 13d) a linear relationship was suggested for the first sixteen weeks. This was confirmed statistically when the coefficient of correlation was observed to be 0·535 which was significant at the 5% level (Snedecor, 1946). The regression line was calculated at $y = 5{\cdot}115 + 0{\cdot}859x$. Over the whole twenty-seven weeks, however, the correlation was not significant ($r = 0{\cdot}381$). The scatter of results over this period suggested a possible curvilinear relationship (when the curve was drawn by hand). This exponential relationship was confirmed when with the use of the Hewlett Packard programmable calculator and programme 70811 for curvilinear correlation, from the Hewlett Packard Library, a coefficient of correlation of + 0·63 was found for all results from 0 to twenty-seven weeks. This correlation was significant at the 5% level. The best curve fit was expressed by the equation $y = - 14e^{- 0{\cdot}05x} + 18$, and is drawn on Figure 13d. From the

Dog	Weeks	Internal mammary artery Forward volume flow (mls per minute)	Left ventricular weight (gm.)	Flow into 100 gm. of left ventricle from implant (mls/100 gm. left ventricle)
45	2	7·7	116	6·6
44	4	5·7	132	4·2
25	5	17·3	135	12·8
40	5	10·8	81	13·3
41	5	13·2	119	11·1
34	8	5·9	105	5·6
31	10	14·8	125	11·8
32	10	16·3	67	24·3
30	11	10·1	114	8·8
26	14	7·5	131	5·7
28	14	33·8	133	25·4
23	14	20·3	164	12·4
24	14	18·2	105	17·3
18	16	32·4	126	25·7
51	25	12·0	82	14·6
48	26	19·0	109	17·4
47	27	12·7	93	13·7

Table 10

Perfusion of 100 gm. of ischaemic left ventricle from the internal mammary artery implanted two to twenty-seven weeks previously in seventeen dogs.

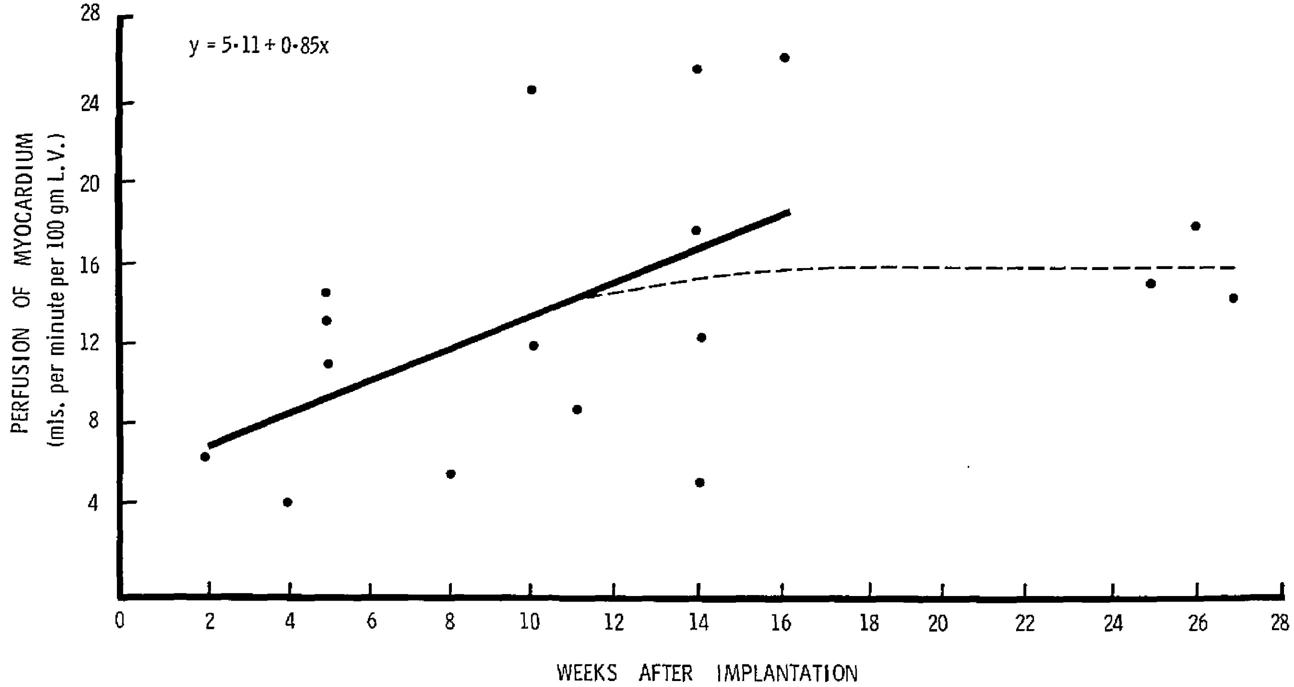


Figure 13d

The effect of duration of implantation on the perfusion of the myocardium from the internal mammary artery. The line is the best fit calculated by digital computer.

equation the exponential is reached at about eighteen weeks.

Comparison of perfusion values before ten weeks with those between ten and twenty weeks after implantation demonstrated a significant increase in the latter group ($t = 2 \cdot 10$, $p < 0 \cdot 05$). No difference could be demonstrated between the perfusion values between ten and twenty weeks with those after this period. When the group before ten weeks was compared with all values from ten to twenty-seven weeks after implantation, the mean value rose from 8·93 mls ot 16·10 mls per minute per 100 gm. of left ventricle, representing an increase of 79% in perfusion from the implant (Table 11). This increase was found to be statistically significant ($t = 2 \cdot 61$, $p < 0 \cdot 01$).

Period	No. in Sample	Range (mls per minute per 100 gm. left ventricle)	Mean (mls per minute per 100 gm. left ventricle)	Standard Deviation	Standard Error of Difference	t	p-value	
Before 10 wks	6	4·2-13·3	8·9	3·63	2·74	2·61	$< 0·01$	Significant difference.
After 10 wks	11	5·7-25·7	16·1	5·81				

Table 11

Myocardial perfusion from the internal mammary artery before and after ten weeks following implantation.

Estimation of the Resistance to Flow experienced by the Blood within the Implant

The resistance to the forward flow of blood through the implanted internal mammary artery is compounded from several different sources. These include the resistance within the implant, the anastomotic vessels between implant and coronary circulation, and the coronary circulation itself. In addition, the compressing forces of the left ventricular wall which vary in degree at different parts of the cardiac cycle, plus the right atrial pressure all must have affected the flow of blood through the implant.

Despite this daunting complexity an estimate of the overall resistance to implant flow in diastole can be obtained by subtracting the right atrial pressure from the mean diastolic pressure in the central aorta (close to the left subclavian artery), and dividing by the mean implant flow in diastole.

i.e. $R = \dfrac{P_1 - P_2}{Qi}$

(Where P_1 = mean diastolic aortic pressure; P_2 = right atrial pressure; Qi = mean diastolic implant flow; R = total resistance in diastole).

The right atrial pressure itself was not measured in each of these dogs but was assumed to have a value between 0 and 5 mm. Hg. This assumed range in values was based on other experiments on anaesthetised dogs where the mean right atrial pressure was found to be within this range, and also on the work of Gregg and Fisher, (1963) who showed that the anaesthetised dog has a right atrial pressure in the range 0 - 8 mm. Hg. The right atrial pressure could have been left out of the calculation for resistance but the latter was estimated at a right atrial pressure of 0 mm. and 5 mm. Hg for completeness. Resistance was measured in mm. Hg per ml. of forward blood flow but is referred in the tables to 'resistance units" The mean diastolic aortic pressure was calculated from the pressure waveform which had been carefully calibrated as previously described. It was taken as one third of the difference between the maximum pressure after the closure of the aortic valve and the minimum diastolic pressure (the diastolic blood pressure) plus the value of the minimum diastolic pressure.

1/3 (Maximum D.P. - Minimum D.P.) + Minimum D.P.

The mean diastolic implant flow was calculated from the mean flow waveform during the same cycle as the aortic pressure waveform mentioned above. Two sets of resistances were calculated, one corresponding to a right atrial pressure of 0 mm. Hg, the other

		diastole (MLS Per Minute)	mm. Hg.	pressure 0 mm. Hg.	pressure 5 mm. Hg.
45	2	4.0	80	20.0	19.0
44	4	4.0	80	20.0	19.0
25	5	10.5	124	11.8	11.3
40	5	8.0	105	13.1	12.5
41	5	12.0	112	9.3	9.0
34	8	5.2	89	17.1	16.1
31	10	8.0	77	9.6	9.0
32	10	12.0	88	7.3	7.0
30	11	7.5	80	10.4	10.0
26	14	6.0	60	9.2	10.0
28	14	26.0	95	3.7	3.4
23	14	14.0	90	6.4	6.1
24	14	16.0	51	3.2	3.0
18	16	25.0	120	4.8	4.6
51	25	10.0	121	12.1	11.6
48	26	18.0	63	3.5	3.2
47	27	8.0	63	7.9	7.2

Table 12

The resistance to blood flow through the internal mammary artery implanted into the ischaemic left ventricular myocardium from two to twenty-seven weeks previously.

to 5 mm. Hg. The results are shown in Table 12.

On plotting the values for resistance against duration of implantation, a linear relationship was suggested (Figure 13e). This was confirmed by calculation of the coefficient of correlation ($r = -0{\cdot}498$ and $-0{\cdot}502$ at 0 and 5 mm. Hg right atrial pressure respectively) which was found to be significant at the 5% level (Snedecor, 1946). The regression equation of this relationship was expressed by the equation $y = 51{\cdot}34 - 0{\cdot}38x$.

From the plot of values for resistance and duration of implantion, it seemed that an exponential curve could also have fitted the relationship. Such a relationship was confirmed by use of the Hewlett Packard programmable calculator. The correlation coefficient was found to be $-0{\cdot}62$ for all values from 0 to twenty-seven weeks after implantation; this coefficient was significant at the 5% level. The best curve fit was expressed by the equation $y = 16{\cdot}5e^{-x/11} + 3$. The relationship between the resistance to flow and the duration of implantation could therefore be expressed both as a linear and curvilinear relationship, but the time relationship is probably the latter. The regression line for the straight function is shown on Figure 13e.

Comparison of the mean resistance before ten weeks and between

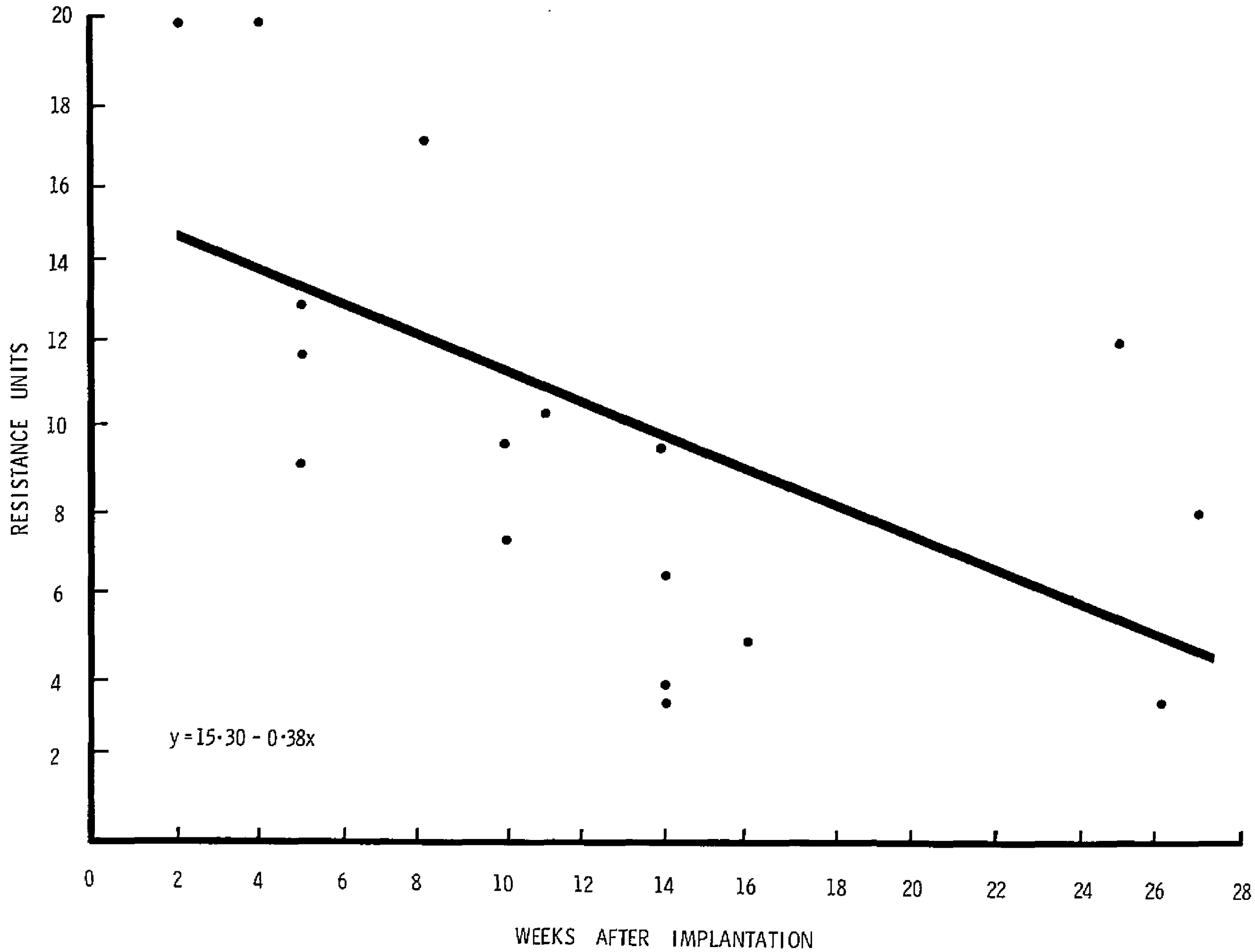


Figure 13e

The effect of duration of implantation on the resistance to flow in the internal mammary artery during diastole at a right atrial pressure of 0 mm. Hg. The relationship can be expressed by linear regression as shown, but the values can also be related by the exponential equation

$$y = 30e^{-x/6} + 3$$ calculated by digital computer.

ten and twenty weeks after implantation, demonstrated a significant decrease in the latter group ($t = 2{\cdot}38$, $p < 0{\cdot}05$). Between the ten and twenty week group and those implanted more than twenty weeks, no difference between their means could be shown.

When those implanted for less than ten weeks were compared with those over ten weeks (up to twenty-seven weeks), there was still a significant difference (Table 13) between the means at both levels of right atrial pressure ($t = 2{\cdot}87$, $p < 0{\cdot}01$ at 0 mm. Hg right atrial pressure and $t = 2{\cdot}82$, $p < 0{\cdot}01$ at 5 mm. Hg right atrial pressure).

Right atrial pressure mm. Hg	Period	No. in Sample	Range Resist. Units	Mean Resist. Units	Standard Deviation	Standard of Error Difference	t	p-value	Remarks
0	< 10 wks	6	9·3-20·0	14·8	4·11	2·31	2·87	< 0·01	Significant difference.
0	> 10 wks	11	3·2-20·8	8·2	4·90				
5	< 10 wks	6	9·0-19·0	14·5	3·82	2·41	2·82	< 0·01	Significant difference.
5	> 10 wks	11	3·0-20·0	7·7	4·74				

Table 13

The resistance to implant bloodflow compared before and after ten weeks following implantation, at 0 and 5 mm. Hg right atrial pressure.

The Dependence of the Left Ventricle on the Implant for its Functional Integrity

In ten of the dogs in which an internal mammary artery had been implanted into an ischaemic left ventricle and studied at intervals up to fourteen weeks following operation, heart rate, cardiac output and stroke volume were measured before and after clamping the graft. The graft was occluded for exactly one minute and at this time the cardiac output and heart rate were measured; from these, the stroke volume was calculated. The observed values for heart rate and stroke volume were compared with those obtained immediately before the graft was clamped. The results are shown in Table 14.

The average stroke volume for the ten hearts with the implant open was found to be 11.56 mls, and that with the implant clamped, 11.35. This represented a decrease of only 1.8% which of course was not statistically significant. The average heart rate remained unchanged at 137 beats per minute. Scrutiny of the electrocardiograph patterns did not reveal any changes in rhythm or in the S-T segment and T wave, nor were any extrasystoles, arterial or ventricular, recorded during this time.

It must be concluded that although it had been demonstrated that

Dog	No. of wks post-implant	Cardiac Output (mls per minute) Implant unclamped	Cardiac Output (mls per minute) Implant clamped	Mean Stroke Volume (mls) Implant unclamped	Mean Stroke Volume (mls) Implant clamped	Heart Rate (beats per minute) Implant unclamped	Heart Rate (beats per minute) Implant clamped
45	2	1,200	1,240	8·0	8·3	150	150
44	4	1,241	1,078	10·8	9·4	115	115
25	5	1,850	1,627	9·25	8·7	200	187
41	5	1,529	1,570	14·3	14·1	107	111
43	8	890	982	6·5	7·2	136	136
31	10	1,120	944	8·9	7·55	125	125
30	11	1,014	1,061	9·43	9·14	107	116
26	14	1,400	1,320	9·3	8·8	150	150
23	14	2,420	2,880	16·1	19·2	150	150
28	14	2,984	2,748	22·95	21·14	130	130

Table 14

The effect of clamping the internal mammary artery implant for one minute, on the cardiac output, stroke volume and heart rate in ten dogs.

these grafts were patent and carried a measurable bloodflow to the myocardium, the cessation of this extra supply of blood for one minute, did not produce any detectable ill effects in cardiac function as far as the measurement of stroke volume and cardiac output were concerned.

Bloodflow through the Anterior Descending Branch of the Left Coronary Artery

Bloodflow through this artery was measured 2 cm. from its origin from the left coronary artery. The technique employed was exactly as for the internal mammary artery bloodflow using the electromagnetic flowmeter method. Zero base-line readings were obtained by clamping the vessel temporarily above and below the flow probe.

The forward volume flow, measured 2 cm. below the origin of the anterior descending branch from the left coronary artery, varied from 12·9 to 32·0 mls per minute in ten dogs, with an average value of 19·6 mls per minute (Table 15). This wide range in values was probably in part a reflection of the relative size of the artery and its area of supply, and also to the presence or absence of early branching.

When the forward volume flow through the left anterior descending branch was compared with the forward volume flow through the internal mammary implant it was found (Table 16) that the flow in the former was significantly greater than in the implant before the tenth post-operative week ($t = 3{\cdot}68$, $p < 0{\cdot}01$) but that there was no significant difference between the flows from the ten week onwards ($t = 0{\cdot}48$, $p > 0{\cdot}30$).

Dog	Flow in anterior descending branch of left coronary artery (mls per minute)	Blood pressure mm. Hg	
		systolic	diastolic
34	32·0	110	75
35	21·0	100	70
36	15·0	105	70
39	23·9	95	75
41	20·8	95	68
42	20·1	100	88
43	15·6	104	85
45	16·7	107	85
46	18·3	90	68
54	12·9	90	75

Table 15

Forward volume bloodflow through the anterior descending branch of the left coronary artery 2 cm. from its origin.

Period	No. in Sample		Means mls per minute		Standard Deviation		Stand. Error of Diff.	t	p-value	Remarks
	Coronary	Implant	Coronary	Implant	Coronary	Implant				
< 10 wks	10	6	19·6	10·1	5·18	4·18	2·35	4·04	< 0·0025	Significant difference.
> 10 wks	10	11	19·6	17·9	5·18	8·03	8·19	0·2	> 0·49	No significa[nt] difference.

Table 16

Statistical comparison between the forward bloodflow in the anterior descending branch of the left coronary artery, 2 cm. below its origin (position of subsequent ligation), and that in the internal mammary artery before and after ten weeks following implantation.

The Proportion of the Total Body Flow Carried by the Anterior Descending Branch of The Left Coronary Artery 2cm. from its Origin

The cardiac output was measured by the electromagnetic flow-meter in the same ten dogs, within one minute after the measurement of the forward volume blood flows through the anterior descending branch of the left coronary artery. During the measurement of the cardiac output in one dog, the heart rhythm altered from sinus to ventricular tachycardia, the data from this dog were omitted from the analysis. The flow in this coronary branch 2 cm. below its origin was expressed per litre of cardiac output (Table 17). In the nine remaining dogs the proportion of the cardiac output carried by the artery ranged from 9.0 to 21 mls. per minute per litre of cardiac output with a mean value of 13.8 and a standard deviation of 3.94.

When the 'proportional' flow in the anterior descending branch of the left coronary artery was compared to that through the implant (Table 18) it was found that there was a statistically significant difference between them before the tenth post-operative week, ($t = 2.49$, $p < 0.025$) but no difference after the tenth week ($t = 1.66$, $p > 0.499$). Thus after the tenth week, the implant carried about the same proportion of the cardiac output to the left ventricle as did the anterior descending branch of the

Dog	Volume flow in anterior descending branch of the left coronary artery mls per minute	Cardiac Output	Proportion of cardiac output mls per minute per litre cardiac output
34	32·0	1,600	20·0
35	21·0	1,000	21·0
36	15·0	1,304	11·4
39	23·9	1,886	12·6
41	20·8	1,797	11·6
42	20·1	1,340	15·0
43	15·6	1,533	10·2
45	16·7	1,200	13·9
54	12·9	1,318	9·0

Table 17

The proportion of cardiac output carried by the anterior descending branch of the left coronary artery 2 cm. below its origin.

Period	No. in Sample		Means (mls per minute per litre cardiac output)		Standard deviation		Stand. Error of diff.	t	p-value	Remarks
	Coronary	Implant	Coronary	Implant	Coronary	Implant				
$<$ 10 wks	9	6	13·8	7·9	3·94	3·8	2·49	2·37	$<$ 0·025	Significa differenc
$>$ 10 wks	9	11	13·8	13·1	3·94	3·08	1·66	0·004	$>$ 0·499	No significa differenc

Table 18

Comparison between the proportion of the cardiac output carried by the anterior descending branch of the left coronary artery, 2 cm. below its origin, and by the internal mammary artery before and after ten weeks following implantation.

left coronary artery prior to its ligation at a point 2 cm. below its origin.

Measurement of the Myocardial Bloodflow from the Anterior Descending Branch of the Left Coronary Artery 2 cm. from its Origin

The left ventricle was weighed in each of six dogs in which the forward volume bloodflow in the anterior descending artery had been measured (Table 19). The forward volume flow was expressed per 100 gm. of left ventricular weight, and was found to vary from 9·6 to 30·5 mls per minute per 100 gm. of left ventricular weight, the four other values were fairly close together, however, and ranged from 14·4 to 17·5. The average flow for the six dogs was calculated at 17·6 mls per minute per 100 gm. left ventricular weight.

When compared with the data observed for the implanted internal mammary artery (Table 20), the quantity of myocardial perfusion from the anterior descending branch of the left coronary artery was statistically greater than that from the implant before the tenth week post-operatively ($t = 2{\cdot}31$, $p < 0{\cdot}025$). But when compared with the perfusion from the implant after the tenth week, the values could not be separated statistically ($t = 0{\cdot}09$, $P > 0{\cdot}475$). Thus only after the tenth week did the implant provide about the same level of perfusion as the anterior descending branch at the level of subsequent ligation.

Dog	Volume flow in anterior descending branch of the left coronary artery (mls per minute)	Left Ventricular Weight (gm.)	Flow into left ventricular myocardium from anterior descending branch (mls per minute per 100 gm. left ventricle)
34	32·0	105	30·5
41	20·8	119	17·5
43	15·6	92	17·0
45	16·7	116	14·4
46	18·3	108	16·9
54	12·9	135	9·6

Table 19

Perfusion of 100 gm. of normal left ventricle from the anterior descending branch of the left coronary artery 2 cm. from its origin.

Period	No. in Sample		Means (mls per 100 gm. left ventricle)		Standard deviation		Stand. Error of diff.	t	p-value	Remarks
	Coronary	Implant	Coronary	Implant	Coronary	Implant				
< 10 wks	6	6	17·6	8·9	6·34	3·63	3·25	2·67	$< 0·0125$	Significant difference
> 10 wks	6	11	17·6	16·1	6·34	5·81	3·20	0·47	$> 0·3$	No significant difference

Table 20

Comparison between the myocardial perfusion from the anterior descending branch of the left coronary artery 2 cm. below its origin, and that from the internal mammary artery before and after ten weeks following implantation into the ischaemic left ventricle.

Measurement of the Resistance to Bloodflow within the Anterior Descending Branch of the Left Coronary Artery, 2 cm. from its Origin

Resistance to bloodflow within the anterior descending branch of the left coronary artery was calculated from the formula:-

$$R = \frac{P_1 - P_2}{Qc}$$

(Where P_1 = mean diastolic aortic pressure in mm. Hg; P_2 = right atrial pressure in mm. Hg; Qc = Volume flow in the anterior descending branch of the left coronary artery in mls per minute).

The right atrial pressure was not measured in each of these dogs but was assumed to have a value in the range of 0 to 5 mm. Hg. This range of right atrial pressure was based on other experiments performed by the author on anaesthetised dogs where the right atrial pressure was found to be within this range. This agrees closely with the observations made by Gregg and Fisher (1963), who found a range in right atrial pressure, in anaesthetised dogs, between 0 and 8 mm. Hg. From the resistance equation, it can be seen that the right atrial pressure could in fact be neglected altogether, but is taken into account in this study for completeness. The resistance was calculated at a right atrial pressure of 0 mm. and 5 mm. Hg respectively. Resistance was measured in mm. Hg per ml. of

Dog	Mean Diastolic Blood Pressure mm. Hg	Mean Flow during Diastole mls per minute	Resistance Units At Right Atrial Pressure 0 mm. Hg	Resistance Units At Right Atrial Pressure 5 mm. Hg
39	78	20·2	3·8	3·6
41	74	19·0	3·9	3·6
42	88	19·0	4·6	4·4
43	88	12·0	7·3	6·9
45	90	13·0	6·9	6·5
46	71	16·0	4·4	4·1
54	78	10·0	7·8	7·5

Table 21

The resistance to flow in the anterior descending branch of the left coronary artery in seven dogs, 2 cm. below the origin of that branch.

