EVALUATION OF ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSMS

by

Akhtar Nasim

MB, ChB (Aber 1990), FRCS (Edin 1994)

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Department of Surgery, University of Leicester, UK.

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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

The work on which this thesis is based is my own independent work except where acknowledged.

Akhtar Nasim
April 1997

Dedicated to my parents

'Blood....appears to carry life to every part of the body, for whenever the whole or a part is deprived of fresh blood it very soon dies'.

John Hunter (1728-93)

Abstract: Evaluation of endovascular repair of abdominal aortic aneurysms

Akhtar Nasim MB. ChB. FRCS (Ed).

Abdominal aortic aneurysms occur in about 3% of the population over the age of 50 years and rupture of these accounts for around 10 000 deaths per annum in England and Wales. Conventional elective repair of abdominal aortic aneurysms is associated with a mortality rate of 5% in most centres. However, in elderly patients and those with co-existing cardiorespiratory disease the mortality rates may reach 60%. Endovascular repair of abdominal aortic aneurysms is a new "minimally invasive technique" that enables aortic aneurysms to be treated without the need for major abdominal surgery. It involves the insertion of a prosthetic graft via the femoral or iliac arteries, which is anchored within the infra-renal aorta with expandable metallic stents, with the aim of excluding the aneurysm from the circulation. The feasibility of this technique was first demonstrated in animal experiments, and subsequently several reports of initial clinical experience have been published.

However, several important questions remain unanswered which have been investigated by this study. Initially a retrospective study was undertaken to assess the current abdominal aortic aneurysm practice in terms of workload, mortality, complications and risk factors, to assess whether there is a role for endovascular AAA repair in Leicester. Then an experimental animal model was developed to investigate the necessity for anchoring the distal end of the graft with a second stent, the effect of placing stents across the renal ostia, and whether inferior mesenteric or lumbar artery backbleeding persists into the excluded aneurysm sac. A study has also been performed to assess the clinical application of this technique. A prospective study was undertaken in 82 consecutive patients referred for elective aneurysm repair to determine the best imaging modality for pre-operative assessment prior to endovascular AAA repair. A comparison was made between computed tomography (CT), magnetic resonance angiography (MRA), colour duplex and intra-arterial digital subtraction angiography (IA-DSA). The morphology of the aneurysm in these patients was assessed to determine the proportion of patients that may benefit from this technique. Finally, the preliminary clinical experience with 3 different endoluminal grafts, one of which was developed in this study, was assessed.

The results presented in this thesis show that work load of AAAs in Leicester has slowly increased over the past decade but there has been no significant improvement in the mortality figures for elective and emergency aneurysm surgery during this period. The results of the animal work show that a distal stent is necessary for complete exclusion of the aneurysm sac, but the safety of deploying stents across the renal arteries remains uncertain. This study also shows that MRA provides the best non-invasive assessment of aneurysm morphology prior to endovascular repair when compared to CT and IA-DSA ($p<0.01$). Only 36% of the patients met the criteria for the currently available tube and bifurcated endoluminal grafts. The initial clinical results show that this technique is feasible and appears to reduce the ischaemia-reperfusion response associated with conventional aneurysm surgery . However, a number of problems have been encountered which need further evaluation prior to widespread use of this technique.

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ABBREVIATIONS

< or >	less than or greater than
%	per cent
AAA	abdominal aortic aneurysm
AD	anno domini
AE	air emboli
AOD	aortic occlusive disease
AP	anteroposterior
ARDS	adult respiratory distress syndrome
ASA	American Society of Anaesthesiologists
BAPN	beta-aminoproprionitrile fumarate
BC	before christ
blo	blotchy
CAD	coronary artery disease
CAM	cell adhesion molecule
CD	colour duplex
CFA	common femoral artery
CHF	congestive heart failure
CIA	common iliac artery
COAD	chronic obstructive airways disease
COPD	chronic obstructive pulmonary disease
cm	centimetre
Cr-EDTA	chromium ethylene diamine tetra-acetic acid
CT	computed tomography
DA	distal anastomosis
DTPA	diethylene triamine penta-acetic acid
ECG	electrocardiogram
ECM	extracellular matrix
EIA	external iliac artery
EM	electron microscopy
ESR	erythrocyte sedimentation rate
et al.	et alia (and others)
EVT	EndoVascular Technologies
GFR	glomerular filtration rate
GGH	Glenfield General Hospital
GI	gastrointestinal
HAA	hospital activity analysis

Hg	**mercury**
HMSO	**Her Majestys stationary office**
IA-DSA	**intra-arterial digital subtraction angiogram**
IIA	**internal iliac artery**
ICAM	**intercellular adhesion molecule**
ICD-9-CD	**International Classification of Diseases, ninth revision, Clinical modification**
Ig	**immunoglobulin**
IL	**interleukin**
ISCVS	**International Society for Cardiovascular Surgery**
kDa	**kilo Dalton**
L	**litre**
LGH	**Leicester General Hospital**
LRI	**Leicester Royal Infirmary**
LT	**leukotriene**
LVEF	**left ventricular ejection fraction**
MHz	**megahertz**
MI	**myocardial infarction**
ml	**millilitre**
mm	**millimetre**
MMP	**matrix metalloproteinase**
MRA	**magnetic resonance angiography**
MRI	**magnetic resonance imaging**
mRNA	**messenger ribonucleic acid**
MUGA	**multigated acquisition scan**
NHS	**national health service**
No.	**number**
OFR	**oxygen free radical**
OPCS	**Office of Populations, Censuses and Surveys**
PA	**proximal anastomosis**
PE	**particulate emboli**
PTFE	**polytetrafluoroethylene**
QALY	**quality adjusted life year**
RA	**renal artery**
RPI	**retroperitoneal incision**
SE	**spin echo**
SMC	**smooth muscle cell**
SVS	**Society for Vascular Surgery (USA)**

TAI	**transabdominal incision**
TIMP	**tissue inhibitor of metalloproteinase**
TNF	**tumour necrosis factor**
UK	**United Kingdom**
USA	**United States of America**
VWF	**Von Willebrand Factor**

PUBLICATIONS ARISING FROM THIS THESIS

PUBLISHED PAPERS

1. **Nasim A**, Sayers RD, Thompson MM, Bell PRF and Bolia A. Endovascular repair of abdominal aortic aneurysms. *Lancet* 1994;**343**:1230-1231.

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3. **Nasim A**, Thompson MM, Sayers RD, Bell PRF. Elective AAA repair and rupture. *Eur J Vasc Endovasc Surg* 1995;**9**:124-125.

4. **Nasim A**, Sayers RD, Thompson MM, Healey P, Bell PRF.Trends in Abdominal aortic aneurysms: a 13 year review. *Eur J Vasc Endovasc Surg* 1995;**9**:239-243.

5. **Nasim A**, Sayers RD, Thompson MM, Bell PRF. Endovascular repair of abdominal aortic aneurysms. *Hosp Update* 1995;131-135.

6. **Nasim A**, Sayers RD, Thompson MM, Bolia A, Bell PRF. Simultaneous endovascular repair of an abdominal aortic and iliac aneurysm. *Br J Surg* 1995;**82**:634.

7. **Nasim A**, Thompson MM, Sayers RD, Bolia A, Bell PRF. Endovascular repair of abdominal aortic aneurysms: an initial experience. *Br J Surg* 1996: **83**;516-519.

8. **Nasim A**, Thompson MM, Sayers RD, Boyle JR, Bolia A, Bell PRF. Late failure of endoluminal aortic aneurysm repair due to continued aneurysm expansion. *Br J Surg* 1996;**83**;810-811.

9. **Nasim A**, Thompson MM, Sayers RD, Bell PRF. Ischaemia Reperfusion Injury. In: Yusuf W, Hopkinson BR, Whitaker SC, Veith FJ (eds) *Endovascular Surgery for Aortic Aneurysms*. London: WB Saunders 1997. Pages 264-272.

10. **Nasim A**, Thompson MM, Sayers RD, Boyle J, Maltezos C, Fishwick G, Bolia A, Bell PRF. Is endoluminal AAA repair using an aorto-aortic (tube) device a durable procedure? *Annales De Chirurgie Vasculaire* (in press)

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PUBLISHED ABSTRACTS

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3. **Nasim A**, Thompson MM, Sayers RD, Thompson J, Fishwick G, Bolia A, Bell PRF. Endoluminal repair of abdominal aortic aneurysm: preliminary experience. *Br J Surg* 1996:**83**;567-8..

4. **Nasim A**, Thompson MM, Sayers RD, Hartshorne T, Bell PRF, Moody AR. Comparison of MR angiography, Computed tomography, Colour Duplex and Arteriography for assessing AAAs prior to endoluminal repair. *Br J Surg* 1996:83;559.

5. **Nasim A**, Thompson MM, Sayers RD, Boyle J, Thompson J, Smith G, Fishwick G, Bolia A, Bell PRF. Is Endoluminal repair of abdominal aortic aneurysms a durable procedure? *Br J Surg* 1996;Suppl 1; Page 4.

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CHAPTER ONE

Abdominal Aortic Aneurysms

1.1 Historical Aspects

Aneurysms have been recognised since ancient times. A clear description of the diagnostic features and management of a traumatic aneurysm can be found in the Ebers Papyrus (2000 BC), one of the earliest known texts (Osler, 1905). The term "aneurysm" is derived from the Greek word *aneurusma* meaning to widen out. Galen (AD 131-200) in his writings defined an aneurysm as a localised pulsatile swelling which disappeared on pressure and wrote *'if an aneurysm be wounded, the blood is spouted out with so much violence that it can scarcely be arrested'* (Osler, 1905). Vesalius (1514-64) made the first clinical diagnosis of aneurysm of the abdominal aorta (Osler, 1905). He asserted in 1555 that a pulsating tumour in a patient's back near a vertebra was a "dilation of the aorta." He was proven correct at the patient's autopsy two years later (Blau *et al.* 1983).

1.2 Definition

Most commonly, an aneurysm (*Figure 1.1* and *Figure 1.2*) is defined as permanent localised dilatation of an artery, but the amount of enlargement required for an artery to be categorised as aneurysmal is controversial. Several definitions have been proposed (Moher *et al.* 1992; Collin, 1990; Sterpetti *et al.* 1987) but the definition which is most widely accepted is that agreed by the ad hoc committee on reporting standards of the Society for Vascular Surgery (SVS) and the North American Chapter of the International Society for Cardiovascular Surgery (ISCVS), who proposed to define arterial aneurysm as "*a permanent localised dilatation of an artery of more than 50% of the normal diameter of the artery*" in question (Johnston *et al.* 1991). However, determination of expected normal diameter is confounded by differences in gender, total body surface area, and other factors. The dimensions of the abdominal aorta have been analysed in large numbers of individuals using CT scan measurements (Ouriel *et al.* 1992), but there is no universal agreement concerning what size constitutes an aneurysm. Moreover, diffusely enlarged arteries are frequently present in patients with aneurysms (a condition known as arteriomegaly, arteriectasis, or dolichomegaly) (Lea Thomas, 1971). Thus, a more generally applicable definition of an aneurysm is dilatation more than twice the size of the more proximal artery.

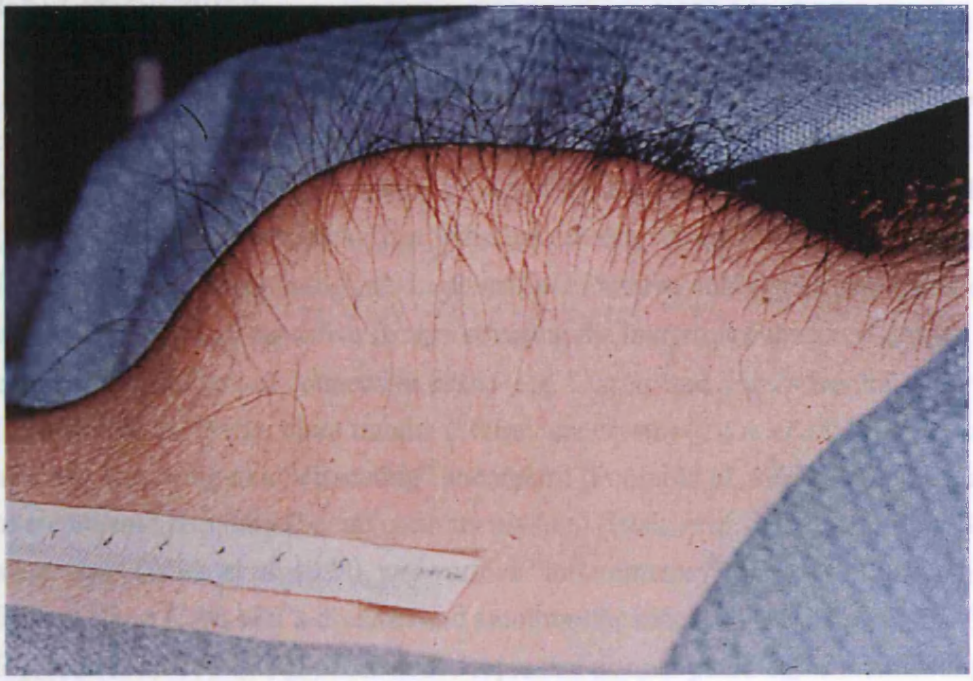


Figure 1.1: *Photograph of an abdomen showing a large abdominal aortic aneurysm presenting as an abdominal mass.*

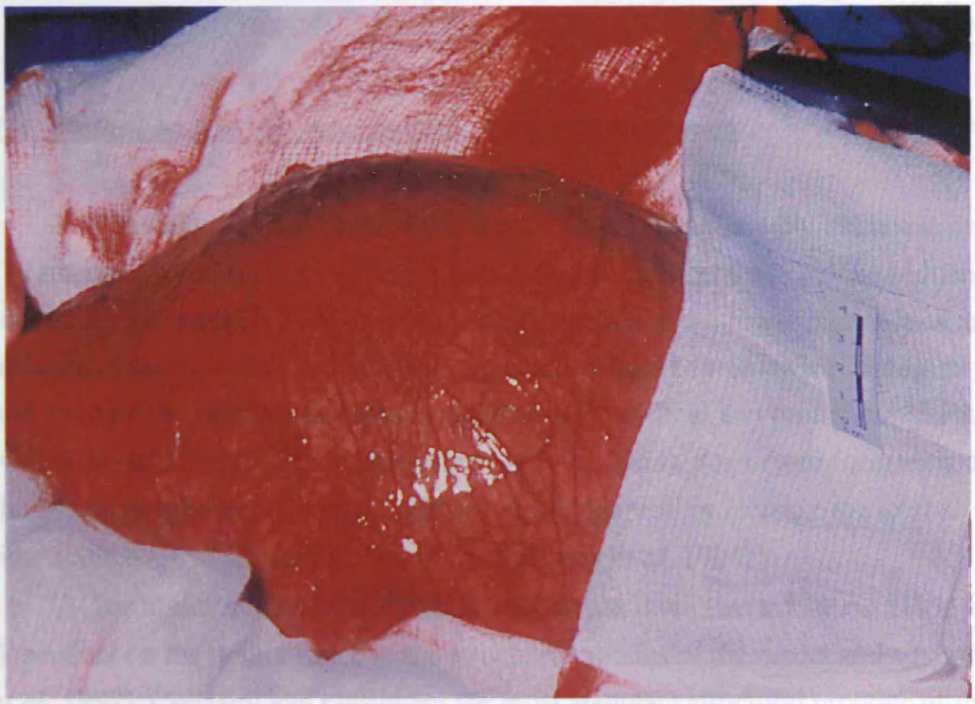


Figure 1.2: *Operative photograph of an abdominal aortic aneurysm.*

1.3 Classification

The ISCVS has recommended that aneurysms be classified by a combination of characteristic factors such as site (e.g. abdominal aorta, popliteal), aetiology, histological features, morphology (e.g. fusiform or saccular), and clinicopathological manifestations (pulsatile mass, thromboembolism, pressure effects, rupture, fistula) (Johnston *et al.* 1991) (*Table 1*). An aetiological classification of arterial aneurysms may include one of a variety of "specific" causative factors affecting the integrity of the arterial wall, such as congenital disorders of connective tissue (e.g. Marfan and Ehlers-Danlos syndromes) (Johnston *et al.* 1991), blunt trauma ("false" aneurysm) (Cook *et al.* 1994), cystic medial necrosis (resulting in a "dissecting" aneurysm) (Ponraj *et al.* 1992), infectious agents such as *treponema pallidum* (i.e. mycotic aneurysms) (Pasic *et al.* 1992), anastomotic aneurysms (Allen *et al.* 1993), and various "inflammatory" diseases (Takayasu's, Behcet's and Kawasaki's disease) and autoimmune reactions (Johnston *et al.* 1991; Rijbroek *et al.* 1994). All of the above represent distinct pathologies manifesting themselves as an aneurysm. However, it is the "non-specific" aneurysm, commonly referred to as an atherosclerotic aneurysm, which is the most prevalent (Reed *et al.* 1992) and the site most often affected is the infra-renal abdominal aorta (Lilienfield *et al.* 1987; Reed *et al.* 1992). This thesis concentrates mainly on this latter entity.

1.4 Pathogenesis of Abdominal Aortic Aneurysms

Clinically, disease of the distal aorta results in anatomically diametric processes: (1) atherosclerotic occlusive disease, in which the atherosclerotic plaque reduces the vessel lumen, impedes blood flow, and results in ischaemia of the lower extremities; or (2) abdominal aortic aneurysm, in which the vessel dilates beyond twice its normal diameter and becomes susceptible to rupture. Accumulation of lipid and protein within the vessel wall is responsible for the former process (Ross, 1993). Aneurysm formation depends on the interplay between factors that either weaken the wall or increase the load on it and the time scale over which they operate (MacSweeney *et al.* 1994b).

The ability of the arterial wall to counter the force exerted by the blood is dependent on the maintenance of the structural proteins of the media and adventitia (Baxter *et al.* 1992). Collagen and elastin are the most abundant structural proteins of the aorta, imparting both strength and distensibility, resulting in uniform distribution of stresses and appropriate viscoelastic responses to pulsatile oscillations. They are arranged in conjunction with smooth muscle cells in multiple concentric elastic lamellae, the basic structural units of the aortic media (Wolinsky *et al.* 1967a; Clark *et al.* 1985). Elastin, as

Table 1: *Classification of arterial aneurysms (Reproduced from Krupski, 1994).*

Shape Fusiform Saccular *Location* Central Peripheral Visceral Cerebral *Aetiology* Degenerative Nonspecific (atherosclerotic) Fibrodysplasia Graft Congenital Idiopathic Tuberous sclerosis Turner syndrome Infection Bacterial Syphilitic Infection of false aneurysm Fungal *Aneurysms associated with arteritis* Systemic lupus erythematosus Takayasu's disease Giant cell arteritis Polyarteritis nodosa Behcet's disease	*Size* Macroaneurysms Microaneurysms *Structure* True False *Inherited abnormality of connective tissue* Marfan's syndrome Ehlers-Danlos syndrome Cystic medial necrosis Berry (cerebral) *Mechanical* Post-stenotic Traumatic Anastomotic Prosthetic *Miscellaneous* Inflammatory Dissecting Aneurysms associated with pregnancy

its name suggests, is easily stretched and can double its length and spring back to its original dimensions. Elastic fibres consist of at least two components: elastin and microfibrillary proteins. Fibrillin is one component of the electron microscopically visible microfibrillar proteins. On the other hand collagen, of which types I and III are the principal forms found in the aortic wall (Menashi *et al.* 1987), has very different properties. Collagen type I and III are capable of forming fibres (also types II and V) and are referred to as fibrillar collagens. Fibrillar collagen has a tensile strength over 20 times greater than that of elastin (Caro *et al.* 1978) and is very difficult to stretch: it cannot extend beyond a small proportion of its original length before structural damage occurs (Dobrin, 1988; Caro *et al.* 1978). Aortic collagen is coiled up in such a way that, initially, the load on the aorta is borne by elastin, resulting in an easily stretched elastic vessel. As the load increases and the vessel continues to stretch, collagen fibres uncoil and are progressively recruited as load bearing elements, so that the vessel becomes ever less distensible (Dobrin, 1988; Caro *et al.* 1978; Burton, 1954).

Smooth muscle cells (SMC's) are the major cell type of the aorta (Galis *et al.* 1994). In conjunction with the adventitial population of fibroblasts they synthesise the important connective tissue components of the extracellular matrix (ECM) including collagens, elastin, and proteoglycans. The close association of elastin, collagen, and SMC's in the aortic media are responsible for the viscoelastic properties that account for many of the static and dynamic mechanical features of the adult aorta (Wolinsky *et al.* 1967b).

Abdominal aortic aneurysms are a disease of degeneration, destruction, and remodelling of the architecture of the aortic wall. Aneurysmal dilatation is accompanied by an overall thickening of the aortic wall in both the tunica intima and adventitia, with a marked loss of extracellular matrix within the tunica media (Baxter *et al.* 1992). A stereological study on segmental histological sections demonstrated that concentrations of both elastin and smooth muscle cells were decreased by 91% in AAAs (He *et al.* 1994). The loss of both elastin and smooth muscle cells contrasts with a clearly visible increase in collagen, and an almost ubiquitous chronic inflammatory infiltrate (Koch *et al.* 1990).

Matrix Protein Changes in AAA

If the aorta were to expand without an increase in the mass of the wall, the attenuation of the wall would be so great that rupture would consistently occur before an aneurysm became two or three times its normal diameter. Rather than undergoing attenuation the thickness of the aneurysm wall is usually increased, except in the very late stages of the disease. Studies of matrix proteins in aneurysm specimens have shown an increase in total protein, microfibrillar protein, and collagen content, together with a marked reduction in elastin concentration, and in the number of medial smooth muscle cells (Baxter *et al.* 1992; Baxter *et al.* 1994; Koch *et al.* 1990).

Sumner *et al.* (1970) were the first to document deficiencies of elastin in aneurysmal tissue (as percentages of solids present in the aortic wall), and numerous subsequent biochemical studies have confirmed the marked segmental elastin depletion seen in aneurysmal histological sections. As a defatted dry weight percentage, the elastin concentration of infrarenal AAAs has been reported by several studies to be only 5-8% (Powell *et al.* 1989; Campa *et al.* 1987; Sakalihasan *et al.* 1993) when compared to the 15-35% of age-matched aortas (Powell *et al.* 1989; Sakalihasan *et al.* 1993). As a ratio to the total insoluble matrix material Gandhi *et al.* (1994) found the elastin concentration of AAAs to be reduced by 90%. Likewise Baxter *et al.* (1992) found the percentage of insoluble elastin to be substantially decreased from 12% in non-aneurysmal disease to just 1% in AAA tissue.

However, on closer examination, contradictory results appear when the distinction between elastin concentration and elastin content is considered. Some authors claim that examining changes in elastin concentration of aneurysmal aorta is misleading because of the concomitant increase in wall thickness with increasing aneurysm circumference (Minion *et al.* 1994). Elastin content, defined by its total weight in a standardised entire circumferential transverse ring of aorta, has been shown to increase in AAA tissue, but owing to a much greater total circumferential increase in protein content the elastin concentration decreases (Minion *et al.* 1994; Baxter *et al.* 1994).

The fibrillar collagen network provides most of the tensile strength of the aortic wall. This network contains principally types I and III collagen (Powell *et al.* 1989) with the tensile characteristics being attributed to type III (Menashi *et al.* 1987). Whilst elastin is the principal load-bearing component under normal conditions (Dobrin, 1988), its depletion in the aneurysmal aorta results in collagen fibres being progressively "recruited" (MacSweeney *et al.* 1994b) as the load increases and the vessel continues to stretch. If there is a continued weakening in tensile strength supplied by the collagen fibres, dilatation progresses until rupture threatens.

Collagen is the principal component of the adventitia of any AAA, regardless of size. As with the rest of the ECM, the relative collagen concentration and absolute collagen content of the aneurysmal aorta has been extensively analysed, with elevated levels in comparison to age-matched controls being widely reported. Minion *et al.* (1994) and Baxter *et al.* (1994) found a 5-fold and 3-fold increase in collagen content respectively whilst Menashi *et al.* (1987) showed an increase in collagen concentration from 62% to 84% of total dry weight. Similarly, He and Roach (1994) found a 77% increase in collagen as a total volume fraction.

As with elastin, the relative change in collagen during aneurysm formation has been the subject of much debate. The high degree of correlation between increasing aneurysm size and collagen content (Minion *et al.* 1994) suggests a causal relationship between collagen synthesis and AAA formation, although this could be a compensatory

response to increased wall stress (White *et al.* 1993). New collagen may be deposited as the wall becomes aneurysmal, since stretch is known to be a stimulus for connective tissue synthesis by vascular smooth muscle cells (Leung *et al.* 1976). That continued collagen deposition and reorganisation is required to compensate for aneurysm growth under a failing tunica media is supported by the findings of McGee *et al.* (1991) who demonstrated accelerated collagen synthesis and deposition in the walls of unruptured aneurysms. They found mRNA levels for the distinct α1-procollagen chains to be increased in AAA tissue extracts (McGee *et al.* 1991). Since elastin gene expression is unaltered in the wall of aortic aneurysms (Mesh *et al.* 1992), these data suggest that discordinate gene expression may contribute to the relative decrease in elastin concentration in aortic aneurysms.

Others have argued that since the ratio of type I to type III collagen is unchanged compared with normal aorta (Menashi *et al.* 1987), and the relative amount of elastin in the aneurysmal media is markedly diminished, selective degradation of elastin in the aneurysmal media gives an apparent dilutional increase in collagen concentration (Menashi *et al.* 1987). It would appear that a combination of both an absolute increase in collagen synthesis and a relative increase due to elastin degradation are responsible for these observations.

Interestingly, the matrix abnormalities associating increased collagen deposition with dilatation seen in AAA tissue are not confined solely to the aneurysmal segment, but are also found in aortic tissue proximal to the aneurysmal site (Baxter *et al.* 1994). Ward (1992) also found mean diameters for the carotid, femoral, brachial and popliteal arteries to be significantly greater in patients with aortic aneurysms than in controls, suggesting that infrarenal aneurysmal disease may be a localised manifestation of a systemic dilating process.

In addition to elastin, collagen, and SMC's, the elastic lamellae are associated with microfibrillar proteins, a family of glycoproteins which envelope the elastic fibres. Several biochemical studies of aneurysmal tissue have shown an increase in content of approximately 20% of an unknown connective tissue protein, most likely to be a microfibrillar protein such as fibrillin (Gandhi *et al.* 1994; Baxter *et al.* 1992; Minion *et al.* 1994). The reasons for the increase in this microfibrillar protein are currently unclear.

The increased turnover in extracellular matrix components observed in the aneurysmal aorta, thought to be due to increased elastolytic (Vine *et al.* 1991) and collagenolytic activity (Busuttil *et al.* 1980), results in a relative imbalance in structural proteins. It is not known whether this imbalance is an important aetiological factor in aneurysm formation, or whether it results from changes such as wall tension and chronic inflammation. However, it is probable that the continued abnormal mechanical properties of AAAs are at least, in part, due to a decrease in the ratio of elastin to collagen, resulting in a functionally compromised aortic wall.

Genetic Factors

Although localisation of AAA to the infra-renal aorta suggests a focal process, there is evidence of systemic abnormalities. This includes generalised dilatation, and elongation of other arteries and aneurysm formation at remote sites such as the popliteal artery (Makherjee *et al.* 1989; Tilson *et al.* 1981; Ward, 1992). Although aneurysm formation in the thoracic aorta may be attributable to well defined abnormalities such as Marfan syndrome (Ramirez *et al.* 1993), AAAs are rarely associated with known connective tissue abnormalities. However, three mutations in type III collagen have been linked to late onset AAA (Deak *et al.* 1991; Kontusaari *et al.* 1990). A systematic search for other fibrillar collagen mutations in more than 100 patients with adult-onset AAAs has not identified another structurally significant mutation (Halloran *et al.* 1995). Two fibrillin mutations have recently been found in association with AAAs (Halloran *et al.* 1995). Given the strong association of fibrillin with elastin, and the markedly higher levels of elastin in the proximal compared with distal aorta, it would seem quite unlikely that fibrillin or elastin mutations would be manifest in the distal rather than the proximal aorta. At present there are no known mutations of the major aortic connective tissue proteins that can account for the frequency of adult-onset AAA.

It seems certain that inheritance of AAA disease is multifactorial, involving a complex interaction between environmental influences and a constitutional genetic susceptibility (Powell *et al.* 1989). Powell *et al.* (1990) analysed patients who were normal, or had aortic occlusive disease or AAA, and found an increased frequency of the haptoglobin alpha-1 allele in AAA patients. Although haptoglobin has been shown to accelerate the hydrolysis of elastin by elastases in vitro, its function in vivo remains unclear. Because the haptoglobin gene maps to the long arm of chromosome 16, other genes on this chromosome may have a more direct influence on AAA formation (Halloran *et al.* 1995). Therefore, although the familial clustering of AAA indicates a hereditary component and several candidate genes have been investigated, the precise genetic basis of aneurysm formation remains unresolved (MacSweeney *et al.* 1994b).

Haemodynamics and Mechanical Factors

The infra-renal abdominal aorta appears to be a preferential site for development of aneurysm. Several anatomical and physiological factors seem to enhance the development of aneurysm at this level.

The strength of the normal aortic wall results from the medial lamellae of smooth muscle cells, tensile collagen, and elastic connective tissue. There is a relative deficiency in the proportion of elastin in this part of the aorta, since the infrarenal aorta contains fewer elastic lamellae in contrast with the thoracic aorta (Wolinsky *et al.* 1967b; Baxter *et al.*

1994), resulting in a stiffer less compliant vessel by comparison. Superimposed upon this is a natural age-related decrease in the distensibility and elasticity of the aorta, owing to the effects of haemodynamic stress imparted during the cardiac cycle (Sonesson *et al.* 1994).

Localised high-pressure zones, due to reflected pressure waves from the aortic bifurcation, may also contribute to the common localisation of aortic aneurysms in the infrarenal segment (Henney *et al.* 1993). The higher pressure waves reflecting off the iliac and other arteries contribute to pulsatile stress in the abdominal aorta, further fracturing the elastic lamellae in the media, and possibly precipitating the development of an aneurysm in a weak wall. An interesting example of this haemodynamic effect was noted in a study of amputees which resulted in an asymmetric flow pattern at the aortic bifurcation and an increased risk of aortic aneurysms (Vollmar *et al.* 1989).