Right atrial press. (mm. Hg)	Period	No. in Sample Coronary Artery Resist.	No. in Sample Implant Resist.	Means Coronary Artery Resist.	Means Implant Resist.	Percentage difference between means	Stand. Deviation Coronary Artery Resist.	Stand. Deviation Implant Resist.	Stand. Error of Diff.	t	p-value	Remarks
0	10 wks	7	6	5·2	14·8	185	1·55	4·11	1·84	5·2	0·0005	Significa differen
0	10 wks	7	11	5·2	8·2	58	1·55	4·90	2·01	1·49	0·05	No significa differen
5	10 wks	7	6	5·5	14·5	164	1·60	3·82	1·73	5·2	0·0005	Significa differen
5	10 wks	7	11	5·5	7·7	40	1·60	4·74	1·97	1·12	.0·1	No significa differen

Table 22

The difference between the implant resistance before and after ten weeks following implantation and the resistance in the anterior descending branch of the left coronary artery calculated at right atrial pressures of 0 and 5 mm. Hg.

forward flow and abreviated in the tables to 'resistance units'. The mean resistance to flow through the anterior descending branch of the left coronary artery (at the point of its subsequent ligation) in seven dogs was found to be 5·20 units with a standard deviation of 1·55 (Table 22). When compared with the resistance to bloodflow through the internal mammary artery before ten weeks from implantation, a significantly smaller value was found in the coronary artery ($t = 5{\cdot}2$, $p < 0{\cdot}0005$ at right atrial pressure of 0 mm. Hg and 5 mm. Hg), but when compared with the arteries implanted for more than ten weeks, no significant difference could be demonstrated ($t = 1{\cdot}49$, $p > 0{\cdot}05$ at right atrial pressure of 0 mm. Hg; $t = 1{\cdot}12$, $p > 0{\cdot}1$ at right atrial pressure of 5 mm. Hg). The resistance to bloodflow through the graft had presumably fallen to about the same level as that through the coronary artery after ten weeks from implantation due to an increase in the number and maturity of the anastomotic vessels connecting the implant to the branches of the left coronary artery within the myocardium which was observed histologically (Section IV).

DISCUSSION.

Bloodflow in Internal Mammary Arteries Implanted into the Non-ischaemic Myocardium

The observation that only three arteries implanted into the myocardium which had not been rendered ischaemic, had a forward bloodflow and that two of these were minute, indicates that the presence of ischaemia was in some way necessary for the extensive development of channels between the implant and the coronary circulation. The proportion of implants with a forward bloodflow (25%) in this study agrees well with that observed by Vineberg (1946) who found that only approximately 20% of vessels implanted into the non-ischaemic myocardium were patent throughout their entire length. The presence of a back flow of arterial blood from 50% of these implants also showed that connecting vessels can arise without the presence of ischaemia of the myocardium.

Flow Patterns in the Long-term Implant

The flow of blood in the long-term implant was pulsatile in character (Figure 11) as it was immediately after implantation (Section II). The main component was a large forward wave which was followed by a small but definite reverse wave in some implants. Examination of the forward flow component demonstrated two subdivisions, a systolic and a diastolic. These two phases of forward flow were also seen in the intact mammary artery before its dissection from the chest wall but in this latter situation they were well defined and discrete (Figure 10). In the long-term implant these components of forward flow were close together and often merged. The general shape of the flow waveform had not changed therefore from that of the immediately implanted artery. It was reported by Provan, Hammond and Austen (1966) that the diastolic component of forward flow increased in magnitude with time. This was not the finding in this study where the diastolic component, was on some occasions, larger than the systolic component but by no means always.

Bloodflow in Long-term Implants

This study demonstrated that not only were 90% of those arteries which were implanted into the ischaemic myocardium for prolonged periods of time patent, but each had a measurable forward bloodflow. Disregarding the particular implant which had not only carried blood to the myocardium but also had made vascular connections with the lef lung, the remainder of the grafts delivered from 5·7 to 33·8 mls of blood per minute to the ischaemic myocardium (Table 6). This range of values was of the same order as that quoted by Vineberg, Munro, Cohen and Buller (1955) who observed a flow of 3 to 21 mls per minute 'up to several months' after operation, by collecting the blood in a graduated burette. A much smaller range (1 to 8 mls per minute) was found by Barner, Harada, Jellinck, Mudd and Kaiser (1967), over approximately the same period of time, using the electromagnetic flowmeter technique. Suma, Hammond, Buckley and Austen (1969), measured internal mammary implant and coronary artery flows in dogs, using the drop-counting method in the non-working heart perfused with a pump oxygenator and constant-pressure blood reservoir, and observed an average flow of 12 mls per minute in one year implants. Since the non-working heart preparation is so physiologically different from that of the intact heart, valid comparisons cannot be made with results obtained in the present study. The only comparable study of implant bloodflow in the literature, where flow values were quoted, was that of Provan, Hammond and Austen (1966), using the electromagnetic flowmeter method, but unfortunately no individual values were given in their paper; the quoted range varied from 1 to 28 mls per minute (mean flow), measured one to thirty weeks following implantation. The range of values observed in the present study was therefore of about similar magnitude. The same workers showed that when the implant flow was graphed against time the resting flow increased in a linear manner in implants older than six weeks, but they did not give the numbers of dogs used in this part of the study and the flow values in their implants. The evidence from the present study would suggest that at least for the first sixteen weeks after implantation there was an increase in forward volume flow with time, but after sixteen weeks the relationship was not clear; the wide scatter of values after ten weeks made it impossible to obtain a fit for an exponential curve. The main reason for this inability was that beyond sixteen weeks, there were values from only three dogs available, and those were at twenty-five, twenty-six and twenty-seven weeks. Two of these dogs had a low mean blood pressure and therefore their forward flow values were probably low for this reason. It was therefore impossible to predict from these figures the height of the plateau above the x-axis.

The significant increase in forward bloodflow in the period after ten weeks confirmed the histological and angiographic evidence of a greater number and maturity of anastomotic connections between the implant and the coronary circulation during this period.

The Proportion of the Cardiac Output carried by Long-term Implants

Measurement of absolute forward flow in the internal mammary implants took no account of differences, between individual dogs, in total bloodflow from the heart due to body size, breed and cardiac efficiency in the presence of a left ventricular infarct. The few published studies on bloodflow in these implants not only gave very little data but made no mention of these factors listed above which might have affected the absolute forward flow. For example, a 15 Kg. dog of inactive habit and with an ischaemic area occupying 50% of the anterior wall of its left ventricle might be expected to have a lower cardiac output than a 20 Kg. running dog with an ischaemic area occupying say 25% of its anterior left ventricular wall.

It has been shown in this study that forward volume flow in the implant varies in a linear fashion with the cardiac output ($r = 0{\cdot}772$, $p < 0{\cdot}001$). Unless the cardiac output in each dog in the study were kept at the same level, then a comparison of forward flow with duration of implantation would be very difficult to make. Since the cardiac outputs in this study varied widely (845 to 2,984 mls per minute), at the time the implant flows were measured, for reasons of anaesthesia, thoracotomy, ischaemia of the left ventricle, variations in size, etc., it might be expected that forward implant flow would also vary widely, for reasons of cardiac output level as well as, possibly, with duration of implantation. It seemed logical therefore, that the proportion of the cardiac output carried through the graft might provide a better index of forward flow through the implant when comparisons had to be made between individual dogs.

The relationship between this 'proportional' flow (mls per litre of cardiac output) and the duration of implantation was found in this study to be in fact a linear one, with a coefficient of correlation ($r = 0{\cdot}531$), significant at the 5% level for all values up to twenty-seven weeks after implantation. This demonstrates that forward flow in the implants increases with time to at least about six months. It would seem therefore, that the curve for absolute forward flow when plotted against duration of implantation probably reached a plateau too early, for reasons attributable to the level of cardiac output at the time when flow was measured, rather than to effects associated with the duration of implantation. The significant increase in mean value for the proportion of cardiac output carried by the implant after ten weeks confirmed the relationship shown by the coefficient of correlation during this time.

Additional Myocardial Perfusion from the Implant

Another surprising finding in this study was that although the total body weights of the seventeen dogs were in the range of 15 to 20 Kg., the left ventricular weights varied from 67 to 164 gm. Since an identical forward implant flow would be of greater benefit to a small ventricle than to a large one, the flow values had to be expressed per 100 gm. of left ventricular weight in order to make real comparisons of the value of the additional perfusion from the implants to the myocardium. This 'additional perfusion' from the implants varied from 4·2 to 25·7 mls per minute per 100 gm. of left ventricle, measured from two to twenty-seven weeks after implantation. The mean value obtained in the group implanted less than ten weeks previously was 8·93 mls per minute per 100 gm. left ventricle, which is considerably less than that quoted by Seeman (1968), who observed an additional flow from the implant to the myocardium of 13·0 mls per minute per 100 gm. left ventricle at six weeks following implantation. No figures are available from the literature for comparison with those from the group implanted longer than ten weeks.

The relationship between the quantity of blood perfusing the myocardium from the implant was shown to be exponential, and from the plot in Figure 13d the 'plateau' was reached at about twelve weeks. This corresponded to a value of 18 mls per minute per 100 gm. of left ventricle, which represents the mean maximum value for myocardial perfusion. This value is remarkably close to the mean value of 17·6 mls per minute per 100 gm. of left ventricle found for perfusion from the anterior descending branch of the left coronary artery at the point of its subsequent ligation (Tables 19 and 20). It would seem from this study that the original mean level of myocardial perfusion from the anterior descending branch of the left coronary artery is reached by the implant at about twelve weeks and the perfusion from the implant remains at about this level thereafter. This might suggest that the maximum perfusion level from the implant is related to that of the anterior descending branch of the left coronary artery which it has 'replaced'. It also means that implantation of the internal mammary artery is an adequate method of perfusing the ischaemic left ventricle in dogs.

Resistance to Bloodflow within the Implants

The high level of resistance to flow through the internal mammary artery in the first few weeks after implantation was most probably due to the small degree of anastomosis with the coronary circulation at this time. As the connections between them became more extensive and mature, so the resistance to flow within the implant decreased until it reached the level of the resistance to flow normally encountered in the intramyocardial branches of the coronary arteries. The values for resistance (mm. Hg per ml flow) plotted before the first ten weeks after implantation, suggested that the resistance was at a maximum in the first four weeks and then fell abruptly to a much lower level at five weeks, to decrease slowly thereafter. There was, however, a significant linear correlation between resistance and duration of implantation at both levels of right atrial pressure throughout the whole twenty-seven weeks ($r = -0{\cdot}498$ and $-0{\cdot}502$). The values could also be expressed as a reducing exponential function with a significant correlation coefficient of $-0{\cdot}62$. This curve, when drawn, was very close to the regression line for the linear equation.
The difference in the mean values in the group before and after ten weeks confirmed that this was a real decrease in resistance with time.

The resistance to flow in the anterior descending branch of the left coronary artery in this study was found to have mean values of 5·2 and 5·5 at right atrial pressure of 0 and 5 mm. Hg respectively (Table 22). This means that theoretically, the resistance to flow in the implant should fall to this level or slightly above. From the regression line in Figure 13e, it can be seen that this resistance would be reached at about twenty-six to twenty-seven weeks.

Comparison between Flow Values in the Implanted Internal Mammary Arteries and those in the Anterior Descending Branch of the Left Coronary Artery

Before the tenth week following implantation of the internal mammary artery into the myocardium, the absolute forward flow, with the proportion of the cardiac output, the perfusion of the myocardium by addition blood from the implant, were all statistically significantly less than the values obtained from the anterior descending branch at the point of its subsequent ligation 2 cm. from its origin from the left coronary artery. In addition the resistance to the flow of blood through the implant at this time was significantly greater than that experienced by blood in the anterior descending artery. After the tenth week, however, none of these parameters could be separated statistically between the implant and the anterior descending artery.

Thus after the tenth week following implantation the volume of blood carried by the implant was comparable with that carried by the anterior descending artery at its point of subsequent ligation, and therefore it took over ten weeks before the implant could restore to the left ventricle the amounts of blood by which it was deprived after ligation of the anterior descending branch of the left coronary artery. In addition, the proportion of the cardiac output removed by this ligation, was carried by the implant after this time. The only part of the circulatory pathway which differed between implant and the coronary artery was the presence of new channels within the implants and the new connections between the latter and the coronary circulation. It again took over ten weeks for the resistance in these new vessels to decrease to the level of resistance offered to coronary blood in the normal situation.

Thus after ten weeks, the implant in about 85% of dogs (seventeen out of twenty implants) became as effective in delivering blood to the 'ischaemic' myocardium as the normal artery of supply 2 cm. below its origin. These observations seem to demonstrate that implanting the internal mammary artery was an excellent method of revascularising the ischaemic left ventricle.

Summary of Section III

The main purpose of this section was to study the bloodflow through the internal mammary artery implanted into the ischaemic and non-ischaemic myocardium for prolonged periods. The proportion of the cardiac output carried by the implant, the extra myocardial perfusion from the implant and the resistance to flow in the implant were also studied. The bloodflow through the anterior descending branch of the left coronary artery at the point of subsequent ligation to produce ischaemia of the left ventricle (2 cm. below the origin of the branch from the left coronary artery) was measured, together with the proportion of the cardiac output carried, in addition to the myocardial perfusion from the branch and the resistance to bloodflow through it. The values obtained were compared with those from the implanted internal mammary arteries. The following conclusions were reached:-

1. 90% of internal mammary arteries implanted into the ischaemic myocardium for periods up to twenty-seven weeks had a measurable bloodflow.

2. Only three of twelve internal mammary arteries implanted into the non-ischaemic myocardium for periods up to thirty-two weeks, had a measurable bloodflow, although the flow was

minute in two of them. Six of these implants had a small backflow from their cardiac end when cut transversely; this blood was shown by gas analysis to be arterial, demonstrating minute connections with the coronary arterial system.

3. In dogs with an ischaemic lesion of the left ventricle, the volume flow varied from 5·7 to 33·8 mls per minute. There was an increase in forward volume flow in the implants at least until the sixteenth week, thereafter there was no apparent increase in flow. The possible reasons for this are discussed. When the volume flow in the anterior descending branch of the left coronary artery measured at the point of its subsequent ligation was compared statistically with bloodflow in the implants, it was shown that prior to ten weeks after implantation the flow in the implants did not reach the level in the anterior descending artery, but after ten weeks no significant differences could be found between the flow in the two vessels.

4. The proportion of the cardiac output carried by the implant increased linearly with duration of implantation.

5. The level of forward flow in the implant increased with the cardiac output in a significant linear relationship.

6. A linear relationship could be demonstrated between the

perfusion of the myocardium from the implant and the duration of implantation only for the first sixteen weeks. An exponential relationship exists for all values up to twenty-seven weeks.

7. The resistance to flow in the implants was found to decrease linearly with duration of implantation until at about twenty-six to twenty-seven weeks it reached the mean level of resistance in the descending branch of the left coronary artery.

8. When the values obtained for the anterior descending branch of the left coronary artery were compared with those of the implants, statistically different figures were obtained before the ten week period; after ten weeks the mean values for the proportion of cardiac output carried, the myocardial perfusion and the resistance to flow in the implant and anterior descending branch of the left coronary artery could not be separated statistically.

9. Cessation of the implant flow to the ischaemic myocardium for a period of one minute did not produce any detectable deterioration in cardiac function.

The significance of these results is discussed and attention drawn to the fact that this study is the first to measure the proportion of cardiac output in the implant, the myocardial perfusion from the implant and resistance to flow in the implant and compare these with values obtained for the anterior descending branch of the left coronary artery. This is also the first time the forward flow measurements in the implant have been analysed statistically and compared with those of the anterior branch of the left coronary artery.

SECTION IV.

MICROSCOPIC OBSERVATIONS IN THE IMPLANT AND THE MYOCARDIUM.

INTRODUCTION

The demonstration that blood flows in the internal mammary artery implant from the moment of its insertion to at least one hour later, and also the observation that in the majority of these grafts bloodflow is present at intervals up to about thirty weeks, is surprising. The microscopic changes occurring within both the implant and myocardium in the immediate post-operative period have received scant attention, whilst those occurring some weeks or months later have been more documented (Vineberg, 1946; Bellman and Frank, 1958; Pearl, Joseph, Citret and Kallemeyn, 1959; Maruyama, Warren, McCombs, Vickery and Brener, 1966; Ahlberg, Seeman and Ahren, 1968). Despite this existing documentation, the sequence of events following implantation up to thirty weeks is not clear. In this section a detailed account is made of changes occurring within the implant and myocardium together with a description of the pattern of small vessel anastomosis between the two. In addition the importance of the adventitial vessels of the implant is stressed; these vessels until now, have received little or no attention in the development of anastomosis between the systemic and coronary circulations after internal mammary artery implantation. The histological features of acute myocardial ischaemia alone have been studied in a small number of hearts, for comparison with the changes observed after the production of ischaemia and subsequent implantation of the internal mammary artery.

Thickness of the Extracardiac Portion of the Internal Mammary Artery Wall

One of the observations made in this work (page 133) is that in internal mammary arteries implanted into the myocardium for prolonged periods of time, there is an increase in the thickness of the tunica intima in the distal part of the artery; these intimal changes were seen to a minor extent in the last distal centimetre of the extracardiac portion of the artery and often to a major extent in the implanted part of the artery. Crucial to the validity of the blood flow measurements made on the artery, is the demonstration that the lumen of the artery had not been encroached upon by a thickened arterial wall.

The measurement of arterial wall thickness has received only scant attention in the literature, but in particular the internal mammary artery has not been studied. From the tables published by Noordergraaf and Horeman (1958) of a variety of human arteries, from the aorta down to vessels 3 mm. in diameter studied histologically, the mean wall thickness of those less than 5mm. in diameter was 11% of the external diameter. In the branches of mesenteric arteries less than 1 mm. in external diameter, Van Citters, Wagner and Rushmer (1962), found a mean wall thickness of 3.5% of external diameter, using a quick freezing histological method. McDonald (1960) pointed out that shortening occurs in excised arteries and a resulting increase in wall thickness could then be expected. To date there has been no published evidence to support or refute this suggestion, but if this does occur then measurements made on histological sections will on these grounds tend to overestimate wall thickness. On the other hand, since fixation of the artery in formalin and other fixatives might be expected to produce some shrinkage, as happens in other tissues, this will further complicate accurate predictions of true wall thickness, especially since uneven shrinkage of longitudinal and transverse components might occur within the arterial wall. The value of 8% of external diameter for wall thickness was obtained for arteries from the aorta to the saphenous artery in the dog was observed by McDonald (1960), calculated from measurements of length from intact arteries followed by determination of wall density. In a series of carotid and femoral arteries in dogs, Petersen, Jensen and Parnell (1960) estimated mean wall thickness in vessels less than 5 mm. in diameter at 11.3% of external diameter, calculated from pressure wave velocity measurements.

In this present study, wall thickness both in the normal internal mammary artery and also in the extracardiac portion of the artery whose distal end was implanted into the myocardium, was measured from histological sections, and expressed as a percentage of the external diameter in order that comparisons be made of vessels within the same range of external diameter.

METHODS

Within ten minutes of cardiac arrest, four blocks of tissue were taken from each of forty dog hearts ranging from twenty-four hours to thirty weeks following implantation of the internal mammary artery into the left ventricular myocardium (Table 23). There were two groups of dogs, the first received an implant only, whilst the second had, in addition, ligation of the anterior descending branch of the left coronary artery. Details of these dogs and the methods employed have already been given in Section I.

The four blocks of tissue taken from each heart were from the following sites. The first was from the implant in the last centimetre of its extramural course. The remaining three blocks were from the left ventricular myocardium and included the tunnel and its contained implant plus surrounding myocardium. Each of the myocardial blocks was cut 1 cm. broad by 1 cm. long, through the whole thickness of the myocardium. The proximal and distal ends of each block were identified by different markings. The first of the myocardial blocks was taken from the first centimetre of the tunnel, that is, that most proximal part of the intra-myocardial course of the implant. The second myocardial block was cut from

Dog	Time after Implantation	Dog	Time after Implantation
3	32 weeks	39	9 hours
5	26 weeks	40	5 weeks
8	26 weeks	41	6 weeks
12	13 weeks	42	3 days
14	10 weeks	43	29 days
16	19 weeks	44	27 days
18	16 weeks	46	3 days
20	14 days	47	27 weeks
22	2 days	49	26 weeks
23	14 weeks	50	26 weeks
25	15 weeks	51	25 weeks.
26	14 weeks	52	24 weeks
30	11 weeks	53	8 weeks
31	10 weeks	55	13 weeks
32	10 weeks	59	18 weeks
33	9 weeks	60	18 weeks
34	8 weeks	61	18 weeks
35	7 days	69	22 weeks
36	2 days	70	19 weeks
38	1 day	71	19 weeks

Table 23

The length of time from implantation of the internal mammary artery in the forty dogs, whose implants and hearts were studied histologically. The first four dogs had no ischaemia of the myocardium, the remainder had ischaemic lesions of the left ventricle.

the mid-tunnel region whilst the last block was taken from the end of the tunnel and included a piece of myocardium beyond the end of the implant.

The blocks of tissue were immediately immersed in 10% neutral formalin and later processed for histological examination. Sections from the blocks were cut and stained with haematoxylin and eosin. In addition, certain sections were also stained with resorcin fuchsin for elastic fibres.

Acute myocardial ischaemia of the anterior wall of the left ventricle was carried out in seven dogs by ligation of the anterior descending branch of the left coronary artery, 2 cms. below its origin, as described previously (page 16), without implantation of the internal mammary artery. The dogs were allowed to survive from one to twenty weeks. Three blocks of tissue were cut from the infarcted area, one at the level of the ligature round the artery, the second in the mid part of the ischaemic area and the third at the apex close to the edge of the devitalised area. Sections were prepared from these blocks as described above, and stained with haematoxylin and eosin.

Measurement of Wall Thickness of Internal Mammary Arteries

Measurement of wall thickness was made on the internal mammary artery in ten normal dogs and also on internal mammary arteries implanted into the myocardium in twenty dogs, for periods up to twenty seven weeks. The segment of artery examined in the latter group was at a distance of 4 to 5 centimetres proximal to the point of entry of the artery into the myocardial tunnel; this was the point (5 centimetres) where blood flow was measured in those arteries. The histological sections were prepared as described above, and stained with haematoxylin and eosin. Measurements of wall thickness and external diameter were made using a binocular microscope with a fitted micrometer eyepiece, at one hundred times magnification. At this magnification the measurements were made to within 1 mm., which represented 0.01 mm. in terms of unmagnified dimension. Since the mean thickness and external diameter in all arteries in both groups were 0.25 mm. and 2.26 mm. respectively, the accuracy was to within 4% for thickness measurement and to within less than 0.5% for that of external diameter. Six measurements were made of each artery.

RESULTS

These are summarised in Table 24.

1. Histological changes in the first seventy-two hours

The changes seen in the first seventy-two hours following implantation of the internal mammary artery into the acutely ischaemic myocardium could be divided into three groups:-

(i) those occurring in the internal mammary artery both in its extramural and intramural course;

(ii) those in the immediate vicinity of the implant;

(iii) those occurring at a short distance (up to 1 cm.) from the implant.

Changes within the implanted artery

These were observed at four levels:-

(a) extramural,

(b) at 0·5 - 1 cm. of the intramural course of the implant,

(c) at 1·5 - 2 cm. of the intramural portion,

(d) at 2·5 - 3 cm. of the intramural portion.

	Event	Time from Implantation
1.	Implant invaded by polymorphs	24 hours. Over in 14 days
2.	Swelling of myocardial cells	24 hours
3.	Hyperaemia of myocardium	24 hours. Over in 14 days
4.	Recanalisation of thrombus in implant	7 days
5.	Disappearance of myocardial cells	2 - 4 weeks
6.	Red blood cells in new channels within implant thrombus	2 - 4 weeks
7.	New channels at end of implant	2 - 4 weeks
8.	Proliferation of intima of implant	2 - 4 weeks
9.	New vessels in intima	2 - 4 weeks
10.	Increase in adventitial capillaries	2 - 4 weeks
11.	Breakdown of elastic tissue in media	10 - 14 weeks
12.	New blood vessels in media	10 - 14 weeks
13.	Maturity reached in blood vessels around implant	16 - 20 weeks
14.	Arteriole-like vessels in implant thrombus	20 - 27 weeks

Table 24

The time sequence in the histological events after implantation of the internal mammary artery.

The features observed in the extramural course of the implant in the first seventy-two hours could be divided into those occurring in the peri-arterial area and those within the lumen. The peri-arterial changes were those of an increasing invasion of polymorphonuclear leucocytes into the soft connective tissue surrounding the artery and into the adventitia, although there was no sign of infiltration of the media or intima by those cells during this time. In all sections up to seventy-two hours there was unclotted blood within the lumen of each vessel although there was evidence of mural clotting at twenty-four hours at some part of each lumen. At forty-eight and seventy-two hours only a small proportion of the blood within the lumen remained unclotted.

In its intramural course the implant at twenty-four hours showed similar changes at the different levels. The adventitial coat contained only a few polymorphonuclear cells although they could also be seen in the intimal or medial layers. The lumen showed in addition to the changes mentioned above in the extramural part of the implant, many more polymorphs grouped around the edge of the lumen. At other places within the lumen very fine, pale stained thrombus was discernible, adherent to the endothelium, and probably of platelet origin. There was no evidence, however, of generalised thrombus formation.

At forty-eight and seventy-two hours the only new change in the implants was the greater numbers of polymorphs in the adventitial coat and to a lesser degree in the media and intima.

Crimping of the implant within the myocardium was seen in one heart. From Figure 14 it can be seen that when this occurs it must predispose to a reduction of flow through the implant and also to its early thrombosis. In the immediate vicinity of the implant at all levels, a small fresh haematoma could be seen surrounding the vessel (Figure 15). This haematoma at its maximum in all of the sections was about 10 mm. in diameter.

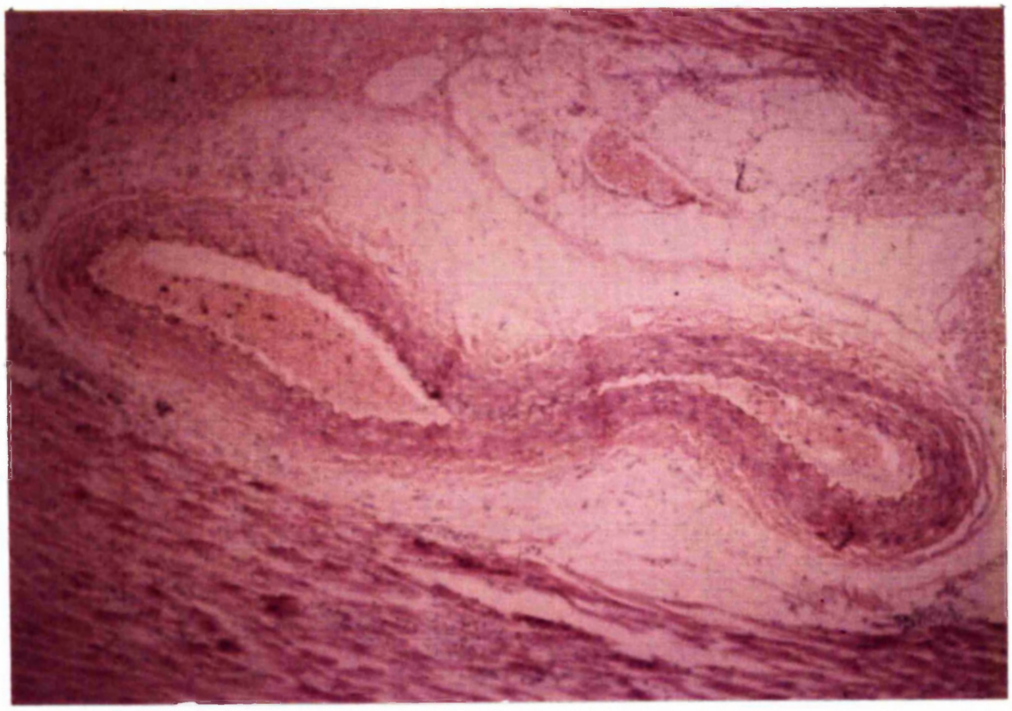


Figure 14

Crimping of the internal mammary artery within the myocardium.

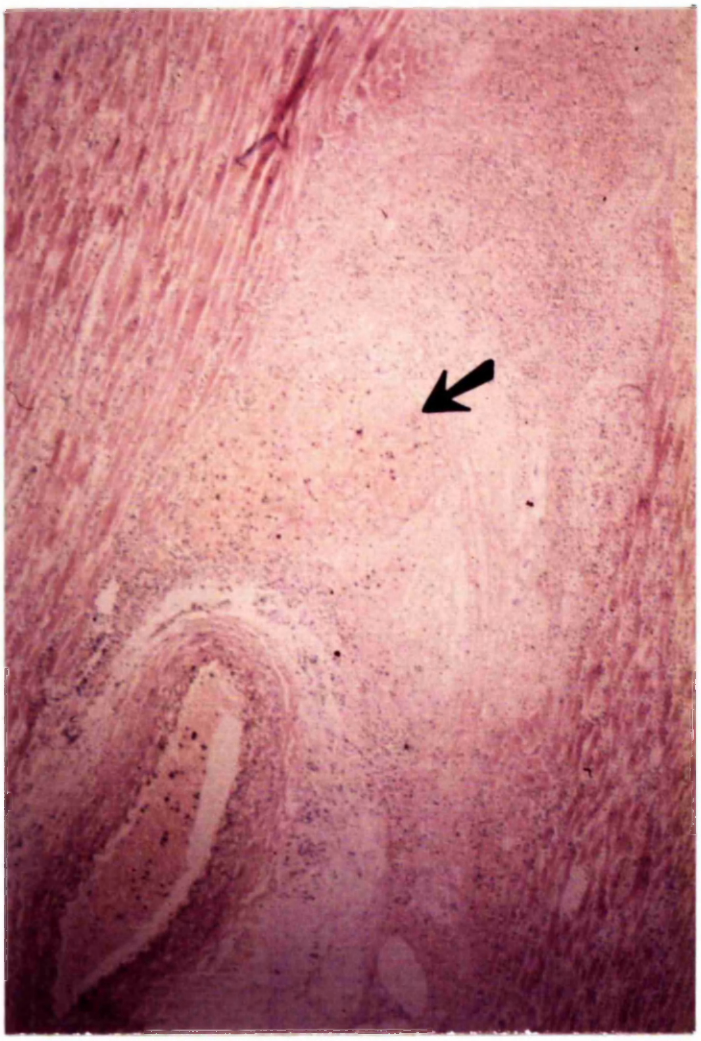


Figure 15a

Fresh haematoma surrounding the internal mammary artery implanted seventy-two hours previously (x56).

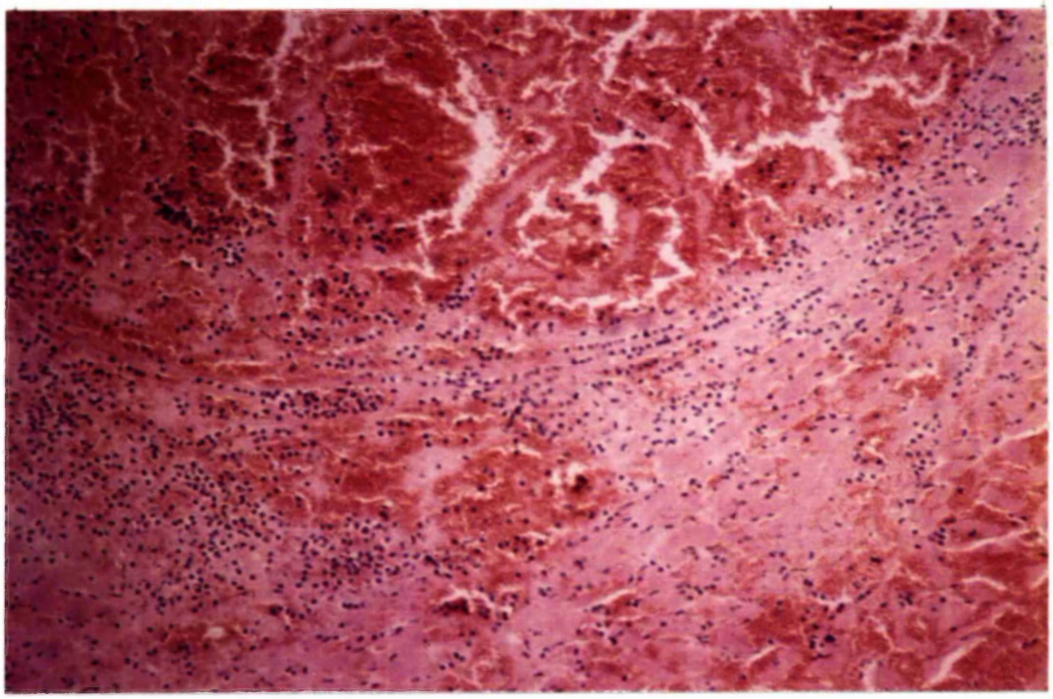


Figure 15b

Higher magnification of the haematoma (x140).

Changes in the vicinity of the implant

The extravasation of blood was partly compartmentalised by fibrin at twenty-four hours, although at seventy-two, the pool of red blood cells was not completely enmeshed by fibrin strands (Figure 16). By the end of seventy-two hours, the extravasated blood was not totally invaded by polymorphs which were present only in places. This suggested that the pool of blood might not in fact be entirely static, but that the constituent cells were in motion.

Radiating from the haematoma were streams of blood cells from ten to about 50 microns in width situated between the myocardial cells (Figure 17). These spaces between cells were on close inspection seen to be lined with endothelial cells and were therefore enlarged capillaries and venules. The capillaries and venules could be seen in places to join each other in a plexus formation (Figure 18) and occasionally to empty into small thin-walled veins (Figure 19). At twenty-four hours, these streams of cells showed no signs of thrombus formation within them but at seventy-two hours, some cells were enmeshed in fibrin. Swelling of myocardial cells surrounding the implant and widening of the spaces between the columns of cells was evident from twenty-four hours and intensified to seventy-two hours. The muscle fibres were in addition, less

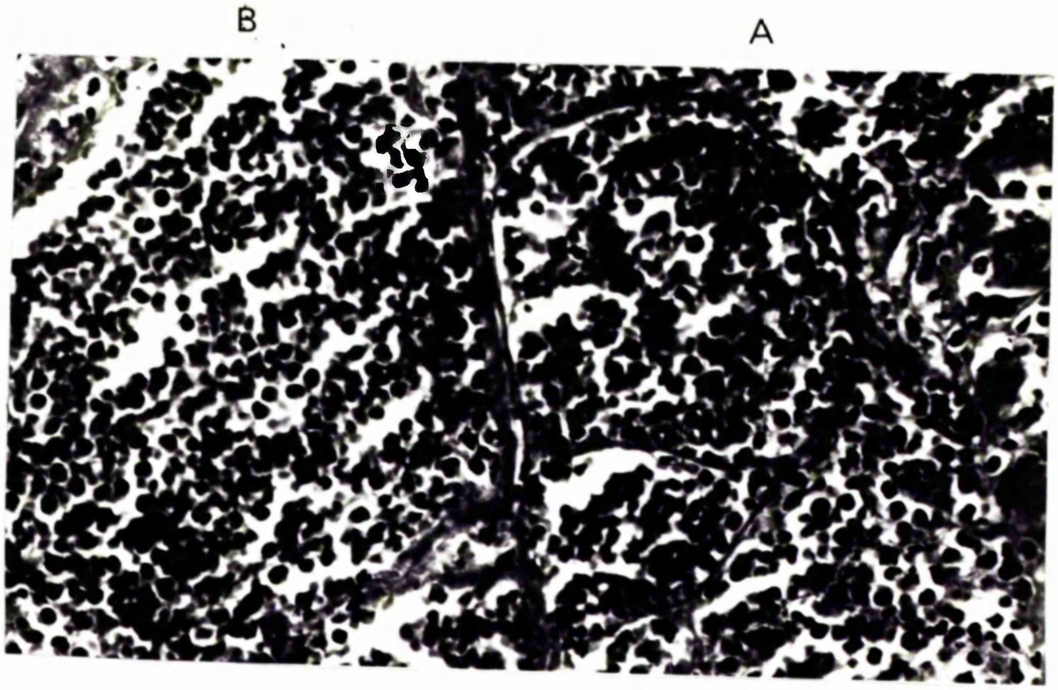


Figure 16

Red cells from the pool of blood surrounding the implant enmeshed in fibrin in area A but not B. (X 130)

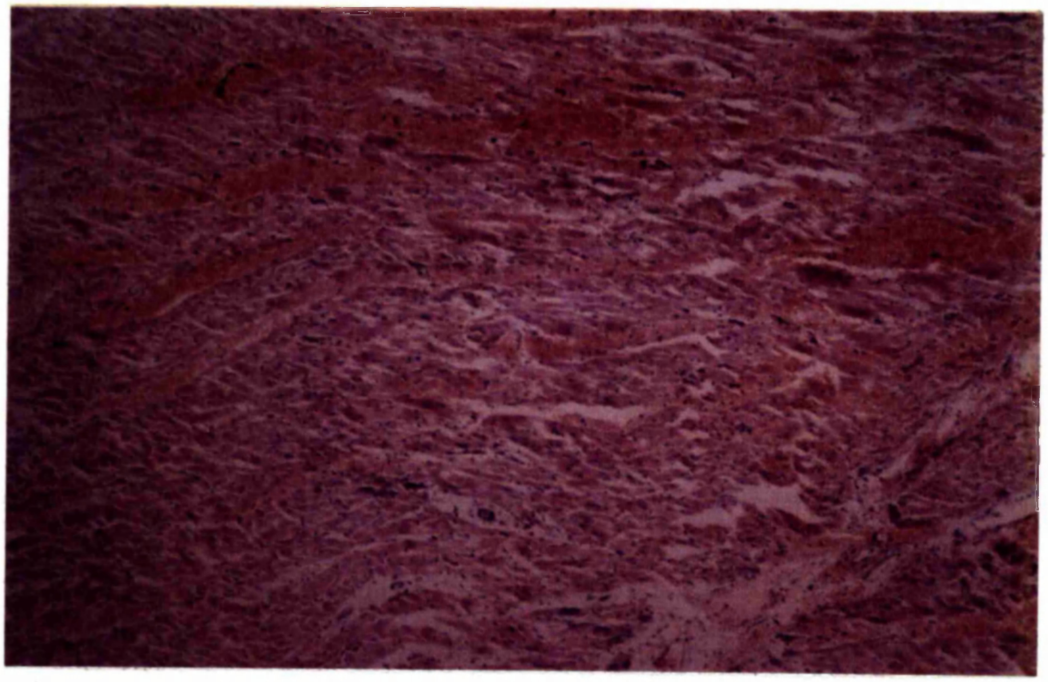


Figure 17

Streams of red cells within enlarged capillaries and venules in the myocardium, seventy-two hours after implantation of the internal mammary artery (x70).

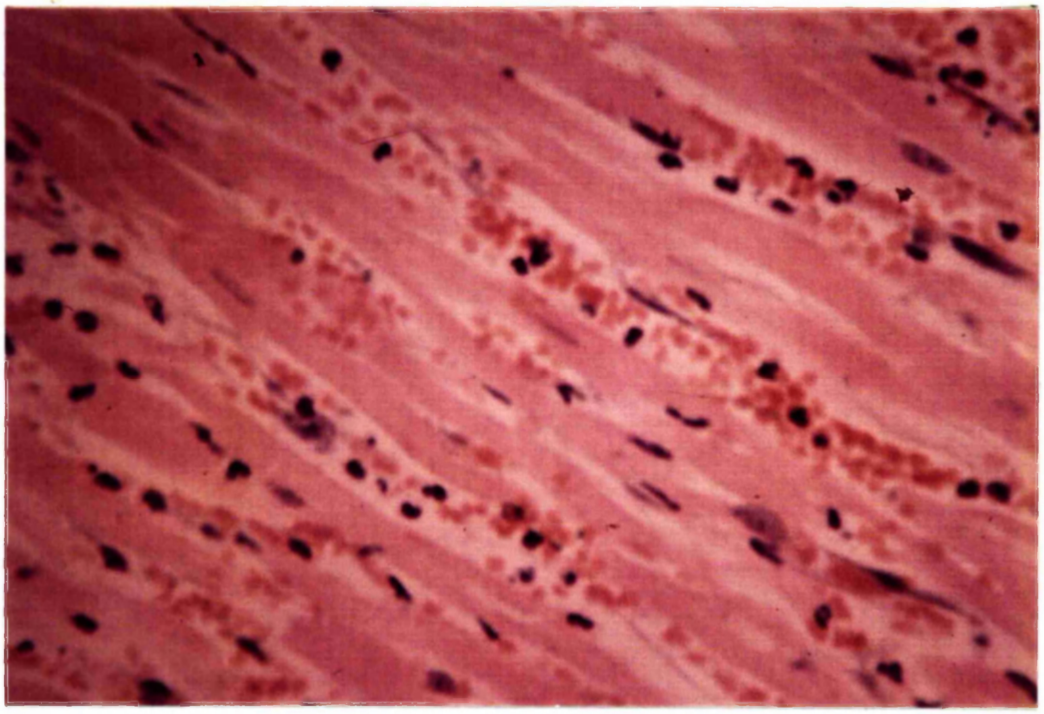


Figure 18

Capillaries and small venules within the myocardium, seventy-two hours after implantation of the internal mammary artery (x280).

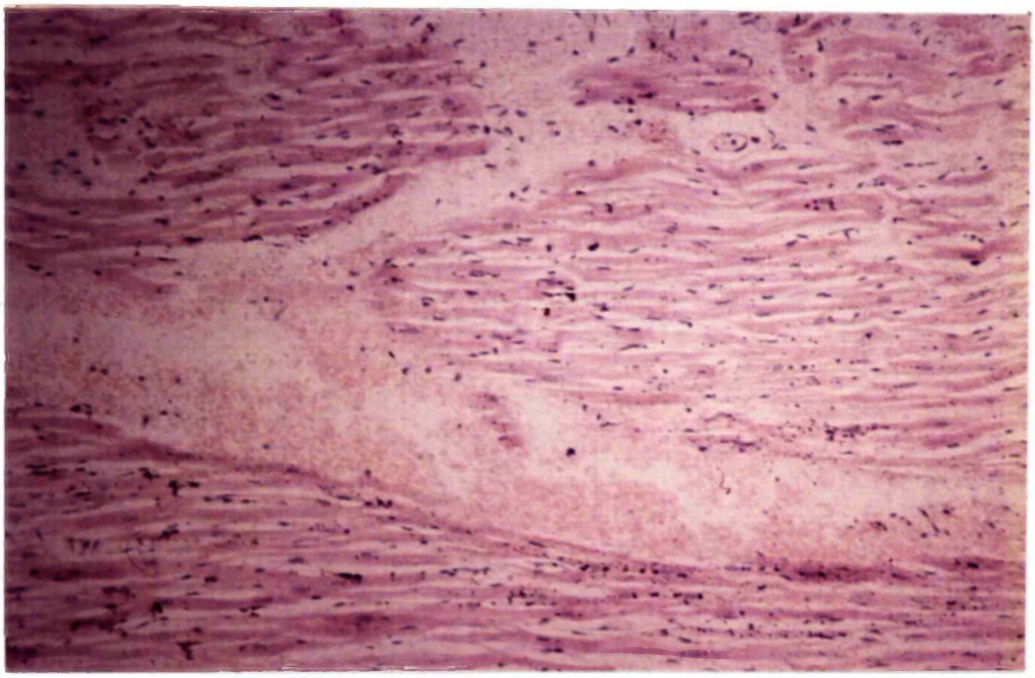


Figure 19

Small thin-walled vein connecting with venule and capillaries, in the myocardium (x140).

eosinophilic than normal. The whole myocardium in the immediate vicinity of the implant was already infiltrated with neutrophil polymorphs at twenty-four hours and quite densely so by seventy-two hours (Figure 20). No mitosis was seen in any cell type in the implant or myocardium from all hearts examined up to seventy-two hours.

Changes at a Distance from the Implant

Examination of the areas of myocardium at some distance from the implant and the haematoma revealed the presence of widened capillaries and small thin-walled vessels between the cords of myocardial cells. There were also engorged veins, arterioles and arteries in the area. The presence of engorged arterioles and arteries suggested that at least part of the increased vascularity of the myocardium was due to reactive hyperaemia. The uniform invasion of the whole area with neutrophil polymorphs was also evident even in the more distant areas of myocardium, and increased in quantity with time.

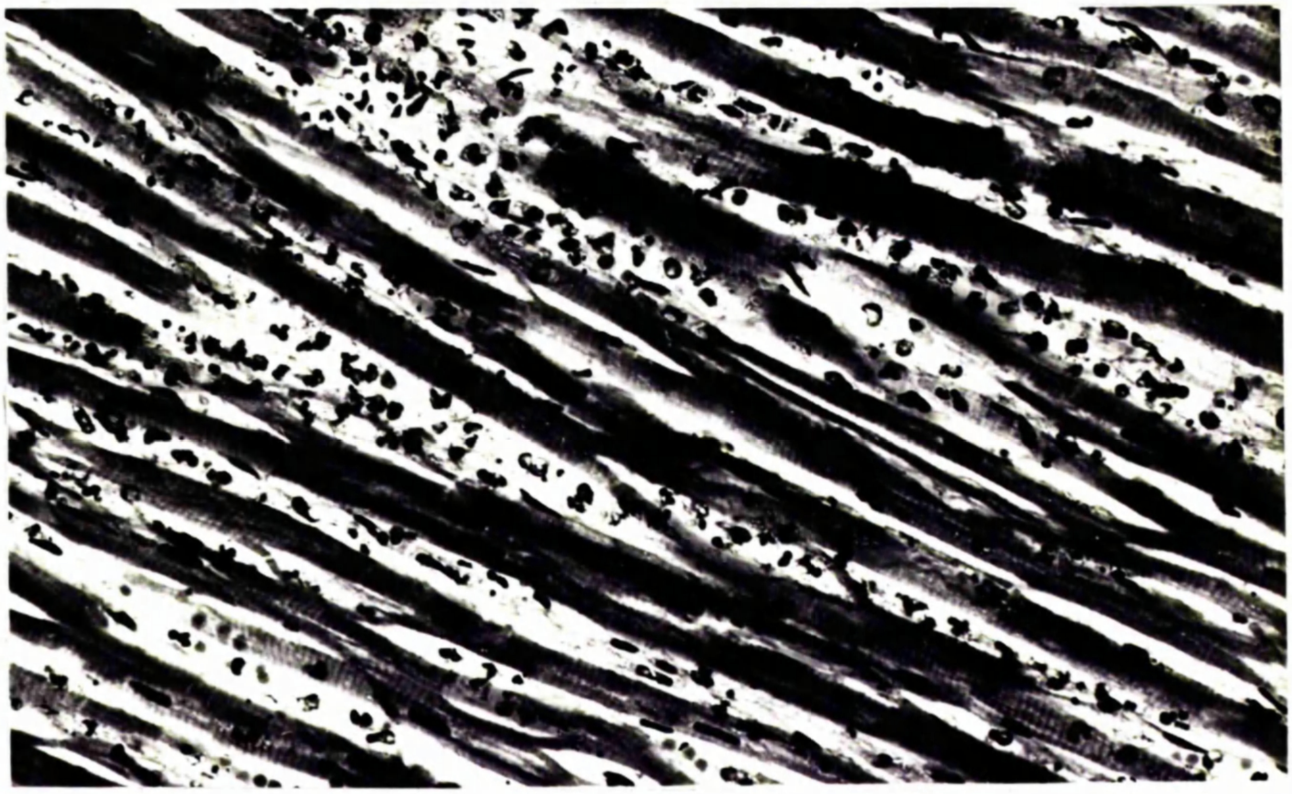


Figure 20

Infiltration of the myocardium by polymorphonuclear cells, mainly neutrophils, seventy-two hours after implantation of the internal mammary artery. (X 280)

II. Histological Picture Between the First and Second Weeks

By the end of two weeks the extramural portion of the implant still remained patent (Figure 21) as did the intramural portions except for the distal part of one implant which was thrombosed but which however, had begun to recanalise (Figure 22). This particular implant had been carried out only seven days previously, so that recanalisation can apparently occur in this short time. The walls of these early channels were thin and lined by flattened endothelial-like cells (Figure 23). No blood cells however could be seen within these vessels at this stage which although hollow might not have communicated with the systemic circulation. At the end of the first week, the capillaries and larger blood vessels of the surrounding myocardium were still observed to be widely open and filled with blood cells; this was taken as evidence of continuing hyperaemia in the vicinity of the implant, although this was no longer observed by the end of the second week.

The leucocyte infiltration which was apparent in the earlier stages was still intense at one week but had abated considerably by the end of the second week. Intact extravasated red blood corpuscles were still in evidence around the implant at the end of the first week but were no longer seen beyond that time.

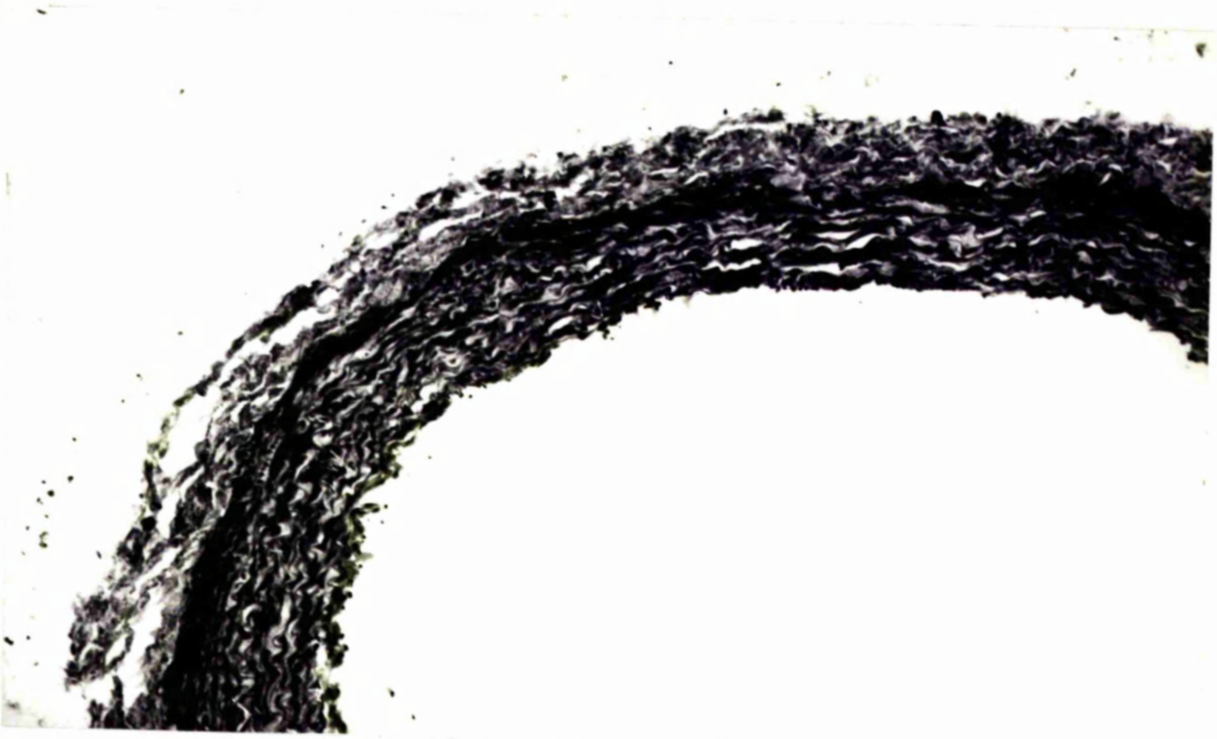


Figure 21

Patent extracardiac part of the internal mammary artery implanted two weeks previously. (X 32)

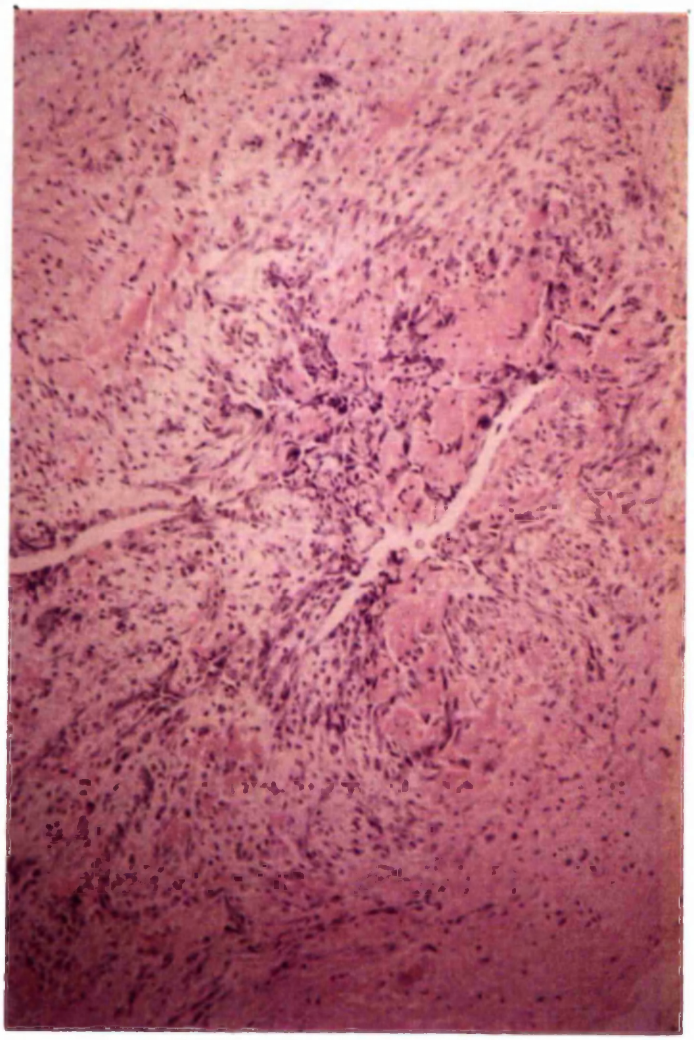


Figure 22

Recanalisation of the distal thrombosed portion of the internal mammary artery implanted one week previously (x140).