The process of dilatation itself perpetuates continued aneurysm expansion. Laplace's Law states that *the circumferential tension in the wall of a cylinder is directly proportional to the pressure within it and to its radius, and inversely proportional to the thickness of the wall.* This creates an unstable situation, with dilatation causing increased loading on the aortic wall and resulting in further dilatation until eventually rupture occurs. Several factors modify this apparently simple process. As the aorta dilates its shape changes from a cylinder towards a sphere. This results in a reduction in the load on the wall. This tends to counteract the effect of the dilatation (Dobrin, 1988). Also as expansion of the aorta occurs over years, during which time remodelling of collagen occurs, it can not be assumed that the volume of the aortic wall will remain unchanged. Hypertension also increases the transmural pressure, further increasing the load on the aortic wall, exacerbating the cycle until rupture eventually occurs (Cronenwett *et al.* 1985; Cronenwett *et al.* 1990).

The Role of Proteolysis

Proteolysis of the critical structural elements of the aortic wall is the basic fundamental process responsible for weakening of the vessel wall. Busuttil and co-workers (Busuttil *et al.* 1980; Cannon *et al.* 1982) were the first to report increased elastolytic activity in AAAs.

The family of enzymes that selectively digest the individual components of the ECM are collectively called the matrixins, or more commonly the matrix metalloproteinases (MMP's), since their catalytic mechanism depends on the presence of zinc at the active site (Woessner, 1991). The proteinase activity of the MMP's is inhibited under physiological conditions by tissue inhibitors of metalloproteinases (TIMP's), a group of endogenous of glycoproteins. The TIMP family includes TIMP-1, a 29-kiloDalton (kDa) glycoprotein, and a smaller inhibitor called TIMP-2. The MMP's belong to three main groups according to their substrate specificity: the collagenases (e.g. MMP-

1) which selectively cleave the fibrillar collagens (types I, II and III); the gelatinases (MMP-2 and MMP-9) which degrade denatured type IV and V collagen (i.e. gelatin) and elastin (Senior *et al.* 1991; Katsuda *et al.* 1994); and the stromelysins (e.g. MMP-3) which are capable of degrading elastin, fibronectin, collagen IV and V, and proteoglycans (Woessner, 1991).

Cohen *et al.* (1988) have extensively studied neutrophil elastase and reported that peripheral neutrophils from patients with AAA exhibit increased neutrophil elastase activity. They also showed that smooth muscle cells from AAA explants secrete increased amounts of elastase in response to stimulation by elastin degradation products (Cohen *et al.* 1992). These findings suggest systemic differences in neutrophil proteolytic activity or mesenchymal cell (smooth muscle cells and fibroblasts) response in patients with AAA. Herron *et al.* (1991) have focused on the role of specific elastolytic enzymes and reported increased activity of the 92-kd gelatinase in AAA tissue homogenates compared with homogenates from normal tissue using gelatin zymography. Vine and Powell (1991) also found increased degradation of radio-labelled gelatin in AAA as compared with normal tissue, but found comparable gelatinase activity in AAA and aortic occlusive disease (AOD). Its activity was unaffected by aldylation (which inhibits TIMP), whereas there was increased gelatinase activity if alpha 2-macroglobulin was blocked in AAA homogenates. When the aneurysm wall was bisected and the plaque was compared with the outer media/adventitia, gelatinase activity was greatest within the plaque in both AAA and AOD. Therefore, these studies suggest increased elastolytic activity in AAA tissue compared with AOD, the more specific assays of elastolytic activity performed by Vine and Powell (1991) localised the elastolytic activity to the plaque in both AAA and AOD. Thus, the destruction of the organised aortic elastin lamellae that occurs in both AOD and AAA is a result of elastolytic activity from the inflammatory process that begins within the plaque.

Busuttil *et al.* (1980) also provided early evidence of increased collagenolytic activity in the aneurysmal aorta. Manachi *et al.* (1987) demonstrated low levels of true collagenase activity in aneurysm tissue collected at elective repair, whereas higher levels were noted in specimens from ruptured aneurysms. Vine and Powell (1991), using Western blots, found that MMP-1 was present in 10 of 10 aneurysm homogenates, 3 of 8 AOD homogenates, and none of the normal aorta homogenates. Irizarry *et al.* (1993) also found increased MMP-1 in AAA tissues as compared with normal or AOD tissue. By immunohistochemistry, the MMP-1 localised to the adventitia. More recently Newman *et al.* (1994b) have reported an increase in activated MMP-1 in AAA tissue compared with normal aorta. All these studies of aortic proteolytic activity suggest increased collagenolytic activity in AAAs.

The localisation of collagenase to the adventitia is not surprising given the prominent adventitial infiltrates found in AAA. Although MMP-1 is a product of

macrophages, it is produced in much greater quantity by mesenchymal cells under the influence of inflammatory mediators (Welgus *et al.* 1990). Cytokines that have been shown to increase MMP-1 synthesis by mesenchymal cells include IL-1β and PDGF (Birkedal-Hansen *et al.* 1993). Of these cytokines, only IL-1β has been specifically identified in AAA tissues (Pearce *et al.* 1992).

The Role of Inflammation

In addition to the changes in proteolytic activity and subsequent protein concentration, abdominal aortic aneurysms are typically characterised by a marked chronic inflammatory infiltrate of varying intensity, ubiquitous throughout the affected aortic wall (Koch *et al.* 1990; Newman *et al.* 1994b; Beckman, 1986). These inflammatory cells have been thought to play a significant role, not only in the direct destruction of the extracellular matrix, but also in their self-perpetuating autocrine activation, and through their cytokinetic paracrine control of native aortic mesenchymal cells.

The locations of the inflammatory cells in AAA and AOD are similar (intima/plaque and adventitia) as are the cell types (macrophages and lymphocytes (Halloran *et al.* 1995). The inflammation in AAA and AOD differ in two ways: (1) the lymphocytes present in AOD are predominantly T-cells, whereas both T- and B-cells have been identified in AAA tissue; (2) adventitial inflammation is a consistent feature of AAA, but is only seen in the more advanced stages of AOD (Koch *et al.* 1990; Ross, 1993). The entity called "inflammatory aneurysm" seems to represent the extreme on a continuum of the periadventitial inflammation that is found in all AAAs (Koch *et al.* 1990).

There are two experimental aneurysm models that suggest that inflammation may have a causal role in AAAs. Gertz and associates (1988) have found that aneurysms can be created reliably in the rabbit carotid artery by applying calcium chloride to the adventitia. This produces a transmural chemical injury that is associated with the same type of periadventitial lymphocytic infiltrate as is found in human AAAs. Aneurysm formation occurred only after the inflammatory response was present. Anidjar and colleagues have shown that infusion of elastase under super physiological pressures produces aneurysms in the rat aorta (Anidjar *et al.* 1990). The aneurysm developed not with the early elastin degradation, but with the ensuing inflammatory response. This suggests that the inflammation and the inflammatory mediators elaborated secondarily in response to chemical and mechanical injury may produce the aneurysm rather than direct elastolysis.

The Role of Atherosclerosis

Although there is a strong association, the role of atherosclerosis in the pathogenesis of AAA remains unclear. Aortic aneurysms have historically been ascribed to

atherosclerosis because individuals with AAA usually manifest atherosclerosis at other sites (coronary artery, cerebral vascular, and peripheral vascular disease). This association is based on common risk factors such as hypertension, smoking and cholesterol (Reed *et al.* 1992; Powell *et al.* 1989); histological features of marked atherosclerotic lesions in AAA tissue (Campa *et al.* 1987); and localisation of aneurysms to the atherosclerosis-prone infrarenal aorta.

Zarins *et al.* (1990) were able to induce AAA formation experimentally in monkeys fed on a lipid-rich atherogenic diet. They found that 4 out of 31 monkeys (13%) who experienced prolonged exposure to an atherogenic diet (12 months) and who were then transferred to a "regression" regimen (a diet containing no cholesterol) and cholestyramine, to lower serum cholesterol, developed aneurysms. In comparison only 1 out of 107 monkeys (1%) on an atherogenic diet (20 months) without subsequent "regression" regime developed aneurysms. Also no aneurysms were found in 44 monkeys serving as controls and eating a normal diet with no cholesterol or fat supplementation. They hypothesised that the matrix fibres in atherosclerotic plaques may provide structural support to the aortic wall where the media is eroded, and that during the period of "regression" of the atherogenic diet the plaques receded removing the support that these lesions could have afforded to the underlying thinned media, resulting in AAA formation (Zarins *et al.* 1990).

In contrast to the thoracic aorta, the infrarenal abdominal aorta contains relatively few vasa vasorum, with appropriate levels of oxygenation and nutrition being provided to these outer layers by pressure filtration from the lumen (Wolinsky *et al.* 1967a). This paucity of vasa has been suggested as a factor that may explain the particular propensity of this segment of the human aorta to develop early and severe atherosclerosis (Reed *et al.* 1992). Consequently, advanced thickening of the intima by atherosclerotic lesions and thrombus could further impede the only source of nutrients to a faltering media, and theoretically exacerbate deterioration of the elastic and collagen architecture of the aortic wall, initiating aneurysm formation. Moreover, accumulation of the atherosclerotic material may occlude the ostia of the vessels supplying what little vasa vasorum originally existed in the infrarenal aorta.

However, separating "cause" and "effect" has proven far more problematical than a superficial examination would lead to believe. A differing school of thought began to develop in the late 1970's (Martin, 1978) with the premise of explaining how the deposition of atheromatous plaque results in occlusive disease in some individuals, and aneurysm formation in others. Tilson (1990 and 1992) and others have argued that aneurysms may become atherosclerotic as a secondary phenomenon to dilatation, since atheromatous plaque is preferentially formed in regions of turbulence and low shear stress, possibly as a result of prolonged contact between blood borne atherogenic factors and the vessel wall (Glagov *et al.* 1988). Tilson (1992) has also proposed that the effects of

smoking and hypertension, risk factors in both atherosclerotic occlusive, and aneurysmal disease, may mediate the promotion of either disease through unique disease-specific mechanisms, dependent on the constitutional susceptibilities to both diseases.

Reports of familial clustering of aneurysmal disease (Clifton, 1977; Speziale *et al.* 1994; Darling III *et al.* 1989) has left little doubt that there must be an important genetic susceptibility factor associated with the hereditary nature of AAA formation. In addition, Ward (1992) observed that AAA patients demonstrated systemic arterial dilatation in peripheral arteries such as the brachial artery at the elbow and the carotid artery beyond its first branch, which are seldom, if ever, involved in atherosclerosis. Such clinical observations and the results of various biochemical studies of possible genetic causes suggest that atherosclerosis is an "effect" of AAAs and that AAAs may be a manifestation of a systemic abnormality. These findings add further support to the view that aneurysmal disease has specific determinants that may be unrelated to the atherosclerotic process and distinguish it from occlusive disease as a unique pathogenetic entity.

Chronic Obstructive Pulmonary Disease and AAA

Patients with chronic obstructive pulmonary disease (COPD), emphysema and chronic bronchitis have been observed to have an increased incidence of AAA (Cronenwett *et al.* 1985; van Laarhoven *et al.* 1993). In a recent study Laarhoven *et al.* (1993) assessed 362 patients with COPD above 64 years of age, and found AAA > 30 mm diameter in 9.9 per cent. Patients with severe disease (forced expiratory volume/vital capacity ratio <55%) had a significantly higher prevalence (19.3%) compared with 7.6% in those with mild to moderately decreased FEV/VC (>55%). One possible explanation is that cigarette smoking may be the common predisposing factor for both conditions. The strong association between smoking and AAA has been recognised for over 20 years (Kahn, 1966; Hammond *et al.* 1969; Doll *et al.* 1976). The toxic components of tobacco consumption associated with aneurysm formation remain to be identified. Serial ultrasonography of screen detected small AAAs has shown that aneurysm expansion rates are greater in patients who continue to smoke and are associated with increased levels of serum cotinine, a nicotine metabolite (MacSweeney *et al.* 1994a). Gaseous and blood-borne products of tobacco combustion contribute to the inactivation of alpha 1-antitrypsin by oxidising the methionine at the central bait region to methionine sulphoxide (George *et al.* 1984; Carrell, 1986). This reduces the ability of alpha-1-antitrypsin to inhibit elastase and alters the normal balance between lung neutrophil elastase and antiprotease activity sufficiently to increase lung elastin degradation (Stockly, 1987). Smoking also alters neutrophil elastase activity in patients with aneurysms. Patients with AAA who smoke have higher level of circulating elastolytic activity and leukocytic granular elastolytic activity than non-smokers with AAA (Cannon *et al.* 1982). Therefore, smoking may

enhance the degradation of the aortic wall by proteolytic enzymes.

A decreased content of elastin in the aortic wall and the lung have been observed in both AAA and COPD (Powell *et al.* 1989; Wright, 1961). The pathogenesis of emphysema is thought to be mainly due to an uninhibited activity of proteolytic enzymes (Wright, 1961; Laurell *et al.* 1963), released by polymorphonuclear leukocytes (Fujita *et al.* 1990). In smokers elevated levels of elastase can be detected in the serum as well as in broncho-alveolar lavage fluid (Weissler, 1987). Therefore enzymatic imbalance may affect both systems but further studies are necessary to explain the suggested co-existence of these two disorders.

1.5 Incidence and Prevalence

In a large autopsy study (24 000 consecutive post-mortem examinations) Darling *et al.* (1977) found AAAs in 2 percent. Similar studies in unselected populations using autopsies, ultrasound examinations, and CT scans have reported a similar prevalence of about 2% to 3% (Johansen *et al.* 1986; Johnson *et al.* 1985; Leopold *et al.* 1972). The coexistence of other vascular pathologies in the study population substantially increases the prevalence of AAAs. Five percent of individuals with symptomatic coronary artery disease have aneurysms, and 10% of patients with peripheral or cerebrovascular disease have AAAs (Cabellon *et al.* 1983; Graham *et al.* 1988; Allardice *et al.* 1988). Patients with peripheral arterial aneurysms (especially those involving the popliteal artery) have a prevalence of AAAs approaching 50% (Anton *et al.* 1986). The mechanical role of high blood pressure in the formation of AAA may seem obvious but reports of prevalence in hypertensives are conflicting. Allen *et al.* (1987) found 5.3% AAAs among 168 hypertensive men and women, whereas Lindholm *et al.* (1985) screened 245 patients and reported a prevalence of 0.4 percent. However, both of these studies did not include a control group and were of limited size. Several studies also suggest that there is increased likelihood of developing AAAs in first-degree relatives (Clifton, 1977; Tilson *et al.* 1984b; Norrgard *et al.* 1984). Investigators have suggested that autosomal dominant, autosomal recessive, and sex-linked inheritance modes of transmission are possible (Tilson *et al.* 1984a). Approximately 18% of patients with AAAs have a first-degree relative affected (Johansen *et al.* 1986; Webster *et al.* 1991b).

The incidence of AAAs world-wide appears to be increasing (Samy *et al.* 1994; Budd *et al.* 1989; Fowkes *et al.* 1989; Naylor *et al.* 1988; Melton *et al.* 1984). In two studies from the Mayo Clinic that examined the period between 1951 and 1980, there was a threefold increase in the prevalence, from 12.2 per 100,000 to 36.2 per 100,000 (Melton *et al.* 1984; Bickerstaff *et al.* 1984). Some of the increase may partly be due to better diagnostic methods, greater clinical awareness and an increase in the number of elderly

people in the catchment population, but the magnitude of the difference suggests a genuine increase (Ernst, 1993). The effect of the ageing population was emphasised by a European autopsy study in which aneurysms occurred with a steadily increasing frequency in men after age 55, peaking at 5.9% in 90 year olds (Bengtsson *et al.* 1992). Women developed an increased incidence of aneurysms after age 70, peaking at 4.5% in 90 year olds.

Mortality data also reflect a real increase in the prevalence of AAAs. For example, compared with 30 years earlier, a 1984 study in England and Wales showed a 20-fold and 11-fold increase in deaths from ruptured aortic aneurysms for men and women, respectively (Fowkes *et al.* 1989). The ratio of male to female death rates decreases from 11:1 in younger age groups to 3:1 in the octogenarians.

1.6 Natural History

There is a natural tendency for an AAA to dilate until rupture occurs, unless the patient dies from other causes (Estes, 1950, Wright *et al.* 1956)). The rate of change in size and risk of rupture of AAAs are of paramount importance when deciding treatment (Bernstein *et al.* 1976; Katz *et al.* 1992; Cronenwett *et al.* 1990; Cronenwett *et al.* 1985). In a large post-mortem study, Darling *et al.* (1977) found that the risk of rupture was proportional to the diameter of the aneurysm. Of 201 aneurysms measuring 4 cm or less, 9.5% ruptured, whereas in the size range 4.1-5 cm the rupture rate was 23.4 percent. *Table 2* summarises the results of several studies which have demonstrated high rupture rates for AAAs greater than 5 cm in diameter (Gliedman *et al.* 1957; Foster *et al.* 1969; Szilagyi *et al.* 1972a; Nevitt *et al.* 1989; Johansson *et al.* 1990; Glimaker *et al.* 1991). The overall mean annual rate of rupture was 8%.

Most of the above studies are either referral-based or autopsy examinations and are subject to considerable selection bias. A population based study by Nevitt *et al.* (1989) followed evolution of 176 patients with at least two periodic ultrasound examinations. They obtained a mean expansion rate of 2.1 mm per year. Only 25% of the patients had their aneurysm expand faster than 4 mm per year. The incidence of rupture was 6% at 5 years, and 8% at 10 years. They also emphasised the fact that risk of rupture during the first 5 years of follow-up was zero for the 130 patients with an aneurysm less than 5 cm in diameter, and 25% for the 46 patients with a diameter of 5 cm or more. These findings were confirmed by Glimaker *et al.* (1991), who also conducted a population-based study in Uppsala, Sweden. They monitored 187 patients with AAA, 110 with aneurysms smaller than 5 cm in diameter and 77 with aneurysms greater than 5 cm. During a median follow-up of 16 months (range 0 days to 9 years), the policy was to recommend operation when the aneurysm reached 5 cm in diameter in low risk patients and 6 cm in high risk patients. In total 11 aneurysms ruptured, only 1 of which was smaller than 5 cm. Thus,

Table 2: *Natural history of large AAAs (>5 cm diameter).*

Author and year	Size (cm)	No. of cases	Death from rupture (%)	Death from other causes (%)	Follow-up (months)
Gliedman 1957	>5	68	49	51	-
Foster 1969	>6	37	51	35	60
Szilagyi 1972	>6	40	42	57	72
Nevitt 1989	>5	46	25	-	60
Johansson 1990	>5	34	41	44	66
Glimaker 1991	>5	77	28	-	36

the rupture rate for AAAs less than 5 cm was below 1% (1/110). The results from these studies and other reported series of small AAAs treated conservatively are summarised in *Table 3*. These findings differ from those of Darling *et al.* (1977), who reported a 9.5% rupture rate in aneurysms measuring 4 cm or less. This discrepancy between the conclusions from the autopsy based data (Darling *et al.* 1977) and the clinical findings in *Table 3* may be due to several factors. The autopsy study was not performed in a geographically defined population and the ruptured aneurysm may have been a salient reason for referral, and hence resulting in over representation.

Besides the diameter of the aneurysm, other indicators of rupture risk have been investigated. Cronenwett *et al.* (1985) followed 76 AAAs, ranging from 40 mm to 60 mm in diameter, and calculated annual rupture mortality risk of 55. Diastolic blood pressure, initial anteroposterior diameter and degree of co-existing pulmonary disease were independent predictors of rupture. Strachan (1991), in a case controlled study compared smoking habits and the diastolic blood pressure of patients with and without aneurysms of the abdominal aorta. An increase in the diastolic blood pressure of 10 mmHg was associated with a 50% increased risk of rupture. He also reported a 15 times greater risk of death from rupture in smokers compared with non-smokers. The morphology of AAAs also influences risk of rupture. Longer fusiform aneurysms have a poorer prognosis than saccular ones (Ouriel *et al.* 1992). Aortic blebs or blisters, consisting of protrusions in the aortic wall and filled with thrombus and debris, are an indication of impending rupture (Hunter *et al.* 1989; Faggioli *et al.* 1994). Also the risk of rupture seems to be higher when there is no evidence of peripheral vascular disease (Martin, 1978).

1.7 Diagnosis

Most AAAs are asymptomatic until rupture occurs, and are diagnosed incidentally during abdominal examination (Collin *et al.* 1988), radiological investigation or at laparotomy for some other condition. An increasing number of AAAs are being detected by abdominal ultrasound examinations performed for non-vascular reasons (gallstone disease, renal disease or prostatism) (Akersdijk *et al.* 1991). Some patients may present with abdominal or back pain, as a sign of acute expansion or impending rupture. However, in the majority of patients who die from AAA rupture, this is the first presentation of the disease (Collin, 1990). Ruptured aneurysms usually present with sudden onset abdominal pain, hypotension, and a pulsatile abdominal mass (Darke *et al.* 1973), and diagnosis is usually obvious. Patients with inflammatory aneurysms are more likely to be symptomatic than unruptured non-inflammatory AAAs (Goldstone *et al.* 1978). Patients with inflammatory aneurysms may present with a systemic illness and complain of general malaise, loss of appetite and loss of weight (Scott *et al.* 1988a). The

Table 3: *Natural history of untreated small abdominal aortic aneurysms.*

Author and year	Size at diagnosis (cm)	No. of cases	Rupture while <5 cm	Follow-up (months)
Bernstein 1984	4-4.9	35	1	28
Delin 1985	<5	20	0	28
Sterpetti 1985	<4.5	26	0	24
Littooy 1989	4-4.9	50	1	35.4
Nevitt 1989	3.5-4.9	75	0	120
Johansson 1990	<5	42	0	61
Brown 1992	4-4.9	139	0	30
Glimaker 1991	<5	110	1	16

inflammatory fibrosis often extends into the retroperitoneum where it may entrap the ureters, producing symptoms and signs of ureteric obstruction (Pennell *et al.* 1985). The duodenum, left renal vein, inferior vena cava, stomach and small and large bowel may also be adherent to the inflammatory mass surrounding the aneurysm, producing a variety of rare symptoms (Crawford *et al.* 1985).

Once a diagnosis of AAA has been made, determination of its size by palpation alone is imprecise (Goldstone, 1991). Ultrasonography is the most common modality used to diagnose and measure AAA diameter (anterior-posterior diameter) (Hallett, 1992; Stevens, 1993), with a sensitivity approaching 100% (Ernst, 1993; Siegel *et al.* 1994). The success of ultrasonography, however, is highly operator dependent (Rubin *et al.* 1993b). Also it may not be reliable in obese patients, those with excessive bowel gas, or those with periaortic disease (Ernst, 1993).

Contrast enhanced computed tomography (CT) is also highly sensitive and specific in the assessment of AAA (Siegel *et al.* 1994; Hojer, 1992). It is also particularly useful when searching for other causes of abdominal pain or an abdominal mass (Hallett, 1992), and preoperatively to determine the proximal and distal extent of an AAA and to define the anatomical relations of the visceral and renal vessels (Todd *et al.* 1991). However, CT scans may over estimate the size of an aneurysm because the measurements are made perpendicular to the body axis and may be distorted if the aorta is tortuous (Todd *et al.* 1991).

Magnetic resonance imaging (MRI) may be a better method of imaging than either ultrasonography or CT, both for accurate aneurysm measurements and for views of the relevant vascular anatomy (Siegel *et al.* 1994). MRI provides coronal, transverse, and sagittal views of the aorta that define the aneurysm and its relations to aortic branch vessels. Furthermore, MRI is non-invasive and does not require ionising radiation. Unfortunately, it is expensive, not widely available, is imprecise in identifying associated occlusive arterial disease, and is contraindicated in patients with pacemakers and those in whom ferro-magnetic clips have been used (Ernst, 1993; Siegel *et al.* 1994).

The use of aortography for diagnosis or determination of aneurysm size is inappropriate because mural thrombi may lead to an underestimation of size or even a misdiagnosis of the presence of an aneurysm (Johnston *et al.* 1991; Pleumeekers *et al.* 1994). Arteriography is indicated when suspecting, juxta- or supra-renal involvement, multiple renal arteries or a horseshoe kidney, mesenteric or renal artery stenoses, or distal arterial occlusive disease (Ernst, 1993; Johnston *et al.* 1991). There are, however, several risks associated with aortography, including contrast induced renal toxicity (or exacerbation of pre-existing renal failure) , distal embolisation and local complications at the arterial puncture site (Rubin *et al.* 1993b).

More recent imaging techniques include MR angiography (a non invasive technique which provides detailed information regarding vessel blood flow) (Durham *et al.*

1993), and three dimensional spiral CT angiography (Rubin *et al.* 1993b), which require further evaluation.

1.8 Complications of AAA

Rupture of an AAA is the most common and catastrophic complication, resulting in a fatal outcome if untreated (Thompson *et al.* 1975; Goldstone, 1991). In one series less than 40% of patients reached hospital alive (Ingoldby *et al.* 1986). In most cases rupture occurs into the retroperitoneal space and patients present with abdominal pain, a pulsatile abdominal mass and hypovolaemic shock (Hojer, 1992; Banerjee, 1993). However, diagnosis is often missed as this triad may not be present in its entirety (Hojer, 1992), or when present may not be recognised, as one of the components predominates (Goldstone, 1991). The retroperitoneal haematoma of ruptured AAAs may contain the leak and produce symptoms characteristic of many other acute abdominal conditions (e.g. renal colic, pancreatitis, cholecystitis, diverticulitis), and may complicate the diagnosis (Moran *et al.* 1987; Kiell *et al.* 1993; Siegel *et al.* 1994). Less commonly the aneurysm ruptures anteriorly into the peritoneal cavity and rapid exsanguination and death are the usual outcome.

Rare presentations include spontaneous rupture into adjacent tissues and viscera, primary aorto-caval (DeBakey *et al.* 1958; Hickey *et al.* 1991; Lanne *et al.* 1992; Mianni *et al.* 1994) and aorto-duodenal fistulae and are seldom diagnosed before surgery. Clinical features suggesting the diagnosis of aorto-caval include an abdominal bruit, high output cardiac failure, acute onset oedema of the legs and haematuria (Lanne *et al.* 1992; Mianni *et al.* 1994). In the majority of cases the diagnosis is not made until torrential venous bleeding is encountered on opening the sac of the aneurysm.

As an aneurysm enlarges it may also cause abdominal pain (75% of patients) due to pressure on adjacent structures, and back pain (69.4% of patients) related to pressure on the vertebrae (Goldstone, 1991). In addition, large aneurysms can actually erode the spine and cause severe back pain even in the absence of rupture (Goldstone, 1991). Compression of adjacent bowel can cause early satiety, and even nausea and vomiting, particularly in relation to inflammatory aneurysms (Scott *et al.* 1988a). AAAs can very occasionally present with lower limb ischaemia secondary to peripheral embolisation of thrombus or atheroma from the aneurysm sac (Johnston *et al.* 1991; Kiell *et al.* 1993). If the emboli are small, peripheral pulses may be preserved and the patient presents with the characteristic mottling of "trash foot". A more dramatic presentation follows acute thrombosis of the aneurysm. This is again a very rare complication and is usually associated with extensive occlusive disease of the distal vessels, and is more likely to occur with smaller aneurysms (Johnson *et al.* 1974).

CHAPTER TWO

Conventional Management Of Abdominal Aortic Aneurysms

2.1 Historical Aspects of Aneurysm Surgery

The first elective operation for treatment of an aneurysm was reported by Antyllus in the second century AD. He recommended application of proximal and distal ligatures to isolate the aneurysm followed by incision of the sac and evacuation of its contents (Osler, 1915). Antyllus also recognised the difference between "true" degenerative aneurysms and traumatic "false" aneurysms. He emphasised the dangers involved in operating on aneurysms and described which varieties were suitable for surgical treatment and those that were not. His recommendations for aneurysm repair remained the basis of direct arterial operations for the next 1500 years.

In the seventh century, details of operative repair of an arterial aneurysm were recounted by Aetius of Amida, a Byzantine writer of the sixth century AD, in his book *De Vasorum Dilatatione* ('On the Dilatation of the Vessels'), now in the Vatican library. Like Antyllus, Aetius noted that the pulsating swellings of arteries could arise spontaneously or following trauma (Haeger, 1988). He described the management of antecubital fossa aneurysms by double proximal ligation, incision of the sac and evacuation of its contents (Erichsen, 1844). In addition he also advised division of the feeding artery, a practice discouraged by Antyllus because of the propensity of the ligatures to slip. Ambrose Pare (1510-1590), who contributed much to the principles of wound care, applied his observations to aneurysm operations. He gave a vivid description of the death of a patient whose brachial artery aneurysm had been treated by application of a caustic, contrary to Pare's advice, resulting in torrential and fatal secondary haemorrhage (Johnson, 1649). Pare's prestigious contemporary, Andreas Vesalius (1514-64), wrote one of the first descriptions of an abdominal aortic aneurysm (Osler, 1915).

In 1590, Peter Lowe (1550-1612), personal physician to King James VI in Scotland and founder of the medical and surgical faculty at Glasgow, reported that one of the highest ranking officers in the Spanish Regiment presented with a peripheral arterial aneurysm. Whereas Lowe prescribed apothecary remedies against its growth, a second physician consulted a barber, who opened the swelling with a lance and 'blood spewed out so violently that the Captain died some hours later" (Haeger, 1988).

The next major contribution to aneurysm surgery was that of John Hunter (1728-1793). Hunter had observed that the blood supply to the horns of the deer changed under different conditions. A rich supply was present when the crest was full, but the blood vessels decreased in number and size when the horns were shed (Murley, 1984). Hunter inferred that reserve vessels (now termed collaterals) might develop in humans if obstruction occurred in their arteries. The first operation based on Hunter's observation was performed in December 1785. A 45 year old coachman was admitted to St. George's Hospital with a pulsatile mass in the popliteal fossa, possibly secondary to repetitive

trauma against the coachman's seat while driving on rough streets. He complained of leg pain on walking and rested frequently, presumably owing to arterial occlusion distal to the aneurysm. Standard treatment at that time entailed above knee amputation, as strongly advocated by another renowned London surgeon, Percival Pott (1779), but Hunter's experiments with deer had suggested that collateral vessels must have formed around the obstruction or the leg would have developed gangrene. Hunter exposed the femoral artery in the sub-sartorial canal (now known as Hunter's canal), and by means of an eyed probe passed two double ligatures around it. The four ligatures thus created were then gently tied. After a bout of local infection, the patient survived and was discharged six months later. The patient died of a fever some eighteen months after the operation. Hunter went on to perform four similar operations out of which three were successful; the fourth patient died 26 days post-operatively. His operation was rapidly adopted by other surgeons and remained the basis of surgical management of popliteal aneurysm until the end of the last century.