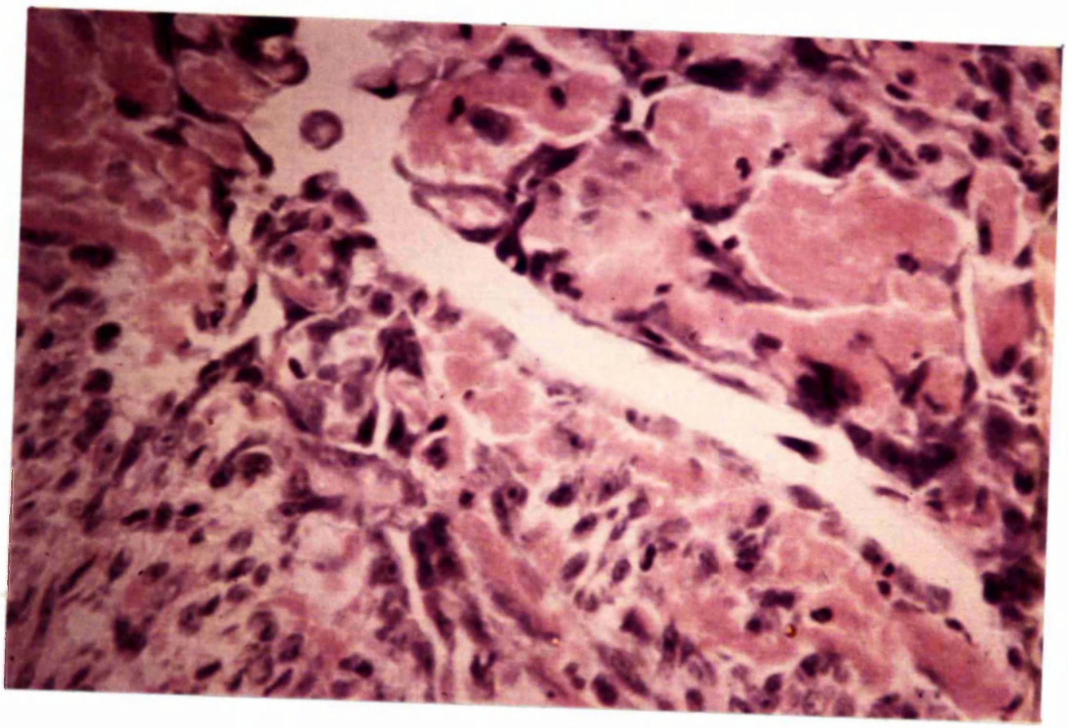


Figure 23

Higher magnification of the new channels seen in Figure 22 (x560).

The area of infarction and necrosis of myocardial cells was more obvious by the end of the first week when the myocardial cells were seen to be pale stained, with loss of cross-striation and swollen, disrupted nuclei. By the end of the second week, the necrotic tissue had almost all been removed, leaving a very loose, pale staining fabric. Amongst this tissue, arterioles, venules and capillaries could be seen, cuffs of normal myocardial cells occasionally surrounding them. Polymorphonuclear leucocytes were still to be found fairly evenly dispersed throughout this area.

III. Histological changes at four weeks

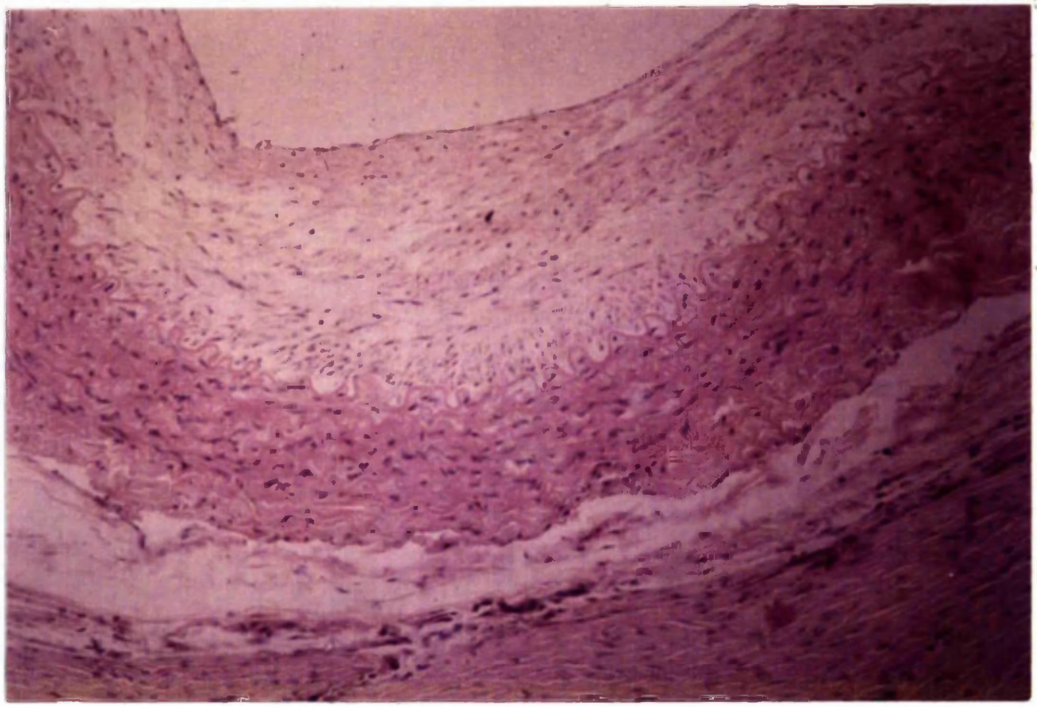
At four weeks the intra-myocardial portion of the implants could be divided into two groups:-

(a) Those remaining patent.

(b) Those which had thrombosed but had recanalised.

The intra-myocardial portion of the implants which had remained patent had a much reduced luminal size. In many cases this had been decreased to almost one-half of the original calibre (Figure 24). This reduction in luminal size was observed to be due to a great increase in the width of the inner coat which in the normal internal mammary artery is exceedingly narrow, consisting usually of a few fine collagen fibres together with other elements of loose connective tissue and the endothelium lining. However, in the patent implant, there was great thickening of this coat due to an increase in the amount of connective tissue. The internal elastic lamina with the elastic and muscular components of the tunica media still remained intact at this stage.

In those implants which had thrombosed but recanalised, the new channels numbered from one to four were present in greater numbers and total cross-sectional area the more distal the observation was made. They were present normally in the middle of the organised thrombosed area (Figure 25) but occasionally they were close to the



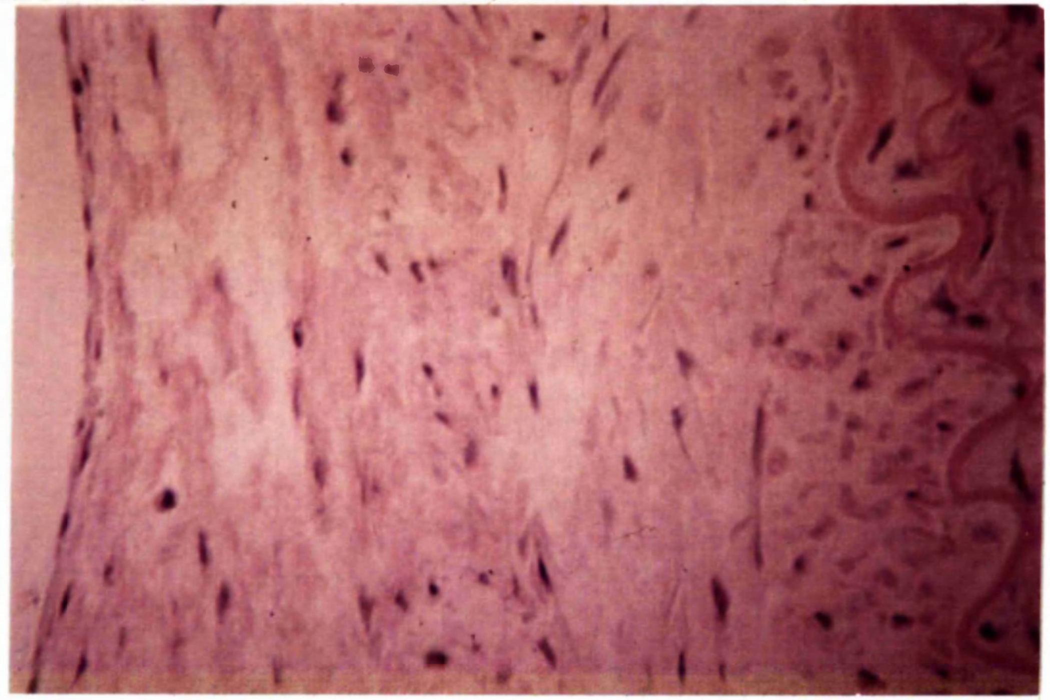


Figure 24

(a) Increase in the thickness of the tunica intima in the intramyocardial portion of the internal mammary artery 4 weeks after implantation. (X 70)

(b) Higher magnification of the thickened intima. (X 300)

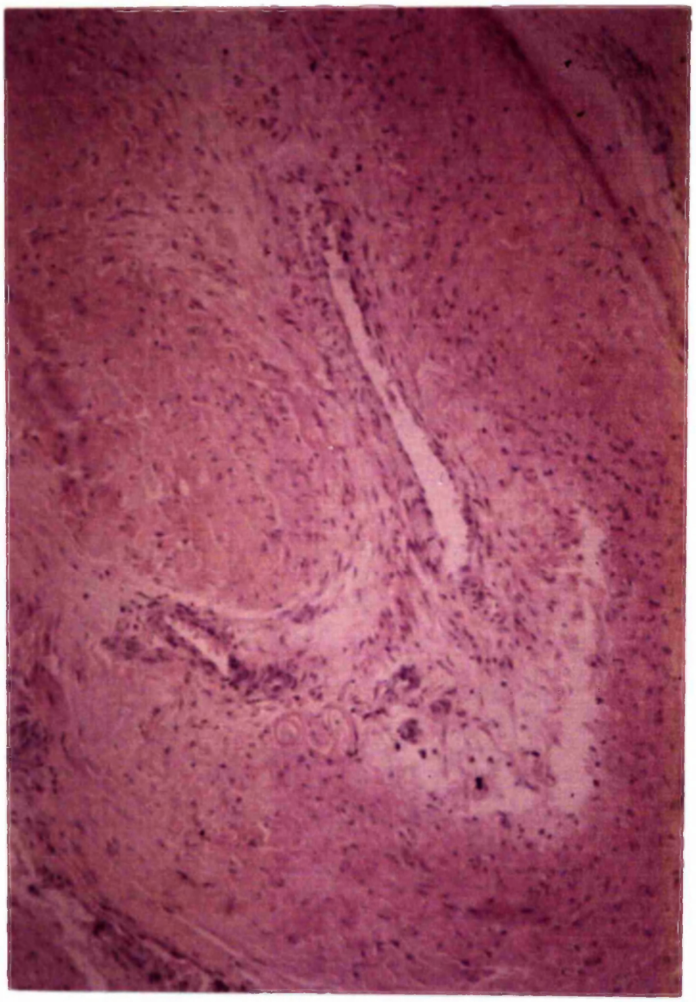


Figure 25

New channels within the thrombosed implant at four weeks (x100).

original endothelium, in a little 'bay' formed by the undulations of the internal elastic lamina and crimped endothelium. This type of channel seemed to utilise the original endothelium as a side wall. At this stage (four weeks) the new channels were still thin-walled but contained red blood cells, and thus evidence of communication with the circulation.

In the intra-myocardial part of all implants whether patent or thrombosed and recanalised, careful scrutiny of the tunica intima revealed in some sections the presence of capillaries and less frequently larger thin-walled vessels up to about 80 microns in diameter (Figure 26), which were not observed in earlier implants. In addition, a well developed plexus of capillaries and thin-walled vessels was evident in the adventitia and immediate peri-implant area, much more developed and extensive than in implants at an earlier stage. In sections of myocardium examined immediately beyond the distal end of this implant, many thin-walled vessels containing red blood cells could be observed (Figure 27). These vessels were grouped together as though they had emerged from the distal end of the implant and from their immature appearance could be differentiated from the intrinsic vessels of the myocardium.

The infarcted area and the haematoma surrounding the implant

Figure 26

New capillaries (arrowed) and a thin-walled vessel (b) in the tunica intima of the implant at four weeks (x280).

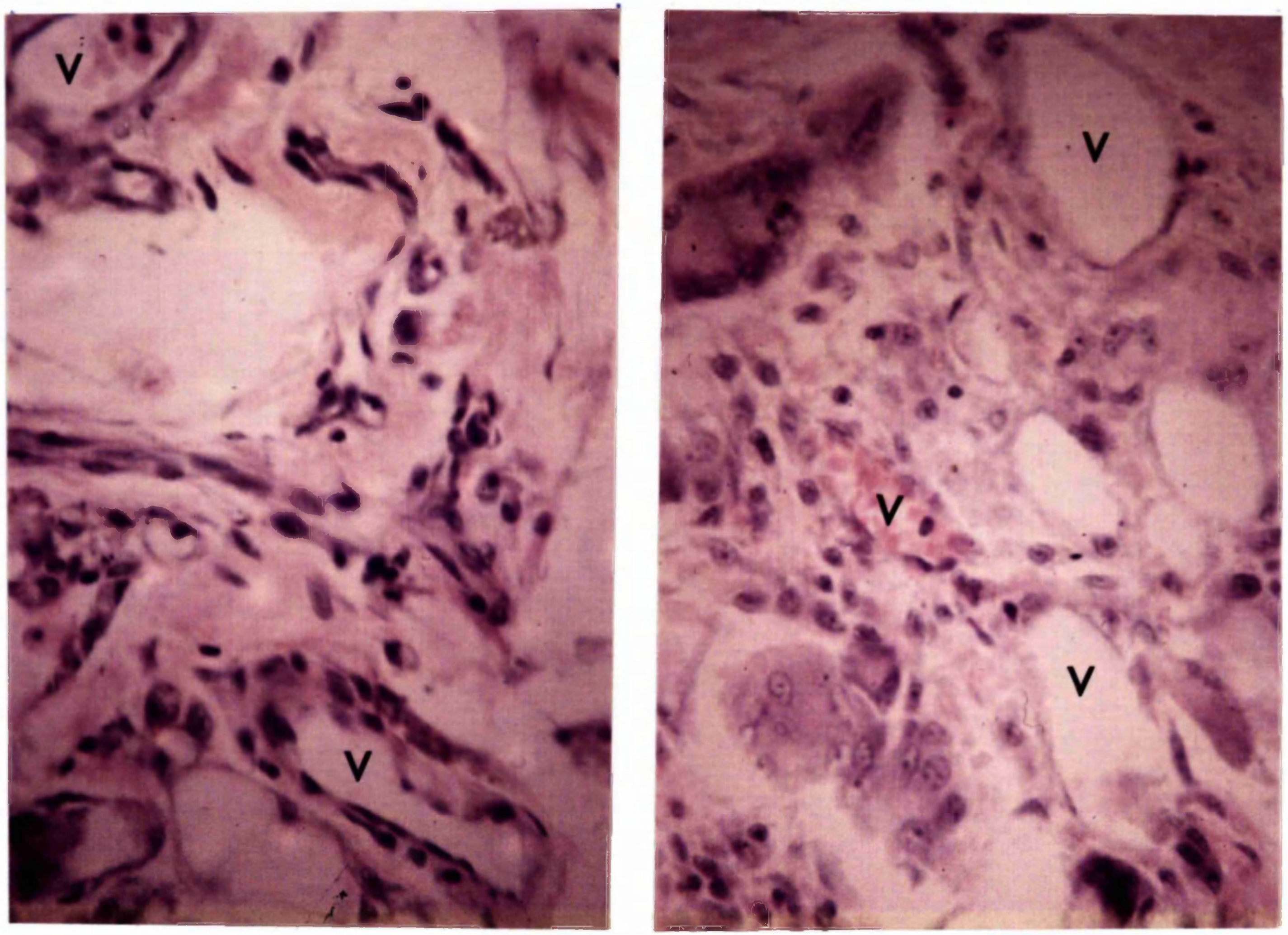


Figure 27

Thin-walled vessels (v) at end of the internal mammary artery implanted four weeks before (x20).

were at four weeks well organised, the myocardial cells having disappeared except for occasional islands of muscle tissue around blood vessels. The whole area was composed mostly of connective tissue in which blood vessels were present in large numbers (Figure 28). The blood vessels of the immediate area around the implant in what was probably the former haematoma area, were mainly thin-walled and from capillary size (i.e. about 6 microns) to about 20 microns in diameter, and well filled with red blood cells. Outside this area was the area of infarction (and possibly surgical trauma incurred during the fashioning of the tunnel). In this region the blood vessels were mainly capillary in type, but also present were the normal arterioles and venules, small arteries and veins of the coronary circulation, grouped together in the classical descriptive manner. These vessels all seemed to be more numerous than normal probably because they were more noticeable amongst the connective tissue of the infarct area than amongst normal myocardial cells.

Figure 28

Area of infarction of the left ventricle, close to the internal mammary artery (not seen) showing large numbers of blood vessels. (X 80)

Figure 29

Very much reduced lumen of the intramyocardial portion of the implant at ten weeks. (X 100)

IV. Histological appearances at ten weeks

By ten weeks there were no striking differences within the implants from those observed at four weeks except that in the patent (non-thrombosed) implants the internal thickening was yet more pronounced in the intra-myocardial portion reducing the lumen in some cases to a mere chink. In addition, the new channels within the thrombosed implants were observed to be more numerous and in some cases obviously branching within the thrombus. In close proximity to the implant the blood vessels which at earlier periods were thin-walled and small, were now thicker walled and much larger (Figure 29). There was also evidence of more mature fibrous tissue within the infarct area.

V. Morphology at fourteen to sixteen weeks

The changes from those at ten weeks were two in number. First, the elastic fibres in the tunica media in the intra-myocardial part were observed to be in various stages of dissolution, varying from simple breaks in these fibres to colour changes and indistinct outlines (Figure 30). Second, accompanying these changes in elastic tissue was distinct evidence of an increase in the number of capillaries and larger thin-walled vessels within the media (Figure 31). This can only be regarded as evidence of an increasing communication between the luminal channels and the blood vessels in the adventitial area.

The ischaemic area was by this time well demarcated and the blood vessels within still numerous, prominent and yet more mature than at ten weeks (Figure 32).

VI <u>Morphology at twenty weeks</u>

By the twentieth week, the new medial vessels were still more obvious but the most striking change found at this time was in the maturity of the vessels around the implant, which was by this time surrounded by vessels of various calibres, the largest of which were certainly larger than arterioles (Figure 33).

VII. <u>Microscopic appearances at twenty-seven weeks</u>

By the twenty-seventh week the only change was in the morphology of the new blood vessels within the implant. Whereas previously these were thin-walled and often of non-circular outline, they were now largely of arteriolar appearance with a well rounded contour and a thick wall (Figure 34). Close inspection of the walls of these vessels showed that they were composed of concentric cells which had the appearance of smooth muscle. The nuclei of the endothelial lining were flattened and small, but those of the wall were spindle shaped and had prominent nucleoli. The origin of these new mural cells was obscure, but they could have originated from cells within the matured thrombus which have been shown in thrombosed veins to be virtually identical with smooth muscle cells (Cliff, 1963 and 1965).

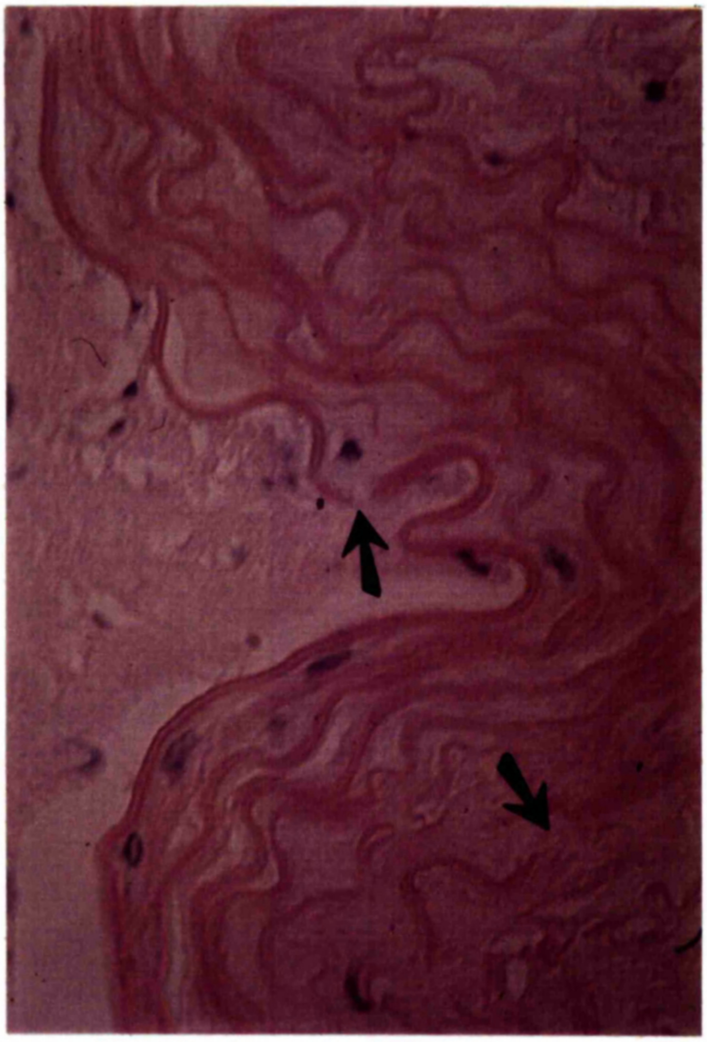


Figure 30

Elastic fibres disintegrating in the tunica media of the implant at sixteen weeks (x520).

Figure 31

Blood vessels in the tunica media of the implant at 14 weeks. (X 240) a b

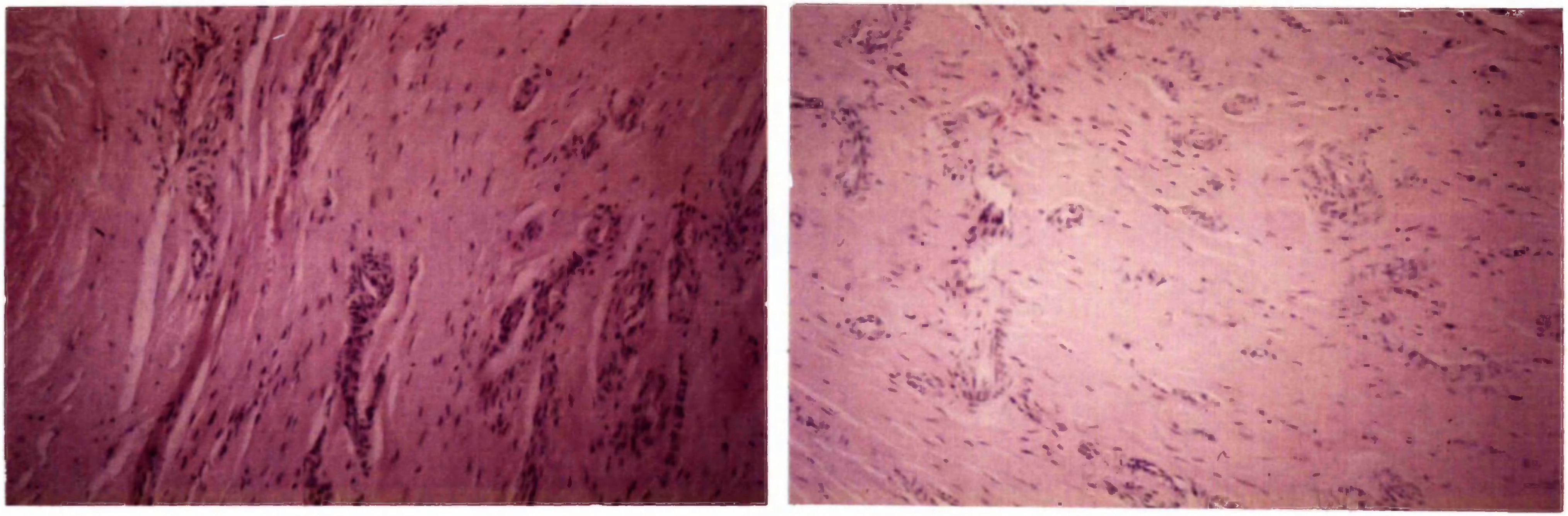


Figure 32

Blood vessels in the infarcted area close to the implant at fourteen weeks (a) and at five millimetres distance (b) (x100).

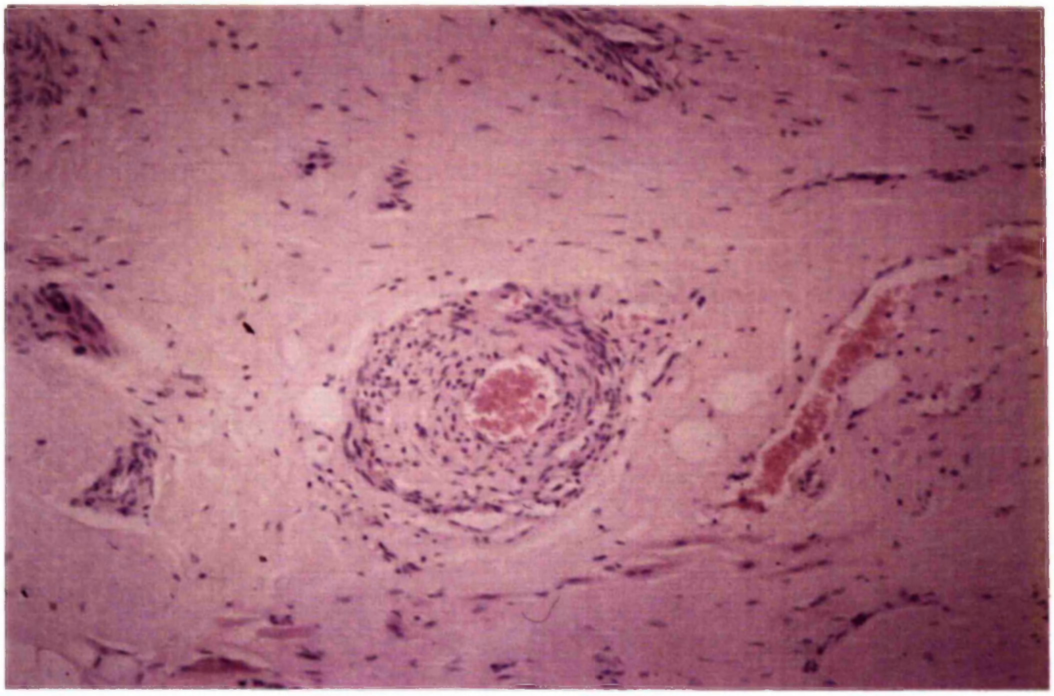


Figure 33

Blood vessels in the immediate vicinity of the implant at twenty weeks (x100).

Histological Changes Observed in the Ischaemic Area in Dogs Without Implantation of the Internal Mammary Artery

The ischaemic areas from the hearts of seven dogs in whom ligation of the anterior descending branch of the left coronary artery had been carried out, as described previously, but without implantation of the internal mammary artery, were examined.

Observations made of the infarcted area of the left ventricle one week following ligation of the anterior descending branch of the left coronary artery, showed that the main histological feature was one of coagulative necrosis of the myocardium. The whole area was pale and stood out in contrast to the darker stained normal surrounding tissue. The whole necrotic area was infiltrated with polymorphonuclear leucocytes, whilst at the edge of the infarct, these cells were in greater numbers. Small areas of intact muscle cells could be discerned but only with difficulty within the necrotic area. Arterioles and venules, some empty, were observed usually close to the islands of intact cardiac muscle.