Astley Paston Cooper (1768-1841), although he is best remembered for his contributions to inguinal hernia repair and female breast anatomy, his most celebrated operation was performed for a leaking iliac artery aneurysm in 1817 (Cooper, 1830). His attempt to ligate the abdominal aorta seemed initially successful, but the patient died suddenly after 40 hours. The autopsy revealed that the ligature had been perfectly placed around the aorta just above the bifurcation. Cooper also reported the first documented case of a spontaneous aortoenteric fistula due to aneurysmal disease and cautioned that patients who present with one aneurysm should be evaluated for the coexistence of others (Cooper, 1830).

In 1804, Antonio Scarpa (1752-1832) wrote a definitive monograph on the classification and diagnosis of arterial aneurysms. About the same time several ingenious treatments were introduced. Giovanni Monteggia (1762-1815) unwisely attempted to cure an aneurysm by injecting a sclerosant into it, which predictably failed because of rapid blood flow. Attempts to thrombose aneurysms by passing electric current between needles stuck into the vessel were begun in 1832 and were still going on in the 1930s. Charles Hewitt Moore (1821-1870), at Middlesex Hospital in London, introduced obliteration of aneurysms by inserting steel wires in 1864, once using 26 yards of the material (Haeger, 1988).

2.2 Development of Current Techniques

Modern treatment of arterial aneurysms was developed in 1888 by Rudolph Matas (1860-1957), in New Orleans. He introduced the operation of obliterative endoaneurysmorrhaphy. His technique involved clamping above and below the aneurysm, opening it, ligating branches from within, and buttressing the wall with imbricating

sutures. This procedure not only cured the aneurysm but also greatly reduced the risk of injury to important surrounding structures (Matas, 1903). By 1906 he was able to report a collective series of 22 obliterative operations, 7 restorative operations (preserving the arterial lumen) with no recurrences, and 5 reconstructive operations with two relapses (Matas, 1906). The first successful proximal ligation of an aortic aneurysm was also performed by Matas in 1923, some 106 years after Astley Cooper's innovative operation (Matas, 1925).

Endoaneurysmorrhaphy paved the way for the current method of intra-saccular reconstruction established by Creech and DeBakey (Creech, 1966). Modern techniques of aneurysm repair were made possible by Alexis Carrel (1873-1948), who demonstrated in animals that a segment of aorta could be replaced with a piece from another artery or vein. On 2 March 1951 Schaffer and Hardin resected an infrarenal abdominal aortic aneurysm using a polythene shunt bypass and a homograft replacement. However, the patient died on the 29th post-operative day from aortic suture line haemorrhage (Schafer *et al.* 1952). On 29 March 1951 Dubost and his team in Paris performed the first entirely successful resection of an infrarenal aortic aneurysm via a retroperitoneal approach (Dubost *et al.* 1952). The third and fourth aortic aneurysm repairs in which both patients survived were both performed on October 25, 1952, one by Ormond Julian's group in Chicago and the other by Russel Brock and associates in London (Julian *et al.* 1953; Brock *et al.* 1953). These were closely followed by DeBakey and Cooley in Houston, who resected six more aneurysms within the next few months with only one death (DeBakey *et al.* 1953). In a series of 17 aortic aneurysm operations, Bahnson from John Hopkins described the first successful repair of a ruptured aortic aneurysm (Bahnson, 1953). In 1953, Voorhees and colleagues introduced a major innovation by substituting Vinyon-N cloth for the unreliable homograft (Voorhees *et al.* 1952). Therefore a new era in abdominal aortic aneurysm surgery had truly begun.

The final chapter in the history of aneurysm surgery involved the development of the currently used *'inlay technique'*. A major problem of the aneurysm resection with graft replacement technique, used by Dubost and associates (1952) and subsequently by several others (DeBakey *et al.* 1953; Julian *et al.* 1953; Brock *et al.* 1953), was the risk of injury to the adjacent structures, particularly the inferior vena cava and the iliac veins, resulting in major haemorrhage. Oscar Creech in 1966 described a modification of the endo-aneurysmorrhaphy developed by Matas. In his paper he gave a detailed account of the "internal" or intra-saccular reconstruction, which has become the standard method of AAA repair (Creech, 1966).

CURRENT MANAGEMENT OF ABDOMINAL AORTIC ANEURYSMS

2.3 Conservative Management of AAAs

The natural history of aneurysms is such that they continue to increase in size until rupture occurs, unless the patient dies from other causes. There is presently no prospective clinical data which suggests that aneurysm growth can be delayed or reduced in man by any known intervention. Before surgical repair of AAAs became established, Estes showed that the 5-year survival rate following diagnosis was only 20 per cent (Estes, 1950). Even in groups turned down for surgery because of severe inter-current disease, the cause of death in over a quarter is still rupture of the aneurysm (Szilagyi *et al.* 1972a; Walker *et al.* 1983). However, the life expectancy following successful AAA repair approaches those of age matched controls (Szilagyi *et al.* 1966). This together with elective mortality rates of less than 5 per cent in most centres (Ernst, 1993), has led to a generally aggressive policy favouring surgery.

Management of Small AAAs

The management of small asymptomatic AAAs continues to be one of the greatest controversies in vascular surgery. In recent years, the improvements in "screening" programmes have led to the identification of many AAAs, most of which are small (Powell *et al.* 1993; Lucarotti *et al.* 1993). Although it is known that the risk of rupture increases as the maximum diameter increases (Darling, 1970; Nevitt *et al.* 1989), the prospective risk of rupture and death is unknown. This creates a dilemma for the surgeon - is it better to operate or monitor the size of the small asymptomatic aneurysm? The ultimate goal of management of patients with AAA is to select for non-operative therapy those patients who will die of other causes before aneurysm rupture and to operate on the remaining group. But aneurysm size has been the usual discriminator for this approach. However, it is evident from a review of the literature that there is considerable disagreement on decisions to operate on aneurysms between 4 cm and 5.5 cm in diameter. Some surgeons consider elective surgery when the AAA diameter reaches 6 cm (Scott *et al.* 1988b) while others advocate operating on any aneurysms greater than 4 cm in diameter (Collin, 1987).

The difficulty in managing small aneurysms arises from the fact that most reports indicate some incidence of rupture regardless of aneurysm size (Ouriel *et al.* 1990; Hallett *et al.* 1993). Darling and co-workers (1977) revealed that almost one quarter of autopsied patients with aneurysms between 4 and 5 cm in diameter had died as a consequence of aneurysm rupture. Some vascular surgeons therefore suggest that even small aneurysms should be surgically repaired (Katz *et al.* 1992; Hollier *et al.* 1992), a belief strengthened

by the fact that mortality after operation of small aneurysms is lower than that for larger ones (Amundsen *et al.* 1989), with better surgical outcomes expected in younger "healthier" patients with fewer co-morbid conditions (McCabe *et al.* 1981). Others recommend a conservative "wait and see" approach with frequent serial radiological measurements in those with AAAs less than 5 cm in diameter and surgical repair if the aneurysm demonstrates relatively rapid expansion (Cronenwett *et al.* 1990; Johansson *et al.* 1990).

However most surgeons agree that there is a grey area of uncertainty concerning the best management of aneurysms of 4 to 5.5 cm diameter in fit patients. In order to clarify this "grey area" of small asymptomatic AAAs, the UK Small Aneurysm Trial was established in 1994 (The UK Small Aneurysm Trial Participants, 1995). Patients with AAAs 3.0 - 3.9 cm in diameter are being followed up every 6 months by ultrasonography. Fit patients with symptom-free AAAs 4.0 - 5.5 cm were randomised to either early elective surgery or to ultrasound surveillance every 6 months. Aneurysms of 5.0 - 5.5 cm are being followed up every 3 months; if the aneurysm diameter exceeds 5.5 cm patients are offered elective repair. Patients considered unfit for surgery are being kept under ultrasound surveillance for aneurysm growth. In addition to determining whether early elective surgery or conservative therapy is the better management modality for small AAAs, the trial has been designed so that several other important issues can be addressed, such as the cost of treatment, the quality of life for each treatment and the identification of factors associated with the rapid growth of small aneurysms (The UK Small Aneurysm Trial Participants, 1995). Although randomisation for the trial stopped in July 1996, results will not be available for a few years.

2.4 Pharmacological Treatment of AAAs

At present there is no specific pharmacological therapy that has been shown to be clinically effective in preventing AAA enlargement and rupture. Pharmacological agents which could slow down or prevent the progression of the disease may have a role in treating patients with small AAAs, those with genetic susceptibility to the development of aneurysms and those individuals in the high risk groups (such as cigarette smokers, hypertensives, and those with peripheral vascular disease).

Beta-Adrenergic Blockade

Experimental work on two models has suggested that the natural history of aneurysm enlargement may be modified by propranolol (Brophy *et al.* 1988; Simpson *et al.* 1968). Simpson and Boucek (1983) investigated the action of various drugs in broad breasted white turkeys fed with beta-aminopropionitrile fumarate (BAPN). BAPN is an inhibitor of lysyl oxidase, an enzyme that catalyses an essential step in the formation of

elastin and collagen links. Broad-breasted white turkeys spontaneously develop hypertension, tachycardia, and atherosclerosis by 5 weeks of age also develop dissecting aneurysms when fed BAPN. BAPN decreases aortic ring tensile strength and causes rupture of the aorta in 44 % of the turkeys but has no haemodynamic effects. Beta-blockade with propranolol decreased heart rate, blood pressure and hence reduced aortic wall tension in this model. In addition it increased aortic tensile strength and limited rupture rate to 1%. The cardio-selective beta-blockers, practolol and sotalol, had similar haemodynamic effects but resulted in 13% and 5% rupture rates, respectively. The authors concluded that the effect of propranolol was independent of its effect on pulse and blood pressure, as the other antihypertensives lacked the protective effect, and they subsequently suggested that there was a direct effect on the cross linking of matrix proteins (Boucek *et al.* 1983). Their data suggested a dose-response relationship between propranolol and aortic tensile strength and increased elastin cross-linking, but not between the cardioselective beta-blockers (sotalol, practolol) and these characteristics (Boucek *et al.* 1983).

The Blotchy (*blo*) mouse, a strain that develops spontaneous aortic aneurysms, has also been used to investigate the effects of beta-blockers. The *blo* mouse has an inherited defect at the mottled locus on the X-chromosome which results in decreased absorption of copper (Hunt, 1974). This results in systemic copper deficiency and decreases the activity of the copper-dependent enzyme, lysyl oxidase, which is responsible for elastin cross-linking (Rowe *et al.* 1977). A deficiency in functional lysyl oxidase renders elastin susceptible to premature destruction, and *blo* mice develop thoracic aneurysms by 4 months of age. Brophy and co-workers (Brophy *et al.* 1988) demonstrated that propranolol could delay the formation of aneurysms in the blotchy mouse. They subsequently showed an increase of 147% in skin elastin and 54% in skin collagen when the mice were treated with propranolol (Brophy *et al.* 1989). Although this suggested to the authors a direct effect of propranolol on tissue metabolism, no direct study of aortic tissue was undertaken nor were haemodynamic parameters measured.

There is limited data of the effect of beta-blockers on aneurysm expansion rates in humans. In a small retrospective study, Leach and co-workers (Leach *et al.* 1988) monitored 27 patients with AAA, 12 of whom were undergoing beta-blocker therapy, over a mean period of 34 months. The expansion rate in patients on beta-blockers was 0.17 cm/year, and 0.44 cm/year for those not receiving beta -blockers. In a larger prospective study that examined variables affecting aneurysm expansion, propranolol produced a less rapid expansion, although this did not reach statistical significance (Cronenwett *et al.* 1989). More recently Gadowski *et al.* (1994) reported a study of 121 patients with infra-renal AAA who had been monitored with serial ultrasound scans over a 14 year period. Of these, 83 patients received no beta-blockers and 38 patients received beta-blockers. The mean expansion rate was 0.3 cm/year in those on beta-blockers and 0.44 cm/year in those

not receiving beta-blockers. However among patients with a large AAA (> 5 cm), those receiving B-blockers had a significantly reduced mean expansion rate (0.36 cm versus 0.68 cm, $p<0.05$).

Although a clear benefit of beta-blockade has been demonstrated in patients with aortic dissections (Wheat, 1988; Pyeritz, 1983), their role in infrarenal AAAs remains unclear. Large scale randomised clinical trials will be necessary to define the effect of beta-blockers on AAA expansion.

Effects of Corticosteroids on AAAs

There is some evidence that steroids may enhance aneurysm formation and predispose to aneurysm rupture. In hamsters treated with steroids to facilitate foetal lung transplantation it was noted that many animals died with massive intra-thoracic or intraperitoneal haemorrhage (Frenkel *et al.* 1959). Histological examination in these animals confirmed that the haemorrhage was due to rupture of an aneurysm of the aorta. Diethylstilboestrol has also been shown to induce aneurysm formation and rupture in turkeys (Beall *et al.* 1963). Work performed on heterozygous female blotchy mice has shown that hydrocortisone induces aortic rupture (Reilly *et al.* 1995). It also induces aortic ectasia and aneurysm formation in normal laboratory mice (Reilly *et al.* 1995).

The exact mechanism of steroid induced aneurysm formation is not known. However steroids are known to impair wound healing, decrease inflammation, decrease overall protein synthesis and decrease collagen synthesis (Cutroneo *et al.* 1981). Steroids decrease collagenase expression and are also known to decrease lysyl oxidase activity in skin which would result in decreased matrix cross-linking (Counts *et al.* 1986).

Aortic aneurysms have also been noted to occur in various diseases commonly treated with corticosteroids. Corticosteroids administered for Dressler's syndrome (an autoimmune response to damaged cardiac tissue following acute myocardial infarction) result in delayed healing and formation of ventricular aneurysms (Bulkley *et al.* 1974). In patients treated for Kawasaki's disease (a generalised vasculitis of unknown aetiology), 65% of those treated with steroids developed coronary artery aneurysms compared with only 20% of patients not treated with steroids (Kato *et al.* 1979). Pregnancy, a physiological condition resulting in increased steroid hormone levels, is associated with aortic dissection (Roberts, 1981; Nolte *et al.* 1995), cerebral aneurysm rupture (Roberts, 1981), and rupture of visceral artery aneurysms (Stanley *et al.* 1986). One exception to this rule is the use of corticosteroids in the treatment of inflammatory aneurysms (Clyne *et al.* 1977; Baskerville *et al.* 1983; Hedges *et al.* 1986). There is some evidence that in these patients corticosteroids reduce the periaortic fibrosis, without causing any increase in the diameter of the lumen (Hedges *et al.* 1986). At present most surgeons use corticosteroids either in patients deemed inoperable at the time of laparotomy or as an adjuvant following

surgical repair. However further controlled trials are required to evaluate the long-term efficacy of steroids for inflammatory AAAs.

Matrix Metalloproteinase Inhibitors

Increased local production of matrix metalloproteinases (MMPs) is a central feature of AAAs (Vine *et al.* 1991; Newman *et al.* 1994c), as discussed in *Chapter 1.* Tetracycline antibiotics inhibit collagenase and other MMPs in vitro, and they effectively prevent MMP-mediated tissue injury in animal models of gingivitis (Golub *et al.* 1983), arthritis (Greenwald, 1994) and other disorders (Greenwald *et al.* 1988). Use of MMP inhibitors therefore, may enable modulation of the pathogenic process in AAAs. Petrinec *et al.* (1995) have undertaken preliminary work with doxycycline, an MMP-inhibitor, to ascertain whether it limited the development of experimental AAA in vivo. They used an elastase induced rat model and treated one group with subcutaneous doxycycline (25 mg/day) and the other with saline. The animals were sacrificed at 0, 2, 7, and 14 days, and AAA diameter was determined. After day 2, the incidence of AAA was reduced from 83% to 8% in doxycycline treated rats ($p<0.01$). Histological evaluation confirmed decreased deterioration of the aortic elastin, in the absence of any effect on the inflammatory infiltrate. Specific assay of 92-kD gelatinase showed marked suppression of this MMP in the doxycycline treated group. Further evaluation of doxycycline is clearly indicated, and at this stage it is too early to forecast the role of MMP inhibitors in the treatment of AAAs.

2.5 Screening for AAAs

Elective repair of AAAs before rupture occurs results in excellent long-term-survival, with an operative mortality below 5% (Johnston *et al.* 1988; Moriyama *et al.* 1994; Hallett *et al.* 1993). On the other hand, up to 60% of patients with ruptured aneurysms die before reaching hospital (Ingoldby *et al.* 1986). When these pre-hospital deaths are combined with the mortality involved with emergency surgical repair the overall mortality rate after rupture may exceed 90% (Thomas *et al.* 1988; Ingoldby *et al.* 1986; Fowkes *et al.* 1989). Indeed ruptured AAAs account for an estimated 10, 000 deaths per year in Britain (Greenhalgh, 1990). For the majority of these patients presenting with ruptured aneurysms the existence of the aneurysm was previously unknown since most aneurysms remain asymptomatic until rupture (Webster, 1994). For these reasons attention has focused on the early detection of asymptomatic aneurysms which permits elective surgical repair based on size and patient risk (Webster, 1994).

The ideal screening programme for AAAs would focus resources on an easily identifiable population, old enough to have developed the disease but young enough to

benefit from prophylactic surgery (Collin, 1993). The Gloucestershire community-based screening programme chose as their target the rather broad population of males aged 65 years (Lucarotti *et al.* 1993). Each patient underwent abdominal ultrasound examination with a portable ultrasound scanner at the general practitioners' surgery by an ultrasound trained radiographer. The study reported an incidence of 1.3% for AAAs 4.0 cm or greater, with an additional 7.1% for "smaller aneurysms" (Lucarotti *et al.* 1993). Lucarotti *et al.* (1993) concluded that this more than justified continuation of the service.

Others, however, have criticised such random screening as cost ineffective and have advocated selective screening programmes as being far more rational and acceptable, based on factors known to increase the probability of aneurysms in specific groups (Webster *et al.* 1991a; Collin, 1993). The screening of recognised high-risk groups such as patients with hypertension (O'Kelly *et al.* 1989), cigarette smokers (Muluk *et al.* 1994; Strachan, 1991) and first-degree relatives of patients with aneurysms (Webster *et al.* 1991a; Cole *et al.* 1989) have yielded far better results. Several studies have also proposed scanning the abdominal aorta during routine peripheral arterial evaluation to be a particularly cost-effective means of screening patients at high risk of aneurysms (Carty *et al.* 1993; Karanjia *et al.* 1994; Hedges *et al.* 1986). For example, when added to routine lower extremity arterial examination in the vascular laboratory, the additional effort for limited aortic scanning was minimal and on average only prolonged the examination by 5 minutes (Hedges *et al.* 1986). Using such opportunistic screening a substantial incidence of unsuspected AAAs has been found in patients with either symptomatic or asymptomatic carotid artery stenosis (Carty *et al.* 1993). One study revealed more than one fifth of patients with carotid stenosis had coexistent aortic aneurysmal disease (Karanjia *et al.* 1994). Other studies have demonstrated that peripheral vascular disease is a reliable marker for AAA (Allardice *et al.* 1988). Schwend *et al.* (1994) advocate the addition of an abdominal ultrasound to the standard duplex imaging for lower extremity arterial evaluation. It is thought that such opportunistic screening in patients presenting with other illnesses might achieve almost as much success as the more formal screening programmes (Collin, 1993). The likely increase in surgical workload from the screening programmes outlined above appears to be small, and may allow a reduction in the number of emergency operations (Scott *et al.* 1994).

The economics of mass screening for AAAs have been analysed in detail by Collin (1990). The cost of screening alone would amount to less than one million pounds per annum for the whole of England and Wales or roughly £100 per aneurysm detected. An additional 4300 elective operations would be required but 1500 fewer emergency operations for ruptured aneurysms would be necessary each year. At £4000 per elective operation the net additional cost for operations would be £8 million. Each year around 20 000 life years would be saved at a medical cost of £450 per quality adjusted life year (QALY). This compares with an estimated cost of £4136 per QALY for the national breast

screening programme (Blamey *et al.* 1986). Given the uncertain aetiology of the disease and its occult nature, neither attempts at prevention nor the introduction of innovative methods of treatment can be expected to have much impact on the number of deaths from this cause. Therefore the essential requirement is to detect a higher proportion of lesions before rupture, when most are asymptomatic, which may be the only effective strategy for reducing the currently high mortality from AAAs.

OPERATIVE MANAGEMENT OF AAAS

2.6 Indications for Surgical Repair

Most AAAs remain asymptomatic until rupture occurs. Elective repair of an asymptomatic AAA aims at preventing rupture, a condition associated with a high mortality. Such prophylactic management requires comparison of the risk of rupture if left uncorrected, to both the risk of surgery and the probability of worthwhile long-term survival unrelated to the AAA (Johansson *et al.* 1990; Limet *et al.* 1991).

Indications for Operation for Asymptomatic AAA

All authorities agree the factor most closely associated with the risk of rupture is aneurysm size. Although there is uncertainty as to the exact risk of rupture for any particular size, estimates range from a very low incidence of 0% to 3% per year for AAAs <5 cm in diameter, to a very significant 20% per year or greater for AAAs >7 cm in diameter (Taylor *et al.* 1987; Hollier *et al.* 1992). As the benefit of AAA repair to prevent rupture is dependent on operative risk, factors increasing risk in individual patients are of importance, and have been delineated by the subcommitte on indications for AAA surgery of the American Joint Vascular Societies (*Table 4*).

For patients with asymptomatic AAA, three treatment options exist: (1) elective repair; (2) observation, reserving repair for rapid expansion in size or occurrence of symptoms; (3) no repair. Which approach is adopted for an individual patient depends on the relationship of risk of AAA rupture (size, expansion rate) to the individual operative risk (age, coexisting medical conditions). In the absence of factors clearly indicating increased operative risk, most vascular surgeons would consider elective surgery when the aneurysm reaches 5.0 cm in diameter (Campbell, 1991). This is also the policy adopted in Leicester. Only in cases of very limited life expectancy, such as disseminated cancer or severe accompanying risk factors, should elective surgery for AAAs be withheld.

In the United States, the threshold for elective aneurysm surgery is lower than in the UK. The subcommittee of the Joint Council of the Society for Vascular Surgery and

Table 4: *Factors resulting in increased risk of perioperative mortality associated with elective repair of AAA.*

Factor	Level I (No increase in risk)	Level II (1-3% increase in risk)	Level III (3-7% increase in risk)
Age 75-80 Age 80-85 Age >85	X	X	X
Stable angina or previous MI with negative objective studies Unstable angina or MI within 6 months Symptoms of congestive cardiac failure	X	X	X
Left ventricular ejection fraction (LVEF) 30-50%% 20-30%% < 20%	X	X	X
Chronic obstructive airways disease (COAD) with normal daily activities COAD with restriction of activities COAD with O2 at home	X	X	X
Creatinine 1.5-2.0 mg/dl Creatinine 2.0-3.5 mg/dl Creatinine > 3.5 mg/dl	X	X	X

(Modified from Hollier *et al.* 1992).

the North American Chapter of the International Society for Cardiovascular Surgery recommend AAA repair in all patients with aneurysms greater than 4 cm in diameter (Hollier *et al.* 1992) (*Table 5*). However, these guidelines have not been adopted in the UK.

The findings of the UK. Small Aneurysm Trial (The UK Small Aneurysm Trial Participants, 1995) may help to clarify the grey area of uncertainty concerning the best management of aneurysms between 4 and 5.5 cm in diameter. In the presence of significant perioperative risk factors, the risk of rupture must be balanced against the risk of surgery. By its very nature, the decision is an individual one, both for patients and surgeons. Few would recommend elective repair of an aneurysm 4.5 cm in diameter in an 80 year old patient with severe coronary and pulmonary disease. Few would not recommend repair of an 8 cm AAA in a 60 year old patient with stable angina. Between these extremes lies a spectrum of individual situations. For some of these patients, observation of AAA by serial ultrasound every 6 months, reserving operation for increasing size or risk of rupture represents a reasonable approach to balancing the risk of surgery against risk of rupture. In most cases, aneurysm repair can be performed safely, despite associated medical risks, by careful preoperative evaluation and preparation, and by careful perioperative monitoring and management.

2.7 Preoperative Assessment

General Assessment

In our centre patients initially undergo simple preoperative investigations including full blood count, serum biochemistry, electrocardiogram (ECG) and chest radiography. Any abnormalities revealed by these routine investigations are then investigated further.

Ischaemic heart disease is a common associated problem in these patients and is the most common cause of postoperative mortality. Therefore it warrants careful assessment and will be discussed in more detail later. Renal function assessment is based initially on the serum urea and creatinine values. If the creatinine is elevated further investigation of the cause is undertaken, with the involvement, where necessary of the nephrologist. Renal artery stenosis should be excluded in these patients with colour duplex scanning or angiography, as this can be dealt with appropriately during aneurysm surgery. Approximately 6% of patients undergoing elective resection are found to have significantly elevated serum creatinine levels (>2 mg/dl) (Lazarus, 1992). Even though pre-existing renal insufficiency has been linked with a higher mortality rate (Katz *et al.* 1994) it

Table 5: *Recommended indications for operative treatment of AAAs by subcommittee of the Joint Council of the SVS and the North American Chapter of ISCVS. After Hollier et al. 1992.*

1. Ruptured AAA

Indications:
-any patient with documented or suspected rupture.
Relative contraindications:
(i) underlying medical condition that would otherwise preclude any significant long term survival (e.g. terminal cancer), (ii) underlying issues relating to quality of life that make repair unreasonable (e.g. demented elderly nursing home patient).

2. Symptomatic or rapidly expanding aneurysm

Indications:
-any patient, regardless of any size, should be considered for aneurysm repair.
Relative contraindications:
- preterminal condition, overwhelming medical problems, or unacceptable quality of life.

3. Asymptomatic aneurysms

Indications:
- aneurysms >4 cm in diameter or a diameter >twice the diameter of the normal infrarenal aorta.
Relative contraindications:
(i) life expectancy of less than 2 years, (ii) overwhelming medical problems, (iii) unacceptable quality of life.
Relative contraindications to repair of small (<5 cm) AAAs:
(i) recent myocardial infarction, (ii) intractable congestive cardiac failure, (iii) severe angina pectoris, (iv) severe renal dysfunction, (v) decreased mental acuity, (vi) markedly advanced age.

4. Complicated aneurysms

Indications:
- embolism, thromboses, fistulisation, or aneurysms associated with symptomatic intraabdominal occlusive disease, regardless of size.
Relative contraindications:
(i) life expectancy of less than 2 years, (ii) overwhelming medical problems, (iii) unacceptable quality of life.

5. Atypical aneurysms

Indications:
- dissecting, mycotic, false, or saccular aneurysms, as well as penetrating ulcers may represent indications for surgical treatment regardless of size.
Relative contraindications:
(i) life expectancy of less than 2 years, (ii) overwhelming medical problems, (iii) unacceptable quality of life.

should not preclude aneurysm repair but rather indicate that the patient may need special perioperative care.

Formal lung function tests and arterial blood gas analysis are performed if associated lung disease (such as COAD) is present or suspected on clinical examination. Chronic obstructive pulmonary disease should also not in itself be viewed as a contraindication to surgery, but instead should identify the patient who will need special postoperative care (Hallett, 1992). Cessation of smoking, the administration of bronchodilators, antibiotic treatment for chronic bronchitis, early extubation and mobilisation will all help minimise postoperative pulmonary complications (Hallett, 1992).

Assessment and Management of Coronary Artery Disease prior to AAA Surgery

As mentioned before coronary artery disease (CAD) is the most common cause of operative death in patients undergoing AAA surgery (Diehl *et al.* 1983; Johnston, 1989). In the Canadian multicentre study of 680 elective AAA repairs, the overall hospital mortality was 4.8% and two-thirds of the operative deaths were related to cardiac complications (Johnston, 1989). The beneficial influence of correcting severe CAD prior to other arterial operations has been shown by several authors (Crawford *et al.* 1978; Hicks *et al.* 1975). Crawford *et al.* (1978) and Hicks *et al.* (1975) described 179 aneurysm repairs in patients who had previous coronary bypass surgery and reported no early deaths and a cumulative 5-year survival ranging from 70 to 87 per cent. Subsequently, Hertzer *et al.* (1984) recommended the most comprehensive yet controversial approach to the evaluation of patients under consideration for elective AAA repair. Cardiac catheterisation was performed in 302 patients, in a prospective attempt to reduce operative risk and late mortality, selected patients with appropriate angiographic lesions underwent myocardial revascularisation as a preliminary or synchronous procedure. Severe surgically correctable disease (>70% stenoses) was found in 42% of patients with clinical disease and in 19% of those with no clinical indications of CAD (Young *et al.* 1986). Therefore in an effort to detect those patients at risk for perioperative myocardial infarct, some authors have advocated the routine screening of all patients with dypyridamole-thallium scans and/or coronary angiography with subsequent coronary revascularisation in those with severe CAD.

In the UK the approach to managing associated CAD varies depending on the individual vascular surgeon and the local facilities. In our centre patients with ischaemic heart disease are referred for anaesthetic opinion. Left ventricular ejection fraction is assessed with an echocardiogram or a radionuclide ventriculograph (MUGA-multigated acquisition scan). A cardiology opinion is sought if recommended by the anaesthetist, to improve the cardiac status of the patient with best medical therapy. Very few patients

proceed to coronary angiography and CABG prior to aneurysm surgery. A thorough cardiological work-up may be feasible with small aneurysms. However, in the case of large aneurysms there is a greater sense of urgency and a comprehensive preoperative assessment may not be possible.

In an ideal situation the preoperative cardiac assessment should follow the same guidelines as used in the United States. Most vascular surgeons there base cardiac work up on the clinical severity of CAD as measured by the presence and severity of angina (Brown *et al.* 1981; Golden *et al.* 1990; Lachapelle *et al.* 1992). Patients are divided into 3 groups : those without any clinical evidence of CAD (Group I), those with mild to moderate CAD [on the basis of previous MI or presence of class I-II angina (New York Heart Association Classification), or an abnormal ECG] (Group II), and those with severe CAD [based on presence of congestive heart failure or class III-IV angina] (Group III). In patients who fell into Group I, Lachapelle *et al.* (1992) found an overall mortality rate of 1.8% and a cardiac mortality rate of 0%. Brown *et al.* (1981) and Golden *et al.* (1990) also showed that in patients with no history of angina or MI, there is no need for extensive cardiac work up. However, patients with severe CAD (Group III), do benefit from coronary angiography and subsequent coronary artery bypass prior to AAA repair (Lachapelle *et al.* 1992; Pairolero, 1989).

A more difficult question concerns the appropriate management of patients with clinically evident CAD that is thought to be of only mild to moderate degree (Group II). There is no reliable test to detect those patients within group II who would benefit from myocardial revascularisation. Radio nuclide measurement of left ventricular ejection fraction (LVEF) has been used by some surgeons. Pasternack *et al.* (1984) found that patients with a left ventricular ejection fraction (LVEF) less than 40% have a 17% incidence of postoperative cardiac events compared with 3.4% if it greater than 40% (Pasternack *et al.* 1984). However, other authors (McEnroe *et al.* 1990; Franco *et al.* 1989; Lachapelle *et al.* 1992) have found no correlation between LVEF and the risk of a postoperative cardiac event. This may be due to the fact that LVEF is a static measurement done at rest and gives no information as to the ability of the heart to withstand ischaemia. Exercise tolerance testing, which is done to reproduce myocardial ischaemia in a controlled setting, has a number of drawbacks. Approximately one third of vascular patients cannot complete the examination because of claudication (Cutler *et al.* 1981; McPhail *et al.* 1988). Even if completed, ST segment depression is not always associated with significant CAD on subsequent coronary angiography (Cutler *et al.* 1981; Goldman *et al.* 1984).

Dipyridamole-thallium scanning has been found to be a useful alternative to exercise tolerance tests (Cutler *et al.* 1987; Boucher *et al.* 1985). Iskandrian *et al.* (1988) have shown that a patient with a negative dipyridamole-thallium scan can undergo operation safely without cardiac complications. If the scan demonstrates a significant area of thallium redistribution, then most authors believe that a coronary angiogram is

warranted (Brewster *et al.* 1985; Fletcher *et al.* 1988). Eagle *et al.* (1989) have shown that dipyridamole-thallium scan is most useful in patient stratification if used on those patients thought to be at intermediate cardiac risk on the basis of the presence of one or two of the following clinical variables: age >70 years, history of angina, diabetes, clinical evidence of CHF, Q wave on ECG, or ventricular arrhythmia requiring medical therapy. Patients without redistribution on dipyridamole-thallium scanning had a similar risk for cardiac events (3%) as those without clinical factors, compared with the 30% incidence of postoperative events in those with redistribution. A dipyridamole-thallium scan can therefore be used to identify those patients in Group II who may benefit from coronary angiography.

2.8 Elective AAA Surgery by Transperitoneal Approach

The transperitoneal approach is the most widely used approach for elective and emergency repair of infrarenal aortic aneurysms (Crawford *et al.* 1981; Soreide *et al.* 1982b; Whittemore *et al.* 1980). Its advantages for aortic reconstruction include easy access to the infrarenal aorta and iliac vessels, the possibility of simultaneous inspection of the intra-abdominal viscera, and the speed of opening and closure. However a number of authors have suggested that this approach takes longer, causes more blood loss, prolonged ileus, increased third-space fluid loss, increased pulmonary complications, and is associated with a longer hospital stay than the retroperitoneal approach (Leather *et al.* 1989; Sicard *et al.* 1987; Shepard *et al.* 1986; Williams *et al.* 1980).

Operative Technique

The choice between a long mid line incision and a wide transverse incision is a matter of personal preference, although there is some evidence to suggest that a transverse incision may reduce hospital stay (Lord *et al.* 1994).

The abdominal cavity is explored for other unexpected pathology. The likelihood of a coexisting malignant tumour or other intraluminal pathology is substantial in this age group, particularly in patients who present with abdominal symptoms that are not clearly due to the aneurysm (String, 1984; Szilagyi *et al.* 1967). The extent of the aneurysm, its upper and lower limits, and the condition of the major adjacent arteries, particularly the renal and common iliac arteries is also determined by palpation.

The transverse colon is then retracted superiorly and the small bowel held to the right, to allow a longitudinal incision of the peritoneum just to the left of the base of the small bowel mesentery to expose the aneurysm. The parasympathetic nerves lie anterior to the proximal left common iliac artery on their way to the pelvis (Weinstein *et al.* 1975). An effort is made to retract these nerves with the peritoneum and minimise damage to them in sexually active men. After the peritoneal incision is completed and the duodenum

mobilised, the small intestine is either packed into the right upper portion of the abdomen or eviscerated and retracted rightward. Self-retaining retraction devices (e.g., Omnitract) may aid good exposure during the operation. After the ligament of Treitz is transected, the inferior mesenteric vein becomes apparent, and it can be divided if necessary. The left renal vein lies in the cephalic direction in a deeper plane. In order to obtain adequate exposure of larger aneurysms, it may be necessary to expose and retract this vein superiorly. Occasionally, the left renal vein may be tightly stretched over the "neck" of the aneurysm. In such cases division medial to the adrenal and gonadal tributaries is usually well tolerated (Anderson *et al.* 1986).

After exposure of an adequate segment of aorta above the aneurysm is obtained and before the aneurysm itself is dissected or otherwise manipulated, control of the iliac arteries is established. Five thousand units of heparin are usually given intravenously in an average sized adult, and the distal vascular clamps are applied first (to prevent distal embolisation from above) followed by the proximal clamp. Good communication with the anaesthetist is essential and they should be warned adequately prior to application of the clamps to enable regulation of the blood pressure. The aneurysm is then opened longitudinally along its anterior surface. The upper end of the incision is then incised horizontally in a T-shape with the lateral extensions just below the neck of the aneurysm. The thrombus and atherosclerotic debris are removed. The value of routine Gram stain and culture of this material in predicting subsequent graft sepsis is unproven (Buckels *et al.* 1985; Eriksson *et al.* 1983; McAuley *et al.* 1984; Schwartz *et al.* 1987). A review of routine cultures from 500 elective aneurysms found that positive cultures did not predict subsequent graft sepsis (Farkas *et al.* 1993).

After clearing the aneurysm sac of its contents, bleeding from lumbar arteries is controlled individually with suture ligatures. Once the collateral flow into the aneurysm sac has been controlled in this manner, the upper anastomosis is performed. A graft of appropriate size is chosen according to the diameter of the non-aneurysmal segment of the aorta and cut to the required length. After completing the upper anastomosis, the distal graft is occluded with a vascular clamp, and the proximal aortic clamp is released briefly to check for suture line bleeding. Particular attention is paid to the posterior aspect of the suture line because it can not be reached again once the distal anastomosis is undertaken. If the iliac arteries are not aneurysmal, only a tube graft is needed. A similar technique is used above the bifurcation, suturing from within the lumen and encompassing both iliac artery orifices within the suture line. If iliac artery aneurysms exist, they are incised anteriorly so that the limbs of the bifurcated graft can be sutured to an oblique ellipse that includes both the internal and external iliac arteries. Care should be taken to ensure distal patency with good back flow before completing each distal anastomosis; heparinised saline is carefully flushed into the distal circulation.

As soon as the first iliac anastomosis is completed, flow into that limb should be

restored, releasing the clamp slowly to decrease "declamping" hypotension. The anaesthetist is given adequate warning prior to this manoeuvre so that any vasodilator infusion can be turned off and adequate fluid volume is given prior to release of the clamp. Although declamping shock is rare if adequate intravenous fluid replacement has been administered, the sudden release of the aortic clamp, allowing blood into the dilated distal bed, and the concomitant venous return of vasoactive substances that have accumulated in the ischaemic tissues may cause hypotension. Flow is released into the internal iliac arteries before the external iliac arteries if both of these arteries have been individually clamped. This has the advantage of diverting any embolic debris into the internal iliac circulation rather than into the legs.

After restoration of flow into the iliac arteries, attention is turned to the circulation of the sigmoid colon. In the rare circumstances when the sigmoid colon appears ischaemic, particularly if the internal iliac arteries are diseased or excluded from the circulation (especially when a bifurcated graft is inserted), an elliptical cuff of the aortic wall around the inferior mesenteric artery orifice is excised and anastomosed to the side of the graft. On occasion, embolisation to the lower extremity can compromise distal perfusion. Prior to closure the feet are inspected to ensure adequate perfusion. A change in perfusion from the preopertive status indicates the need for thromboembolectomy. Finally the remaining aneurysmal sac is trimmed and sutured around the graft to provide a natural tissue barrier over the prosthesis followed by closure of the retroperitoneum.

2.9 Elective AAA Surgery by Retroperitoneal Approach

The retroperitoneal approach to the abdominal aorta has been advocated by some surgeons because of improved operative morbidity and hospitalisation (Rob, 1963; Sharp *et al.* 1987). This technique was first described by John Abernathy, in 1796, when he tried unsuccessfully to ligate an external iliac artery aneurysm using this approach (Abernathy, 1804). Retroperitoneal procedures on the aorta and iliac arteries were performed at the inception of modern vascular surgery. Dubost (1952) and Oudot (1951) used a retroperitoneal approach for exposure of the distal aorta and iliac arteries in their initial reports. In 1963, Charles Rob reported 500 cases of aortic reconstruction using the retroperitoneal approach, and observed a better postoperative course in these patients compared with those undergoing transperitoneal aneurysm repair (Rob, 1963).

Operative Technique

The patient is positioned in a semilateral position with the left side up. The shoulders are fixed at approximately 60 degrees to the horizontal plane by means of a sand

bag under the left shoulder, while the pelvis is rotated posteriorly so that it lies approximately 45 degrees to the horizontal plane. A suction beanbag device may aid in maintaining this position (Chang *et al.* 1988). The operating table can be rotated towards or away from the operating surgeon, to achieve a more or less lateral position. Use of a kidney bridge to break the table increases the space between the costal margin and the iliac crest. This position gives good access to the retroperitoneum and both groins if necessary.

A number of different incisions have been described for the retroperitoneal approach to the aorta (Rob, 1963; Shumaker, 1972; Helsby *et al.* 1975; Taheri *et al.* 1983; Risberg *et al.* 1989; Metz *et al.* 1978) but an oblique flank incision is the one currently favoured by most surgeons (Sharp *et al.* 1987; Williams *et al.* 1980; Leather *et al.* 1989; Shepard *et al.* 1986; Chang *et al.* 1988; Sicard *et al.* 1989). This incision extends in a curvilinear fashion from the lateral border of the rectus muscle anteriorly adjacent to the umbilicus to the eleventh interspace posteriorly. The incision is deepened posteriorly through the lower fibres of the latissimus dorsi and the underlying edge of the serratus posterior inferior and anteriorly through the external and internal oblique muscles. The lumbar fascia is incised posteriorly to expose the loose fat of the retroperitoneal space.

The retroperitoneal space is then developed inferiorly by blunt finger dissection separating the posterior peritoneum from the iliopsoas muscle taking care to stay anterior to the epimysium of the psoas muscle. This enables exposure of the inferior aorta just above the bifurcation and the left common and external iliac arteries. The dissection is then extended proximally, developing the plane between the iliopsoas muscle and the peri-renal fascia with its enclosed fat. Some surgeons advocate mobilisation and medial displacement of the left kidney and ureter, thus exposing the entire infra-renal aorta (Leather *et al.* 1989; Shepard *et al.* 1986; Chang *et al.* 1988).

After systemic heparinisation, the iliac arteries are controlled initially to minimise the potential for distal embolisation (Leather *et al.* 1989). If there is any difficulty in placing an external clamp on the right iliac artery, control can be achieved later, after opening the aneurysm sac, by using intraluminal balloon catheter occlusion. The neck of the aneurysm is approached from its posterior aspect. The large lumbar branch of the left renal vein is identified, suture ligated and divided. The plane posterior to the neck of the aneurysm is developed by blunt dissection close to the vertebral body. The anterior plane is similarly opened. If supracoeliac control is necessary the dissection proceeds proximally along the aorta towards the left crus of the diaphragm, which is divided in the long axis of the aorta (Shepard *et al.* 1986).

The aneurysm sac is then opened longitudinally along its posterolateral wall and a tube or bifurcated graft inserted, after controlling the back bleeding from the lumbar and inferior mesenteric arteries by suture ligation. An alternative technique, involves exclusion of the aneurysm and end-to-end anastomosis between the divided proximal and distal aorta and the graft. The aneurysm is over sewn to exclude it (Leather *et al.* 1989). The latter

technique overcomes the blood loss associated with opening the aneurysm sac (Leather *et al.* 1989).

In patients with iliac aneurysms or iliac occlusive disease, distal anastomoses are carried out to the iliac or femoral arteries as necessary. The right limb of a bifurcated graft can be easily passed in a retroureteric fashion into the right iliac or femoral area (Sicard *et al.* 1987). Shepard *et al.* (1986) advocate anastomosing the distal limbs of a bifurcated graft to the external iliac arteries as it is easier and avoids the complications of a groin incision. This is achieved on the left side through the retroperitoneal incision and on the right side through a small right lower quadrant incision.

2.10 Transabdominal Versus Retroperitoneal Approach

The proponents of the retroperitoneal approach argue that it results in a smoother, shorter, and less complicated post-operative recovery with a lower incidence of complications (Rob, 1963; Helsby *et al.* 1975; Taheri *et al.* 1983; Shumaker, 1972; Metz *et al.* 1978). There are only 2 prospective randomised studies comparing surgical approaches to the abdominal aorta (Cambria *et al.* 1990; Sicard *et al.* 1995). Cambria *et al.* (1990) performed a prospective randomised study comparing transabdominal (n=59) and anterolateral retroperitoneal approaches in patients undergoing elective abdominal aortic reconstruction. Although they were unable to demonstrate statistically any important differences between the two approaches, they did observe a trend towards reduced mortality, morbidity, postoperative ileus and hospital stay in the retroperitoneal group. More recently Sicard *et al.* (1995) reported results of a similar randomised trial comparing the transabdominal incision (TAI) to the retroperitoneal incision (RPI) for aortic surgery. One hundred and forty-five patients were randomised, with 75 (41 with AAA and 34 with aortoiliac occlusive disease) in the TAI group and 70 (40 with AAA and 30 with occlusive disease) in the RPI group. The incidence of intraoperative complications was similar for both groups. However, the incidence of prolonged ileus ($p = 0.013$) and small bowel obstruction ($p = 0.05$) was higher in the transabdominal incision group. Overall, the RPI group had significantly fewer complications ($p < 0.0001$). The overall postoperative mortality rate (two deaths) was 1.4%, with both occurring in the TAI group ($p=0.51$). The RPI group also had significantly shorter stays in the intensive care unit ($p <0.006$), a trend toward shorter hospitalisation ($p = 0.10$), lower total hospital charges ($p < 0.02$), and lower total hospital costs ($p < 0.02$). There was no difference in pulmonary complications ($p = 0.71$). In long-term follow-up (mean 23 months), the RPI group reported more incisional pain ($p = 0.056$), but no difference was found in incisional hernias ($p = 0.297$). The authors concluded that the RPI approach for abdominal aortic surgery was associated with fewer postoperative complications, shorter stays in the hospital and intensive care unit, and lower cost.

There are a number of drawbacks to the retroperitoneal approach. Positioning the patient on the operating table may take some time. It also does not allow adequate exploration of the abdominal cavity and its contents to exclude other pathology. Also operating on the aorta via the retroperitoneal approach is technically demanding, access to the right renal artery is difficult, and exposure of the right iliac system may require an additional right lower incision.

2.11 Repair of Ruptured Abdominal Aortic Aneurysms

Rupture is the most frequent and lethal complication of abdominal aortic aneurysms. Rupture of an abdominal aortic aneurysm is responsible for 1.3 per cent of all deaths in men over 65 years of age (Department of Health Statistics, HMSO, 1983) accounting for around 10, 000 deaths per annum in England and Wales (Fowkes *et al.* 1989).

Without surgical treatment rupture invariably results in death. Even with surgical intervention the mortality remains high. The mortality rates in most centres approach or exceed 50 % (DiGiovanni *et al.* 1975; Hildebrand *et al.* 1975; Fitzgerald *et al.* 1978; Pilcher *et al.* 1980; Fielding *et al.* 1981; Castleden *et al.* 1985; Thomas *et al.* 1988; McCready *et al.* 1993; Johnston, 1994b; Samy *et al.* 1994). Once rupture occurs many patients do not reach hospital alive, therefore the overall mortality of ruptured aneurysms may exceed 90% (Johansson *et al.* 1986; Mealy *et al.* 1988; Budd *et al.* 1989). There are some reports of better results with ruptured aneurysms, but most of these are from major centres in which the time and distance involved in transfer of patients may select out the worst cases before arrival (Lawrie *et al.* 1979; Darke *et al.* 1973; Hoffman *et al.* 1982; Naylor *et al.* 1988). Lawrie and colleagues (1979) reported a 14.8 per cent mortality rate for 61 consecutive emergency aneurysm operations, but less than 30 per cent of the patients were hypotensive (systolic pressure < 100 mm Hg) on admission and less than 45 per cent were hypotensive at any time prior to operation. Darke and Eadie (1973) reported a 29 per cent mortality rate from the London Hospital, however despite excluding emergency cases that had not been hypotensive, there were no instances of free intraperitoneal haemorrhage in their series. In a community wide experience from a large US city, Hoffman *et al.* (1982) reported a 38.2 per cent operative mortality for ruptured aortic aneurysm. Thus, the operative mortality for ruptured aneurysms differs in various centres, probably because of the different patient populations, variability in pre hospital care and transport, delay in treatment, and difference in the experience of surgeons.

In the past two decades there has been little improvement in the operative mortality for ruptured aneurysms, despite improvements in anaesthesia and post-operative care (Crawford *et al.* 1981; Johansson *et al.* 1994; Katz *et al.* 1994).

Diagnosis of Ruptured AAA

Early diagnosis is important in improving the outcome of ruptured aortic aneurysms. Several authors who have examined the causes of death have identified an increased mortality rate for patients who are incorrectly diagnosed on admission (Bodily *et al.* 1985; Hoffman *et al.* 1982; Lawrie *et al.* 1979). In the series reported by Hoffman *et al.* (1982), those patients in whom the initial diagnosis was correct or the aneurysm was suspected from the outset, the mortality rate was 35 %. Whereas those patients in whom the diagnosis was incorrect or a cardiopulmonary event was suspected, the mortality was 75 percent.

The classical clinical triad of abdominal or back pain of sudden onset, hypotension, and a pulsatile abdominal mass, is only present in about half of the patients. Sudden onset of abdominal pain is the most common symptom (Darke *et al.* 1973; Gloviczki *et al.* 1992) and about half of the patients have back pain. A ruptured aneurysm should be considered in any patient above 50 years of age presenting with sudden onset abdominal pain, back pain, or hypotension, especially those with other risk factors for atherosclerosis. Patients with a perforated viscus may also present with shock and dramatic abdominal pain, however, signs of peritonitis with rigidity of the abdominal wall are striking features of perforation. Even if the initial diagnosis of a ruptured abdominal aortic aneurysm is incorrect, it is important to note that most conditions that cause abdominal pain and shock require urgent abdominal exploration. Myocardial infarction, pulmonary embolism, and acute pancreatitis should also be included in the differential diagnosis.

The diagnosis of ruptured aneurysm is more difficult when hypotension is absent and the patient presents with abdominal or back pain alone. In stable patients with ruptured aneurysm, a pulsatile mass may be felt, usually to the left of the mid line and above the umbilicus (Rutherford *et al.* 1989). Abdominal distension in a hypotensive patient should also arouse suspicion of a ruptured aneurysm. Most patients will likely be distended from the retroperitoneal or intraperitoneal blood and secondary ileus, although they may only have mild tenderness and guarding. This distension may obscure imaging of the aneurysm by ultrasound examination. Also as most aneurysms usually rupture to the left of the base of the mesentery, the resulting haematoma often forms to the left and may dissect downward and present as a tender left lower quadrant mass, which may be mistaken for diverticulitis with or without perforation (Rutherford *et al.* 1989). The retroperitoneal haematoma may cause compression and irritation of the nerve roots, causing testicular pain or radiation of pain to the genitals, particularly to the left. Such presentations may lead to a mistaken diagnosis of lumbosacral radiculopathy (Wilberger, 1983), strangulated inguinal hernia (Merchant *et al.* 1981; Banerjee *et al.* 1989), or ureteric colic (Moran *et al.* 1987).

Ultrasound examination may be useful in confirming the diagnosis in

haemodynamically stable patients and visualises the aneurysm in 90 per cent of cases (Johansen *et al.* 1991; Creech, 1966; Osler, 1905). However the ultrasound is not accurate in determining the presence or absence of rupture. If the diagnosis is still uncertain and the patient is haemodynamically stable, a CT scan may be performed (Johnson *et al.* 1986; Raptopoulos *et al.* 1987; Senapati *et al.* 1986; Weinbaum *et al.* 1987). The basic approach to the diagnosis must be modified according to the urgency of the situation as judged from the patient's haemodynamic stability on admission. If hypotension predominates, then resuscitation should be commenced and the patient should be prepared and transferred to the operating theatre as soon as possible. In patients presenting with predominately pain, there may be more time to pursue the diagnosis and exclude other causes.

Resuscitation of Ruptured AAAs

Patient transfer to the operating theatre should not be delayed by prolonged resuscitation in the casualty department. The lower the blood pressure and the poorer the response to resuscitation, the more urgently the patient needs to be transferred to the operating theatre. Resuscitation may then be continued in theatre by the anaesthetist while the surgeon prepares the patient for laparotomy.

Resuscitation follows the same guidelines as for any condition causing major haemorrhage. Blood should be taken for cross-matching and routine haematology and biochemistry. Crystalloid infusion should be begun via a large-bore cannulae in the antecubital fossae. In addition to the peripheral venous cannulae, a central venous catheter and an arterial line should also be inserted, if possible, before the operation begins. A urinary catheter is placed to monitor urine output.

Crystalloid infusion should be followed by whole blood transfusion as soon as the blood becomes available. However the volume of intravenous fluids infused in hypotensive patients in the preoperative period is controversial (Crawford, 1991; Friedman *et al.* 1992; Bickel, 1989). Most vascular surgeons would agree that intravenous fluids should be administered with caution before placement of the aortic cross clamp. Elevating the patients systolic pressure beyond 80-100 mmHg may contribute to more blood loss through the rupture site. When large volumes are given, the blood should ideally be externally warmed during infusion, to minimise hypothermia and the consequent haemodynamic disturbances and coagulopathy (Patt *et al.* 1988). Platelet dysfunction is the primary abnormality responsible for hypothermia induced coagulopathy (Valeri *et al.* 1987). This may result in a poor outcome in such patients (Davies *et al.* 1993). Specific blood component therapy (fresh frozen plasma, platelets, cryoprecipitate) to correct the underlying disorder may also be necessary, particularly after re-establishment of vascular continuity.

Operative Technique

A long midline skin incision, from the xiphoid to the pubis, should be made. If the patient has been, or is unstable and, particularly if the abdomen is distended, care should be taken in opening the abdomen. In this situation the skin and subcutaneous tissues and then the fascia should be opened in layers, before entering the peritoneum, to maintain the tamponade effect until the last possible moment in case free intraperitoneal rupture has occurred.

The success of the operation is determined by the speed and manner in which proximal aortic neck control is gained. Once the tamponade effect of the abdominal wall (in case of free intraperitoneal rupture) or the retroperitoneum (in case of large contained haematoma) is lost, there may be rapid haemorrhage from the rupture site. The abdominal aorta can be isolated at the level of the diaphragm or at the infrarenal segment. Rapid control of the upper abdominal aorta below the diaphragm should be obtained if the patient is unstable, if there is free intraperitoneal bleeding, or if the retroperitoneal haematoma extends superiorly to the level of the renal vein. Control is gained by incising the avascular portion of the gastrohepatic omentum, retracting the left lobe of the liver medially, and compressing the aorta against the spine using a fist, retractor or an aortic compressor (Crawford, 1991). After proximal control has been achieved, the patient is rapidly resuscitated with crystalloid solution, blood, fresh frozen plasma, and platelets. A renal dose of dopamine may also be commenced and prophylactic antibiotics given. Both the surgeon and the anaesthetist work simultaneously to gain haemodynamic control.

Control of the infra-renal aorta is then obtained in a similar manner to that used for elective repair. The neck of the aneurysm is dissected bluntly distal to the renal arteries, and an aortic clamp is placed. The haematoma often pushes the overlying retroperitoneal structures anteriorly, facilitating this manoeuvre. A large Foley catheter can also be inserted during the operation directly through the infrarenal aorta, immediately after opening the sac of the aneurysm to gain temporary control.

After obtaining control of the proximal aorta, the aneurysm is incised, and the thrombus from the aneurysm is carefully removed to avoid embolisation. Distal control may be achieved with balloon catheters inserted into the two iliac arteries or simply by the vertical placement of vascular clamps without attempts to encircle the iliac arteries. Having obtained proximal and distal control, bleeding from the lumbar arteries is controlled by tamponade while the anaesthetist catches up with the volume losses and the cardiac function is restored.

The aortic reconstruction does not differ from elective repair. A tube graft should be inserted wherever possible. The natural history of isolated iliac aneurysms is different

from those of small iliac aneurysms associated with an aortic aneurysm. In cases of abdominal aortic aneurysm rupture small iliac aneurysms may be ignored as very few need subsequent revision to a bifurcated graft (Glickman *et al.* 1982; Provan *et al.* 1990). In view of these findings, it is reasonable to ignore mild aneurysmal changes in the iliac arteries and insert a tube graft.

2.12 Complications of AAA surgery

Early Complications

(a) Intraoperative Haemorrhage

Most of the blood loss occurs because of rupture or from coagulopathies (Bernhard *et al.* 1983). The infrarenal aorta is surrounded by a number of major veins (the left renal vein superiorly, the inferior vena cava, gonadal, and inferior mesenteric vein laterally, and the iliac veins located inferiorly). Occasionally accidental venous injury may give rise to blood loss. Mobilisation and retraction of the left renal vein may be necessary to gain control of the proximal aorta. In some cases the left renal vein may be ligated to facilitate exposure and control of a high aortic aneurysm. However, this may be complicated by loss of the kidney or haemorrhage if the left adrenal gland and adrenal veins are injured during retraction (Rastad *et al.* 1984). Venous anomalies are also common (Bartle *et al.* 1987; Brener *et al.* 1974) and may complicate aortic surgery. A retroaortic left renal vein or a posterior branch of the renal vein occurs in around 2 per cent of cases, and the absence of the vein in its normal anterior position should alert the surgeon to this anomaly. A bifid left sided inferior cava can also be a site of injury and major haemorrhage. Therefore care must be taken during dissection to identify these anomalies rather than discovering them through inadvertent injury.

Proximal anastomotic haemorrhage may occur, particularly in patients with a high lying short necked aneurysm and severe degeneration of the aorta at this site. Therefore care must be taken during anastomosis to prevent iatrogenic weakening. After the anastomosis is completed it should be checked for leakage and any bleeding points sutured after re-application of the proximal clamp.

Major intraoperative haemorrhage usually increases cross-clamp times and contributes to coagulopathy. Intraoperative blood loss correlates directly with postoperative morbidity and mortality (Diehl *et al.* 1983; Johnston, 1989). Intraoperative rupture of the aneurysm is rarely a problem when preliminary control of the proximal and distal vessels is obtained prior to the dissection of the aneurysm itself.

(b) Aortic Declamping Shock

Severe hypotension after restoration of blood flow to the legs can lead to myocardial ischaemia, infarction, or cardiac arrest in the presence of severe coronary artery disease (Rutherford, 1984). This complication can be avoided by good communication between the surgeon and the anaesthetist during the procedure. With adequate volume management and increased awareness of this phenomenon, prolonged declamping hypotension is now seen rarely during elective aortic aneurysm repair (Reiz *et al.* 1979; Bush *et al.* 1977). However, it remains much more of a problem with ruptured aortic aneurysms.

(c) Renal Failure

Acute renal failure following aneurysm repair is a rare but serious complication, and results in death in 50 to 90 per cent of affected patients (McCombs *et al.* 1979; Abbott *et al.* 1975; Porter *et al.* 1966). Advanced age, ischaemic heart disease, occlusive renal artery disease, and decreased functioning renal mass, and poor tolerance of dialysis contribute to the poor prognosis in patients with this complication. Renal failure is now relatively rare following elective infrarenal aortic aneurysm surgery. Avoidance of intraoperative hypotension, improved volume resuscitation, and the shorter period of aortic occlusion required with the endoaneurysmal technique have contributed to improved outcome.

The two main aetiological factors are: nephrotoxicity and ischaemic injury (Porter *et al.* 1966; Miller *et al.* 1987). Ischaemic injury is the most common insult to the kidney and can occur from hypovolaemic or cardiogenic shock, extended period of supra-renal clamping or atheroembolisation to the kidney. Nephrotoxic injury usually results from radiographic contrast agents, perioperative antibiotics, haemoglobinuria secondary to transfusion reactions, or myoglobinuria secondary to skeletal muscle necrosis. Acute renal failure can present as oliguric, polyuric (high output) or late oliguric failure (Porter *et al.* 1966; Miller *et al.* 1987). Oliguric renal failure usually follows an ischaemic insult and is characterised by the formation of 200 to 400 ml of urine per day, a rapid rise in plasma urea and creatinine, metabolic acidosis, and hyperkalaemia. Polyuric renal failure is most commonly seen after aortography, administration of nephrotoxic antibiotics such as aminoglycosides, or renal microembolisation during proximal aortic clamping. The production of large volumes of dilute urine (1.2 to 1.8 L per day) is common. Acidosis and electrolyte imbalance are less likely in high output renal failure, and the plasma urea and creatinine rise more slowly. The prognosis is much better for polyuric than oliguric renal failure, because the renal insult is usually less severe and dialysis may not be required. Late oliguric renal failure manifests initially as high output failure and then

progresses to a state similar to oliguric failure, after an additional insult such as myocardial infarction with low cardiac output, respiratory failure, sepsis, or hypotension secondary to renal dialysis (Miller *et al.* 1987). The prognosis is extremely poor in late oliguric acute renal failure, and dialysis is almost always necessary.

Prevention of renal failure requires the recognition of risk factors, preoperative preparation, and careful operative monitoring and management. Patients with poor renal reserve or extensive renal vascular disease and those with an aneurysm, clot, or severe atheromatous degeneration of the juxta-renal aorta are at high risk for the development of acute renal failure (Dean *et al.* 1984; Diehl *et al.* 1983; Hallett *et al.* 1987; Tarazi *et al.* 1987). Extensive monitoring and maintenance of intravascular volume are essential to prevent hypotension and a low cardiac output during the operative period. A good diuresis should be established with intravenous hydration before aortic cross clamping. There is some evidence to support the beneficial effect of intravenous mannitol when it is given prophylactically 15 to 30 minutes prior to aortic cross clamping (Miller *et al.* 1987). Mannitol acts as a oxygen-free radical scavenger that may have an additional role in preventing renal failure (Miller *et al.* 1987). If hypotension occurs with an adequate filling pressure, the myocardium should be supported with adrenergic receptor-stimulating drugs such as low dose dopamine, which also is a renal vasodilator.