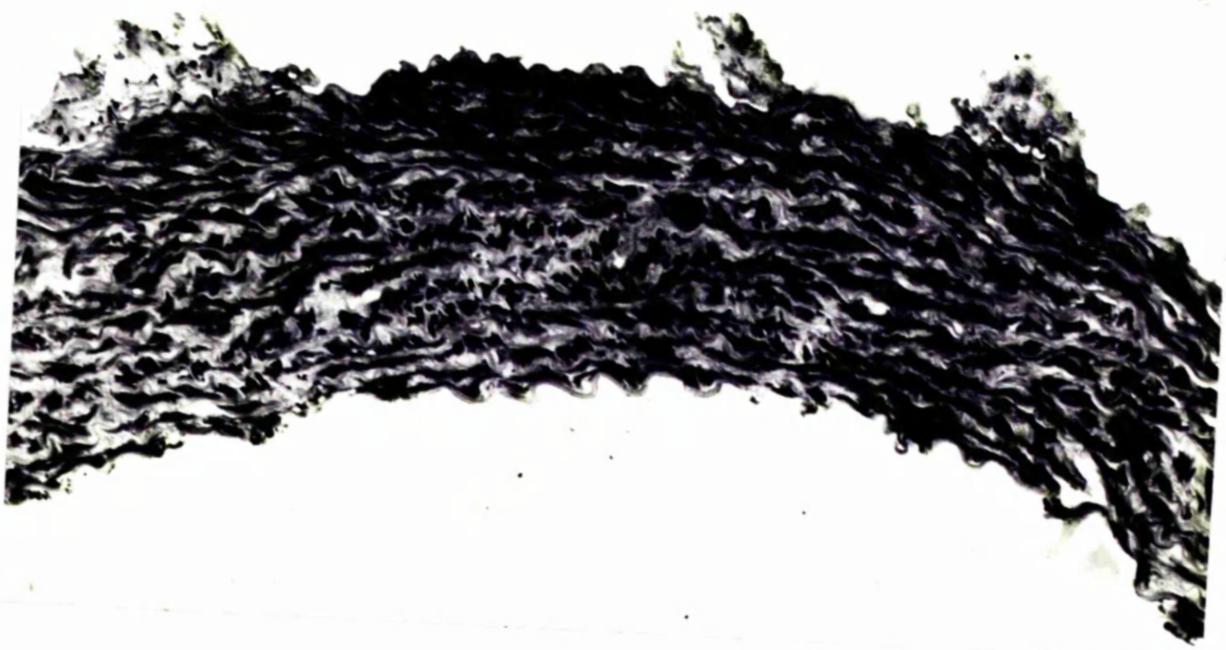
At the end of the second week, the picture had changed dramatically, the necrotic muscle had disappeared except in very small areas, leaving behind a very loose pale staining tissue, which probably represented the fibbous skeleton of the myocardium, within which many capillaries could be seen. Larger blood vessels, of arteriole and venule size could be more clearly seen against this pale background. The edge of the infarct area was clearly defined at this time.

By the fourth week, the whole area looked more dense, due to an increase in connective tissue elements. Very few polymorphonuclear cells and macrophages could be seen, although capillaries seemed to be present in larger quantity. The larger blood vessels did not seem to be increased in number.

At the end of the sixth week, the histological picture had changed only in two respects, first the connective tissue within the area was much more dense, giving the whole area a much more solid appearance, and second, there seemed to be an increase in the numbers of small arterioles. By the tenth week, the infarct had been converted into a sheet of dense collagen tissue in which larger numbers of capillaries and small blood vessels stood out against a very pale background. The picture was unchanged in the two other dogs at sixteen and twenty weeks.

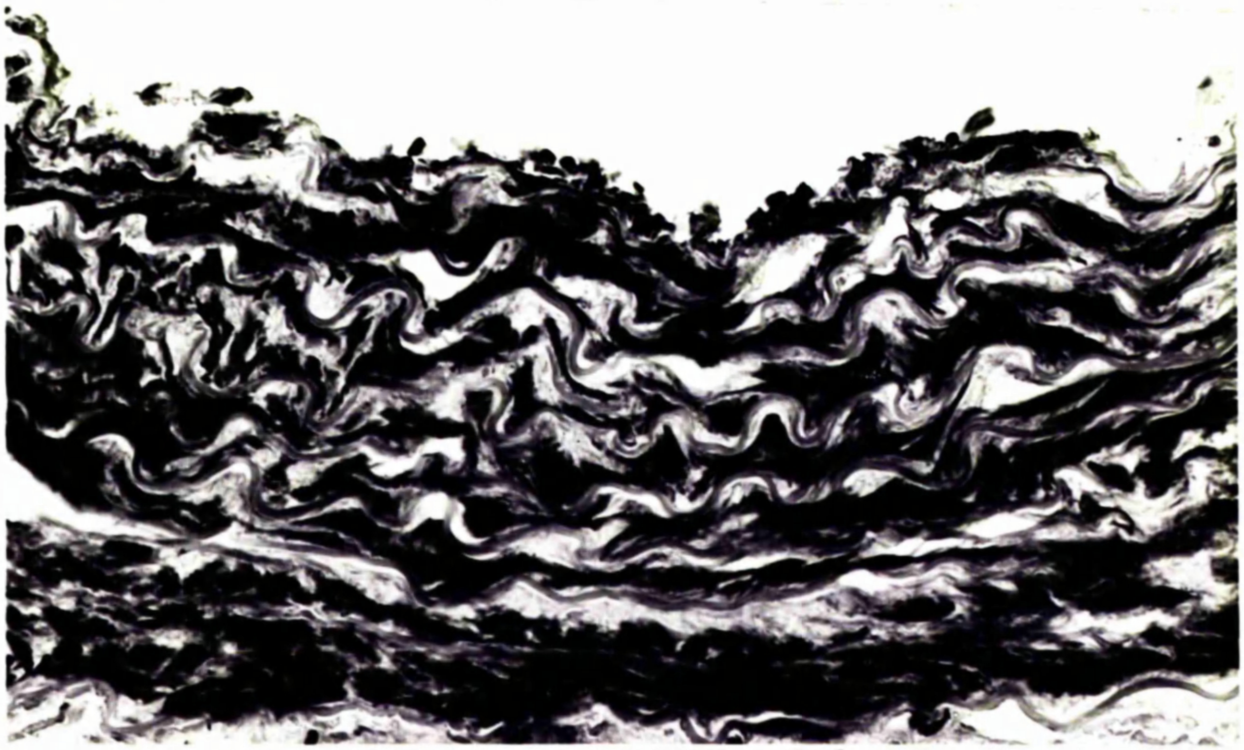
Measurement of Wall Thickness and External Diameter

These were made on twenty implanted internal mammary arteries in their extracardiac course, 4 to 5 centimetres proximal to the point of entry into the myocardial tunnel, and also on ten normal internal mammary arteries. The results for the individual vessels are given in Table 24a. In the implanted group, the external diameter varied from 1.8 to 3.0 mm., with a mean of 2.15 mm., the thickness of arterial wall had a range of 0.15 to 0.3 mm., with a mean of 0.24 mm. The thickness expressed as a percentage of external diameter varied from 7.5 to 16.0%, with a mean of 11.04% (standard deviation 2.20). In the normal internal mammary arteries, the external diameter range was from 2.0 to 3.0 mm. (mean 2.48 mm.); the thickness of the arterial wall varied from 0.16 to 0.38 mm. (mean 0.27 mm.). The mural thickness expressed as a percentage of external diameter varied from 8.0 to 15.5%, with a mean value of 10.85% (standard deviation 2.39). Using the student t-test with Bessel's correction for small numbers of values, the difference between the two groups was found to be not significant ($p > 0.40$; $t = 0.214$).



Cross section through the wall of the normal unimplanted internal mammary artery. (X 120)

Cross section through the wall of the extracardiac portion of the internal mammary implant, 5 cms from the heart. (X 120)



High power view of the wall of the extracardiac portion of the internal mammary implant, 5 cms from the heart, showing very thin intima. (X 240)

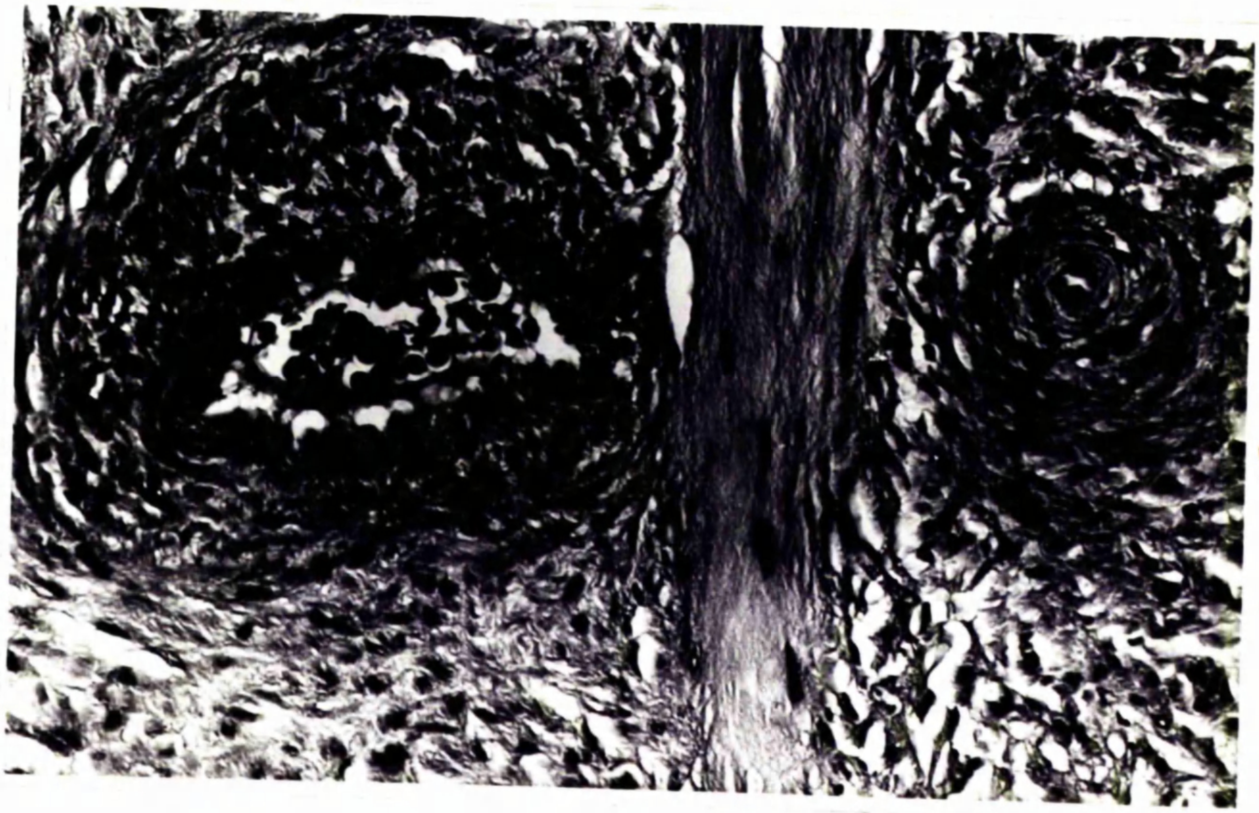


Figure 34

Arteriolar appearance of the new blood vessels within the thrombosed lumen of the implant, at twenty-seven weeks. (X 240)

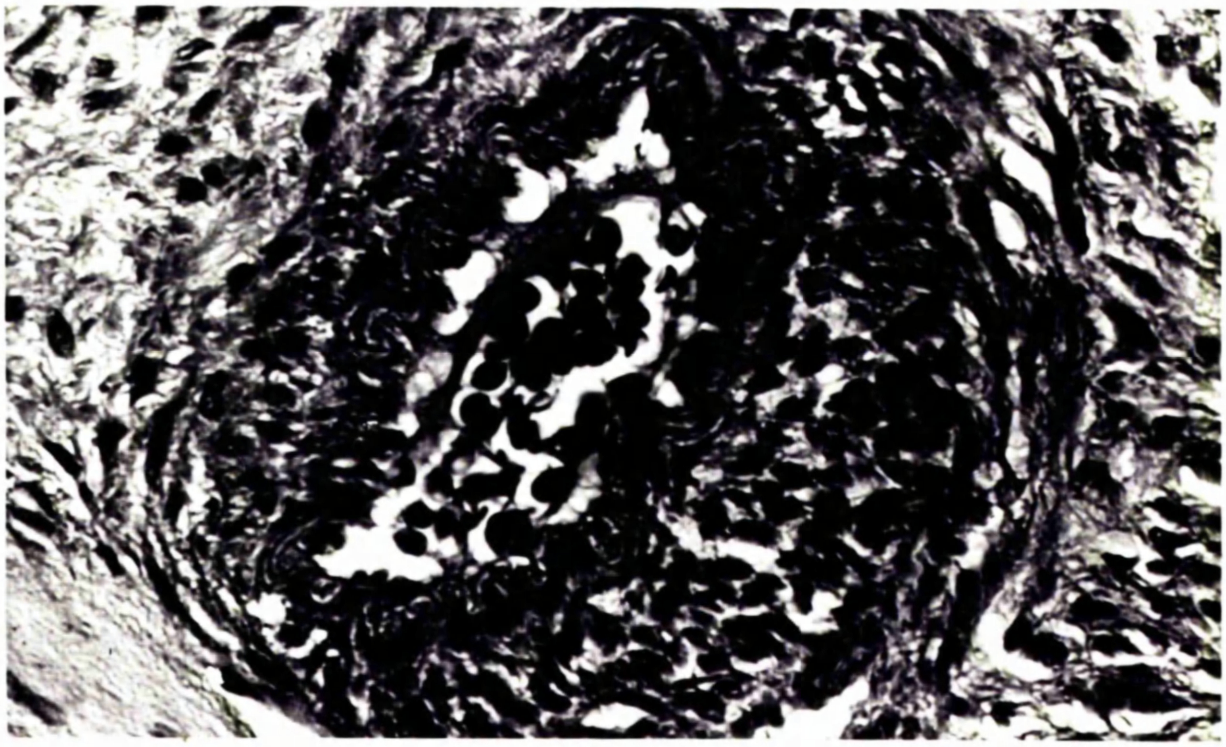


Figure 35

Higher magnification of the blood vessel seen in Figure 34 showing the endothelial nuclei. (X 500)

Figure 36a

The edge of the infarcted area showing the loose tissue from which the muscle cells have been removed; more normal myocardium can be seen above. (X 80)

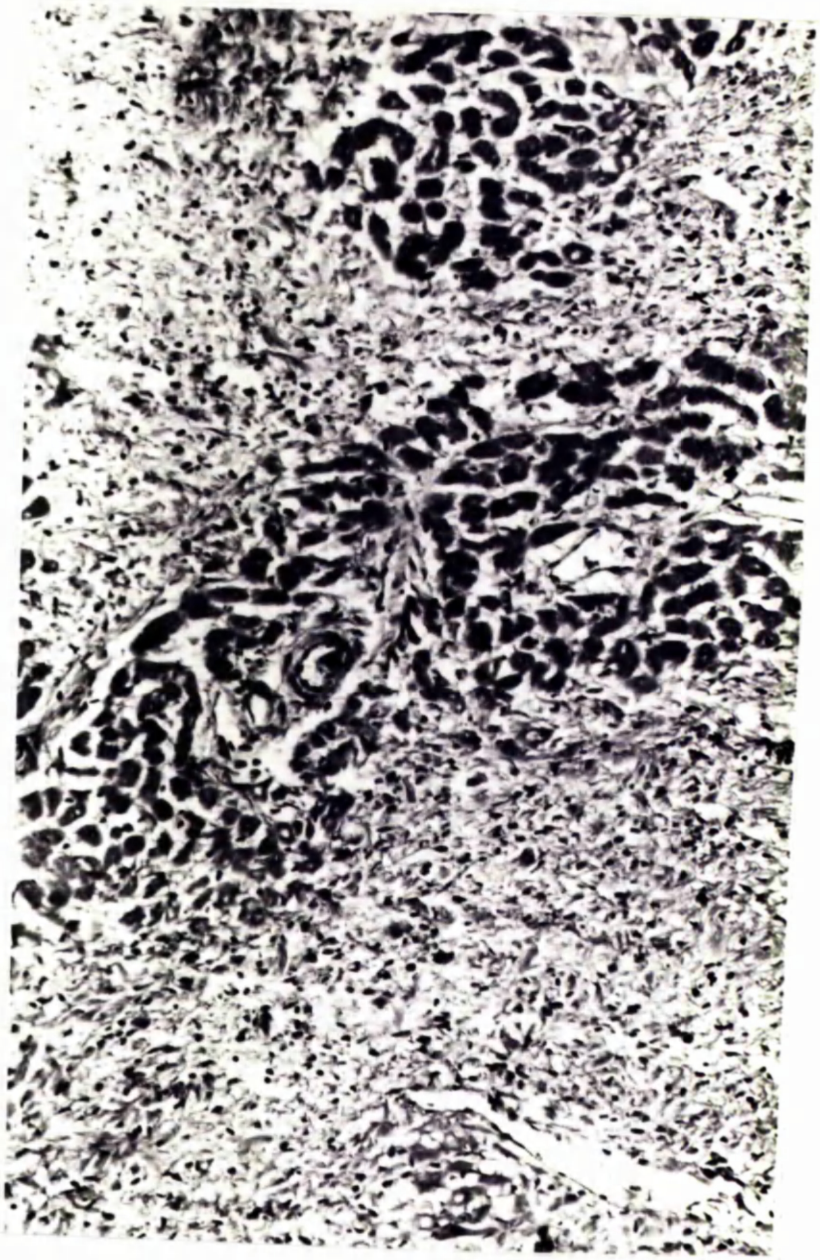


Figure 36b

Islands of cardiac muscle containing prominent blood vessels within a sea of infarcted tissue. (X 80)

DISCUSSION

Absence of Complete Occlusion of the Graft by Thrombus

In the first twenty-four hours following the implantation of the internal mammary artery, the most surprising feature of this study was the absence of complete occlusion of the implant by thrombus formation. In certain sections, evidence of thrombus formation was observed but was limited to small areas of the lumen adjacent to endothelium. By forty-eight and seventy-two hours this 'partial' clotting process had increased to include most of the cross-sectional area of the lumen. At no time, however, was it observed that the whole lumen was entirely thrombosed, there was always a small area even at seventy-two hours which was free of fibrin and in which the blood cells were of normal appearance.

The absence of total thrombus occlusion of the implant in the first twenty-four hours indicates that either the flow of blood through the implant had ceased but that there was inhibition of the clotting mechanism by some anti-coagulant process, or that there was some flow of blood through the graft. Although it has been shown experimentally that blood in ligated segments of arteries tends to remain fluid (Hanser, 1913; Mehrota, 1953), the presence, however, of small areas of clot formation at twenty-four hours, plus the gradual increase in that process over the succeeding forty-eight hours is rather against the anti-coagulant hypothesis in this setting. One is therefore forced to the view that the static pictures of histology represent a situation where in the early stages there is some bloodflow through the implant but as time passes, there is a gradual 'silting-up' of the vessel by thrombus formation probably due to slowing of bloodflow through it. If there is flow through the graft in the first seventy-two hours, no matter how small a quantity per minute, a large quantity of blood must either be accommodated within the myocardium or in some way pass through it during these three days; but the blood must eventually find a route through to the venous system of the heart wall. Even if the flow through the graft were as small as 1 ml. per minute throughout the first twenty-four hours, then 60 mls per hour, or a total of almost one and a half litres of blood would accumulate within the myocardium in the first day.

Extravasation of Blood within the Myocardium

The pool of blood cells lying around the implant in the first seventy-two hours measured some 10 mm. in diameter at a maximum in all of the sections examined. Since the tunnel through the myocardium was at the very most, 4 cm. long, the largest extravasation within the myocardium could not have measured more than

$$\frac{22}{7} \times 0{\cdot}5^2 \times 4 = 3{\cdot}10 \text{ mls of blood}$$

Even admitting a large error in these calculations, it is clear that if this quantity of blood represented the total blood which had passed from the implant into the myocardium then bloodflow in the implant must have ceased within the first few minutes of the mammary artery being placed within the tunnel in the myocardium. The strong evidence of bloodflow in the extramural portion of the graft from actual measurements of flow by the electromagnetic flowmeter method detailed earlier in this work suggests that bloodflow continues in the graft for at least one hour following implantation (see Section II).

The finding that the haematoma itself at twenty-four hours is only in part compartmentalised by fibrin strands and that even by seventy-two hours is still not completely enmeshed, suggests that either some local anti-coagulant or fibrinolytic factor is active, or that the pool of extravasated blood is not static but in motion, or indeed that a combination of these factors is at play.

Polymorphonuclear leucocyte behaviour in the vicinity of the implant

The behaviour of the polymorphonuclear leucocytes in their relationship to the haematoma was also interesting. In this study these cells had not invaded the haematoma in the first twenty-four hours and indeed at this time were present only in scant numbers on the edge. At the end of three days, only small parts of the extravasation were infiltrated with white cells, although a fairly large population of these polymorph cells were to be found throughout the myocardium surrounding the implant at this time.

The observations made on the implant itself including the absence of generalised thrombus occlusion of its lumen, the surprisingly small size of the haematoma with the absence of complete fibrin enmeshment throughout its structure, plus the apparent reluctance on the part of the polymorphonuclear leucocytes to invade the haematoma, pointed to the conclusion that the pool of blood lying outwith the implant was not entirely static in the first twenty-four hours.

The presence of greater quantities of thrombus within the implant itself by seventy-two hours, together with the presence of neutrophil polymorphs in small areas of the haematoma surrounding the implant at this time, suggested that there was a gradual curtailment of flow by this time.

Changes in the Blood Vessels Within the Myocardium

The most striking feature seen in the blood vessels of the myocardium was their dilatation. These changes were evident by the end of twenty-four hours following implantation and were most pronounced by the end of the third day continuing for at least one week. By the end of the second week, these vessels were of normal dimensions. The changes in the blood vessels strongly resembled those of reactive hyperaemia which is seen when damage to the cells of an organ or tissue occurs. This view was strengthened by the observation that arterioles as well as capillaries and venules were dilated. This reactive hyperaemia was most likely in response to acute ischaemia of the myocardium, plus the trauma inflicted on the myocardium by the tunnelling process.

The pool of blood surrounding the implant may act, in part, as a small reservoir in diastole when it is augmented from the implant. In systole when the implant flow (like that of the coronary arteries) is halted or even slightly reversed, the myocardium may squeeze this reservoir and in part disseminate it through the 'spaces' in the myocardium. These 'spaces' in the myocardium were shown histologically to be small blood vessels from about 6 microns to about 20 microns in diameter.

During the tunnelling process, great numbers of these vessels must have been cut across, leaving the open ends in direct contact with the blood flowing from the implant. Thus a pathway for blood from the implant might well have been established. This hypothesis is supported at least in part by the histological and flow studies.

On casual observation it might seem that the blood vessels of the myocardium were engorged with extra blood from the implant, but close examination showed that the arterioles of the myocardium were also widened and packed with blood cells. Thus the blood within the capillaries and venules might have been a mixture of implant blood plus a relatively greater contribution from the arterioles swollen from reactive hyperaemia.

Vineberg (1946) claims that blood from the implant flows into large thin-walled spaces which he called sinusoids, and from these to the myocardial capillaries and hence on to the venous system. These sinusoids were not identified in the present study. Spaces were seen occasionally around the implants in the early stages, but these were irregular in shape and appeared to be artefacts made in the tunnelling process. Apart from the blood in the haematoma, the remainder of the red blood cells were found to be in vessels which had a thin endothelial lining. These dilated thin-walled vessels between the columns of cells were capillaries and venules. The presence of sinusoids is not essential however, in the concept of a pathway from implant to the venous system in the early post-implant period.

Changes Observed in the Ischaemic Myocardium

The histological picture of the changes observed in the ischaemic myocardium in this study was complicated by the presence of the implant and its associated trauma to the myocardium, plus the presence of the haematoma surrounding the implant. In order to clarify what changes were brought about by the implant and what changes were brought about by the ischaemic process, a limited study (on seven dogs) was carried out for comparison in which only the ligation of the anterior descending branch of the left coronary artery was carried out without implantation of the internal mammary artery. This study of the changes effected by ischaemia alone was made from the end of the first week to the twentieth week, and the results have been described above.

Essentially the cardiac muscle fibres of the left ventricle were swollen and pale at twenty-four hours following ligation of the anterior descending branch of the left coronary artery and implantation of the internal mammary artery. By seventy-two hours this process had intensified. In places actual dissolution of cells could be observed. The early histological changes of myocardial infarction have been described at length by Lodge-Patch (1951). As early as twenty-four hours neutrophil polymorphs could be seen throughout the myocardium, increasing in numbers up to at least the third day. Careful observations by other workers have shown infiltration by these cells from as early as six hours following sudden coronary artery occlusion.

By twenty-four hours, however, an apparent paradox exists in the observation that within a sea of dying and dead muscle cells there were great numbers of vessels swollen with blood cells. This reactive hyperaemic process, however, was probably in response to the presence of damaged cells which liberate some substance (thought to be similar to the histamine-like substance in the skin) but perhaps some other chemical in the myocardium. The hyperaemic process occurred too late to be of significance in the resuscitation of muscle cells in the area, since the great majority of these would not be viable one hour following coronary artery occlusion, but would have been of value in keeping muscle cells on the fringe of the ischaemic area viable..

The changes observed in the ischaemic myocardium not in the immediate vicinity of the implant, were no different from those in the ischaemic myocardium in which no artery had been implanted at any stage, with two exceptions. First, in the implanted group at one week, the small vessels within the ischaemic area were more enlarged with blood, and secondly, from the fourth week there seemed to be larger numbers of vessels of arteriole size, and smaller, in the ischaemic area close to the site formerly occupied by the haematoma surrounding the implant, than in those hearts with ischaemia alone. This second difference was an observation which was not made more concrete by enumeration of these vessels, since this would have involved a more extensive study in greater depth, if a more meaningful conclusion were to be drawn, than from distinct impression. Whether those thin-walled vessels had their origins from within the infarct area or from those proliferating in the haematoma area is not known. Connections between those two sets of blood vessels were not seen histologically, but there was angiographic evidence of communication between the implant and the vessels within the ischaemic area, observed by the presence of a "blush" produced by contrast medium filling the small channels within this area (page 189).

The Fate of the Haematoma

By the end of the second week following implantation, the red cells of the haematoma area were no longer to be seen, and gradually over the subsequent few weeks this area became filled first with a loose and then later, a more dense connective tissue. This fibrous area merged with the connective tissue of the adventitial coat of the implant so that it was difficult to define the dividing line between them. Similarly on the outer side it merged with the connective tissue of the ischaemic myocardium. Within the connective tissue of the organised haematoma, large numbers of small vessels appeared. This subject is discussed at greater length below.