Mortality in patients developing acute renal failure has not decreased despite the use of haemodialysis, which often serves only to prolong the time to death after this complication. Pre-operative renal insufficiency is the only independent risk factor for postoperative acute renal failure (Miller *et al.* 1987), therefore, maintenance of optimal haemodynamics is critical in these patients.

(d) Gastrointestinal Complications

Some degree of ileus occurs after any major abdominal procedure. The most dreaded intestinal complication of aortic aneurysm surgery is "ischaemic colitis," which usually involves the sigmoid colon and occurs rarely in patients undergoing elective aneurysm repair (Bast *et al.* 1990; Diehl *et al.* 1983; Johnston, 1989), and 7% to 10% of patients undergoing repair of a ruptured aneurysm (Ernst, 1983; Ernst *et al.* 1976; Ernst *et al.* 1978; Schroeder *et al.* 1985; Welling *et al.* 1985; Bast *et al.* 1990). Several factors contribute to this complication, with the most important being interruption of the primary or collateral blood supply of the left colon by atherosclerosis, embolisation, thrombosis, ligation, or stretch injury to the left colonic mesenteric vessels (Ernst *et al.* 1976; Welling *et al.* 1985). Stenosis or occlusion of the superior mesenteric artery (SMA), the absence or lack of a meandering artery, or congenital absence of a continuous marginal artery of Drummond at the splenic flexure can predispose to left colonic ischaemia if a patent inferior mesenteric artery (IMA) is ligated. In addition, severe stenosis, occlusion or

ligation of the internal iliac arteries may also contribute to left colonic ischaemia because of diminished flow to the inferior and middle haemorrhoidal arteries, which also serve as a source of collateral blood flow through communications with the superior haemorrhoidal arteries. Operative findings that suggest a potential problem with left colonic ischaemia are the absence of brisk back-bleeding from a patent IMA after the aneurysm has been opened, a stump pressure in this vessel of less than 40 mm Hg, or a dusky-appearing rectosigmoid colon on completion of aortic reconstruction (Ernst *et al.* 1978). Under such circumstances perfusion to at least one internal iliac artery should be preserved (Ernst, 1983) and reimplantation of the IMA should be undertaken. Other modalities which may have a role in perioperative detection of sigmoid ischaemia are laser Doppler flow measurement of the mesenteric vessels (Krohg-Sorensen *et al.* 1989), and sigmoid tonometry to detect changes in the intramucosal pH (Soong *et al.* 1993).

Occasionally, the colon appears dusky and poorly perfused in the unstable, hypotensive, hypothermic patient after repair of a ruptured aneurysm. Under such circumstances, the abdomen may be closed, and either a colonoscopy or a second look laparotomy performed the next day (Hermreck, 1989). Extensive mucosal ischaemia noted on colonoscopy or transmural infarction at the time of re-exploration is an indication for resection.

Post-operatively, colonic mucosal ischaemia usually presents as bloody diarrhoea, fever, tachycardia, and leucocytosis. Colonoscopy should be performed under such circumstances to establish the diagnosis of colonic ischaemia and evaluate its extent (Ernst *et al.* 1976). If only patchy mucosal changes are observed then continued close observation and support with antibiotics and hydration may be all that is required. Extensive mucosal necrosis, signs and symptoms of systemic toxicity, and increasing abdominal tenderness are indications for re-operation.

(e) Ureteric Injury

Injury to the ureter is very rare and occurs during redo aortic surgery in patients with marked perigraft fibrosis, in inflammatory aneurysms or during emergency operation for a ruptured aneurysm (Henry *et al.* 1978; Lambardini *et al.* 1967; Schubart *et al.* 1985; Sacks *et al.* 1988). The most common site for injury is where the ureter traverses the iliac vessels near their bifurcation (Kleinhans *et al.* 1985). Injury to the ureter can be avoided by identifying the ureter before mobilising the iliac artery, and by maintaining a plane of dissection as close as possible to the iliac arteries. These precautions are especially important when the aneurysm involves the iliac arteries.

Clinically, ureteral injury may present with loin pain, impaired renal function, pyrexia and leucocytosis. An ultrasound scan or an intravenous urogram may reveal hydronephrosis. A retrograde pyelogram will reveal the site of obstruction or kinking. If

ureteric obstruction or injury is demonstrated then a urologist should be involved in the further management of this. A temporary stent can sometimes be placed retrograde in the kinked or partially occluded ureter and may resolve the problem. If the ureter is completely occluded, a nephrostomy tube can be placed percutaneously to protect the kidney before definitive repair is undertaken in the high risk patient. Ureteric obstruction in inflammatory aneurysms may be managed by ureterolysis at the time of aneurysm repair (Boontje *et al.* 1990), but this is not advocated by all surgeons (Pennell *et al.* 1985; Crawford *et al.* 1985).

(f) Embolisation or Thrombosis of the Distal Arterial Tree

Atheromatous debris and clot are present in virtually all aneurysms and can extend well above and below the aneurysm in the presence of severe atheromatous degeneration of the aorta. Therefore all structures distal to the diaphragm are at risk of embolisation. Acute lower limb ischaemia following aneurysm surgery occurs in 0.6 to 9.5 per cent of patients (Imparato, 1983; Strom *et al.* 1984). Showers of microemboli in to the foot can lead to 'trash foot', or 'trash buttock' if the embolisation occurs to the trunk via the internal iliac artery, both of which are dreaded complications. Embolisation can occur during manipulation and mobilisation of the aneurysm, during aortic cross-clamping and during unclamping (Jarrett, 1989).

Starr *et al.* first demonstrated the importance of distal clamping prior to placing a proximal clamp (Starr *et al.* 1979). They noted that this manoeuvre could prevent the distal arterial embolisation that would occur if the proximal clamp dislodged juxtarenal aortic thrombus (Starr *et al.* 1979). With this technique Starr and colleagues reported an embolisation rate of 0.23 per cent.

Avoidance of heparin anticoagulation during aneurysm repair, such as during emergency operations, can result in distal arterial thrombosis during the period of cross-clamping. In addition, thrombus formed above the proximal clamp can be flushed into the lower extremities when blood flow is restored. To minimise this possibility, flushing manoeuvres should be performed prior to unclamping. Creation of an intimal flap from the arterial clamp that crushes a calcified plaque within the vessel is a common pitfall. If backbleeding is not present during flushing manoeuvres, distal embolisation or thrombosis may have occurred. Embolectomy or thrombectomy with a Fogarty balloon catheter should be attempted at this point but may be difficult because the iliac arteries are often tortuous.

(g) Paraplegia

This complication is very rare after elective infrarenal aortic surgery, with reported

incidence ranging from 0 to 0.9 per cent (Diehl *et al.* 1983; Hands *et al.* 1991; Johnston, 1989; Picone *et al.* 1986; Szilagyi *et al.* 1978). The basis for this complication is not fully understood but three factors appear important: interruption of the blood supply to the anterior spinal artery, shock, and bilateral internal iliac artery occlusion. The principal source of blood supply to the spinal cord in the abdominal area arises from the accessory spinal artery (*the artery of Adamkewicz*), which supplies the anterior spinal artery. Normally this arises at the T-8, L-1 level and is more commonly injured during thoracic or thoracoabdominal aneurysm repair. Occasionally, this important collateral vessel may arise as low as L-4 level and can be interrupted inadvertently during AAA repair. Classically, the anterior spinal artery syndrome is characterised by paraplegia, rectal and urinary incontinence, and loss of pain and light touch sensation but sparing of vibration sense and proprioception.

Prevention of paralysis secondary to interruption of an anomalous artery of Adamkiewicz is probably not possible short of performing selective spinal angiography in all patients undergoing AAA repair, which also carries a risk of paralysis (Doppman, 1993). Shock secondary to massive haemorrhage and prolonged suprarenal clamping of the aorta greatly increase the risk of paralysis. Another possible mechanism for lower extremity paralysis following AAA repair has been suggested by Iliopoulos *et al.* (1987) and Picone *et al.* (1986). Acute interruption of the internal iliac artery system by exclusion, thromboses, and ligation was found to result in neural deficits ranging from bilateral lower extremity weakness to monoplegia and paraplegia. This again illustrates the importance of maintaining the patency of at least one internal iliac artery by grafting, angioplasty, or endarterectomy.

(h) Infected Aortic Prosthesis

Prosthetic graft infection is the most dreaded complication of vascular surgery. Overall rates for major graft infection average around 2 per cent, ranging from less than 1% to 6% in published series (Hoffert *et al.* 1965; Szilagyi *et al.* 1972b; Goldstone *et al.* 1974; Lorentzen *et al.* 1985; O'Hara *et al.* 1986; Earnshaw, 1991). The organisms implicated in most graft infections include gram-positive organisms (*Staphylococcus epidermidis, S. aureas*), gram-negative organisms (*E. coli, Salmonella, Pseudomonas, Enterobacter*), and even fungi (McCann *et al.* 1993; O'Hara *et al.* 1986; Bandyk *et al.* 1984; Lorentzen *et al.* 1985; Yeager *et al.* 1985; Anderson *et al.* 1984; Bernhard, 1980). In the absence of an aortoenteric fistula, *S. epidermidis* is the primary organism cultured in the majority of graft infections (Yeager *et al.* 1985).

The source of contaminating organisms and the factors responsible for graft infection have been extensively investigated in recent years (Bergamini *et al.* 1988; Bunt, 1983; Malone *et al.* 1975; Schmitt *et al.* 1986; Webb *et al.* 1986). Selwyn and Ellis (1972)

performed a study of various disinfectants, and found that a considerable number of resident bacteria survive despite thorough treatments. Staphylococcus epidermidis is one of the most common organisms of normal skin flora, and because the skin cannot be sterilised completely, may account for the predominance of this organism in graft infections (Bandyk *et al.* 1984; Bergamini *et al.* 1988; Schmitt *et al.* 1986). It is postulated that mucin production by this organism also facilitates adhesion to the prosthetic vascular grafts (Schmitt *et al.* 1986). Other sources of graft infections include infected lymphatics, aneurysmal sac contents, the gastrointestinal and genitourinary systems, and blood-borne organisms.

Graft contamination is more likely to occur in the early post-operative period as bacterial adhesion is facilitated by absence of a pseudointima internally and incorporation of graft with fibrous tissue externally (Malone *et al.* 1975). Therefore it is important to protect the graft with prophylactic antibiotics in the early post-operative period, which have been shown to reduce the incidence of this serious complication (Ilgenfritz *et al.* 1988).

An infected graft may manifest clinically as fever, leucocytosis, and malaise within days of insertion (early graft infection) or as abdominal pain, abdominal or groin mass, a draining groin sinus, or as a vasculoenteric fistula (O'Hara *et al.* 1986). The discharge from the sinus should be cultured, and appropriate tests such as a sinogram, CT scan of the abdomen, and a gallium or indium labelled-leucocyte scan performed to localise the infection (Mark *et al.* 1985). The presence of a fluid collection or gas around the graft on CT scan or the concentration of indium or gallium around the graft strongly suggests graft infection.

The treatment of infected aortic grafts is difficult and is associated with a high morbidity and mortality. There are two schools of thought regarding management of aortic graft infection: conservative versus radical. The former approach involves placing gentamicin beads in the infected field or adjacent to the graft for 1-2 weeks. This method has been described in small series and isolated case reports in combination with graft excision to lower the risk of aortic stump blowout, and as a conservative method for treating localised groin infections (Bailey *et al.* 1987; Reilly *et al.* 1989). Morris *et al.* (1994) have suggested treating graft infection with prolonged, high dose, local antibiotic irrigation therapy, systemic antibiotic treatment, surgical debridement, and graft conservation. The one year survival rate in their series was 80%, but the series only consisted of 10 patients. However further evaluation of this method is necessary before adopting this conservative approach.

The radical treatment consists of total graft excision, over sewing of the aortic stump, and extra-anatomic bypass (O'Hara *et al.* 1986; Blaisdell *et al.* 1963; Louw, 1963; Conn *et al.* 1970; Trout *et al.* 1984; Yeager *et al.* 1985; Goldstone, 1987). However, this management is technically complex and is associated with an early mortality rate of 24% to

45% (Jamieson *et al.* 1975; Spanos *et al.* 1976; Liekweg *et al.* 1977; Cormier *et al.* 1980; Casali *et al.* 1980; Downs *et al.* 1983; Ricotta *et al.* 1991; Quinones *et al.* 1991). A mortality rate of 17% following graft excision, debridement and in situ replacement was reported by Walker *et al.* (1987). Although a later series from the same unit presented less optimistic results with a mortality rate of 83% in severe graft infections (Jacobs *et al.* 1991). The major causes of death were recurrent sepsis and secondary haemorrhage due to aortic stump blowout. Other problems include prolonged hospital stay (Lorentzen *et al.* 1985, reported a mean of 90 days), multiple operations (1.4 to 2.6), and high amputation rates (Szilagyi *et al.* 1972b; Goldstone *et al.* 1974; Lorentzen *et al.* 1985; O'Hara *et al.* 1986; Quinones *et al.* 1991; Reilly *et al.* 1987). Another technique which has been used with some success in our centre is total graft excision and in situ replacement with a rifampicin bonded prosthesis (Naylor *et al.* 1995). This treatment has also been used in other centres with good early results (Torsello *et al.* 1993; Strachan *et al.* 1991). However the numbers treated so far are small and long term follow-up data is lacking.

(i) Impotence

This is a recognised complication of aortoiliac reconstruction and AAA repair (Harris *et al.* 1965; May *et al.* 1969; Spiro *et al.* 1979; Hallbrook *et al.* 1970; Machleder *et al.* 1975; Flanigan *et al.* 1982; Flanigan *et al.* 1982; Miles *et al.* 1982). The patients complain of failure to ejaculate or retrograde ejaculation with orgasm. The sexual dysfunction is thought to occur as result of ischaemia secondary to diversion of pelvic blood flow and or autonomic nerve injury during aortoiliac dissection (Depalma, 1982). The pre sacral sympathetic nerves responsible for antegrade ejaculation originate from the thoracolumbar sympathetic chain and course over the left anterolateral portion of the infrarenal aorta, the IMA, the distal aorta, and the left common iliac artery. Sabri and Cotton (Sabri *et al.* 1971) and DePalma (1982) have demonstrated that sparing of the para-aortic and superior hypogastric nerve plexuses during aortoiliac reconstruction by careful dissection reduces the incidence of postoperative sexual dysfunction. Preservation of internal iliac artery blood flow also decreases the incidence of impotence following aortoiliac reconstruction (Queral *et al.* 1979).

(ii) Late Complications

(a) Anastomotic Aneurysm

Para-anastomotic aneurysms involving the abdominal aorta are a recognised complication following AAA repair (Gautier *et al.* 1992; Mehigan *et al.* 1985; Mikati *et al.* 1990). The reported incidence of this complication following bypass grafting for AAA or

aortoiliac occlusive disease ranges from 0.2 % to 15 % (Gautier *et al.* 1992; Mehigan *et al.* 1985; Mikati *et al.* 1990). True para-anastomotic aneurysms usually occur after bypass grafting for aneurysmal disease (Curl *et al.* 1992; Edwards *et al.* 1992). Allen *et al.* (1993b) reviewed 31 cases with para-anastomotic aneurysms, and found 6 patients with true aneurysms, all of whom had dilatation after surgery for an AAA. Such aneurysms may result from inadequate resection of the infrarenal aorta at the time of the initial operation. An alternate theory is that true aneurysms are a result of continued degeneration of an inherently abnormal vessel.

False aneurysms may develop as a consequence of defects in the artery, suture or graft. Factors implicated in their development include choice of suture material, prosthesis dilatation, type of anastomosis (end-to-side), severity/progression of atherosclerosis (multilevel disease), vessel versus graft compliance mismatch, and infection (periprosthetic, aortoenteric fistula) (Briggs *et al.* 1983; Gaylis, 1981).

A high index of suspicion is required for early diagnosis of a para-anastomotic aneurysm. The patient may be asymptomatic or present with abdominal/back pain. Most para-anastomotic aneurysms are detected late and therefore are large at the time of diagnosis, with an average size of approximately 7 cm (Allen *et al.* 1993). They may present with rupture, but the prognosis in such cases is poor (Plate *et al.* 1985; Sladen *et al.* 1987). Both CT scanning and ultrasonography are useful for diagnostic purposes, although the latter is operator dependent (Hilton *et al.* 1982; Gooding *et al.* 1981; Turnispeed *et al.* 1982; Mark *et al.* 1982). Elective surgical repair of a para-anastomotic aneurysm is the treatment of choice, as these lesions progressively increase in size and rupture with time (Sladen *et al.* 1987). Operative complications are common and increase in the urgent setting or if other aortic graft complications are present (e.g. aortoenteric fistula, graft infection) (Dennis *et al.* 1986; Curl *et al.* 1992; Plate *et al.* 1985; Treiman *et al.* 1988). The role of routine screening of patients following AAA repair to detect this condition at present remains controversial.

(b) Aortoenteric Fistula

Fistulae between the aorta and the gastrointestinal tract are a dramatic and often lethal complication of aneurysm repair (Busuttil *et al.* 1979; Champion *et al.* 1982; Connolly *et al.* 1981; Henry *et al.* 1978; Reilly *et al.* 1985; O'Hara *et al.* 1986; Peck *et al.* 1992). They occur in 0.55 to 2 % of all patients who undergo aortic reconstruction (Bunt, 1983). The duodenum is the commonest site of the fistula (Reilly *et al.* 1984), although it can involve any part of the small or large bowel. Several factors are thought to play a role in this complication including graft infection (Busuttil *et al.* 1979), suture-line failure with false aneurysm formation (Gaylis, 1981; Treiman *et al.* 1988), and failure to interpose viable tissue between the graft and the gastrointestinal tract. Graft infection may occur as

result of soilage of the prosthetic material via a graft-enteric communication either from a bowel injury at the time of the original operation, or more commonly, as a result of erosion of the bowel by long-term contact with the pulsating prosthetic graft (Bunt, 1983; Kleinman *et al.* 1979).

Gastrointestinal bleeding or unexplained sepsis is the usual presenting feature. A definitive diagnosis of fistula is only possible in a small proportion of patients (Peck *et al.* 1992). Upper GI endoscopy may be helpful in establishing the diagnosis and excluding other causes of haemorrhage such as a duodenal ulcer (Mir-Majdlessi *et al.* 1973; Baker *et al.* 1976; O'Mara *et al.* 1977; Peck *et al.* 1992). Abnormal findings at endoscopy include an extraenteric pulsatile mass, punctate ulceration and or haemorrhage at the distal duodenum and even visualisation of the intraluminal graft. Arteriography, computed tomography, and indium-labelled white cell scan may also be helpful in establishing diagnosis (Peck *et al.* 1992; Kleinman *et al.* 1979; Perdue *et al.* 1980). However, none of the tests are reliable, and early diagnosis requires a high index of suspicion, in any patient with a graft and a gastro-intestinal bleed.

Surgical intervention is associated with a mortality of 33% to 85% in most series (Bunt, 1983; O'Hara *et al.* 1986; Moulton *et al.* 1986; O'Donnell *et al.* 1985). Surgical intervention involves separation of the involved bowel from the aortic prosthesis. Management of graft infection is along the same lines as described previously for infected aortic prosthesis.

(c) Graft Limb Occlusion

Graft thrombosis is a rare problem following aneurysm repair (Bernhard *et al.* 1983; Moore, 1982; Tchirkow *et al.* 1978). Most perioperative graft failures result from technical errors. Intimal flaps and plaque dislodgement at the distal anastomosis are the most common causes for graft failure following aneurysm repair (Moore, 1982). Large, loose, calcified plaques should be removed to prevent dislodgement and graft occlusion, but care must be taken to prevent an intimal flap. In some instances, it is necessary to tack the intima with sutures to prevent this problem. In patients with claudication, angiographic assessment of the outflow vessels must be obtained prior to aneurysm repair to select the appropriate place for distal anastomosis.

Graft thrombosis that occurs hours or days after the operation usually presents as a cold, pulseless leg. The patient should be heparinised and returned promptly to the operating theatre. In the majority of cases, the cause for graft thrombosis can be found and corrected at the distal anastomosis site. The graft limb can then be thrombectomised and flow re-established. Occasionally, poor runoff secondary to occlusion of the superficial femoral artery and extensive disease of the profunda femoris is responsible for graft failure. A femoropopliteal bypass may be necessary to improve flow and long-term

patency under these conditions. If the graft limb cannot be thrombectomised with restoration of good inflow, or if thrombosis occurs in a graft limb that is anastomosed to the iliac artery, the abdomen must be reopened and the cause corrected.

Graft failure that occurs months or years after AAA repair is usually attributable to poor runoff from progression of distal occlusive disease, pseudoaneurysm formation, neointimal hyperplasia, or excessive build-up of graft pseudointima (Moore, 1982). In such cases angiography is mandatory before undertaking reconstruction.

2.13 Inflammatory Aneurysms

Inflammatory AAAs are characterised by a triad of thickened aneurysm wall, extensive perianeurysmal and retroperitoneal fibrosis, and dense adhesions of adjacent abdominal organs(Pennell *et al.* 1985; Crawford *et al.* 1985; Sterpetti *et al.* 1989). Inflammatory AAAs represent 3% to 10% of all abdominal aortic aneurysms (Crawford *et al.* 1985; Sterpetti *et al.* 1989; Nitecki *et al.* 1996), and have a distinct tendency to occur in men. The male to female ratio varies from 30:1 to 6:1 depending on the series (Pennell *et al.* 1985; Sterpetti *et al.* 1989; Stella *et al.* 1993; Gans *et al.* 1993). Inflammatory aneurysms are typically larger and more symptomatic than non-specific AAAs (Walker *et al.* 1972). The triad of abdominal or back pain, weight loss, and an elevated erythrocyte sedimentation rate (ESR) in patients with AAA is highly suggestive of an inflammatory aneurysm (Nitecki *et al.* 1996). Entrapment of the ureters in the retroperitoneal fibrotic process is common and occurs in varying degrees. Stella *et al.* (1993) reported involvement of the ureters in the periaortic mass in 53% of the patients with inflammatory aneurysms as documented by CT scan. Obstructive uropathy affects 10% to 21% of patients with inflammatory AAAs (Pennell *et al.* 1985; Crawford *et al.* 1985; Sterpetti *et al.* 1989; Boontje *et al.* 1990).

Preoperative diagnosis of inflammatory AAAs is the exception and occurs in only 13% to 33% of patients (Pennell *et al.* 1985; Sterpetti *et al.* 1989; Boontje *et al.* 1990; Gans *et al.* 1993). Although its sensitivity is not absolute, the abdominal CT scan is the most reliable radiological study to detect aneurysmal wall thickening ("inflammatory halo") and perianeurysmal soft tissue changes suggestive of an inflammatory AAA (Pennell *et al.* 1985; Crawford *et al.* 1985; Gans *et al.* 1993; Cullenward *et al.* 1986). Most studies report retrospective readings after the inflammatory aneurysm has been discovered operatively.

The optimum treatment of inflammatory AAAs is replacement grafting, which is possible in most cases. However, the periaortic fibrosis may render the dissection hazardous and the identification of the adjacent structures difficult. Such technical difficulties may cause intraoperative complications, such as uncontrollable haemorrhage or damage to the surrounding structures (such as renal vein, duodenum and ureter). The

aneurysm may also be deemed inoperable and the attempted repair abandoned by less experienced surgeons. The operative mortality is therefore greater than that associated with non inflammatory AAAs, and ranges from 3% to 30% (Walker *et al.* 1972; Crawford *et al.* 1985). However, with operative techniques that minimise dissection of the duodenum and ureters, the operative mortality rate approaches that reported in a large review of non inflammatory AAAs, 1.4% to 6.5% (Ernst, 1993). Reports of non operative management with corticosteroids include only case reports or small series of patients deemed inoperable at the time of laparotomy (Clyne *et al.* 1977; Baskerville *et al.* 1983; Hedges *et al.* 1986). In one such study by Baskerille at al., five patients were observed while on oral corticosteroids (Baskerville *et al.* 1983). During the 18 month period of surveillance by abdominal CT scans, one patient underwent emergent operation for signs of rupture. No follow-up longer than 18 months is offered in the remaining patients. Also no controlled clinical trials have evaluated the long-term efficacy of steroids for inflammatory AAAs. Therefore the role of corticosteroids in the management of inflammatory AAAs remains uncertain.

Controversy exists regarding the cause and pathogenesis of inflammatory AAAs. Recent studies suggest that inflammatory aneurysms may represent the extreme end of an inflammatory process responsible for both the inflammatory and non inflammatory AAA (Rose *et al.* 1981; Pennell *et al.* 1985). Emerging data support this theory and suggest a primary inflammatory response to an unknown antigen present in the aortic wall. This response is characterised by infiltration of the aortic wall by macrophages, T lymphocytes, and B lymphocytes that activate proteolytic activity through the production of cytokines (Pasquinelli *et al.* 1993; Rizzo *et al.* 1989; Newman *et al.* 1994b; Newman *et al.* 1994a). This inflammatory process may be accentuated in certain persons with environmental risks (e.g., smoking) or a genetic predisposition. However further studies are required to better characterise these factors and the molecular and cellular mechanisms at play in the pathogenesis of inflammatory AAAs.

2.14 Late Survival and Quality of Life Following AAA Surgery

The long-term results for elective AAA treatment in terms of life expectancy and quality of life compared to the general population have been well documented (DeBakey *et al.* 1984; Szilagyi *et al.* 1966; Hicks *et al.* 1975; Fielding *et al.* 1981). A 5 year survival rate of around 70% has been reported in several large series (Fielding *et al.* 1981; Soreide *et al.* 1982b). Fielding *et al.* (1981) followed up 243 patients and reported an overall 5-year survival of 64.8%; 68.1% in elective cases, 57.1% in ruptured cases, and 66% in the acute cases. The key determinant of late survival after aneurysm repair is coronary heart disease (Hollier *et al.* 1984; Roger *et al.* 1989). Roger *et al.* (1989) found that by 5 years after aneurysm repair 60% have either sustained a myocardial infarction or died. These

dismal results contrast with those for patients with no evident coronary heart disease or prior cardiac bypass grafts, who have a 70% survival at 5 years, a 60% survival at 8 years, and only a 15% risk of a cardiac event (Roger *et al.* 1989).

The quality of life after AAA surgery has been investigated by several authors (Appleberg *et al.* 1980; Treiman *et al.* 1982; van Ramshorst *et al.* 1990; Rohrer *et al.* 1988; Magee *et al.* 1992). Some studies have concluded that patients had a prompt return to their pre-operative life-style in the majority of cases. Rohrer *et al.* (1988) used objective quantifiable methods to show that the quality of life for survivors of ruptured AAA was similar to that following elective aneurysm surgery. These findings were also confirmed by Van Ramshorst *et al.* (1990), who showed that patients surviving operation for ruptured AAA had an equal perception of their quality of life compared to patients undergoing elective AAA surgery. The long-term survival and quality of life documented in patients surviving elective and emergency AAA resection, therefore strongly supports an aggressive approach towards the management of AAAs.

2.15 Summary

In this chapter the historical developments as well as the current status of open aneurysm surgery has been described. Considerable advances have been made in the management of AAAs since the first successful repair undertaken by Charles Dubost in 1951. Although mortality rates for conventional aneurysm repair are commonly below 5%, the procedure remains debilitating and expensive (Breckwoldt *et al.* 1991). Most patients with AAA are elderly and other co-morbid conditions such as cardiac, pulmonary and renal disease. These patients tolerate abdominal operation, aortic clamping and general anaesthesia poorly.

The introduction of a simpler and safer approach for repair of AAA would make it reasonable to take a more aggressive approach to the management of AAAs, and may reduce the mortality from aneurysm rupture and lower the morbidity and mortality rates for elective repair. The aim of this thesis is to investigate whether AAA repair by endovascular techniques is feasible, less invasive and associated with lower complication rates compared with standard open repair. The concept of endovascular AAA repair is discussed further in the next chapter. The aims and scope of this thesis will be described in more detail in *Chapter 4.*

CHAPTER THREE

Endovascular Repair Of AAA

3.1 Historical Perspective

Endovascular treatment of AAA predates open repair, when in 1864 Hewitt Moore (1821-1870), at Middlesex Hospital in London, placed 75 feet of wire (*Figure 3.1*) into an aneurysm in order to stimulate thrombosis (Haeger, 1988). Later in 1879 an Italian physician, Corradi, attempted coagulation by passing an electrical current through a wire inserted into an aneurysm, and this technique was applied widely with sporadic success until the 1950s (Blakemore, 1951). High rupture rates and thrombosis of the outflow vessels led to the era of open aortic surgery, with endoaneurysmorrhaphy via an abdominal or flank approach becoming the accepted standard (Creech, 1966).

There have been many further attempts to simplify the management of patients with AAA to reduce the perioperative morbidity and mortality. Blaisdell and colleagues introduced the concept of bypass and ligation of aneurysm using the extracavitary approach of axillo-bifemoral reconstruction (Blaisdell *et al.* 1965). This technique was abandoned because of continued aneurysm perfusion of several patients with subsequent rupture. This concept was re-examined by Leather and colleagues (1979), who also abandoned this procedure because of poor results. Later sutureless intra-luminal grafts (*Figure 3.2*) were used by some surgeons as part of an open surgical approach, in an attempt to reduce the time required to perform aorta-to-graft anastomoses and hence reduce the aortic clamp time (Oz *et al.* 1989). These grafts are composed of rigid polypropylene rings attached to each end of a Dacron graft. After the abdomen has been opened, the graft is placed directly into the surgically opened aneurysm and secured with a ligating tie around the portion of the vessel that overlies the grooves in the rings (Oz *et al.* 1989; Dureau *et al.* 1978; Albaza *et al.* 1978). An alternative sutureless intraluminal prosthesis uses an elastic end ring, therefore obviating the need for posterior aortic wall dissection and placement of a ligating tie (Matsumae *et al.* 1988). Compared with the standard surgical repair it has been claimed that these permit AAA repair in less time and with less blood loss (Lemole *et al.* 1984; Goddard *et al.* 1985). Reduction in clamp time may minimise time dependent complications including cardiac problems, renal failure and gastrointestinal complications. In addition this grafting technique appeared particularly helpful in the management of suprarenal or ruptured aortic aneurysms, in which speed is important, and in affecting technically difficult anastomoses to friable aortic tissue. However because of the thickness of the support rings there have been problems with proper sizing while maintaining adequate flow and ring displacement. Also as the abdomen must be entered, periaortic dissection performed, and general anaesthesia employed, the overall magnitude and duration of the procedure is not significantly reduced, and these devices are not in common use.