Changes Observed in the Walls of the Implant

In those implants which had remained non-thrombosed, at about four weeks following implantation, there was a small increase in the thickness of the intima in the last centimetre of the extracardiac portion of the internal mammary artery but a greater increase in that within the myocardial tunnel. This increase was mainly due to proliferation of the connective tissue elements, and produced a gradual encroachment of the walls of the implant on the lumen of the vessel which gradually, over the succeeding weeks, reduced to a chink in the middle of the implant in which blood cells could still be found. The obliteration of the lumen by intimal hyperplasia has been noted previously in studies of experimentally ligated vessels (Hanser, 1913; Mehrota, 1953). In the mature implant of say ten weeks or more, this central much reduced lumen could easily be mistaken for a new channel produced by the process of recanalisation. Careful scrutiny however, of the endothelial lining of the channel revealed that it was in direct communication with the now much folded and disintegrating original endothelium almost obscured in the obliterated part of the original lumen. In this way the original route, however reduced in size, remained open, connecting the systemic circulation above to the myocardium below. It was probable that the folded endothelium of the obliterated part of the original lumen might well be a source of new capillary growth. In those implants, which either wholly or in part thrombosed early, the tunica intima retained its original size and contour. The intimal proliferation occurring in the patent vessel was not observed in these implants.

The mechanism involved in the observed changes in the intima of patent implants is obscure, but perhaps may be related to the following:-

1. Interference with the blood supply to the intima due to the removal of the artery from its natural bed, where the arterial wall receives at least some blood for its own nourishment from peri-arterial plexuses of small blood vessels. Dissection of the artery from this bed could jeopardise the blood supply to the walls of the artery.

2. The presence of a reduced blood flow through the implant. The intima probably obtains at least part of its nutritional and gaseous requirements directly from the lumen of the artery. When the flow has been slowed or completely stopped, this may result in proliferation of connective tissue elements in the intima.

3. <u>Pressure increases across the implant wall</u>. Since the myocardium increased resistance to bloodflow through the implant, the blood pressure within the implant must have been redistributed, in part, through the walls of the implant. The increase in transmural pressure might in some way have stimulated growth of connective tissue in the intima.

The increase in connective tissue bulk in the intima was not accompanied by similar changes in media, which remained remarkably unaltered in appearance until about fourteen weeks following implantation when the elastic fibres in that coat began to disintegrate. At first only the occasional elastic fibre was observed to be broken, this was followed by a gradual disruption of the great majority of the elastic fibres. Dissolution of these fibres then occurred so that by about twenty weeks, elastic fibres were not discernible in the walls of the implant. This gradual disintegration of the elastic tissue could have been due to disuse atrophy or again to poor nourishment. The smooth muscle cells of the tunica media were more difficult to define even in the earliest implants but these too had certainly disappeared by the twentieth week. By the twenty-sixth week the walls of the original implant were in many cases difficult to distinguish from the connective tissue surrounding the implant, except that they retained a slightly more eosinophilic appearance.

The two easily noticeable changes in the adventitial coat were the increase in the amount of connective tissue together with a re-orientation of its constituent fibres into concentric shells almost parallel to the curvature of the implant in transverse section. It was difficult, as was stated earlier, to differentiate between the connective tissue of the adventitia and that of the organised haematoma. The other obvious change was the great inrease in the number of blood vessels in and around the adventitia, but this subject will be discussed separately.

New Vessel Formation around the Implant

Around the implant within the myocardium, an increasing number of blood vessels made their appearance from about the fourth week. These vessels were at first of capillary size or a little larger and had thin walls. Over the next twenty weeks they increased in size and gradually approached, mingled and became indistinguishable in the later stages from the adventitial vessels. From the angiographic study presented later, it was obvious that at least some of these vessels (if not all) eventually represented the anastomosis between the graft and the myocardial vessels.

The origin of these small thin-walled vessels outwith the adventitial coat of the implant was not clear but geographically they came to occupy the area in which the haematoma was originally situated. It is thought, at present, that new blood vessels can arise only from pre-existing endothelium (Florey, 1970). It is unlikely that their origin was from the adventitial vessels since at about four weeks although these small vessels were present, they were well separated from the adventitial vessels; only at about ten weeks were these two groups of vessels found close together.

When the myocardial tunnel was fashioned, large numbers of large and small intramyocardial vessels must have been traumatised and many transected. These multiple foci of breached endothelium could therefore theoretically have been potential growth points for capillary sprouts. These new vessels would grow into the surrounding myocardium and also into the organising haematoma perhaps attracted there in particular, by some chemotropic factor present in the haematoma.

The new vessels of the myocardium therefore arise in the area close to the implant possibly because of the damage inflicted on blood vessels in the vicinity during the construction of the intramyocardial tunnel. The stimulus to initial capillary growth may therefore be the presence of damaged endothelium and the direction of capillary growth may be determined by chemical attraction from the haematoma. In the same way the new vessels arising from the adventitial plexus and also from within the implant itself may be attracted into the haematoma area, where they meet and anastomose with the new capillaries from the myocardial vessels.

The formation of new blood vessels within the lumen of the implant

All implants in this study either retained their patency or were recanalised. In only two implants was evidence of total thrombus occlusion observed without recanalisation, but that was confined to the distal part of the vessel, the proximal reaches including both the extramural and intramural portions remained patent. The changes brought about in the lumen of the patent vessels have already been discussed.

In the thrombosed implants recanalisation was observed as early as the end of the first week. The number and maturity of these new channels increased with time until about twenty weeks following the implantation. During this period these new conduits evolved from small empty vessels with very thin walls, consisting of no more than endothelium at about two weeks and were observed to have red blood cells within them at four weeks. They underwent a branching and intercommunication phase with the other new channels present within the lumen by the tenth week and possibly connected with the new vessels of the intima from as early as the fourth week. From the tenth to the twentieth weeks the vessels in the new channel system became larger and thicker walled but between this point and twenty-seven weeks, many matured into rounded thick walled vessels indistinguishable from arterioles. The new vessels arising from within the implant lumen could be seen issuing from the end of the implant into the surrounding connective tissue from as early as four weeks. Since these vessels all had red blood cells within them they obviously communicated with those in the connective tissue around the termination of the implant and possibly also with the small new vessels within the implant wall. Occasionally new vessels within the lumen of a thrombosed branch of the implant could be observed with red blood cells within them. Thus a well developed circulation of small size vessels up to arteriole level existed at least between the lumen of the implant and the vessels of the connective tissue area at the distal end of the implant. This circulation possibly also included the vessels within the implant wall.

The Origin of New Channels within the Implant Lumen

As has been discussed above, there were two types of channel found within all implants. The first type was really the shrunken remains of the original lumen which had not thrombosed. The lumen had decreased in size because of a great increase in the connective tissue elements of the intimal layer. In some places the original lumen had been obliterated completely, leaving the endothelium lining from opposite sides of the original lumen in close apposition to each other. The possible reasons for this intimal proliferation have already been discussed. In addition to the shrunken lumen remaining a functioning conduit for bloodflow, the folded 'excluded' endothelium in the peripheral obliterated region of the original lumen might be a source of neocapillary formation.

The second type of channel found within the implants were indeed new channels. They appeared within the substance of the organised thrombus which occluded part of the implant. The origin of these new vessels was obscure, but in this study they appeared as early as two weeks following the implantation and took about twenty more weeks to evolve into vessels indistinguishable from arterioles. The early morphology of these vessels was that of the simplest blood vessel possible, they consisted merely of an endothelial-like lining surrounded by a few strands of connective tissue fibres. Since these new vessels had not been observed to carry blood cells in the first week or so of their development it must be assumed that either each had no lumen or that they were not connected to the systemic or coronary circulations. Close examination however suggested that they were hollow, and therefore that they were, at two weeks, not connected to blood-carrying vessels.

Some of these new channels even at two weeks seemed to be much wider than capillaries, and were about 20 to 25 microns in their greatest diameter. So not only were at least some of the vessels hollow but some were also much larger than capillary vessels. This was not the morphology which one expected of new capillaries arising either from cells within the organised thrombus or from sprouting capillaries invading the thrombus. From these origins, small solid cords of capillaries would be expected rather than hollow vessels capable of growing to 20 or more microns in diameter by some ten to fourteen days. What then were the origins of these new vessels?

One possible explanation for the early appearance of these wide new channels is that they were in fact the clefts in the original clot, endothelialised either from invading cells or by extensions from the endothelium of the implant. The more likely of these two possibilities is that the original endothelium extended into the thrombus and naturally followed the paths of least resistance - the clefts and that the latter became endothelialised gradually until a whole network of endothelialised but empty channels were present.

Some authorities have suggested that the organised thrombus within arteries is recanalised from extensions of the vasa vasorum, from the walls of the vessel (Dible, 1958). All internal mammary arteries in this study observed microscopically up to the fourth week following implantation had no visible vessels in the tunica media or tunica intima. It is unlikely therefore that the vasa vasorum (if these vessels exist in the inner coats of the internal mammary artery) have any place in the recanalising process in this vessel. At a later stage it may be that the endothelium of the new channels produces capillary sprouts although there is no evidence for this at the moment. The appearance of blood cells within the new channels by the fourth week of course indicates connection of this system to the circulation either by these new channels opening to the surface of the organised thrombus in contact with blood in the implant above the occlusion, or with capillaries in the implant wall (which are certainly present by four weeks) or with vessels in the myocardium at the distal end of the implant or at the cut ends of the original branches of the implant.

Two other less obvious sources of new capillary formation and/or endothelialisation of the thrombus clefts are from:-

1. the myocardial vessels and

2. the adventitial and peri-arterial vessels of the implant.

It was observed in many thrombosed implants that the new channels were larger and in some cases more numerous in the more distal parts. This could suggest that the new channels originated distally and grew proximally. This might have been because the thrombus occurred first in the distal parts of these implants then proceeded proximally, and therefore the new channels in the distal parts were more mature. Another possible explanation is that the new vessels were formed from the ingrowth of vessels from outside the implant and grew through the cut distal end of the implant either as sprouts or endothelial extensions into the clefts. This theoretically could also occur through the cut ends of branches of the implant. The two types of vessel outside the implant which could provide the ingrowth of new capillaries or endothelium as mentioned above were either myocardial vessels in close proximity to the implant or the adventitial vessels of the implant itself which would of course be cut when the internal mammary artery was transected prior to implantation. Myocardial vessels in the vicinity of the implant would also be cut across when the tunnel was being fashioned. These cut vessels, myocardial or adventitial, might then grow into the thrombus through the openings (end or branch) in the implant.

Blood Vessels in the Implant Wall

No vessels were observed in the tunica media and intima until the fourth week when one or two small capillaries appeared in the intimal coat. It was not until the fourteenth week that vessels were seen in the medial coat. By sixteen weeks there were many [illegible] and slightly larger thin-walled vessels within the two coats in some implants. Also occurring about the fourteenth week, as discussed above, was the beginning of the process of breakdown of the elastic and possibly also smooth muscle tissue of the implant wall. Whether new vessel formation and ingrowth into the implant wall was connected with the disintegration of the constituent tissue in this region can only be guessed at but it is possible that the new ingrowth of vessels occurred because either the physical barrier of elastic and smooth muscle was removed or some chemical constituent of the breakdown products of these tissues stimulated new vessel growth.

The origin of these new vessels was from four possible sources, first they might arise from progenitor cells within the intima and media, or second they might arise from the intimal endothelium. Third, vessels might grow into the wall from the lumen of the implant which during this time was the seat of intense endothelial proliferation. The last possibility is that they represented invasion of the implant wall by the vessels in the adventitia and surrounding tissues. Initially capillary-size vessels appeared only in the intima. These probably did not originate from the external vessels. During the intense proliferative growth phase at fourteen weeks many small vessels appeared in the tunica media and by two weeks later, the intima was also well supplied with these new capillaries. Thus the order of appearance of vessels in this second phase of new capillary formation (the first was at four weeks and as mentioned above, was limited to about one or two capillaries in the intima only) suggests that ingrowth of external vessels into the media was followed by a further increase in intimal vessels. These new vessels in the walls of the implant obviously represented a new interconnection between the external vessels and the lumen of the implant. Since this phenomenon of mural vascularisation occurs in the extramural as well as in the intramural parts of the implant it must be assumed that the adventitial vessels participated in this phenomenon although myocardial vessels in close proximity might also have been involved. Thus by the sixteenth week the circulation within the lumen of the implant was in direct connection with the vessels of the adventitia and possibly also with those of the myocardium through the walls of the implant.

Role of the adventitial vessels

The internal mammary artery has a rich supply of small blood vessels in its adventitial coat. When the artery was dissected from the chest wall, inevitably small pieces of tissue from surrounding structures mainly connective tissue and fat, remained adherent to it. Microscopically this tissue is also rich in small blood vessels. It is likely that there are rich connections between the adventitial plexus and this peri-arterial network of small vessels. The dissection of the internal mammary artery from its natural environment must therefore have caused transection of great numbers of these vessels, leaving countless tiny points of potential endothelial new growth.

At the end of the fourth week after implantation into the myocardium, microscopy revealed the presence of greatly increased numbers of capillaries, arterioles and venules forming a rich plexus of blood vessels around the implant. This enhanced network of vessels could be seen both in the extramural and in the intramural portions of the implant. The proximal origins of this plexus were probably numerous and would include the small blood vessels of any tissue or organ with which the implant came into contact. Even after careful dissection of the internal mammary back to the subclavian artery prior to implantation, it was common to find it later firmly adherent to surrounding structures such as the thymus gland, the lung, anterior chest wall, posterior parietal pleura or the pericardium.

The continuation of the rich plexus which can be seen even with the naked eye on the external walls of the aorta and subclavian artery however, must remain the most important contribution to the circumferential external plexus of the implant. This external plexus of small blood vessels thèrefore extends from the subclavian peri-arterial network into the myocardial tunnel after implantation of the internal mammary artery, but is reinforced by anastomosis with the vascular system of any structure with which it has close contact.

The proliferations of the constituent vessels of this plexus at the fourth week following implantation may signal an increase in the amount of blood flowing through this system towards the myocardium. The connections of this peri-arterial plexus at its distal reaches were not well defined but at this stage it did not seem to be connected transmurally to the lumen of the implant. As has been discussed previously, however, it might have been connected with intra-luminal channels either through the natural side branches of the implant or at the distal cut end of the implant. It might have been connected even at this stage with the vessels either of the haematoma surrounding the implant or with the vessels of the myocardium.

By the tenth week, the peri-arterial vessels were larger and had thicker walls, providing further evidence of increased peri-implant bloodflow. These more mature vessels could be observed not only close to the implant within the myocardium, but also in close proximity to the large numbers of surrounding small thin-walled vessels. These thin-walled vessels could have been extensions of the peri-arterial plexus into the surrounding area of what was haematoma or into the ischaemic myocardium itself. On the other hand, these small vessels could have been extending from the myocardial vessels towards the peri-arterial plexus. What is certain is that the peri-arterial plexus (or its extensions) at this stage, was in close proximity and possibly connected with, the vessels of the myocardium.

The peri-arterial system of vessels could thus conceivably play a direct role in the nutrition of the myocardium, in that blood might pass directly through this system to the myocardial vessels without traversing the main lumen of the graft at any point. This could be the case especially in the presence of an occluded graft. On the other hand, blood might pass from the adventitial vessels through the transmural anastomosis into the lumen distal to an occluding thrombus thus re-establishing at least in part, an intraluminal circulation.

The part played by this peri-arterial plexus of blood vessels may well have been underestimated by previous workers. No references can be found to the role which this system might play in the evolution of transmural connection between the luminal channels and myocardial vessels or indeed in the possibility that the peri-arterial system itself might be a source of a new blood supply to the heart. The arguments posed against the efficacy of internal mammary artery implantation in the clinical setting, in recent years have, in the main, been based on the observation that in the group of patients with angiographic evidence of occlusion of the graft, a percentage of these patients were symptomatically improved. This improvement has hitherto been ascribed to the placebo effect of the operation, and has led to further conviction in many centres that perhaps a percentage of patients with angiographic evidence of graft patency have improved also only by this placebo effect.

From the discussion on the source of the peri-arterial network it was seen that contributions to it could theoretically come from a wide area, anastomosing with the plexus of vessels surrounding the implant. It would therefore be very difficult to visualise this system of vessels by an injection of radio-opaque dye into the lumen of the internal mammary implant. Indeed it is difficult to see how it could be achieved by any known means. The possible contribution to the nutrition of the ischaemic myocardium by the peri-arterial plexus should therefore be borne in mind in assessing the efficacy of the internal mammary implant, especially in the presence of an occluded main lumen.

Discussion

Wall Thickness of Implanted and Normal Internal Mammary Arteries

No difference could be demonstrated by the statistical method between the wall thickness expressed as a percentage of external diameter of normal internal mammary arteries and the implanted internal mammary artery at a point between 4 and 5 centimetres proximal to the place of entry into the myocardial tunnel. This finding re-inforced the microscopical impression that the tunica intima and other arterial coats did not seem to be thickened in the implant at this distance from the heart. Since the tunica intima was slightly increased in thickness in the distal centimetre of the extracardiac portion of the artery and more thickened within the tunnel, it was imperative to establish that the implant wall was not thickened at the site where blood flow measurements had been made. Any increase in mural thickness at this point would have seriously upset the calculations made for blood flow measurements, since the cuff-type flow probes are calibrated on normal vessels (with a normal wall thickness). The blood flow measurements made in the implanted internal mammary arteries in this study, were therefore valid. This precaution of establishing the presence of a normal mural thickness dimension was not made in any of the studies of blood flow through internal mammary artery implants made by the other workers whose results are discussed.

The mean wall thickness of 11.04% of external diameter observed in the implanted arteries 4 to 5 centimetres from the heart and that of 10.85% for normal internal mammary arteries was the same as that calculated from the tables given by Noordergraaf and Horeman (1958) for a variety of human arteries less than 5 mm. in diameter, and very close to the figure of 11.3% calculated from the data given by Petersen, Jensen and Parnell (1960) for canine carotid and femoral arteries less than 5 mm. in external diameter. The value of 8% of external diameter for wall thickness given by McDonald (1960) for arteries from the aorta to the saphenous artery in dogs could be a reflection of the larger external diameter of these vessels, larger arteries might have a relatively thinner wall. On the other hand the technique used by McDonald of measuring the external diameters of the arteries before removing them for density measurements, to calculate mean wall thickness, circumvents possible discrepancies due to an increase in wall thickness from shortening of excised segments of artery and from the effect of histological fixatives.

Summary of Section IV

The main object of this section was to study the histological changes in the internal mammary artery after implantation into the ischaemic left ventricle for periods up to twenty-seven weeks, and the effect on the vascular morphology of the surrounding myocardium. From these microscopical studies, the following conclusions were reached:-

1. There was evidence of absence of complete occlusion of the implant by thrombus formation in the first seventy-two hours following implantation. This was in accord with the observation made in Section II that there was flow in the implant immediately following implantation.

2. The presence of only a small extravasation of blood in the vicinity of the implant within the myocardium, the absence of leucocyte infiltration, and limited partitioning of its substance with fibrin, suggested that at least in the first three days this pool of blood was not static but might have been in movement in the first seventy-two hours.

3. The blood from the implant may have moved through the myocardium, at this time, within the dilated capillaries observed between myocardial cells. Columns of red cells were

seen radiating into the surrounding myocardium from the pool of blood around the implant.

4. Hyperaemic changes were observed in the myocardium until about the second week following coronary artery occlusion and implantation of the internal mammary artery. During this time swelling followed by dissolution of myocardial cells within the ischaemic area was obvious.

5. Further changes in the lumen of the graft were studied up to twenty-seven weeks after implantation. The lumen either remained patent in its intra-myocardial part, but reduced in size due to proliferation of the intima or became thrombosed and subsequently recanalised. Thickening of the intima was first noticed in the last centimetre of the extracardiac portion of the internal mammary artery, never in the proximal reaches. No evidence was seen of a thrombus occlusion of the extramyocardial part of the implant nor of a non-recanalised thrombus of the implant within the ventricular wall. Recanalisation of the thrombus was observed as early as one week after implantation but no red cells were evidence within these new channels until the fourth week. Capillaries appeared within the thrombus and, with increasing time after implantation, some of them enlarged, gained what seemed to be a smooth muscle coat and became indistinguishable from arterioles. The origins of these

vessels are discussed.

6. Vascularisation of the wall of the implant began about the fourth week with the appearance of a small number of capillaries in the intima. It was not until the fourteenth week that capillaries were observed in the tunica media; two weeks later an increase in the number of capillaries was obvious in the intimal coat. The order of appearance of these new vessels suggested that there were two phases of capillary ingrowth, the first at four weeks into the intima, from the endothelium of the implant lumen, followed by the second phase ten weeks later by extension of adventitial capillaries into the media and possibly later into the intima. By sixteen weeks there was evidence of a well developed transmural plexus of small blood vessels probably connecting the lumen of the implant with the adventitial plexus.

7. An increase in the number of small blood vessels around the intramyocardial portion of the implant was noticeable from about the fourth week, increasing in quantity and maturity with time. These vessels were in the area around the implant formerly occupied by the 'haematoma'. It is suggested that these vessels probably arose from vessels of the

myocardium injured at the time of implantation of the graft, and possibly also from the plexus of blood vessels in the adventitial coat of the implant. There may have been a local factor within the haematoma which attracted growth of surrounding blood vessels into its substance.

8. A credible pathway for blood from the lumen of the implant to the vessels of the myocardium is described and discussed.

9. The role of the adventitial vessels of the implant in the revascularising process is stressed. The adventitial plexus of blood vessels extends from the structures surrounding the implant in its extracardiac course, to the termination of the implant within the myocardium. This plexus itself may be a new source of blood for the myocardium. In addition, as mentioned above, the vascularisation of the wall of the implant is probably dependent on the ingrowth of vessels from the plexus, and also the plexus may be the vital link between the implant and the surrounding myocardial vessels. The importance of the adventitial vessels has not hitherto been emphasised.

SECTION V.

AN ANGIOGRAPHIC STUDY OF THE IMPLANT AND ITS CONNECTIONS WITH THE CORONARY CIRCULATION.

INTRODUCTION

Angiography of the implanted internal mammary artery was the logical extension of opacification of the coronary arteries by similar techniques first performed safely and with precision in human patients by Sones in 1958. Implanted internal mammary arteries were clearly shown to be patent and to have formed anastomoses with the coronary circulation in many cases years after the operation (Sones and Shirey, 1962). The evaluation of the effectiveness of the internal mammary artery implant by angiographic techniques has been challenged recently by Dart, Kato, Scott, Fish, Nelson and Takaro (1970). These workers noted that the intensity of opacification by contrast medium and the extent of anastomoses between the implant and the coronary arteries could be varied by altering the position of the tip of the catheter relative to the orifice of the internal mammary artery and also by changing the injection pressure of the catheter medium.

Preliminary experiments in the present study in which injection of contrast medium was made into the internal mammary implant in the intact, anaesthetised dog showed that angiographic detail of anastomoses between implant and coronary circulation was very difficult to achieve. Another disadvantage in using this method, from the point of view of studying the nature and extent of this anastomosis, was that blood in the coronary arteries would dilute the contrast as it passed from implant into the coronary circulation, thus making visualisation more difficult. For these reasons the excised, beating heart preparation was used to study the details of anastomosis.

The seventeen dogs studied in this section also had implant blood flow measurements carried out prior to angiography. This provided an opportunity to study the relationship between the extent and pattern of the anastomosis and the blood flow through the implant. In addition in some dogs it was possible to study the relationship between angiographic assessment and the resistance to implant blood flow.

MATERIALS AND METHODS

Angiographic examination of the internal mammary implant was carried out in seventeen dogs, three of which had no ischaemic lesions of the left ventricle. The remaining fourteen had ischaemia of the anterior wall of the left ventricle. The method used initially was to introduce a thin polythene catheter into the implant at its commencement with the left subclavian artery after the final blood flow measurements had been made. An injection of 2 mls. of 68% urografin was carried out, at about 120 mm. Hg. pressure, into the fine tube and on into the implant. It soon became apparent that in those heart where anastomoses had occurred between the implant and the coronary arteries, that blood flowing in the coronary arteries from the aorta would dilute the dye and therefore render visualisation of fine channels difficult. Secondly, retrograde filling of one coronary artery could cause an admixture of blood and dye to run backwards through the coronary tree into the aorta if the injection pressure exceeded the aortic blood pressure.

In such circumstances, this small amount of dye could in part be flushed down both coronary arteries during the next diastolic period. If this happened then some visualisation of the other parts of the coronary arterial system might occur, giving rise to erroneous impressions.

For these reasons, therefore, it was decided that the heart with the whole length of the implant should be removed from the thoracic cavity and implant angiography be carried out in the isolated fresh preparation. All connections between the heart and surrounding structures were quickly severed and the heart and implant removed to the X-ray table where the thin polythene tubing was swiftly introduced into the lumen of the implant, about 7 cm. from its central end. The tubing was then connected to the flushing system and quickly washed through with physiological saline at 120 mm. Hg. pressure to remove all blood from the interior of the implant and its connections. At this point it may be added that each heart was still beating but at a much reduced rate, usually between five and twenty times per minute. The radio-opaque medium (68% urografin) was then injected at the same pressure into the implant and two exposures taken with a thirty second interval between them. The heart was washed in physiological saline again to remove excess contrast medium and the procedure repeated. Four exposures were therefore made on most hearts, but in a small number only two were carried out.

The radiological equipment used was an ordinary portable X-ray machine. The heart was laid on the X-ray cassette placed on a small table. The correct focal distance from the X-ray tube to the heart, the voltage, current and timing were all found by trial and error in the first specimens. Two to three seconds after the dye was injected, the first exposure was made, the cassette was then manually exchanged for another and the second film taken, with practice this could all be achieved within ten seconds. The heart was washed as described and the process repeated.

Grading of Implant Angiograms

The system used to grade the extent of myocardial revascularisation from the internal mammary implant was modified from that of Dart, Kato, Scott, Fish, Nelson and Takaro (1970). The scoring index was based on the extent and degree of opacification of blood vessels and had six categories measured from 0 to 5 (Table 25). Grade 0 represented opacification of the graft alone without any coronary vessels showing. The presence of a blush of very fine vessels around the implant within the myocardium was given a grading of 1. If a large branch of a coronary artery was visualised, this was grade 2. Grade 3 indicated filling of the distal end of the anterior descending branch of the left coronary artery (this artery filled retrograde in the ischaemic group since it was ligated proximally). When the whole of the anterior descending branch of the left coronary artery was filled (below the point of ligation in the ischaemic group), this scored grade 4. If in addition to opacification of this branch, the circumflex branch of the left coronary artery was filled, the maximum score, grade 5, was used.

Grade	Vessels outlined
0	Implant only.
1	Implant surrounding 'blush' of small vessels.
2	Implant one branch of a coronary artery. other than anterior descending branch.
3	Implant distal end of anterior descending branch.
4	Implant filling of anterior descending branch below occlusion.
5	Implant filling of anterior descending branch below occlusion. circumflex branch filled.