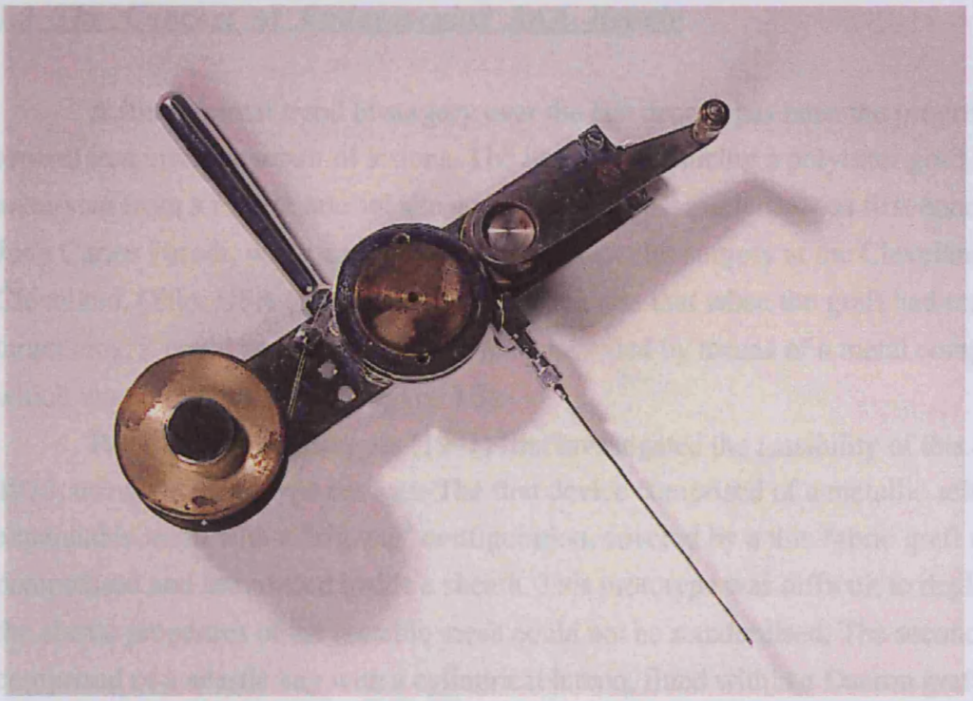


Figure 3.1: *Photograph of the device used for introducing wire into an aneurysm to stimulate thrombosis. This particular device belonged to Mr J.T. Rowlings, Retired General Surgeon, Sheffield Hospitals.*

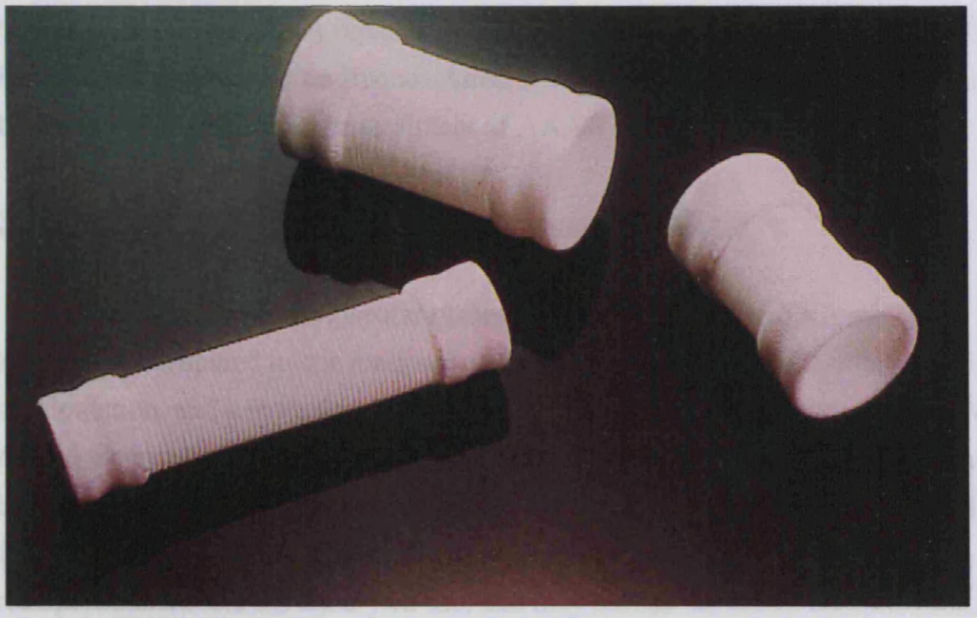


Figure 3.2: *A photograph of the sutureless intraluminal prosthesis (Bard Ltd., Crawley, West Sussex, UK), which is placed directly into the surgically opened aneurysm and secured with a ligating tie.*

3.2 The Concept of Endovascular AAA Repair

A fundamental trend in surgery over the last decade has been the progression toward less invasive repair of lesions. The idea of introducing a polyester graft into the aneurysm from a remote arterial site under fluoroscopic guidance was first conceived by Juan Carlos Parodi, while he was a resident in vascular surgery at the Cleveland Clinic, Cleveland, Ohio, USA (Parodi, 1997). The idea was that when the graft had reached the target area, it could be anchored and both ends sealed by means of a metal component, which would replace suture (*Figure 3.3*).

Parodi and his colleagues (1991) first investigated the feasibility of this concept in 1976, using two prototype devices. The first device comprised of a metallic self-expandable mesh with a "zig-zag" configuration, covered by a thin fabric graft that was compressed and introduced inside a sheath. This prototype was difficult to deploy because the elastic properties of the metallic mesh could not be standardised. The second device comprised of a silastic bag with a cylindrical lumen, fitted within a Dacron graft. This bag was introduced into prosthetic AAAs in dogs, and then distended by the injection of silicone into the bag. However, this method was associated with prompt thrombosis of the aorta in all experimental animals. The project was abandoned at the time due to the disappointing initial results.

Parodi and colleagues re-initiated their project in 1988 when balloon-expandable stents became available. After evaluating the technique in animal experiments, the first human endovascular AAA repair was performed successfully on September 1990, at the Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina. This marked the beginning of a new era in the treatment of AAAs.

3.3 Possible Advantages of Endovascular Repair

Transfemoral endovascular placement of a graft to treat AAA may offer 2 principal advantages compared to conventional aneurysm repair: the absence of intra-peritoneal manipulation, and a reduction in the aortic occlusion time. Avoidance of a laparotomy may reduce the incidence of post-operative ileus and abdominal adhesions. Aorto-enteric fistula is an unusual but recognised complication of reconstructive aortic surgery (O'Hara *et al.* 1986; Reilly *et al.* 1984). Endoluminal graft placement avoids incision of the retroperitoneum and the aneurysm sac, and may reduce the above complication. Obviation of periaortic dissection should also reduce accidental injury to the bowel and ureters (Goldstone, 1991) and eliminate the incidence of surgically induced impotence (Weinstein *et al.* 1975; Depalma, 1982). The risk of deep venous thrombosis and pulmonary embolism may be reduced due to the avoidance of prolonged bed rest and retroperitoneal

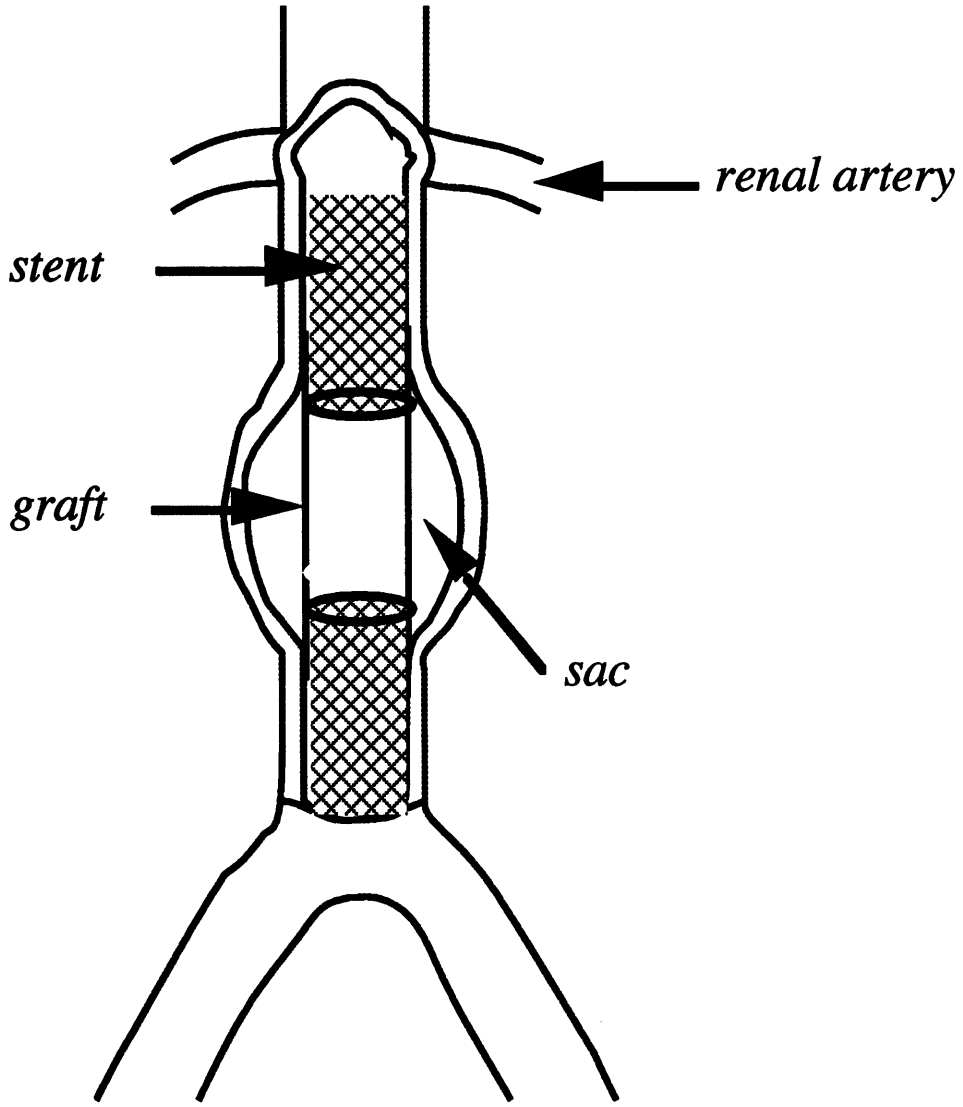


Figure 3.3: *Diagrammatic representation of a 'Parodi' graft-stent combination placed within the infra-renal aorta to exclude the aneurysm sac from the circulation. In this particular design, the graft is composed of Dacron and is anchored at either end by a balloon expandable Palmaz stent. (After Parodi et al.* 1991)

dissection in the predominantly geriatric patient population (Payne *et al.* 1985). Use of a much smaller incision should reduce the post-operative analgesia requirements and allow earlier mobility.

During endovascular repair, the aorta is only occluded during stent deployment, which leads to a "clamp" time of less than 5 minutes. Aortic cross-clamping is associated with an abrupt rise in left ventricular end diastolic pressure, which may be exaggerated in some patients who exhibit cardiac dysrhythmias and sub-endocardial ischaemia (Smith, 1992). Reduction in the duration of aortic cross-clamping may therefore decrease 'clamp'-related cardiac ischaemic events. Similarly, prolonged aortic clamping and subsequent reperfusion, results in the generation of oxygen free radicals, which have been implicated in the genesis of multiorgan failure following AAA repair (Murphy *et al.* 1992). It is tempting to hypothesise that by utilising endovascular repair to limit the duration of aortic occlusion, the extent of the ischaemia-reperfusion syndrome would be minimised.

Endovascular repair can potentially be performed under local anaesthesia. As well as reducing morbidity and mortality rates, endovascular repair may result in less hospitalisation and a shorter convalescent period after discharge. This may reduce the overall cost of aortic aneurysm surgery.

3.4 Technology of Endovascular Graft Placement: Vascular Stents

As mentioned before, a critical element of the endovascular prosthesis is the stent. For a graft to be inserted from a remote site, it must be folded and compressed into a small delivery system. In its collapsed state the graft cannot function as a conduit through the aorta. Endovascular graft placement has been made possible by advances in stent technology. The stents can be used to open the graft and create a haemostatic seal with the native blood vessel.

Although repair of injured arteries with tubular conduits was described by Abbe (1894) and Blakemore (1942), Dotter (1969) was the first to describe the insertion of an endoluminal stent from a remote location in 1969. Dotter's coilsprings were designed to support recently dilated arteries and prevent rapid stenosis. Early trials were performed by insertion into canine popliteal arteries. In these studies the device showed a tendency to thrombosis.

Technological advances in the 1980's prompted further research into use of stents, when Maass *et al.* (1982;1983; and 1984) started experimenting with self expanding spring coils. In the past decade several stents designs have been developed and tried in animal experiments (Dotter *et al.* 1983; Cragg *et al.* 1983; Wright *et al.* 1985; Palmaz *et al.* 1985; Palmaz *et al.* 1986; Rousseau *et al.* 1987; Strecker *et al.* 1987). There are, in general, three types of intravascular stents. *Thermal memory stents* (e.g. Cragg EndoPro

System 1, Mintec, Freeport, Grand Bahamas, Bahamas; -*Figure 3.4*) are composed of Nitinol, an alloy of nickel and titanium. They change shape when exposed to a warm environment (such as blood) to adopt a configuration of predetermined shape. Spring loaded, or *self expanding stents* [e.g. the Gianturco (*Figure 3.5*); Cook inc., Bloomington, IN, USA or the Wall stent; Schneider Inc., Mineapolis, MN, USA] are generally made from stainless steel wire. They are pre-loaded into a sheath, and are deployed into the target vessels by retracting the sheath (*Figure 3.6*). Plastic or *balloon expandable stents* [e.g. the Palmaz stent (*Figure 3.7*); Johnson and Johnson Interventional Systems, Warren, NJ, USA] are constructed of a malleable metal such as annealed stainless steel. They are expanded beyond their elastic limit by a coaxial balloon. Desirable characteristics of stents relate to their deliverability, versatility and biocompatibility. Specifically, a biocompatible stent is non-thrombogenic, promotes rapid endothelialisation, and discourages myointimal hyperplasia. The stent which we have used in our animal work and also employed in some of the clinical work is the Palmaz stent. Histological studies of the Palmaz stent in canines have demonstrated that immediately after implantation, the electropositive stent is covered by fibrin and thrombus. At 1 week the fibrin is colonised with immature endothelial cells. From 3 to 8 weeks, myofibroblasts and proliferating fibroblasts dominate, followed by regression of the matrix over the next 24 weeks. By 32 weeks the stent is covered by a thin neointima (Schatz *et al.* 1987).

Until the conception of endovascular AAA repair, use of intraluminal vascular stents was restricted to occlusive disease. With percutaneous transluminal angioplasty (PTA) alone, a number of problems were encountered including abrupt closure, dissection, and difficulty in treating heavily calcified lesions and total occlusions (Potkin *et al.* 1988). Intraluminal stents have been used to improve the results obtained with PTA alone. Stents have been used to treat occlusive disease in various arteries including the aortoiliac segment (Palmaz *et al.* 1992), renal arteries (Bacharach *et al.* 1995), carotid artery (Diethrich *et al.* 1996), and coronary arteries (Puel *et al.* 1987b).

3.5 Experimental Evaluation of Endovascular AAA Repair: Animal Studies

Before application of the technique in humans, endovascular AAA repair was extensively evaluated using several stent-graft designs in animal models. Balko and colleagues (1986) were the first to demonstrate that AAAs could be treated by transfemoral placement of an intraluminal prosthesis. In three sheep, artificial aneurysms were created by suturing a Dacron patch to a long aortotomy, starting from 1 cm below the renal arteries and ending 1 cm above the aortic bifurcation, after ligating the bleeding lumbar arteries. The aneurysms were successfully excluded from the arterial circulation using a polyurethane graft with a Nitinol or stainless steel frame providing attachment to the aortic wall. The graft was inserted into the aorta from the femoral artery via a 15F catheter. Graft

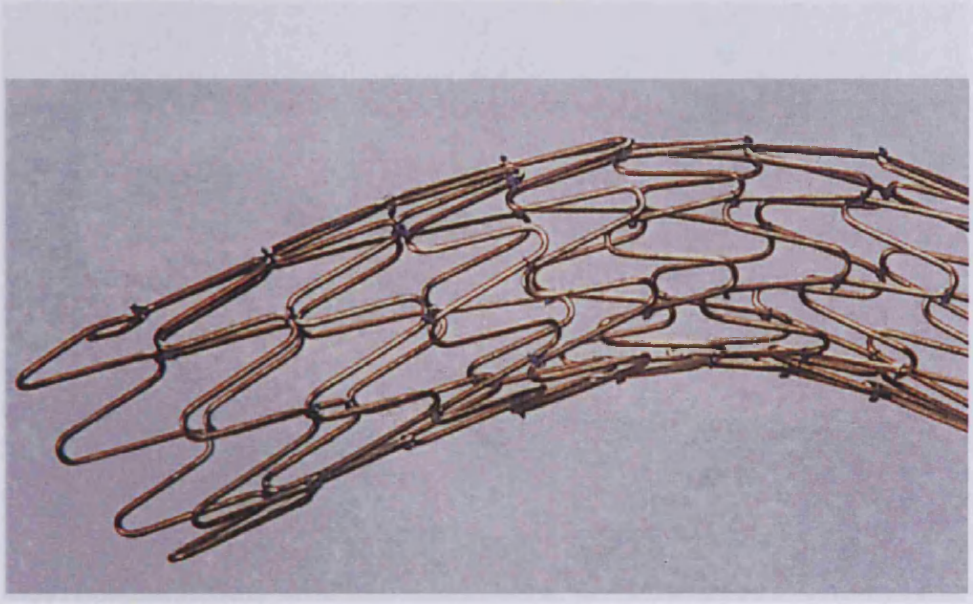


Figure 3.4: *The Cragg Endo Pro System (Mintec, Freeport, Grand Bahamas, Bahamas); an example of a thermal memory stent constructed from Nitinol.*

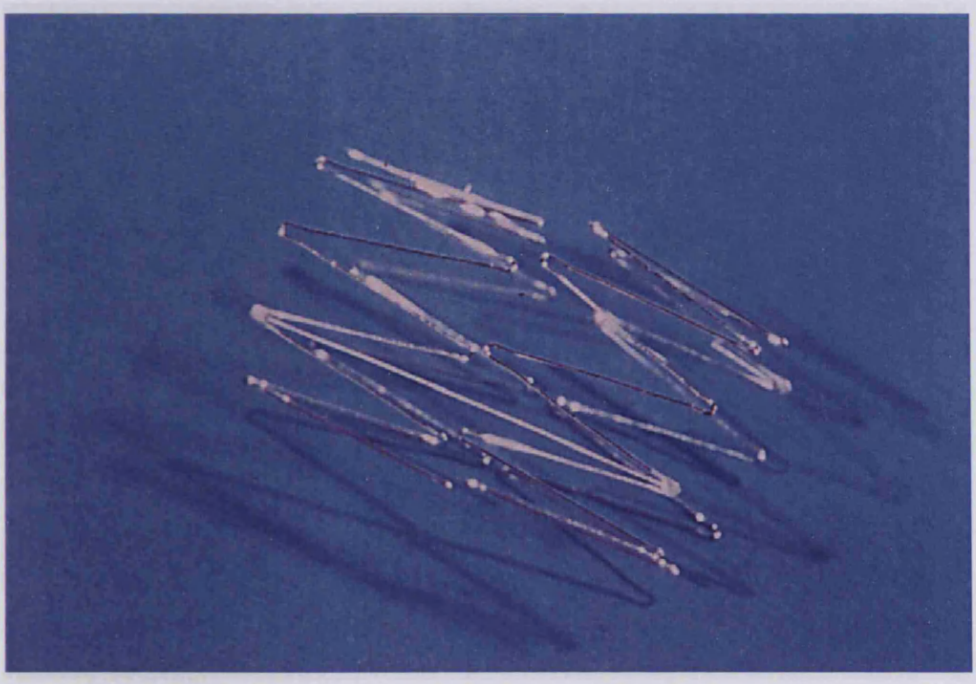


Figure 3.5: *The Gianturco stent; a self expanding stent made from stainless steel.*

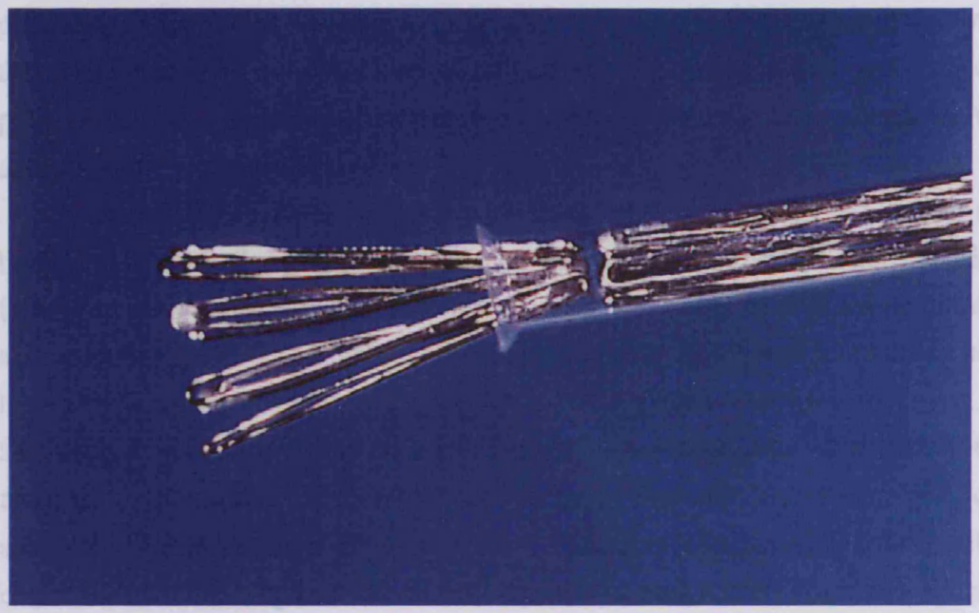


Figure 3.6: *A Photograph illustrating the self expansion of the Gianturco stent as the sheath is withdrawn.*

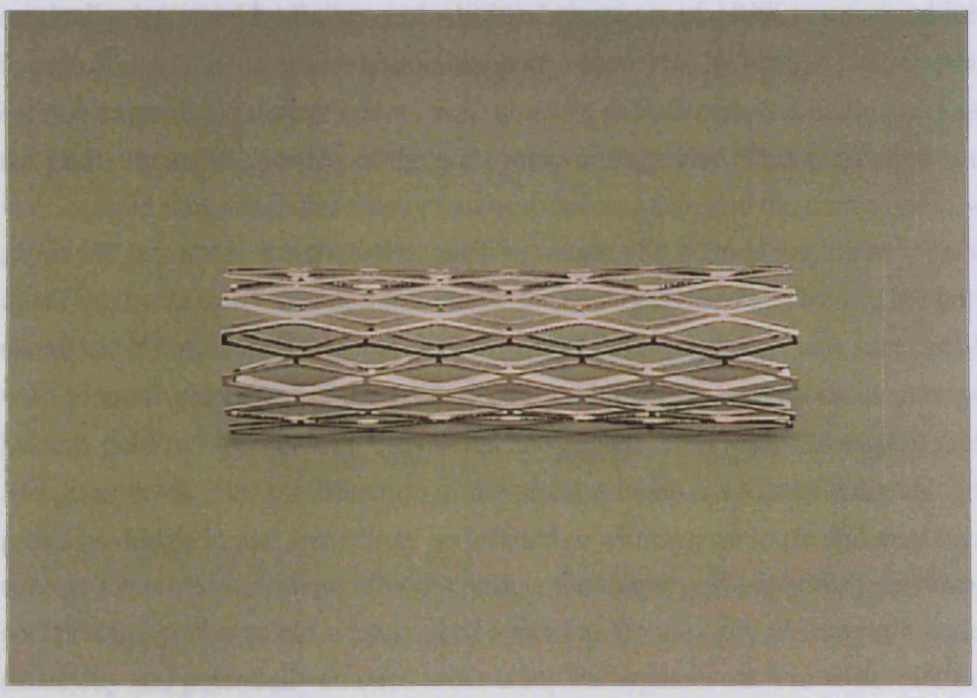


Figure 3.7: *The Palmaz stent; a balloon expandable stent made from annealed stainless steel.*

placement was satisfactory in all cases and no acute complications were encountered. A similar methodological approach was adopted by Lawrence (1987), who used multiple Gianturco stents covered with a Dacron tube graft to form a long expandable intraluminal prosthesis. This device was inserted transfemorally into normal canine abdominal and thoracic aortae, with excellent immediate patency. No complications occurred following placement of an abdominal prosthesis but two out of three thoracic procedures were complicated by aortic perforations.

One of the concerns with using intraluminal devices is the occlusion of the side branches, in particular the renal arteries, covered by the endoluminal graft. Mirich *et al.* (1989) reported treatment of experimental aortic aneurysms in dogs using Gianturco wire stents that had been covered by a porous nylon graft in an attempt to maintain patency of the aortic branches covered by a graft. Grafts were placed across the aneurysm using fluoroscopic guidance, and in one dog, the graft was placed over the orifice of the left renal artery. Animals were then followed for up to 7 months. Incomplete graft expansion and cephalic migration occurred in one dog, leading to bilateral renal artery occlusion and death. In the remaining animals, the aneurysm was successfully excluded, no luminal narrowing occurred, no graft migration was seen, and renal and lumbar arteries in the area of the graft appeared to be patent on follow-up angiograms. However, histological evidence of renal ischaemia was seen in the kidney that was covered by the graft.

The introduction of balloon expandable stents led to modification of the technique originally described by Balko *et al.* (1986). Laborde *et al.* (1992) performed intraluminal bypass of a prosthetic canine abdominal aortic aneurysm by using a Dacron graft with a balloon expandable stent (*Palmaz stent*) attached to both ends (cranially and caudally) of the graft, the middle portion of the graft being unsupported. This graft-stent combination was inserted transfemorally through an introducer sheath and the cranial stent was expanded just above the aneurysm neck by means of a balloon angioplasty catheter. The distal stent was then expanded just below the aneurysm sac and fixed to the aortic wall just above the bifurcation. Technical deployment of the bypass graft was successful in all cases with accurate placement of the graft-stent combination. In several cases, however, the Dacron graft twisted between the cranial and caudal stents with subsequent graft stenosis and thrombosis. This modification of the prosthesis did have several advantages over the previous design in that stents may be inflated to a known pressure and may be able to capture the aortic wall more effectively than the longer self-expanding prosthesis. In addition the graft was not supported by a stent in the majority of its length which increased flexibility and potentially enabled more complex bypasses such as aorto-bifemoral grafts to be performed.

Later, Parodi *et al.* (1991) developed an endoluminal graft comprising a specifically designed thin walled Dacron graft sewn to a Palmaz stent. The graft partially overlapped the stents, so that stent expansion pressed the graft against the aortic wall,

creating an impermeable seal (*Figure 3.3*). This graft-stent combination was mounted coaxially on a balloon angioplasty catheter and deployed into the aorta through a sheath with a haemostatic valve, which was introduced via a femoral arteriotomy. This device was experimentally tested in a canine prosthetic aneurysm model. Arteriography after graft placement showed successful graft exclusion and flow through the graft lumen. Gross examination of these grafts at 6 months showed good patency and demonstrated thrombus in the space between the graft and the aneurysm. Scanning electron microscopy of the inner surface of the graft revealed endothelialisation of the stent and the portion of the graft in direct contact with the aortic wall. In contrast, the portion of the graft in contact with the thrombus within the aneurysm was not endothelialised and was covered with a thin layer of fibrin clot.

Initial feasibility studies concentrated mainly on tube (aorto-aortic) endoluminal grafts. Chuter *et al.* (1993) were the first to pioneer the transfemoral introduction of a bifurcated graft. Their graft comprised a thin walled woven polyester with 2 longitudinal marker lines allowing axial orientation during insertion. A self expanding stent (Gianturco-Z-stent) was used for graft attachment. The proximal orifice of the graft was sutured to small coils on alternate limbs of the stent. Bifurcated grafts were inserted in 8 dogs, 4 with distal stents and 4 without. The grafts were inserted via a femoral arteriotomy and a contra-lateral femoral arteriotomy was also required for deployment of the second graft limb. All were inserted successfully with good patency into the iliac arteries. There were no angiographic signs of perigraft leaks in grafts with or without a distal stent. The accuracy of graft placement was not assessed but this study demonstrate the feasibility of a bifurcated system and extended the application of endoluminal aneurysm bypass.

3.6 The Initial Clinical Experience

A mentioned before, Parodi *et al.* (1991) were the first to report successful exclusion of AAAs by using an endoluminal technique in humans in 1991. This represented a major achievement and Juan Parodi is now regarded as the "creator' of endovascular AAA repair (J Endovasc Surg Editorial, 1997). It took over a decade from conceptualisation of the endografting principal, to the actual patient application of this technique (Parodi, 1997). Soon after Parodi reported his early work (Parodi *et al.* 1991), other researchers rapidly initiated investigative efforts towards evaluating this technique not only in high risk patients but anyone with AAA who could be treated with this exciting new technology. Several types of prosthesis (aorto-aortic, bifurcated, and aorto-uni-iliac) have been evaluated and early experience from several centres world-wide has been published (Parodi, 1995; Chuter *et al.* 1997; Moore *et al.* 1996; Blum *et al.* 1997; May *et al.* 1995b; Dereume *et al.* 1997).

The Parodi System of Endovascular Grafting

The original Parodi device consisted of a Palmaz balloon expandable stent (4.6 mm in diameter and 3.5 cm in length) and a specially designed, thin walled, knitted Dacron graft (Barone Industries, Buenos Aires, Argentina) (Parodi *et al.* 1991). The graft was sutured to the stent in such a way to overlap two thirds of the length of the stent so that on stent expansion the graft was pressed against the aortic wall, creating a watertight seal. The graft stent combination was mounted on a balloon catheter consisting of a 9 French, polyethylene shaft and one or two polyethylene valvuloplasty balloons (3.5 cm long and either 16, 25 or 30 mm in diameter). This device was introduced transfemorally over a 0.038 inch super stiff guidewire, via a 21 French Teflon sheath, 45 cm in length with a haemostatic valve. Once at the level of the proximal neck, the sheath was withdrawn and the cephalic balloon inflated. The balloon was kept inflated under low pressure to expand the folded graft. The catheter was then moved caudally, where the second balloon was inflated, deploying the distal stent to anchor the graft at the aortic bifurcation.