Table 25

Grading system used in implant angiograms.

Results

All dogs studied angiographically had implants which were patent at the proximal end. This allowed in each case the thin catheter to be inserted within the lumen without difficulty. Of the three dogs studied from the non-ischaemic group, two were f und to have radiologically patent implants but without visualisation of coronary vessels, i.e. grade 0 (Table 26). These two dogs had no measurable blood flow in their implants. The other had an angiographic score of '2' and a forward blood flow in the implant of 2 ml. per minute.

Of the fourteen implants studied from the ischaemic group, three had no demonstrable radiological connections with myocardial vessels, yet all three had a forward blood flow, 18.2, 33.8 and 4.0 mls. per minute (Table 26). In one of these dogs (dog 69) the implant was adherent in its middle third to the upper lobe of the left lung which was removed still attached to the graft. The blood flow had been measured, in this implant, between the adherent lobe and the heart, but the radio-opaque dye had been injected proximally to the lobe of the lung. It was found surprisingly, that the blood vessels within this lobe were completely visualised when the plate

Dog	Weeks	Angiographic grade	Implant Flow (mls per minute)
11	9	0	2.0
2	29	2	0.0
3	30	0	0.0
45	2	1	7.7
44	4	4	5.7
40	5	5	10.8
34	8	2	5.9
*33	9	5	not obtained
31	10	5	14.8
32	10	4	16.3
30	11	5	10.1
23	14	5	20.3
24	14	0	18.2
26	14	5	7.5
28	14	0	33.8
18	16	4	32.4
**69	22	0	4.0

* arrhythmia during flow measurement   ** lung adherent to implant

Table 26

Angiographic grading and implant blood flow in seventeen dogs. The first three dogs in the table had the internal mammary artery implanted into normal left ventricular myocardium, the remainder had ischaemia of the left ventricle.

was developed (see Figure 12). The blood flow in this implant was found to be very small (4.0 mls. per minute) probably because the resistance was much higher in the myocardium than in the adherent lobe of lung, so that the injectate too flowed preferentially into the latter.

A measurable blood flow was demonstrated in each of the other two radiologically occluded implants (18.2 and 33.8 mls. per minute). In each of these two dogs, the implant and left ventricle were examined histologically. Both implants showed extensive recanalisation with red blood cells within each of the new channels. In addition there were intramural communicating vessels prominent in one of the implants with well developed new blood vessels surrounding both implants. In these two implants, therefore it should have been possible to demonstrate radiological connections with surrounding myocardial vessels. One possible explanation for this anomaly is that the end of the catheter within the implant lumen had become obstructed by the occluding but recanalised thrombus and therefore dye failed to be injected into the new channels, or that the injection was made beneath the intima following traumatisation of the delicate inner lining of the implant by the end of the catheter, a happening not unknown in human angiography.

Non-occluded Implants in the Ischaemic Myocardium

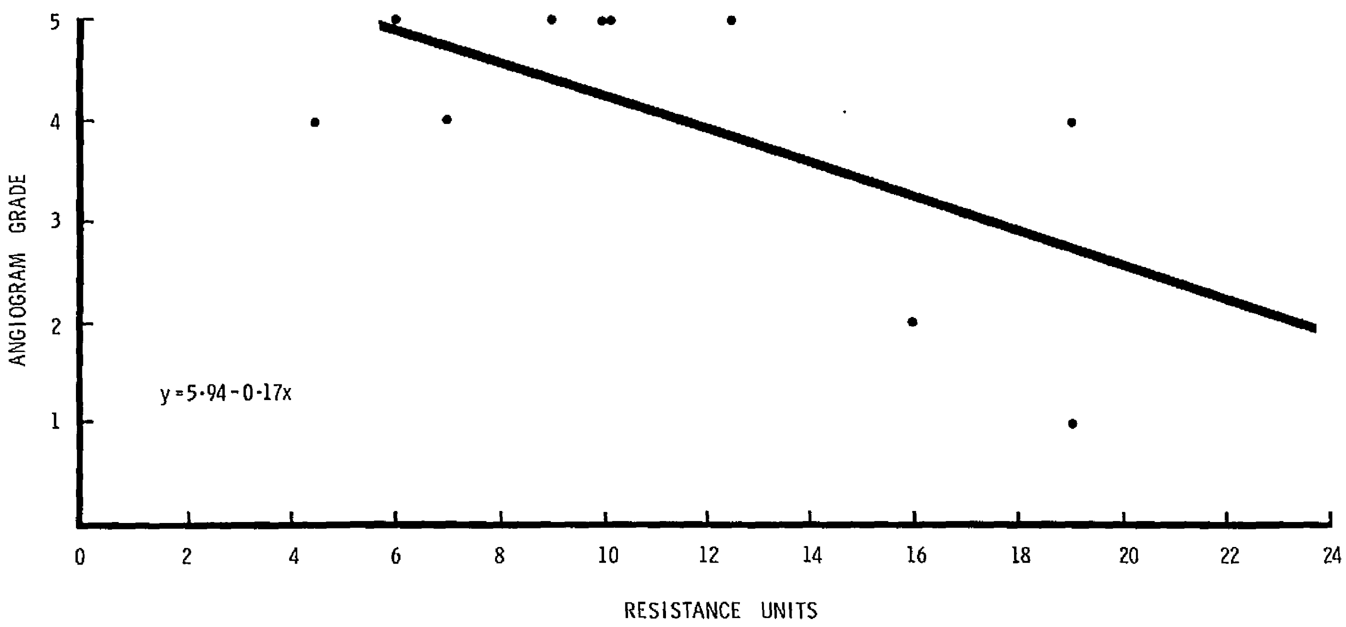
Of the remaining eleven patent and communicating implants in this group (Table 26) there was one implant in grade 1, one in grade 2, none in grade 3, three in grade 4 and six in grade 5. In ten out of those eleven anastomosing implants, blood flow measurements had also been carried out. In the eleventh dog (No 33), the presence of arrhythmias invalidated the graft blood flow measurements. The flow in the ten remaining implants varied from 5.7 to 32.4 mls. per minute. On comparing the angiographic grading (which is based on the extent of opacification) with forward blood flow through the implants, it was observed that in all implants with flows greater than 7.7 mls. per minute, thegrading was at least 4. In addition, two implants with flows less than 7.7 mls. per minute showed maximum opacification of the branches of the left coronary artery. The exact relationship therefore between the flow in the implant and the extent of the implant's anastomosis with the branches of the left coronary artery was not clear, but in general where an implant had a blood flow of 10 mls. per minute or more, there was clear evidence from the angiograms of filling of the anterior descending branch of the left coronary artery below the point of ligature, with in addition, in four out of six angiograms, opacification of the circumflex branch.

There was a linear correlation between the extent of opacification of the branches of the left coronary artery and the resistance to blood flow encountered between the implanted internal mammary artery and the right atrium.

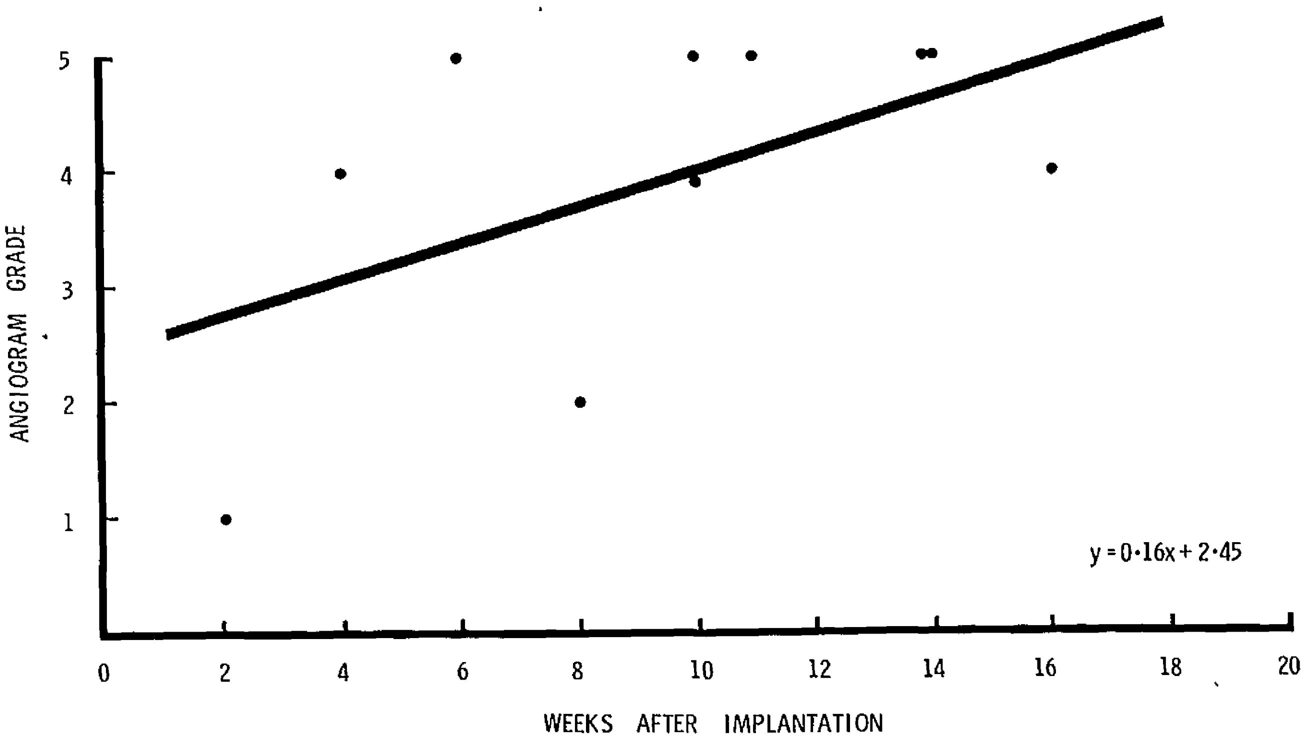
Dog	Weeks	Angiographic grade	Resistance Units At right atrial pressure 0 mm. Hg.	At right atrial pressure 5 mm. Hg.
45	2	1	20.0	19.0
44	4	4	20.0	19.0
40	5	5	13.1	12.5
34	8	2	17.1	16.1
31	10	5	9.6	9.0
32	10	4	7.3	7.0
30	11	5	10.4	10.0
23	14	5	6.4	6.1
26	14	5	9.2	10.
18	16	4	4.8	4.6

Table 27

Angiographic grading and implant resistance in ten dogs with ischaemia of the myocardium of the left ventricle.



The extent of opacification of the branches of the left coronary artery with increasing resistance in the internal mammary artery implant.



The extent of opacification of the branches of the left coronary artery with duration of implantation of the internal mammary artery.

The regression equation connecting resistance to blood flow with the extent of opacification was calculated as $y = 5.94 - 0.17\ x$, with a statistically significant coefficient of linear correlation ($r = -0.63$, $p < 0.01$).

When the extent of opacification was studied with respect to duration of implantation it was found that at nine weeks and above, all implants (except those radiologically occluded) showed connections with the anterior descending branch of the left coronary artery below the point of ligation and that in five of these seven implants, the circumflex branch was also opacified. Evidence of connections between the implant and both branches of the left coronary artery was observed in one dog (No. 40) as early as 5 weeks. When the values were analysed statistically, a linear correlation was found between the duration of implantation and the extent of opacification of the left coronary arterial tree; the linear regression equation was found to be $y = 0.16\ x + 2.45$, with a statistically significant correlation coefficient ($r = 0.54$, $p < 0.05$).

Discussion

The Use of the Ex-vivo Beating Heart Preparation in Experimental Implant Angiography

In this study, angiography was performed with relatively unsophisticated apparatus, on the newly removed and beating dog heart, a technique for which the author can find no published references. These heart preparations were observed to beat at a rate of between five and twenty per minute for about three to four minutes. Since the heart chambers were empty of blood, the force of systolic contraction of this ex-vivo preparation was much reduced. The pressure exerted in the coronary arteries from the myocardium must also have been much reduced, and thus the resistance to the flow of contrast largely removed. In this setting, the flow of radio-opaque dye from the implant at 120 mm. Hg (about physiological mean blood pressure in the dog) through anastomotic channels to the branches of the coronary arteries should be relatively high and should therefore demonstrate radiologically the full extent of these interconnections. This technique using an opaque dye injection at physiological pressures would tend therefore not to produce rupture of small delicate anastomotic channels or plough artifactual tracks through the myocardium, giving rise to false angiographic appearances. The pressure of injection of the contrast has been found to be all important in the demonstration of connections between the implant and the coronary circulation. It has been demonstrated by Dart, Kato, Scott, Fish, Nelson and Takaro (1970) that in the intact dog, full anastomotic opacification was not observed unless injection pressures were used which produced a 200% elevation of implant flow rate. It follows that if a study of the full extent of the anastomoses is to be made, large unphysiological rises in injection pressure must be used in the intact dog, a practice which for reasons given above may give rise to small vessel trauma and misinterpretation. The absolute height of injection pressure alone, however, will not determine how well the anastomotic channels are opacified but rather it will be the difference in pressure between implant and the coronary vessels. If the latter be reduced to zero (or near zero) then a smaller injection pressure can be used, with consequently less chance of damage to the newly formed small vessels. In the non-survival experiment, therefore, the ex-vivo beating heart preparation fulfils these conditions, with the added advantage that in the removed heart the surrounding radio-opaque structures do not obscure the radiological picture.

Figure 37

Implant angiogram after only two weeks following implantation. Fine anastomotic channels arrowed.

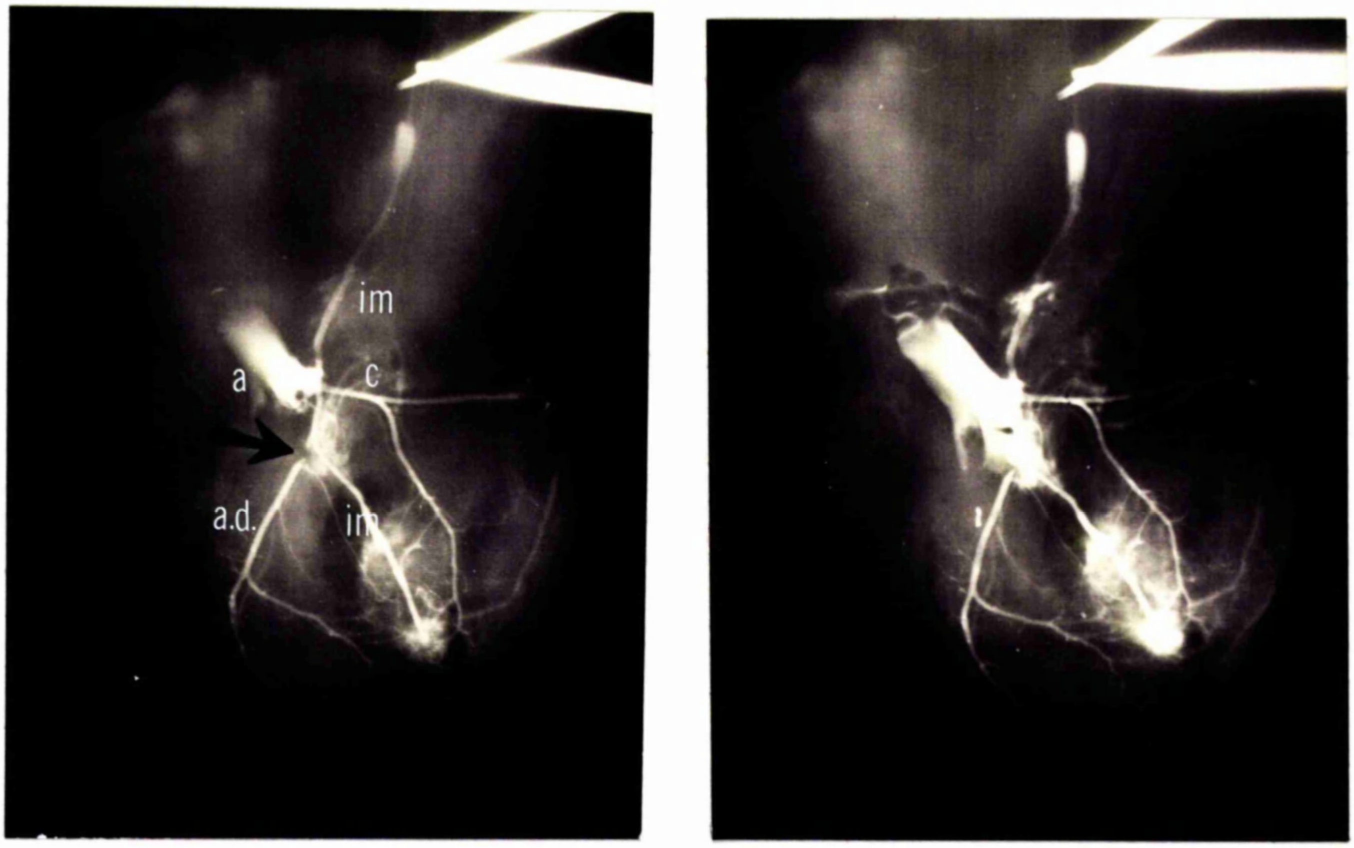


Figure 38

Implant angiograms at two and ten seconds after injection. Communications between implant (im) and both the anterior descending (ad) and circumflex branches (c) of the left coronary artery at four weeks clearly seen. Point of ligation of the anterior descending branch is arrowed. "Blush" of fine vessels within ischaemic area and retrograde filling of aorta (a) are also apparent.

The Demonstration of the Nature and Extent of the Anastomosis between Implant and Coronary Circulation

The angiographic appearances observed in this study confirmed that anastomosis did occur between the internal mammary implant and the coronary arteries, and amplified the bloodflow measurements and histological findings made on the implants reported and discussed previously (Section III and IV). Very fine anastomotic channels (Figure 37) limited to one small area surrounding the graft were found as early as two weeks following implantation in one dog (dog 45) in which the graft was also shown to have a small forward bloodflow (Table 26). Connections between the implant and both anterior descending and circumflex branches of the left coronary artery were observed as early as the fourth week following implantation (Figure 38). Extensive anastomoses between the graft and both of these large branches was the rule beyond ten weeks after operation in the ischaemic group (Figure 39). In two angiograms small channels could be seen extending across the interventricular septum to the wall of the right ventricle, but in no case was the right coronary artery ever visualised (Figure 40). A single well placed graft therefore was found capable of providing free anastomoses between the implant and all vessels supplying the anterior wall, the inferior surface and possibly at least part of

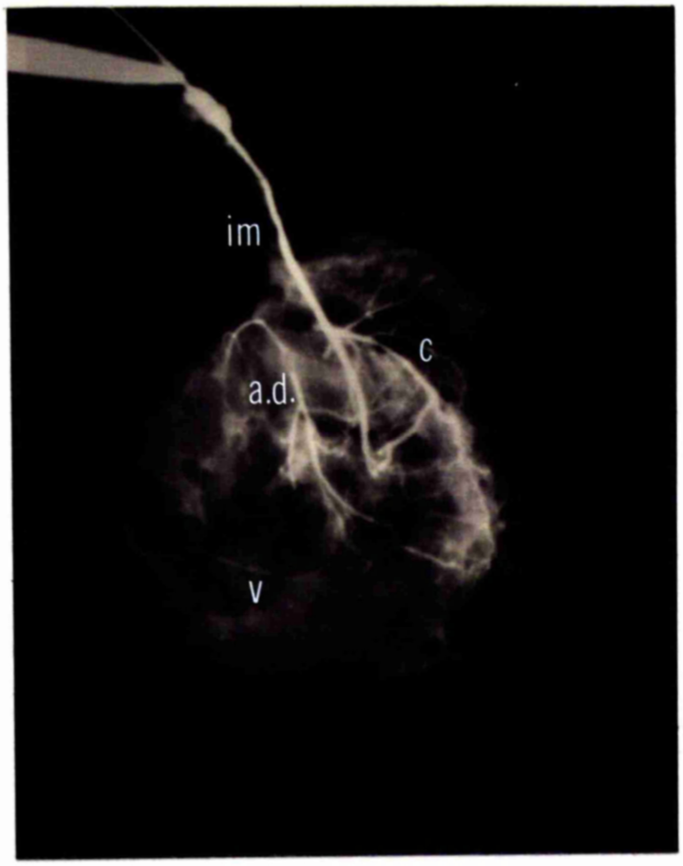


Figure 39

Implant angiogram at ten weeks. This oblique vein shows extensive anastomoses between implant (im) and branches of the left coronary artery (ad and c). Small veins are also outlined (v).

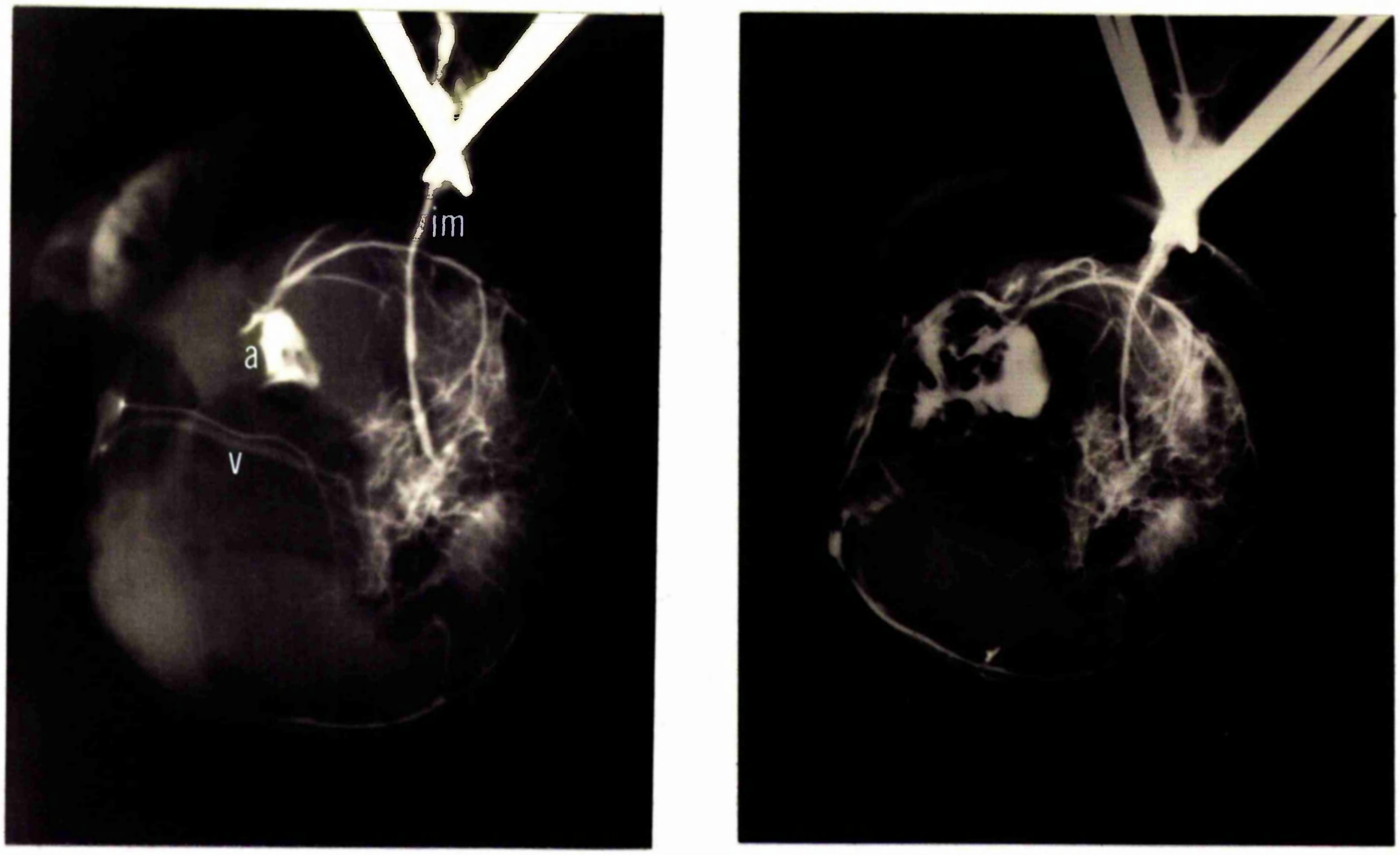


Figure 40

Implant angiograms taken at two and ten seconds after injection. These oblique veins show extensive anastomoses between implant and both branches of the left coronary artery. Retrograde filling of the aorta (a) shown. No filling of branches of right coronary artery. Veins (v) clearly visible draining towards right atrium.

the posterior surface of the left ventricle in the dog with an ischaemic myocardium.

In all grafts which were in connection with coronary artery branches, the new channels from the implant came from the whole length of its visualised intramyocardial portion, although the last centimetre of the graft arborised most profusely with surrounding vessels (Figure 41). Each implant was inserted into the ischaemic area close to the anterior descending branch of the left coronary artery, but despite this, no angiogram showed the anterior descending branch alone visualised, or more clearly than the circumflex branch. Since the terminal branches of the two major divisions of the left coronary artery meet at the apical area of the left ventricle, it might therefore be thought that the circumflex branch would be visualised by radio-opaque dye from the terminal branches of the anterior descending branch, but this did not seem to the case in this study. As many new vessels passed from the implant to the circumflex branch as to the anterior descending branch (Figure 41). In addition to these new vessels which were mainly about 0·5 mm. in internal diameter (i.e. about 50% of the inside diameter of each of the two main divisions of the left coronary artery) and which varied from two to as many as eight in number, there was also a 'blush' of tiny blood vessels in the

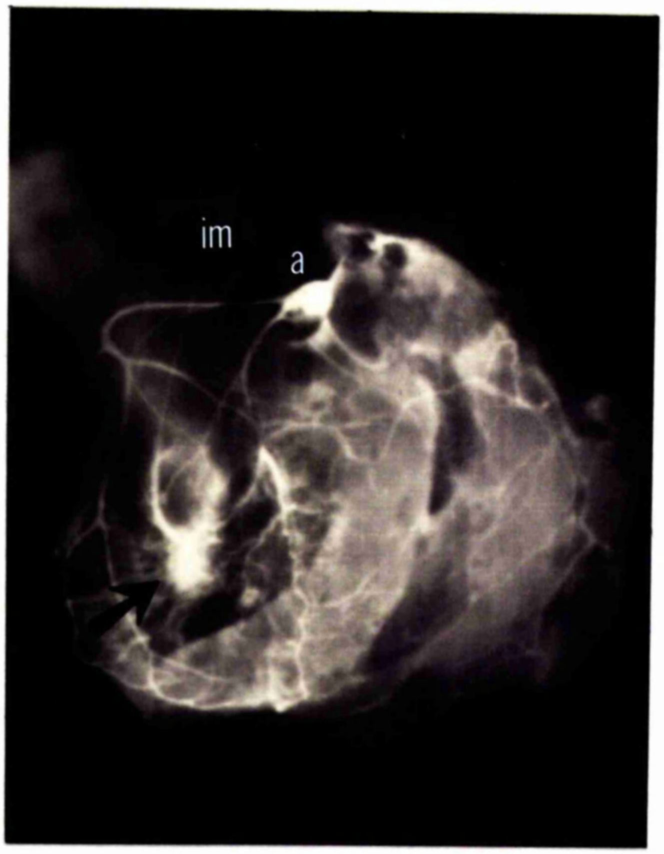


Figure 41

Left lateral implant angiogram five seconds after injection. The last centimetre of the implant (arrowed) shows largest number of small anastomotic channels. Aorta (a) fills retrograde from branches of the left coronary artery. Five weeks after implantation.