Based on the initial clinical experience, Parodi made a number of modifications to the above device (Parodi, 1995). The graft was subsequently sutured to the stents overlapping half of the length of the stent. The distal stent was deployed separately after anchoring the graft with a single proximal stent and distending it along the entire length. Also the Teflon sheath size was reduced to 18 French.

During the period September 1990 to June 1995, Parodi treated 88 patients (66M: 12F) with AAAs using endovascular grafts (Parodi *et al.* 1997). In 8 patients, a proximal stent alone was used. However some of these patients were found to have persistent reflux distally into the aneurysm on follow-up. In view of this, subsequent procedures were undertaken using proximal and distal stents. Out of the 88 patients, 45 had an aortoaortic graft reconstruction, 38 had an aortoiliac stent-graft, 2 had an aorto-bi-iliac-graft and 3 patients had a thoracic stent graft. The tapered aortoiliac graft was used to treat patients with insufficient distal aortic cuff, aortoiliac aneurysms or associated iliac aneurysms. In these patients the contralateral common iliac artery was occluded with a detachable balloon and a femorofemoral bypass was performed to complete the revascularisation. Initial success was obtained in 84% of aortoaortic implantations and in 75% of aortoiliac procedures. Patients with successful procedures recovered rapidly, had breakfast the next morning, and walked within 24-48 hours after the procedure. Of the 88 patients, 18 (2%) were considered initial failures. Microembolisation was encountered in 3 cases, two of whom died of multiorgan failure and one died suddenly 2 days following the procedure. In the latter patient post-mortem examination revealed intestinal ischaemia and renal infarcts. Perigraft leaks were noted on follow-up in 5 patients (3 proximal, 2 distal). Two of the patients with proximal leaks have subsequently died, one from cardiac insufficiency and the other from a ruptured aneurysm. Other complications included groin haematoma

(2), injury to the external iliac artery (1) and lower limb embolisation (1). Patients with successful procedures were discharged 3 or 4 days following the operation.

Devices Evaluated in Our Centre

The initial experience in Leicester has involved the use of 3 devices: the EVT tube graft, the aorto-uni-iliac system combined with a femorofemoral crossover graft, and the Mintec bifurcated system. A brief description of the EVT and Mintec system is given below. The aorto-uni-iliac system which I developed in Leicester as part of the work for this thesis, will be discussed in detail in Chapter 8.

The EndoVascular Technologies' (EVT) Device

The concept for this device was patented by Lazarus in 1988 (1988 and 1992). It comprises a woven polyester graft with metal attachment systems affixed to both ends (*Figure 3.8*). The attachment system consists of a self-expanding cylindrical metal frame with a series of angled metal attachment hooks. The attachment systems are each packed within metal capsules which are attached to the catheter delivery system. A balloon angioplasty catheter is incorporated into this co-axial system, and is used to fix the hooks into the aortic wall (*Figure 3.9* and *Figure 3.10*). This delivery system is introduced over a guide wire, through a specially designed 27 French sheath. The sheath is designed to be inserted via a femoral arteriotomy over a guide wire, and advanced into the lower portion of the abdominal aorta. Accurate positioning of the endoluminal graft is performed under digital fluoroscopic control, and is further aided by the use of a specially designed proprietary marker board (*Figure 3.9*). Patient selection and graft sizing are based on pre-operative contrast enhanced computed tomography (CT) and digital subtraction angiography with a marker catheter. However, only patients with a proximal aortic cuff of 15 mm or greater, distal aortic cuff of 10 mm or greater and an iliac artery diameter of 7.7 mm or greater are suitable for treatment with this device (Moore *et al.* 1996).

The MinTec System (Stentor)

This is a flexible self-expanding prosthesis constructed from Nitinol monofilament wire (nickel-titanium shape memory alloy) which is annealed into a tubular zig-zag configuration (Blum *et al.* 1996). The stent frame is covered with a low permeability, woven polyester fabric. The device comes in two designs, a bifurcated and a tube graft (*Figure 3.11*). The leading and trailing ends of the stent frame are tagged by a platinum marker which allows for proper positioning of the implant. Fixation hooks placed outside

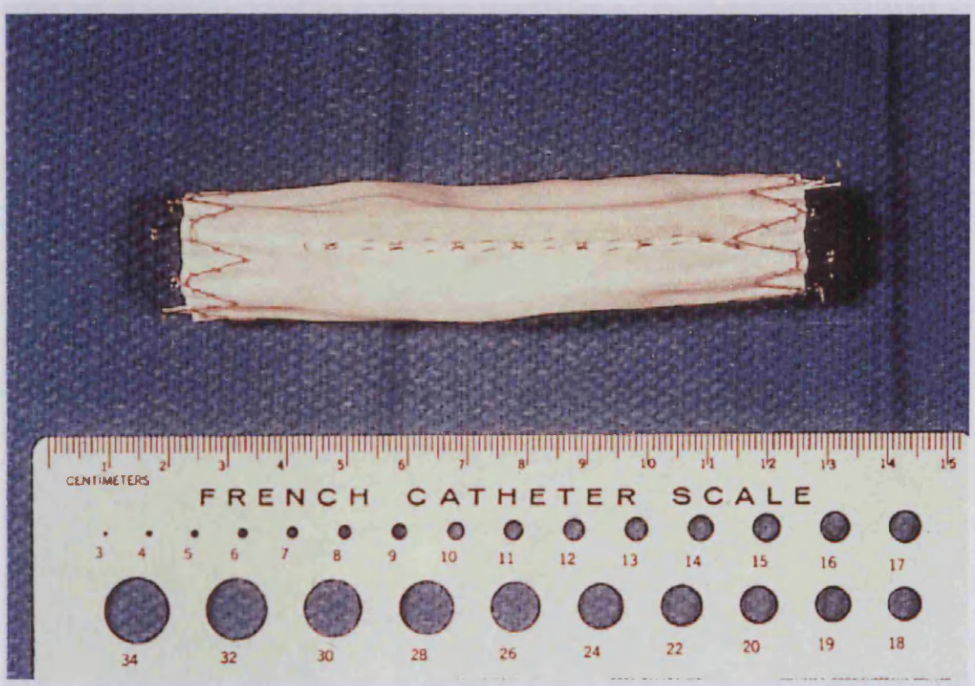


Figure 3.8: *A photograph of the EVT tube graft, showing the fixation pins which are designed to be driven into the aortic wall during graft deployment.*

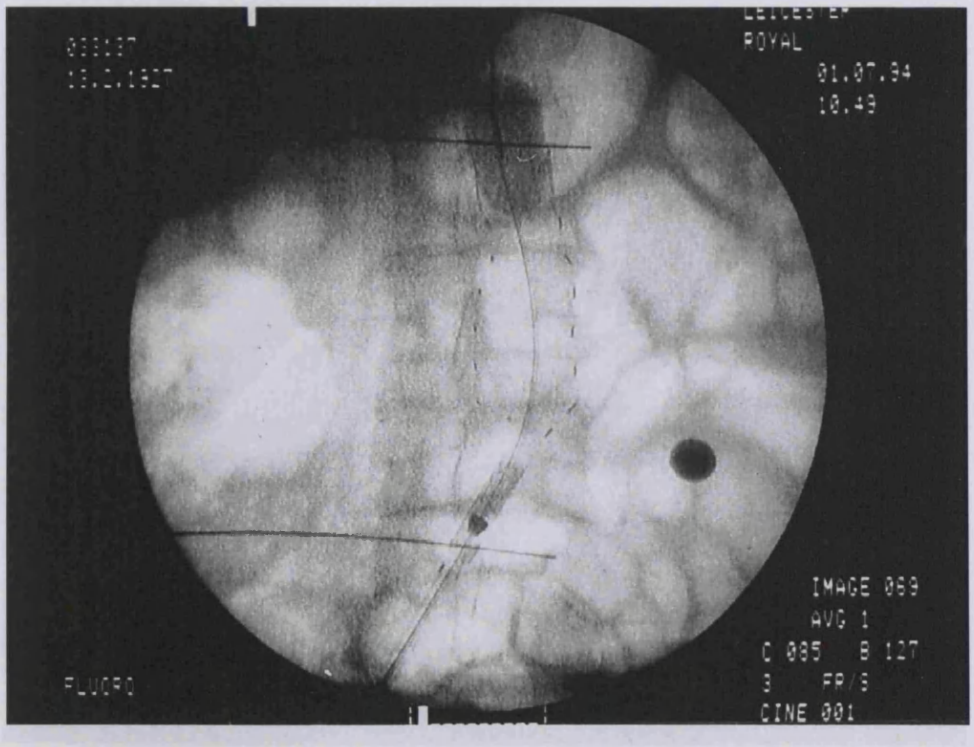


Figure 3.9: *Radiographic image showing the deployment of the proximal attachment system, aided by balloon inflation. Note the radio-opaque markers positioned at the level of proximal and distal aortic cuffs.*

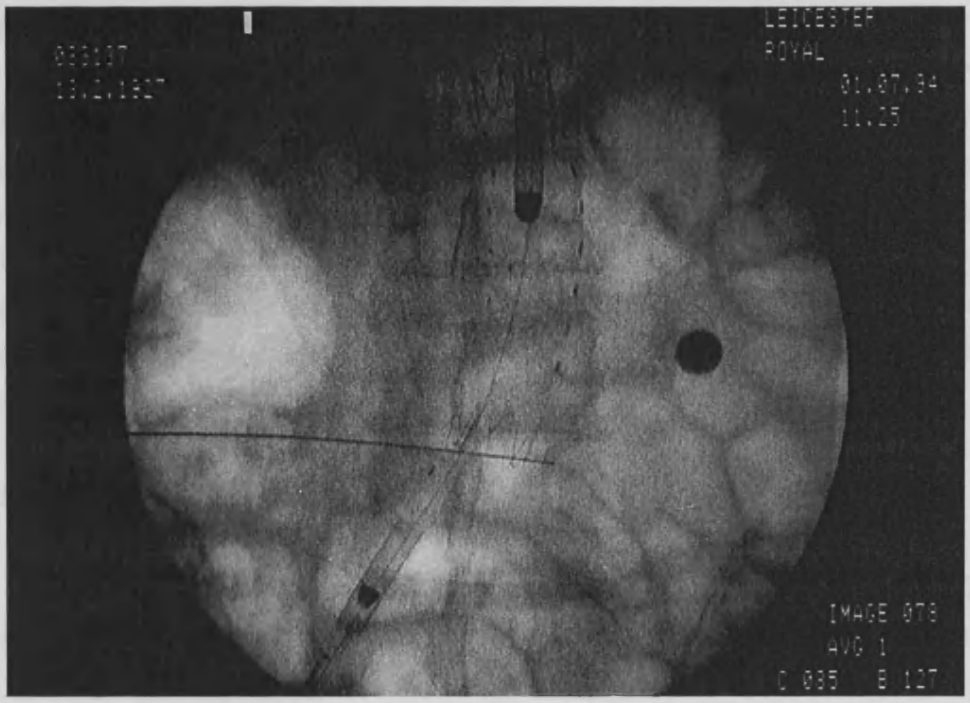


Figure 3.10: *Deployment catheter being withdrawn after deployment of the tube graft.*

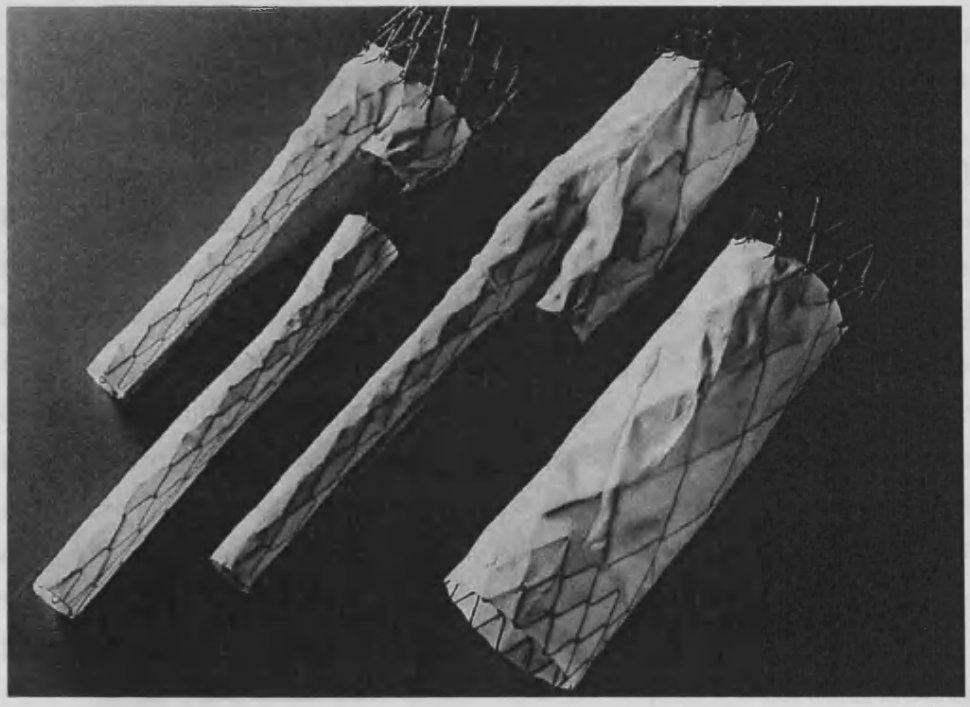


Figure 3.11: *A photograph of the Mintec device (Stentor™ straight and bifurcated systems), consisting of a Nitinol frame covered with a polyester graft material.*

the fabric covered section of the device allow the leading part of the stent to anchor into the proximal neck.

The bifurcated device comprises of two components, the aortic section with a single limb and a second limb, which are introduced separately and coupled in vivo. The juncture into which the two sections are connected is tagged by platinum markers to aid correct coupling. These devices are introduced through an 18 French delivery catheter that is withdrawn to expose the Nitinol frame which expands at blood temperature. A balloon on the distal end of the delivery catheter permits the aorta to be obstructed above the renal arteries during deployment, and for subsequent modelling of the proximal section of the stent frame into the aortic neck.

Initial Clinical Results

Over 500 endoluminal AAA repairs have been performed world-wide. *Table 6* summaries the early results from some of the major centres evaluating this technique.

3.7 Discussion

Since Juan Parodi's initial successful clinical experience, endovascular grafting for AAAs has become a technique of great interest to vascular surgeons and interventional radiologists. Although this technique appears very attractive to both surgeons and patients, it feasibility, safety, effectiveness and durability must be scientifically proved before it can be recommended for widespread use.

Parodi (1995), Chuter *et al.* (1997), Moore *et al.* (1996), Blum *et al.* (1997), and Dereume *et al.* (1997) have reported that endovascular repair of aortic aneurysms is feasible, reasonably safe, and effective (*Table 6*). However, a number of complications have been encountered. Parodi (1995) recorded 10 treatment failures among 50 patients, including 4 procedure related deaths. Three of these deaths were as a consequence of embolisation during insertion of the endovascular graft. On the other hand, using newer techniques for passing the catheter over a wire, Moore *et al.* reported no operative deaths and only a 4% incidence of minor emboli in the EVT North American phase 1 trial (Moore *et al.* 1996). More recently Blum *et al.* have reported similar results, with a 10% rate of major or minor complications, including one death. Five of the 154 patients had macroembolic or microembolic events (Blum *et al.* 1997).

Leaks due to incomplete sealing between the graft and the aorta at either end of the graft have required late conversions to open procedures in several centres (Moore *et al.* 1996; Parodi, 1995; Lunec *et al.* 1985). Late explantation of the graft has been necessary in approximately 6 per cent of patients in whom leaks have persisted, causing either the AAA to enlarge or the graft to migrate (Matsumura *et al.* 1997). Another cause for concern

Table 6: *Summary of the early results obtained with the principal devices under evaluation*

	Parodi 1995	Chuter 1997	Moore et al 1996	Blum et al 1997	Dereume et al 1997
aorto-aortic graft	36*	0	46	21	19
aortoiliac and fem-fem bypass	14	0	0	0	15
bifurcated graft	0	52	0	133	3
Total attempted	50	52	46	154	37
Early conversion (<30 day)	10	3	7	20	2
Late conversion (>30 day)	1	10	2	0	
Overall	11	13	9	20	
Median AAA diameter (range)-cm	-	-	-	-	5.8
Median age (range)-years	73 (57-87)	-	71.6 (54-84)	68 (41-90)	73
Complications:					
Myocardial infarction	1	1	1 (2)		1
Pulmonary complications	1				2
Groin haematoma	2			1	2
Injury to femoral or iliac artery	1	1	8 (17)	2	2
microembolisation	3 (all died)		2 (4)	3	2
renal failure		1		1	2
Graft thrombosis		5 (converted)		2	1
Colonic ischaemia	1				1
Perigraft leaks:					
Early (<30 days)	5	5	17 (9 resolved)	17	13
Late (>30 days)	3	7		7**	
Proximal	3			5	
Distal	5			4	
Median hospital stay (range)-days	-	-	3.8 (1-13)	-	-
Early mortality (<30 day)	4	3	0	1	1
Late mortality (>30 day)	1	0	0	0	1
Overall	5	3	0	1	2

** 8 patients were treated with proximal stent only*

*** 4 leaks due to tear in graft fabric and 3 due to reperfusion of the aneurysm through lumbar arteries.*

in the study reported by Blum *et al.* (1997) were the 8 leaks resulting from tears in the polyester fabric covering the stents, suggesting that thin walled grafts may not be durable.

At present follow-up in all reported series has been relatively short, averaging only 13 months in the study by Blum *et al.* (1997), 14 months in the study by Moore *et al.* (1996), and 17 months in Parodi's study (1995), whereas follow-up for conventional repair of AAA extends well above 10 years (Ernst, 1993). Therefore, before endovascular AAA repair is adopted as an effective alternative to conventional aortic reconstruction, longer term follow up is necessary.

3.8 Summary

In this chapter the development of endovascular AAA repair and the initial clinical results from several centres have been described. The endovascular treatment of AAAs by endovascular techniques is clearly an exciting prospect which promises much for the future. However several limitations have been encountered, including device size, design, and lack of anatomical suitability. Some of these problems will be further addressed in this thesis.

CHAPTER FOUR

Scope And Design Of The Thesis

Endovascular AAA repair is a revolutionary "minimally invasive technique" that enables aortic aneurysms to be treated without the need for major abdominal surgery. In the previous chapter the preliminary clinical results have been described which have demonstrated that this technique is feasible. On the basis of these results it has been suggested that this technique may have the potential to dramatically reduce the morbidity and mortality associated with conventional surgery and allow medically unfit patients to be treated.

This thesis has evaluated several aspects of endovascular aneurysm repair which are presented in the next five chapters. The scope and design of the thesis is briefly outline below. The methods used to achieve these aims will be described in more detail in the relevant chapters.

4.1 Retrospective Review of Conventional AAA Surgery in Leicester

In chapter 5, I have presented two retrospective studies to assess whether there is a need for this technique in a leading UK vascular surgery centre. The first study looks at the overall vascular workload of AAAs in Leicester over a 13 year period from 1979 to 1991, by reviewing the hospital activity analysis (HAA) data. From this data, information regarding patients age, sex, presentation (elective or emergency), length of hospital stay, discharge and mortality was collected. The second study involved a more detailed review of patients who underwent AAA repair at Leicester Royal Infirmary NHS Trust between January 1981 and December 1993. The case notes of all patients were retrieved and a detailed proforma was completed. Data was collated on presentation, diagnosis, treatment, complications and survival. Statistical analysis was performed after seeking advice from a medical statistician. The aim of these studies was to answer the following questions:

(i) What is the current AAA practice in terms of workload, mortality, complications and risk factors?

(ii) Could endovascular techniques improve on this by offering an alternative for elderly and high risk patients?

4.2 Experimental Animal Work

In chapter 6, I have presented the experimental animal work which was undertaken while I was employed as a research fellow in the Department of Surgery.

The early experimental work described in chapter 3 demonstrated the feasibility of

aortic aneurysm repair by transfemoral insertion of a stented graft. However several important questions remain unanswered which I have investigated in this thesis. Firstly, the necessity for anchoring the distal end of the graft with a second stent was not known when this work was commenced. Some of the reported studies had used a distal stent and others had left the distal end unstented at the bifurcation. At that time we thought that it was possible that reversed arterial flow into the aneurysm sac might occur if the distal end of the graft was not stented, which might lead to continued aneurysm expansion.

Secondly, the majority of AAAs begin just below the renal arteries. The effects of partially or totally covering the renal ostia with the proximal stent are unknown. It has been suggested that covering the origins of the renal arteries will not impede renal artery blood flow because of the meshed nature of the stent. However, this question needed further investigation.

Thirdly, the inferior mesenteric and lumbar arteries, which are branches of the aorta arising from the aneurysm sac, often remain patent. During surgical repair of an aneurysm, these vessels backbleed into the opened aneurysm sac and are controlled by suturing the ostia. In the animal models described in chapter 3, a section of the infra-renal aorta was excised and replaced with a prosthetic graft whose shape simulated an aortic aneurysm. Several weeks after implantation, the stented graft was inserted into the aneurysm model. This prosthetic aneurysm model does not have mesenteric or lumbar arteries arising from the sac and is therefore not totally analogous to the human situation. Therefore, it is possible that in the human situation, continued backbleeding from the mesenteric and lumbar arteries might occur into the sac which might lead to continued expansion and possible rupture of the aneurysm. Alternatively it is possible that the mesenteric and lumbar arteries would thrombose shortly after insertion of a stented graft thus preventing continued backbleeding.

The experimental animal work was divided into 3 separate studies. The first experiment was designed to investigate the following aspects:

(i) To design an aneurysm model which allows lumbar back-bleeding to be investigated.
(ii) To assess whether a single proximal stent technique allows adequate aneurysm exclusion.
(iii) To assess whether the infra-renal aortic stent graft has any deleterious effects on renal function.
(iv) To assess whether femoral artery blood flow is affected by the endoluminal graft.

The second experiment was performed to assess:

(i) Whether use of a proximal and a distal anchoring stent would completely exclude the aneurysm sac.

(ii) If reflux of blood from around the distal end of the graft was abolished, whether lumbar artery back-bleeding would occur into the aneurysm sac and prevent sac thrombosis.

The third experiment was performed to assess:

(i) The effect of stent deployment across the renal arteries on renal function.
(ii) To examine the microscopic incorporation and long term effects of the stents on the renal artery ostia.

4.3 Radiological Imaging and Aneurysm Morphology

For endovascular aneurysm repair to be successful, the morphology of the aorta and iliac arteries must be shown to be suitable for the system being used and the size of the prosthesis must be correct in every detail. In order to deliver the graft stent combination via the femoral artery into the aneurysm, the iliac arteries must be patent. Atherosclerotic occlusive disease may co-exist with aneurysmal disease and lead to stenoses or occlusion of the iliac arteries. Therefore each patient requires pre-operative assessment of the iliac vessels in order to ensure that the graft-stent combination can be delivered into the aneurysm.

Successful deployment of the proximal stent at the neck of the aneurysm requires a sufficient length of normal aorta between the renal arteries and the aneurysm to anchor the stent. For endovascular repair, it is essential to measure pre-operatively in each patient, this length of normal aorta available to anchor the proximal stent. Also the aneurysm may not be confined solely to the abdominal aorta. The aortic bifurcation may be dilated and iliac aneurysms may be present.

Prior to introduction of endovascular aneurysm repair, a pre-operative ultrasound scan was used to measure the size of aneurysms and this investigation also provided some information about the diameter of the aortic bifurcation and iliac arteries. However, this information was then confirmed by direct inspection at open operation. A final decision could then be made as to the type of graft required which may be a straight 'tube' graft if the iliac arteries were of normal calibre or a bifurcated graft if iliac aneurysms were present. For endovascular repair, an accurate assessment of the aortic bifurcation and iliac arteries is required pre-operatively in order to select the appropriate graft .

Also during conventional aneurysm surgery, inspection of the inside of the aneurysm after proximal and distal clamping allows the surgeon to determine the diameter of the graft to be used and cut it to the required length. For endovascular repair, pre-operative knowledge of the diameter of the aortic neck and the distance from the proximal neck to the aortic bifurcation is essential so that an appropriate size and length of graft can

be selected.

In chapter 7, I have presented the results of a prospective study to assess the ability of conventional contrast-enhanced computed tomography (CT), magnetic resonance angiography (MRA), colour duplex (CD), and intra-arterial digital subtraction arteriography (IA-DSA) to visualise AAA morphology. This study was conducted in a consecutive series of 82 patients with non-ruptured aneurysms who were due to undergo elective aneurysm repair at Leicester Royal Infirmary NHS Trust. Symptomatic aneurysms were excluded to avoid unnecessary delay in the management of these patients. All patients were given a detailed explanation of the study and the investigations involved and gave consent. Detailed measurements were obtained from all the imaging modalities and a proforma completed for each patient. Aneurysm morphology was also to assessed to determine the proportion of aneurysms that might be suitable for endovascular repair. The principal aims of this study were:

(i) What is the best imaging modality for assessing AAAs for endovascular repair?

(ii) Are the femoral and iliac vessels suitable for insertion of the devices?

(iii) Is the proximal neck (the cuff of undilated aorta between the lowermost renal artery and the start of the aneurysm) suitable?

(iv) Is the distal neck (segment of normal aorta between the lower end of the aneurysm and the bifurcation) suitable?

(v) What proportion of the aneurysms are suitable for endovascular repair?

4.4 Initial Clinical Experience

In chapter 8, I have presented the initial clinical results of endovascular AAA repair in Leicester. Over a 26 month period from March 1994 to April 1996, endoluminal AAA repair was attempted in 29 patients (28 male, 1 female). Data was gathered in a prospective manner in all patients intra-operatively and post-operatively. Detailed follow-up assessment with Computed tomography and Colour Duplex was performed. Ethical Committee approval was obtained and all patients gave consent. The aims of the clinical work presented in this thesis were to investigate:

(1) Whether pre-operative radiological assessment provides adequate visualisation of the aneurysm morphology for endovascular repair.

(2) An endoluminal device which can be applied to a greater proportion of the patients.

(3) The technical problems associated with this technique.

(4) The incidence of peripheral embolisation during deployment of the devices.

(5) The early complications associated with this technique.

(6) The early changes in aneurysm morphology following endovascular repair.

4.5 Ischaemia Reperfusion Injury

It has also been proposed that the ischaemia-reperfusion response associated with conventional aneurysm surgery may be negated to a large extent by endoluminal AAA repair. In chapter 9, I have presented the results of a study to assess whether the metabolic response during surgery differs between conventional and endovascular AAA repair. This was investigated by quantifying oxygen free radical and cytokine production in a non-randomised cohort of patients.

4.6 Final Discussion, Conclusions and Future Work.

Finally in chapter 10, I have discussed the main findings arising from this thesis and the direction of future research.

CHAPTER FIVE

Retrospective Review Of Conventional AAA Surgery In Leicester

5.1 Workload of AAAs in Leicester Over a 13 Year Period

Introduction

Over the last 30 years there has been a progressive increase in the number of recorded deaths from AAA in England and Wales (Collin, 1988; Johansson *et al.* 1994) despite an increase in the number of elective AAA repairs. Several factors may account for this increase including the age of the population at risk, the ratio of males to females, the presence of known cardiovascular risk factors, greater awareness by general practitioners and greater use of ultrasound scanning for investigation of abdominal complaints.

The reported incidence of aneurysms of the abdominal aorta varies from 3.0 per 100, 000 person years in women to 117.2 per 100, 000 in men aged 55 years or over (Fowkes *et al.* 1989; Castleden *et al.* 1985). The reported mortality from AAA varies between 0.91 per 100, 000 person years in women and 47.1 per 100, 000 person years in men (Lilienfield *et al.* 1987; Budd *et al.* 1989). These results are based on hospital discharge and mortality statistics.

One of the controversial issues in vascular surgery over the last decade has been the repair of aneurysms in the over eighties. It has been suggested that patients over the age of 80 years of age with ruptured AAA are unlikely to survive surgery and, therefore, should not be operated on (Buck *et al.* 1987). However, as the general population ages, more octogenarians will present with abdominal aortic aneurysm.

The aim of this study was to establish:

(i) The trends in AAA surgery over a 13 year period.

(ii) To assess the current AAA practice in Leicester in terms of work load and mortality.

(iii) To assess the mortality in the over eighties to see if endovascular techniques could benefit this group of patients.

Patients and Methods

There are three hospitals in the Leicestershire Health Authority that provide vascular services: Leicester Royal Infirmary (LRI), Leicester General Hospital (LGH) and Glenfield General Hospital (GGH). Throughout the period of the study vascular surgery was undertaken at LRI and LGH. At GGH vascular surgery was only available from 1982 onwards. During the period of the study the population of Leicestershire increased from

836 300 in 1979 to 890 800 in 1991.

Data for this study was obtained from the Hospital Activities Analysis (HAA) database of the Leicestershire Health Authority from 1979 to 1987 and the Trent Regional Information System from 1987 to 1991. Data was complete for each year except between September 1986 and April 1987 for which no data was available. The two databases contain information on all patients discharged from hospitals serving the Leicestershire Health Authority, and each patient is coded according to diagnosis and treatment. The diagnostic codes are based on the International Classification of Diseases, ninth revision (*Table 7*), clinical modification (ICD-9-CM) and the treatment codes are based on the Office of Populations, Censuses and Surveys (OPCS) classification of surgical operations, second, third and fourth revisions (*Table 8*). These databases provide information on the patient's name, age, sex, presentation (elective or emergency), length of hospital stay, discharge and mortality.

Using the two databases information was obtained on all patients admitted for AAA surgery between 1979 and 1991. The diagnostic search-profile criteria are shown in *Table 7* and the treatment search-profile criteria are shown in *Table 8*. Patients were only included in the study if they had both a diagnosis and treatment code. In addition, only patients admitted to the 3 hospitals (LRI, LGH and GGH) under general and vascular surgeons were included. Patients with thoracic and thoraco-abdominal aortic aneurysms admitted to the regional cardiothoracic unit (Groby Road Hospital), which is situated on a separate site, were excluded.

Statistical Analysis

For the years 1986 and 1987, data were complete for 8 months of the year rather than the full year. It was assumed that there was no seasonal variation in abdominal aortic aneurysm surgery, and the figures for these years were multiplied by 1.5 to produce estimated rates for the full calendar year. The rates for each year were calculated by using the mid-year estimated resident population for Leicestershire, for the relevant year, as the denominator. Differences in the rates of variables with time were analysed by regression with year as the independent variable and rate as the dependent variable.