Figure 42

Implant angiogram ten weeks after operation, showing the area of 'blush' between the implant (arrowed) and the circumflex branch (c) of the left coronary artery. The veins (v) are well filled.

ischaemic area interposed between the implant and the circumflex vessel (Figures 38 and 42). It is highly possible that the implant and the circumflex circuit were connected additionally through this network of small vessels. The prevailing hypothesis is that new channels from the implant link preferentially with arterial vessels which have a lower blood pressure within than without the implant, that is the movement of new blood within the myocardium is from an area of high diastolic pressure, to that of a low diastolic pressure. This hypothesis is not supported by the observations made in this study in which only the anterior descending branch was ligated, and in which therefore only this branch and its tributaries were at low pressure. The circumflex branch on the other hand was at normal pressure and yet seemed to receive as many anastomotic channels from the implant as did the anterior descending branch. The controlling mechanisms which decide the direction in which the new vessels grew from the implant therefore included at least one factor other than that of the pressure gradient.

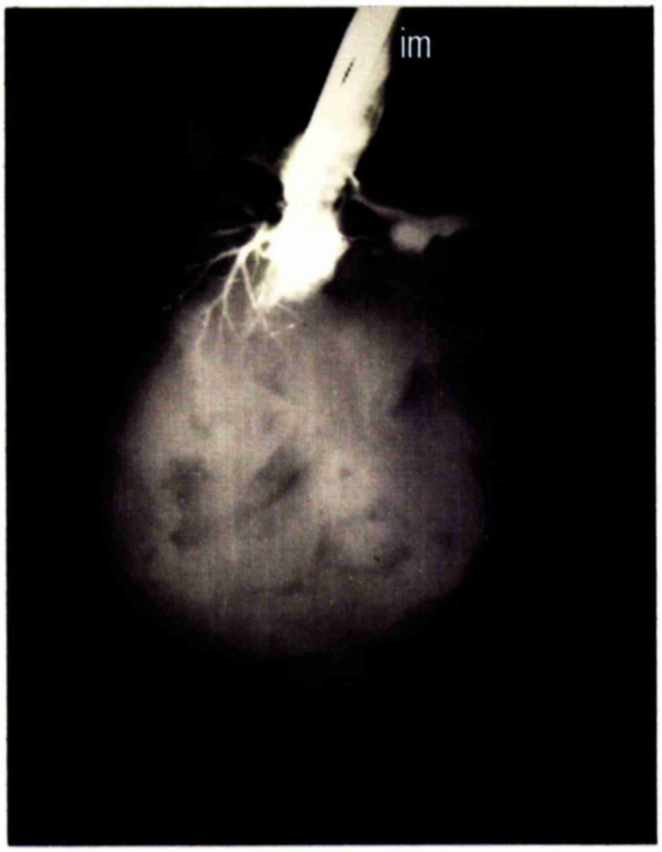


Figure 43

Implant angiogram showing minimal revascularisation of the left ventricle. No connections made with major branches of the left coronary artery.

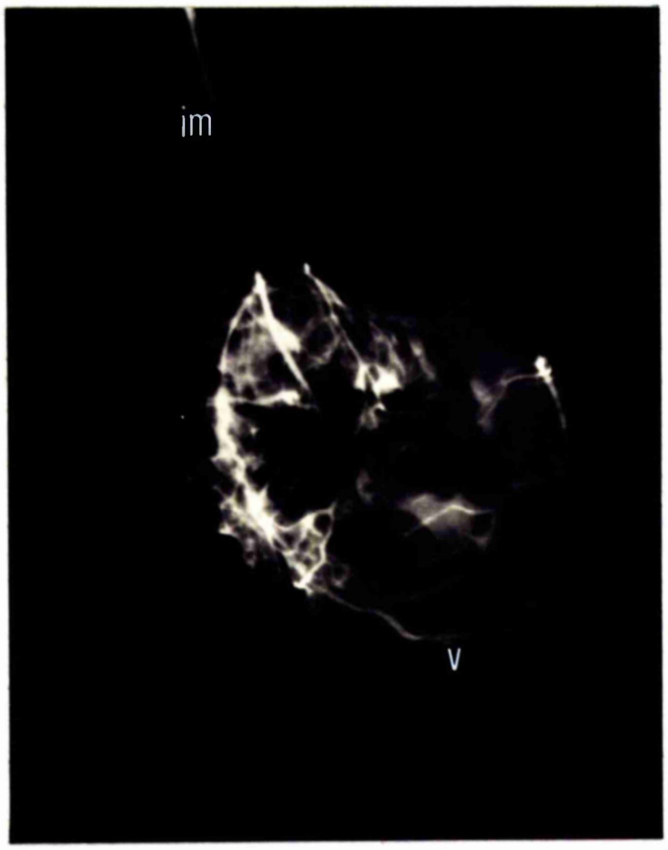


Figure 44

Left lateral implant angiogram demonstrating extensive revascularisation of the left ventricle, with filling of cardiac veins (v).

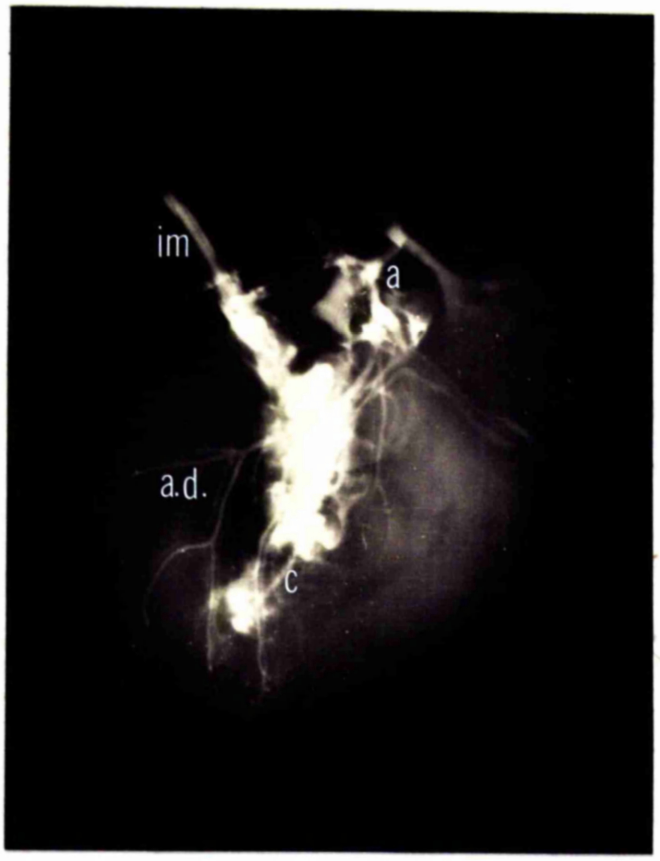


Figure 45

Implant angiogram showing both branches of the left coronary artery thinly outlined.

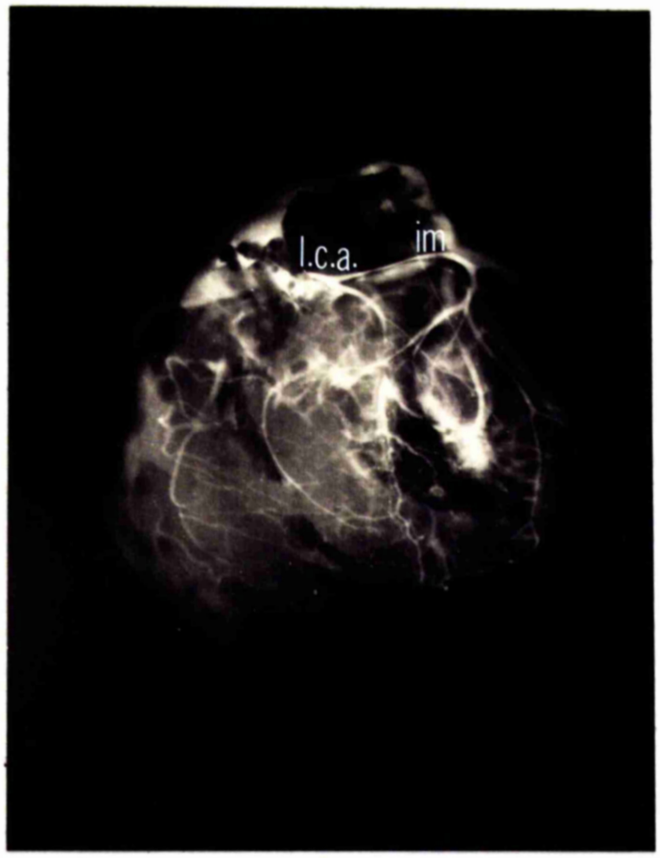


Figure 46

Implant angiogram showing extensive opacification of the branches of the left coronary artery.

The Pertinence of Injection Pressure Levels to the Opacification of Anastomotic Channels between Implant and Coronary Arteries in the Human Patient

If from the observation that very high injection pressures at unphysiological levels are required for full visualisation of connections between implant and the coronary circulation, then by extrapolation the same probably holds in the human subject. It follows that in many cases full radiological visualisation of all implant connections may not be reached. Good quality implant angiograms are, at best, not as clearly outlined as conventional coronary cine-angiograms. Hence the detection of new channels between implant and myocardium in the situation, where, for some reasons, full and extensive anastomosis has not occurred, becomes increasingly difficult. Many new channels may therefore remain undetected by conventional techniques, and the implant diagnosed as occluded. Patients with angiographically labelled 'occluded' implants have in many cases been symptomatically improved and have been said to have benefited only from the placebo effect of the operation. This has been one of the main arguments used against the operation of direct artery implantation. It may be therefore that at least some of these patients have in fact a small bloodflow through the graft to the myocardium undetected by the only practical radiological means available at present to them.

The Importance of Ischaemia in the Development of New Vessels from the Implant

It has been shown already in Section II that forward volume bloodflow was much greater in the group of dogs in which ischaemia of the left ventricle had been produced. The angiograms from the dogs without ischaemic lesions of the myocardium showed that development of new channels from the implant was either absent or of a limited nature, confirming the findings in the measurement of bloodflow in these implants. The presence of an ischaemic lesion in the myocardium is thus conducive to the more extensive development of new channels from the implant.

The Relationship of the Angiographic Appearance to Blood Flow Through the Implant

The failure to demonstrate anastomotic connections between the implant and the coronary arterial tree in three out of the fourteen implants in which there was a measurable forward blood flow was most probably due to technical reasons. There is no doubt that there was blood flow through these implants and although this was small in one (4.0 ml. per minute) it was much larger in the other two (18.2 and 33.8 ml. per minute). Before and after the flow measurements were made, zero flow was established by cross-clamping the implant above and below the flow demonstrating that after removal of the clamps the output from the flow meter was in fact from flow signals. It has also been shown by histological examination that the wall thickness in these implants had not increased at the point where flow was measured indicating that the flow measurements were valid. In addition, histological examination of the intra-myocardial portion of the implants revealed the presence of a narrowed but patent lumen in one implant, and extensive re-canalisation of thrombus within the other two; in all three, red blood cells were present within the lumen. In these implants it should have been possible to demonstrate the vessels which were providing the run-off for the blood flow. The reasons discussed above which might account for the non-visualisation of the connecting vessels in these dogs, namely preferential flow of contrast into the adherent lung in one dog and the wedging of the end of the catheter within the extracardiac course of the implants in the other two, either in re-canalised thrombus or underneath the implant endothelium, are the most likely explanations.

In the ten implants in the ischaemic group which were shown angiographically to anastomose with surrounding intra-myocardial vessels and which had a measurable blood flow, a linear relationship could not be demonstrated between the extent of opacification of the branches of the left coronary artery and forward blood flow through the implants with blood flows less than 10 ml. per minute, but in those with greater flows, the anterior descending branch (below the occluding ligature) was always filled, with, in addition, the circumflex branch in four out of six dogs. These findings are therefore in agreement with those of Dart and his colleagues (1970).

The significant linear correlation between the resistance to flow within the implants and the extent of opacification of the branches of the left coronary artery from the implant, was probably a reflection of the calibre and numbers of new channels connecting them. As a greater number of new pathways developed between the implant and myocardial vessels, and as they increased in diameter with maturity, so the resistance to blood flow through the implant and hence to that of the radio-opaque medium from the implant to the coronary arterial branches would decrease.

The factor which will determine the ease with which blood will pass through the implant, its connections with the coronary arterial branches and finally those latter vessels themselves, will be the resistance to flow offered by these various vessels. Dart and his colleagues (1970) showed that there was no correlation between flow and the extent of opacification of these vessels by angiography (and the results in this study agree with this) but they did not study the relationship between resistance in the circuit and the distribution of contrast medium. The angiographic picture as shown in the present study is therefore a better indication of resistance through the implant and its connections than with flow through the system.

The observation that a statistically significant linear correlation existed between the extent of opacification of the left coronary arterial branches and the duration of implantation was not totally unexpected, since it had already been shown earlier in this thesis (page 84) that the resistance to blood flow within the implants decreased significantly with the duration of implantation. The relatively crude assessment of the extent of anastomosis by angiography therefore provided some confirmation of the relationship between resistance to flow and duration of implantation, but in addition, amplified this information by illustrating the inter-connections between the branches of the left coronary artery especially within the area of ischaemia.

A Possible Theory on the Evolution of Connections between the Implant and the Coronary Circulation

The present study indicated that the development of the pathway from the lumen of the internal mammary artery implant to the coronary circulation could be divided into two distinct parts:-

1. The development of new vessels within and in the immediate vicinity of the implant.
2. The connection of the implant with the coronary circulation.

1. The Development of New Vessels in and around the Implant

This subject has been discussed already in Section IV. Basically these new vessels were probably derived from two sources, the lumen of the implant and the adventitial vessels. The lumen of the intramural part of the implant rarely remained widely patent; it was either considerably narrowed by intense proliferation of the intima or it thrombosed and was recanalised. The new channels within the thrombus were probably formed from cracks in its substance, which then endothelialised from the patent lumen above or from intra-myocardial vessels at the open end of the graft. Endothelial buds from these new channels might have further vascularised the thrombus and possibly also invaded the intima of the implant at a later stage.

The adventitial vessels proliferated to form a rich plexus in outer coat of the implant and at a later stage grew in two directions, into the medial coat of the implant (and possibly farther to link with the patent lumen or the rich new network of intraluminal vessels) and also outward to anastomose with surroundi vessels in the old haematoma and in the myocardium. The importance of the adventitial vessels in the vital link between the implant lumen and the small vessels of the myocardium cannot be in the opini of the author, overstressed. At open parts of the implant (the outside branches and at the end of the implant), the new intralumina vessels probably connected directly with vessels in the vicinity.

The establishment of this first stage of the new pathway was probably the most crucial in whole new system, since failure to make contact with the vessels in the myocardium would prevent new blood entering the myocardium. It may be that in some cases that althoug there was failure to establish adequate communication between the lumen and the myocardial vessels, the adventitial plexus of the implant connected with the latter, providing at least some extra blood for the myocardium. In such instances, these connections would not have been outlined by angiography.

The controlling mechanisms in this first stage of revascularisation are unknown. The stimulus to neocapillary formation is probably chemical, and derived either from the breakdown of tissue or secreted by certain cells in the vicinity. In addition, the maturation of these capillaries to arteriole-like vessels is likewise probably under chemical regulation. A chemical substance which promotes new blood vessel growth has been discovered recently (Schaper, 1970, unpublished) but it is not known whether this or a similar substance is involved in the control of new vessel formation in these circumstances.

2. The Connection of the Implant with the Coronary Circulation

Even in the absence of ischaemia of the myocardium, new blood vessels made their appearance within the implant and also between the implant and the surrounding myocardial vessels. One must therefore assume that ischaemia per se, is not necessary for the production of these new vessels. An ischaemia lesion of the myocardium, however, appears to encourage more extensive connections between implant and intramyocardial vessels and also promotes the appearance of larger and more mature anastomotic vessels.

In the ischaemic myocardium, changes were also evident in the arteries within and around the ischaemic area. The existence of a diffuse network of anastomotic channels linking the branches of the coronary arteries with each other was apparently first demonstrated by Spalteholtz in 1924. These intercommunicating channels which are normally small are much more evident in the ischaemic heart, both in experimental animals and in the human subject (Fulton, 1964; Barold 1965; Estes, Entman, Dixon, Hackel and Durham, 1966). The view of Blumgart and Zoll (1961) that the coronary arteries could be considered as end-arteries since the anastomotic channels were deeme too small to have functional significance, is therefore no longer tenable in the ischaemic heart. The angiograms in the present stud clearly showed that there was an extensive anastomosis between the two major branches of the left coronary artery (Figures 38 to 42, 44 and 46). There was no evidence however of interconnections between the terminal branches of the left and right coronary arteries.

Therefore in the ischaemic myocardium of the left ventricle, a widespread network of vessels connecting the terminal branches of the anterior descending coronary artery and the circumflex artery already existed. An internal mammary implant therefore, well placed within this area, has access to a ready made system for conducting extra blood to the ischaemic area. In addition, it has been shown that there is an actual increase in the number of collateral vessels within an ischaemic area in the heart (Schaper, Schaper, Xhonneux and Vandesteene, 1969), further augmenting possible bloodflow to the part.

Once the centrifugally directed new blood vessels from the implant had made connection with the vessels of the myocardium, probably at capillary level at first, blood would tend to flow during diastole from the implant towards the ischaemic area because of the higher diastolic pressure in the implant. With increasing maturity and number of implant connecting vessels, the ischaemic area, since it is an area of low bloodflow and pressure, would provide an extra point of 'run-off' for implant blood which would pass through this area (possibly providing nourishment to myocardial cells not yet destroyed) and hence to effluent veins. The pressure gradient between the area immediately surrounding the implant and the ischaemic area would ensure a flow of blood between those points. As the implant anastomosis improved, so the flow to the ischaemic area would improve.

With this increase in the flow of blood through the capillary bed between implant and the ischaemic area, certain capillaries would become larger and develop into arterioles as occurs in the development of interarterial anastomotic channels in the coronary circulation within an ischaemic area (Schaper, Schaper, Xhonneux and Vandesteene, 1969). Thus a new blood supply from the implant to the area of need would be effected and become mature. Such a scheme based on a theory of pressure gradients between the implant area and ischaemic area is simple in concept and need not invoke chemical mechanisms.

In the same way, blood probably also flows to the ischaemic area from those parts of the myocardial vascular bed supplied by non-occluded coronary arteries. In time, therefore, the vascular bed in the ischaemic area may become a connecting bridge between the implant and the branches of non-occluded coronary arteries. This area of 'blush' was very prominent in some angiograms (Figure 38). On the edges of this ischaemic area, direct connections between the implant and the branches of neighbouring coronary arteries may develop (Figure 38). The direction of flow between these two points in this situation will depend on which end of this anastomosis was at the lowest pressure. Such anastomoses, although taken to be a sign of the efficacy of the implant, may not in fact be entirely beneficial, for two reasons

1. If the direction of flow is from implant to coronary artery all of this extra blood may or may not reach the ischaemic area, a portion of it may flow to other areas of the myocardium in less need.

2. If the direction of flow is from coronary artery to the implant, then the flow in the implant may be reversed or decreased, especially in the early stages of development.

Summary of Section V

The principal object of Section V of this thesis was to study the connections between the internal mammary implant and the coronary circulation in the non-ischaemic and ischaemic myocardium using a simple angiographic technique on an excised but still beating heart preparation. The extent of this anastomosis was estimated by a relatively uncomplicated grading system and the estimated degree of revascularisation compared with measurements of implant blood flow and resistance. The conclusions drawn from these experiments were as follows:-

1. Angiography revealed the presence of anastomotic vessels between the implant and the branches of the left coronary artery.
2. Ischaemia of the left ventricle was more conductive to the more extensive development of new channels from the implant.
3. Three radiologically occluded implants from the group with ischaemia of the myocardium were known to have a measurable blood flow. Possible reasons are given to explain why false negative results were observed in these implants.

4. A statistically significant linear correlation existed between the extent of opacification of the branches of the left coronary artery and the duration of implantation.

5. A linear relationship could not be demonstrated been the angiographic appearance and the measured blood flow through the implants. In those implants with flows greater than 10 ml. per minute, the anterior descending branch always filled, together with the circumflex branch in a further four out of six dogs.

6. A statistically significant linear correlation was shown to exist between resistance to blood flow and the degree of opacification of the left coronary artery branches; as the former decreased so the latter became more extensive.

These observations have been discussed and where applicable their significance in the interpretation of implant angiograms in human subjects stressed. In addition, a theory is advanced based on histological and angiographic observations made in this study, and from the findings of other workers, of the evolution of the pathway between the lumen of the implant and the coronary circulation.

CONCLUSION.

CONCLUSION

A forward flow of blood through the internal mammary artery, newly implanted into the ischaemic myocardium of the left ventricle, can be detected and measured by the electromagnetic flowmeter. Increasing the number of tunnels within the myocardium did not augment this flow nor the proportion of the cardiac output carried by the implant. Analysis of the flow patterns obtained from all newly implanted arteries demonstrated that the flow was pulsatile and consisted of a large forward flow wave, followed in a few implants by a small reverse flow. The forward wave had two components, systolic and diastolic, which were always separate and distinct.

Observations made on internal mammary arteries implanted into the ischaemic myocardium for periods up to twenty-seven weeks showed that all were patent in their extracardiac course and ninety per cent were patent in their intracardiac course. Implantation into the non-ischaemic myocardium for prolonged periods of time produced a forward flow in 25% of arteries but in two of these, this was minut The presence of ischaemia of the myocardium therefore encouraged the circulation from the implant to the myocardium. Forward flow arteries implanted into the ischaemic myocardium varied from 5·7 to 33·8 mls per minute. The proportion of cardiac output carried by graft increased significantly, whilst resistance to flow in the gra decreased significantly in a linear fashion with duration of implantation over the whole twenty-seven weeks. A significant line increase in forward volume flow in the graft could be demonstrated only in the first sixteen weeks following implantation. Perfusion of the myocardium from the graft has an exponential relationship with duration of implantation.

When forward flow, proportion of cardiac output, perfusion per 100 gm. of left ventricle and resistance to flow were measured in the anterior descending branch of the left coronary artery at the point of subsequent ligation and compared with those of the implants, significant differences between their means were found only the grour implanted for less than ten weeks. After this time therefore, the implant flow, the proportion of the cardiac output carried, the amoun of myocardial perfusion from the implant and the resistance to flow within the implant reached levels whose mean values could not be shown to be significantly different from those of the coronary artery at the level of occlusion. As far as these measurements are concerned, the implanted internal mammary artery therefore appeared to become a reasonable substitute for the occluded portion of the anterior descending branch of the left coronary artery, after the tenth week following implantation. Measurements made of wall thickness of implanted internal mammary arteries on histological sections from the site where blood flow was determined, were not significantly different from those of unimplanted internal mammary arteries. The blood flow measurements made on the implanted arteries were therefore valid.

Microscopic examination confirmed patency of the arteries in the first seventy-two hours after implantation and showed the presence of a small pool of blood around the intra-myocardial port of the implant, with columns of red cells radiating from it into the myocardium. The histological picture suggested that this pool of blood was not static and that it was part of a passive circulation of blood from the implant through the myocardium. A study of the microscopic changes within the implant and surrounding ischaemic myocardium for periods up to twenty-seven weeks revealed that the lumen of the intra-myocardial portion of the graft either remained patent but reduced in size due to proliferation of the tunica intima or had become thrombosed but recanalised; the extracardiac portion of all implants was patent on histological examination.

Small blood vessels made their appearance within the thrombosed lumen of the implant and some evolved gradually into vessels indistinguishable from arterioles. At about the fourth week, the first phase of vascularisation of the implant wall occurred probably from the lumen of the implant, followed by a more intense and complete second phase beginning about ten weeks later; this latter ingrowth of capillaries was probably from the adventitial plexus of blood vessels in the implant. There was also a noticeable increase in the number of small blood vessels around the intra-myocardial portion of the implant from about the fourth week, situated in the area occupied formerly by the haematoma. These blood vessels increased in number and maturity with time and were probably the connecting vessels between implant and the coronary arterial circulation. The adventitial plexus of blood vessels of the implant may play a greater role in revascularising the myocardium than hitherto suspected, first in carrying blood to the myocardium from outside the heart, second in helping to vascularise the wall of the implant, and finally in making possible connections with vessels surrounding the implant. Thus a pathway for blood may be established between the lumen of the implant and the vessels of the surrounding myocardium.

Angiographic studies made on the implants clearly showed the existence of anastomotic vessels with the branches of the left coronary artery in the presence of ischaemia of the left ventricle.

All arteries implanted for more than ten weeks into the ischaemic myocardium had established anastomosis with the anterior descending branch of the left coronary artery below its point of ligation, and also with the circumflex branch of the same artery in the majority of cases. A statistically significant linear relationship was demonstrated between decreasing resistance to blood flow within the implants and the increasing extent of opacification in the branches of the left coronary artery from implant angiograms. A significant linear relationship was also established between the time since operation and the extent of opacification in the branches of the left coronary artery from the internal mammary artery implant.

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ACKNOWLEDGEMENTS

These studies were carried out when holding the post of Lectur in Cardiac Surgery at the University of Glasglow and were performed at the Wellcome Surgical Research Laboratory, University of Glasgow

I render my sincere thanks to Professor W. A. Mackey for his support, advice and encouragement, and to Dr A. M. Harper and his staff at the Wellcome Surgical Research Laboratory, without whose help this work would not have been possible. I wish to thank in particular, Mr Gordon Littlejohn for setting up much of the electronic and other equipment used during this study; Miss Brenda Robinson, who so ably combined the roles of anaesthetist, surgical assistant, theatre sister, animal nurse and technician; Miss Joan McLeod and Mrs F. Crossling who assisted with most of the radiographic studies. Technical assistance with some of the experiments, was also given by Mr A. Smith and Miss Isabel Docherty

Cardiovascular Surgical Unit, Glasgow Royal Infirmary. The photography was carried out with the assistance of Mr W. Towler, Royal Infirmary, Glasgow and Mr B. Richards, National Heart Hospita London. Mrs Theresa Read, Institute of Cardiology, London helped with the laborious task of mounting the figures.

I am indebted to Mr S. W. G. Reeves, Principal Lecturer, Portsmouth College of Technology for his calculations on exponentia curve fitting for some of the experimental data.

Professor Peter Harris, Institute of Cardiology and National Heart Hospital, London, gave much advice on bloodflow interpretatio and on statistics.

My sincere thanks are extended to Miss Sally Read who typed the manuscript.