Table 7: *Office of Populations, Censuses and Surveys (OPCS) codes used to identify patients with abdominal aortic aneurysm.*

OPCS code	**Operation**
5523	Operations on abdominal vessels (graft, repair or reconstruction)
883.0	Repair or excision of aneurysm
883.3	Excision or destruction
883.4	Excision with re-anastomosis
883.6	Excision with graft or prosthesis
884.0	Repair of artery
884.1	By-pass graft
884.2	Repair by tissue graft, not elsewhere classified
884.3	Repair by prosthesis
884.4	Excision with re-anastomosis
884.5	Suture of artery
L184	Emergency replacement of aneurysmal segment of infrarenal aortic aneurysm
L185	Emergency replacement of aneurysmal segment of abdominal aorta
L186	Emergency replacement of aneurysmal aortic bifurcation/ aorto-iliac segment
L188	Other specified emergency replacement of aneurysmal segment of aorta
L189	Unspecified emergency replacement of aneurysmal segment of aorta
L194	Replacement of aneurysmal segment of infrarenal aortic aneurysm
L195	Replacement of aneurysmal segment of abdominal aorta by anastomosis
L196	Replacement of aneurysmal aortic bifurcation
L198	Other specified replacement of aneurysmal segment of aorta
L199	Unspecified replacement of aneurysmal segment of aorta
L233	Plastic repair of aorta using patch graft
L258	Other specified open operations on aorta

Table 8: *International Classification of Diseases, ninth revision (ICD-9), codes used to identify patients undergoing surgery for abdominal aortic aneurysm.*

ICD-9 code	Disease classification
441.3	Abdominal aneurysm, ruptured
441.4	Abdominal aneurysm without mention of rupture
441.5	Aortic aneurysm of unspecified site, ruptured
441.6	Aortic aneurysm of unspecified site without mention of rupture

Results

Over the 13-year period 1979-1991, a total of 727 patients were admitted to the three hospitals with AAA. Of these 410 (56.4%) patients were admitted for elective repair and 317 (43.6%) presented with rupture. *Table 9* shows the number of AAAs admitted for each year. There has been a significant increase (*Figure 5.1*) in both elective and ruptured abdominal aortic aneurysms ($p < 0.05$ and $p < 0.0002$, respectively).

Age and Sex

The overall sex distribution was 5.5:1 male to female. The ratio for elective and ruptured AAAs was 7.5:1 and 4:1 respectively. There was a significant difference between median age of presentation in men (70 years) and women (77 years). Also sex distribution changed dramatically with age for both elective and ruptured AAAs (*Table 10*). The overall median age was 71 years (range 31-97 years). The median age for elective AAA repair was 70 years (range 31-89), and 74 years for ruptured AAAs (range 48-97 years). *Table 11* shows the change in the median age of patients admitted with AAA over the study period. Overall there was a significant increase in the median age of patients over the study period ($r^2 = 0.53$, $p < 0.005$). There was no significant increase in the median ages of elective ($p = 0.09$) and ruptured AAAs ($p = 0.054$) over the study period.

Table 9: Total number of elective and ruptured AAAs admitted for each year. Values in parentheses are rates per 100 000 population.

Year	Total*	Elective**	Ruptured***
1979	22 (2.6)	14 (1.7)	8 (0.9)
1980	30 (3.6)	18 (2.1)	12 (1.4)
1981	26 (3.0)	22 (2.6)	4 (0.5)
1982	46 (5.3)	26 (3.0)	20 (2.3)
1983	43 (4.9)	24 (2.8)	19 (2.2)
1984	51 (5.9)	30 (3.5)	21 (2.4)
1985	66 (7.6)	40 (4.6)	26 (2.9)
1986	65 (7.5)	43 (3.3)	22 (1.7)
1987	106 (11.9)	68 (5.1)	38 (2.8)
1988	83 (9.4)	39 (4.9)	44 (4.9)
1989	54 (6.1)	20 (2.2)	34 (3.8)
1990	58 (6.5)	24 (2.7)	34 (3.8)
1991	77 (8.6)	42 (4.7)	35 (3.9)

*$r^2 = 0.54, p < 0.004$
**$r^2 = 0.30, p < 0.05$
***$r^2 = 0.73, p < 0.0002$

Figure 5.1: *Rate of AAAs admitted per 100 000 population of Leicestershire over the study period. Points are fitted with best fit regression line.*

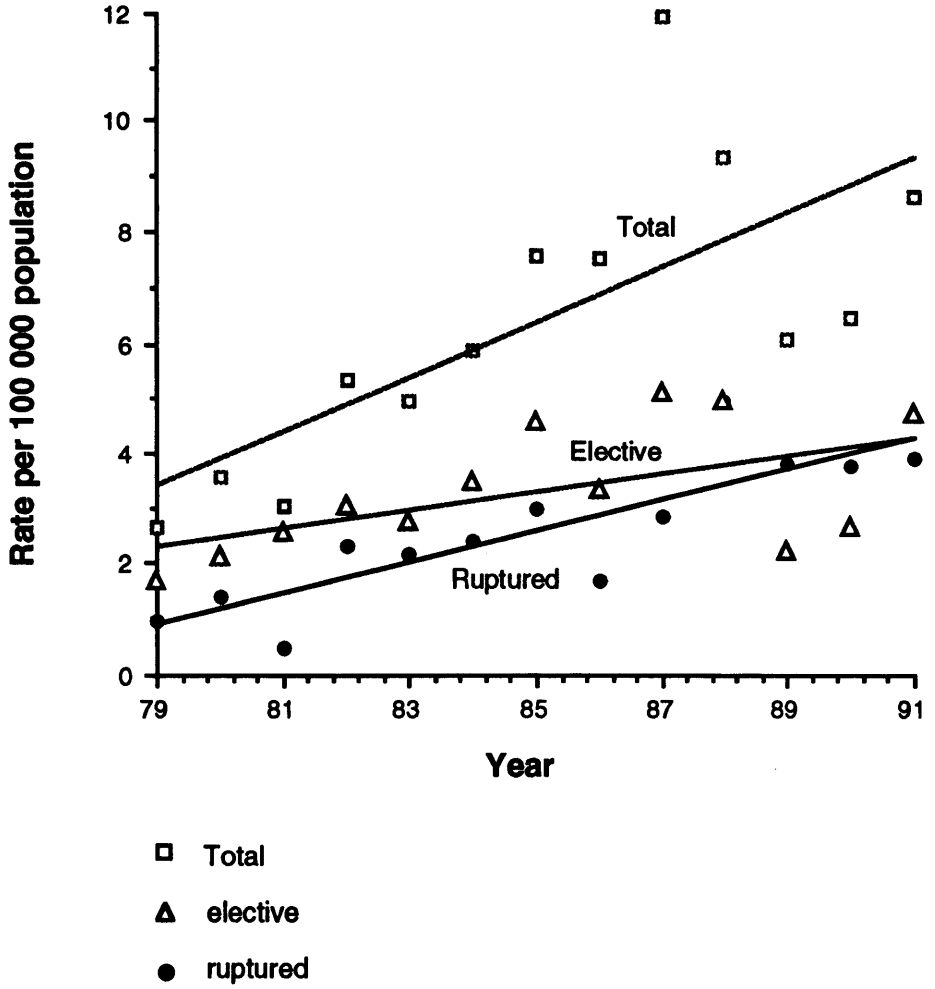


Table 10: Male to female ratio for elective and ruptured AAAs according to age.

Age group	Elective M:F ratio	Ruptured M:F ratio	Overall M:F ratio
<64	15.7:1	46:0	23.3:1
65-74	8.9:1	4.8:1	6.86:1
75-84	4.1:1	3:1	3.44:1
>85	2:1	1:1	1.13:1

Table 11: The median age of patients admitted with AAA from 1979-1991.

Year	Median age of all AAAs (years)*	Median age of elective AAAs (years)**	Median age of ruptured AAAs (years)***
1979	69.5	69.5	70.5
1980	70.5	67.5	73.5
1981	70	70	59
1982	72.5	71	73.5
1983	68	65.5	72
1984	70	68.5	73
1985	70	70	71
1986	70	68	75
1987	71	70	72
1988	73	70	74
1989	74.5	69	78
1990	74	74.5	74
1991	74	71.5	76

* $r^2 = 0.53, p < 0.005$
** $r^2 = 0.23, p < 0.09$
*** $r^2 = 0.30, p < 0.054$

Mortality

Table 12 shows the hospital mortality of elective and ruptured AAAs for each year. Four hundred and nine patients (56%) underwent elective repair with an overall mortality of 8.8% (including patients with symptomatic but non-ruptured aneurysms who required urgent surgery). There was no significant change ($p = 0.06$) in the mortality of elective repair during the study period (*Figure 5.2*). Three hundred and eighteen patients (44%) were admitted with ruptured AAA with an overall mortality of 57.7% (including patients who were deemed medically too unfit for surgery). There has been no significant change ($p = 0.4$) in the mortality of ruptured AAAs (*Figure 5.2*) during the study period .

Mortality of patients undergoing elective AAA repair and those presenting with rupture was analysed according to age and sex (*Table 13*). There was an increase in the percentage mortality of elective and ruptured AAAs with increasing age in both males and females.

Hospital stay

For those patients surviving elective aneurysm repair the median hospital stay was 14 days (range 6-85 days). The median hospital stay for those patients surviving emergency repair was 17 days (range 8-60 days).

Discussion

This study shows that there has been an increase in the workload of AAAs over the 13 year period in Leicester. This may partly be due to better diagnostic methods, greater clinical awareness and increase in the number of elderly people in the catchment population. This is reflected by the increase in the median age of the patients (69.5 years in 1979 to 74 years in 1991) in the study. However the trends observed in this study and those of others (Samy *et al.* 1993; Fowkes *et al.* 1989; Budd *et al.* 1989) suggest that there is probably a true increase in the incidence of aortic aneurysms. Establishment of community screening programmes for aortic aneurysms may in the long term provide a true picture of the changing prevalence of this condition.

The overall mortality for elective repair was 8.8 percent. However this figure includes patients with symptomatic ('acute') aneurysms which have a mortality of 10-15% in most centres (Campbell *et al.* 1986). One of the limitations of the HAA data was that it was not possible, from the diagnostic codes, to distinguish between symptomatic ('acute') and elective aneurysms. The overall mortality for ruptured AAAs was 57.7 percent. This

Table 12: Percentage hospital mortality of elective and ruptured AAAs for each year. Values in parentheses are the number of deaths.

Year	% mortality of elective AAA repair *	% mortality of ruptured AAAs**
1979	14.3 (2)	62.5 (5)
1980	22.2 (4)	91.7 (11)
1981	9.1 (2)	25 (1)
1982	15.4 (4)	65 (13)
1983	4.2 (1)	68.4 (13)
1984	6.7 (2)	66.7 (14)
1985	7.5 (3)	57.7 (15)
1986	7.0 (3)	63.6 (14)
1987	5.9 (4)	34.2 (13)
1988	10.3 (4)	63.6 (28)
1989	10 (2)	61.8 (21)
1990	4.2 (1)	47.1 (16)
1991	9.5 (4)	54.3 (19)
Overall mortality	**8.8%**	**57.7%**

** $r^2 = 0.27, p > 0.05$*
*** $r^2 = 0.027, p > 0.5$*

Figure 5.2: *Comparison of hospital mortality of elective ($r^2 = 0.27, p > 0.05$) and ruptured ($r^2 = 0.027, p > 0.5$) AAAs in Leicester from 1979-1991. Points are fitted with best fit linear regression line.*

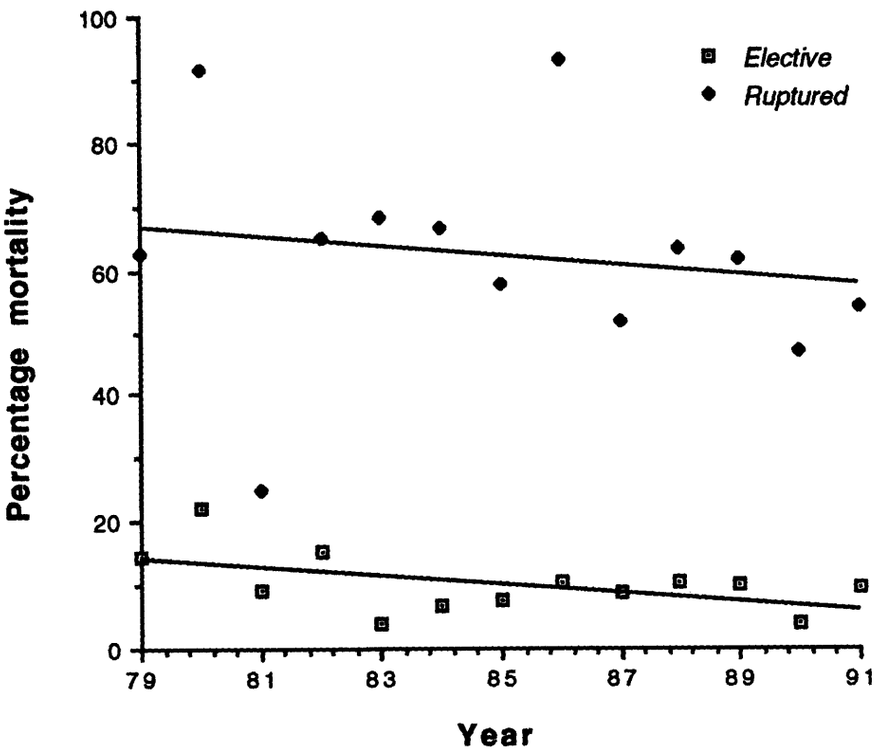


Table 13: Percentage mortality for elective and ruptured AAAs according to sex and age group. Values in parentheses are the number of deaths.

Sex	Age range	% Elective mortality	% Ruptured mortality
Males	<64	5.3 (5)	45.6 (21)
	65-74	6.2 (10)	44.8 (39)
	75-84	21.6 (16)	73.9 (65)
	>85	50.0 (1)	86.7 (13)
Females	<64	0	0
	65-74	0	50.0 (9)
	75-84	22.2 (4)	86.2 (25)
	>85	0	78.6 (11)

figure includes patients who were deemed medically too unfit to undergo surgery, those dying in casualty and those that died on the operating table. Again this was a limitation of the HAA data and probably gives a slightly higher figure for rupture mortality than is actually the case. Also in the early years of the study period, AAAs in our centre were also operated on by general surgeons and higher surgical trainees (registrars and senior registrars) until the introduction of a vascular rota. However there is no data to see if there has been any change in mortality.

There was no significant change in the mortality of ruptured AAAs over the study period. The high mortality may partly be due to more elderly patients (> 80 years) presenting to the hospital with rupture and this is reflected by an increase in the median age of patients (70.5 years in 1979 to 76 years in 1991), although this did not reach statistical significance (p=0.054). The outcome of surgery in these patients is difficult to predict preoperatively (Harris *et al.* 1991), because it is difficult to assess patients fully when they present with rupture. Also despite successful surgery many develop cardiac failure, renal failure and coagulopathy post-operatively. Therefore as surgical reconstruction offers the only chance of survival, surgery should invariably be offered. However the poor outcome of surgery with increasing age is reflected in our study (around 80 percent mortality in > 85 years age group compared with < 45 percent mortality in the 65-74 age group).

Summary

It is clear from this study and other reported series that hospital mortality of ruptured AAAs remains high and there has been little improvement over the last decade despite advances in surgery and anaesthesia. The results also suggest that there has been no significant reduction in the mortality of elective AAA repair over the same period. However, the latter finding may have been influenced by the relatively small number of patients in each year and the inability to separate true elective aneurysms from symptomatic non-ruptured aneurysms. Another finding of this study was the poor outcome of both elective and emergency surgery with increasing age. Therefore any technique which reduces the operative insult may help reduce the mortality in patients with rupture and in the elderly group of patients. Endovascular repair, if proven to be feasible and effective, may benefit these groups of patients in the future.

5.2 A Detailed Review of AAA Surgery at Leicester Royal Infirmary

Introduction

The hospital activity analysis (HAA) data is very crude and is only good when looking at overall trends. To get a more accurate idea of the results AAA surgery in Leicester, this study examined the surgical treatment of all AAAs presenting to the Leicester Royal Infirmary over a 13 year period, in order to document the diagnosis, treatment, complications and mortality of AAAs.

Over the last 2 decades, there have been major advances in the treatment of AAAs based upon changes in pre-operative diagnosis and assessment; intra-operative surgical and anaesthetic techniques and post-operative care. This study examines:

(i) whether any of the above advances have had any impact on the results of aneurysm surgery in Leicester.
(ii) To identify those variables associated with a worse outcome; and
(iii) The proportion of patients who constitute a 'high" risk group, and may benefit from less invasive surgery using endovascular techniques.

Patients and Methods

Patients who underwent AAA repair at Leicester Royal Infirmary between January 1981 and December 1993 were identified from the Leicester Royal Infirmary Vascular Studies Unit audit, death certificate records and the records of the surgical wards, operating theatres, intensive care unit and Accident and Emergency department. The case notes of all patients who underwent AAA repair were reviewed to obtain data on presentation, diagnosis, treatment, complications and survival.

Elective surgical repair was defined as a planned procedure in a patient admitted from the vascular surgical waiting list. Urgent repair was defined as surgery in a patient admitted as an emergency with a symptomatic or tender AAA which was not ruptured at operation. Ruptured aneurysm was defined as a retroperitoneal leak or free intraperitoneal rupture. Mortality was defined as death during the initial hospital admission either at Leicester Royal Infirmary or after transfer for renal dialysis at Leicester General Hospital.

Statistical analysis

In order to examine differences in demographics, risk factors and presentation, the patients were divided into 2 groups: 1981-87 (group A) and 1988-93 (group B). In addition, logistic regression was used to identify associations between patient outcome (death, coagulopathy, cardiac, respiratory or renal failure) and risk factors. Single variable

analysis was performed first and those variables associated with outcome at the $p<0.05$ level of significance were entered into a multiple logistic regression model to identify those variables which were independently associated with outcome using the backward stepwise selection procedure.

Results

During the 13 year period from January 1981 to December 1993, 689 patients underwent surgery for AAA at Leicester Royal Infirmary. Data was unavailable for 18 patients, which left 671 patients for further analysis. The demographic data for the 2 groups is shown in *Tables 14* and *15*. The preceding symptoms and clinical presentation of patients in the 2 groups is shown in *Table 16*. Pre-operative investigations (ultrasound or CT scan) were performed in 15 out of 125 patients with ruptured AAAs in group A compared to 44 out of 153 in group B (chi square, df=1, $p=0.007$)(*Table 17*). The operating surgeon was a vascular surgeon in 633 patients (94%). The maximum transverse diameter of AAA was 6 cm (range 3.6-13 cm)(measured in 423 patients pre-operatively). There were 641 atherosclerotic AAAs (96%) and 30 (4%) inflammatory aneurysms. Six hundred and fifty nine AAAs were infrarenal (98%) and 12 (2%) were suprarenal. A graft was inserted in 638 patients (95%), 339 (53%) tube and 299 (47%) bifurcated. Thirty three patients (5%) died during surgery before a graft could be inserted. Three patients were deemed inoperable; 1 elective patient (age 77y, male, 7.6 cm AAA) with a suprarenal AAA extending to the diaphragm, 1 urgent case (age 76y, male, 7 cm AAA) with an inflammatory suprarenal AAA and one ruptured case (age 79y, male) with a retroperitoneal leak and infarcted small bowel). Sixty patients (9%) required further operative procedures on 66 occasions during the same hospital admission; these included 24 elective cases (8%), 8 urgent cases (10%) and 28 ruptured AAAs (10%). Six patients returned to theatre on 2 occasions; 2 elective AAAs and 4 ruptured AAAs. The indications for further surgical intervention are shown in *Table 18*. There were 23 deaths in these 60 patients who returned to theatre (38%) (5 elective, 2 urgent and 16 ruptured). Major post-operative complications are shown in *Table 19*. The overall median hospital stay was 11 days (range 1-93). The overall mortality was 182 patients (27%); 21 elective patients (6.7%), 13 urgent patients (16%) and 148 ruptured patients (53%) (*Table 20*). There were no significant differences in mortality in group A compared to group B for each of the 3 aneurysm types (elective, urgent, ruptured). *Table 21* shows cause of death. Fifty patients (7%) died during surgery (2 urgent AAAs, 48 ruptured AAAs) and 1 ruptured AAA survived the first operation but died during re-exploration for intra-abdominal bleeding. Multiple regression analysis showed that cardiac and renal failure were significantly associated with death in the elective group (both $p<0.0001$) and that cardiac, respiratory or renal failure were significantly associated with death in the ruptured group (all $p<0.05$).

Table 14: *Demographic data for patients with aortic aneurysms between 1981-87 (n=291). Figures in parentheses are percentages.*

	Elective	**Urgent**	**Ruptured**	**Total**
Number of patients	136 (47)	30 (10)	125 (43)	291
Males	109	26	107	242 (83)
Females	27	4	18	49 (17)
Median age [range]	68 [45-82]	72.5 [51-84]	71 [53-90]	
Risk factors:				
Hypertension	51	12	37	100 (34)
Ischaemic heart disease*	34	10	32	76 (26)
Diabetes mellitus	5	1	5	11 (4)
Cerebrovascular disease**	11	0	13	24 (8)
Intermittent claudication	41	3	10	54 (19)
Smoking:				
Current	60	18	40	118 (41)
Ex	67	11	73	151 (52)
Never	9	1	12	22 (8)

* *angina pectoris, myocardial infarction, arrhythmia, congestive cardiac failure, coronary artery bypass surgery*

** *transient ischaemic attack, amaurosis fugax, cerebrovascular accident, carotid endarterectomy*

Table 15: *Demographic data for patients with aortic aneurysms between 1988-93 (n=380). Figures in parentheses are percentages.*

	Elective	**Urgent**	**Ruptured**	**Total**
Number of patients	177 (47)	50 (13)	153 (40)	380
Males	148	37	130	315 (83)
Females	29	13	23	65 (17)
Median age [range]	70 [52-86]	72.5 [58-90]	74 [52-89]	
Risk factors:				
Hypertension	77	24	58	159 (42)
Ischaemic heart disease*	64	19	51	134 (35)
Diabetes mellitus	6	1	6	13 (3)
Cerebrovascular disease**	24	6	10	40 (11)
Intermittent claudication	58	13	8	79 (21)
Smoking:				
Current	64	21	52	137 (36)
Ex	98	26	90	214 (56)
Never	15	3	11	29 (8)

* *angina pectoris, myocardial infarction, arrhythmia, congestive cardiac failure, coronary artery bypass surgery*

** *transient ischaemic attack, amaurosis fugax, cerebrovascular accident, carotid endarterectomy*

Table 16: *Preceding symptoms and clinical findings in patients with AAAs.*

	Elective [n=313]	Urgent [n=80]	Ruptured [n=278]
1981-87			
Number of patients	136	30	125
Abdominal pain	26	23	115
Back pain	34	18	96
Distal emboli	0	1	0
Palpable abdominal mass	122	26	120
Mass noted by patient	29	3	5
Shock*	0	0	84
1988-93			
Number of patients	177	50	153
Abdominal pain	23	40	132
Back pain	36	37	119
Distal emboli	0	0	0
Palpable abdominal mass	154	44	142
Mass noted by patient	17	2	3
Shock*	0	1	96

** systolic blood pressure < 100 mmHg*

Table 17: *Pre-operative investigations in 671 patients who underwent AAA surgery. CT = computer tomography.*

	Elective [n=313]	**Urgent [n=80]**	**Ruptured [n=278]**
1981-87			
No. of patients	136	30	125
Ultrasound scan	114	14	14*
CT scan	26	7	1*
1988-93			
No. of patients	177	50	153
Ultrasound scan	170	35	42*
CT scan	12	9	2*

p=0.007, Chi square, df=1

Table 18: *Indication for further surgical intervention in 60 patients on 66 occasions.*

Intra-abdominal bleeding	25
Lower limb ischaemia	21
Intra-abdominal sepsis	8
Wound dehiscence	4
Intra-abdominal bleeding & leg ischaemia	1
False aneurysm	1
Hydronephrosis & hydroureter	1
Graft infection	1
Upper gastrointestinal bleed	1
Intestinal obstruction	1
Acute renal failure (suspected renal artery thrombosis)	1
Haematuria & clot retention	1

Table 19: *Incidence of major post-operative complications in 671 patients. Figures in parentheses are percentages.*

Cardiac	212 (32)
Respiratory	202 (30)
Renal	90 (13)
Coagulopathy	48 (7)
Ischaemic leg	23 (3)
Deep vein thrombosis	14 (2)
Cerebrovascular accident	12 (2)
Ischaemic colon	8 (1)
Wound dehiscence	6 (1)
Pulmonary embolus	3 (<1)

Table 20: *Mortality rates for AAA repair. Figures in parentheses are percentages.*

	Elective n=313	**Urgent n=80**	**Ruptured n=278**
1981-87			
No. of patients	136	30	125
Died	6 (4)*	6 (20)**	65 (52)***
1988-93			
No. of patients	177	50	153
Died	15 (8)*	7 (14)**	83 (54)***

* $p>0.05$, chi square, df=1

** $p>0.05$, chi square, df=1

*** $p>0.05$, chi square, df=1

Table 21: *Causes of death (n=182). Figures in parentheses are percentages.*

Cardiac failure	67 (37)
Cardiac failure & coagulopathy	22 (12)
Cardiac & respiratory failure	16 (9)
Cardiac & renal failure	15 (8)
Renal failure*	15 (8)
Coagulopathy	15 (8)
Respiratory & renal failure	11 (6)
Respiratory failure	5 (3)
Other**	16 (9)

** renal failure was defined as a rise in the post-operative serum creatinine level of >100 mmol/litre when compared with the pre-operative figure or the need for dialysis.*

*** usually a combination of the above*

Discussion

These data show that the 671 patients in this study were a typical group of patients who undergo AAA repair in that the majority were elderly and male (median age 71y, 83% male) with associated risk factors such as smoking, ischaemic heart disease, cerebral and peripheral vascular disease (Joffre *et al.* 1986; Akkersdijk *et al.* 1994; Katz *et al.* 1994; Samy *et al.* 1994; Naylor *et al.* 1988; Johnston, 1994a; Samy *et al.* 1993; MacSweeney *et al.* 1993). However, only 4% of patients in this study had diabetes mellitus whereas patients with occlusive peripheral vascular disease have a much higher prevalence of this disease. Although the median ages were similar in groups A and B, the prevalence of ischaemic heart disease has increased significantly from 26% in group A (1981-87) to 35% in group B (1988-93)($p=0.01$, chi-square, $df=1$). Overall 53% of patients in this study were non-elective cases (41% ruptured, 12% urgent). This reflects the fact that LRI is the only one of the 3 acute hospitals in Leicester with an Accident and Emergency department and therefore treats the majority of ruptured aneurysms. Other studies have reported that the majority of AAAs continue to be operated upon in the United Kingdom as emergencies (Fielding *et al.* 1981; Naylor *et al.* 1988) and although a national screening programme has been called for, the role of screening the population (Allen *et al.* 1987) or high-risk groups (MacSweeney *et al.* 1993; Bengtsson *et al.* 1989; Webster *et al.* 1991a) to try to reduce the numbers of ruptured AAA and thus overall mortality remains controversial (Collin, 1993; Harris, 1992).

In the elective group, 60 patients (44%) in group A and 59 (33%) in group B had complained of abdominal or back pain prior to operation. Similarly 122 (90%) patients in group A and 154 (87%) in group B had a palpable AAA. Although these symptoms may not be related to the AAA, there is evidence to show that 26% of patients who subsequently present with a ruptured AAA have been admitted to hospital and examined in the preceding 2 years without their AAA being diagnosed (Craig *et al.* 1993). Thus careful abdominal examination in any elderly patient admitted to hospital with abdominal symptoms may increase the diagnostic rate of elective AAAs.

In most patients with ruptured AAA the diagnosis is easily established and prompt treatment should not be delayed by pre-operative investigations. A few patients present with abdominal and back pain, cardiovascular stability and a non-palpable AAA. If the diagnosis remains in doubt then the safest policy is to proceed to laparotomy although the differential diagnosis includes conditions such as myocardial infarction and acute pancreatitis in which emergency laparotomy is inappropriate. However, better access to medical imaging (ultrasound or CT scan) should improve pre-operative diagnosis of AAAs. During the study period, 24 hour access to ultrasound in the Accident and Emergency department together with rapid access to CT scanning was introduced. This has led to an increase in the number of patients with suspected ruptured AAA (who were

cardiovascularly stable) undergoing these investigations (12% in group A and 29% in group B)(p=0.007, chi-square, df=1).

Fifty nine (9%) patients underwent further surgical procedures on 65 occasion; the commonest indications being intra-abdominal bleeding and lower limb ischaemia. The most common procedures performed at second operation were embolectomy, control of bleeding vessels and repair of anastomotic bleeding. Second operations after AAA repair are associated with a high mortality which was 38% in this study (Slootmans *et al.* 1994; Ng *et al.* 1994). The most common post-operative complications were cardiac (32%), respiratory (30%) and renal failure (13%). The overall mortality was 6.7% in the elective group, 16% in the urgent group and 53% in the ruptured group. Although the mortality rates do not appear to have changed significantly between groups A and B, more high-risk patients with ischaemic heart disease underwent surgery in group B (Johansson *et al.* 1994). Mortality figures after AAA surgery must be interpreted with care (Campbell, 1991) and many studies do not separate the urgent group. However, overall the results from this series are similar to the reports of other groups (Joffre *et al.* 1986; Akkersdijk *et al.* 1994; Drott *et al.* 1992; Katz *et al.* 1994; Samy *et al.* 1994; Greenhalgh, 1990; Fielding *et al.* 1981; Naylor *et al.* 1988; Johnston, 1994a). Although many of the deaths are caused by multi-system failure, cardiac causes alone account for 37% of deaths with cardiac events in conjunction with either coagulopathy, respiratory disease or renal failure accounting for 12%, 9% and 8% of deaths respectively. It is well established that cardiac events are a significant cause of post-operative mortality but there is also evidence to show that respiratory failure (Calligaro *et al.* 1993) and coagulopathy (Davies *et al.* 1993; Milne *et al.* 1994) carry a grave prognosis. In this series, logistic regression analysis showed that for elective AAAs cardiac and renal failure were significantly associated with death and for ruptured aneurysms cardiac, respiratory or renal failure were significantly associated with death.

Summary

This study confirms that the hospital mortality of ruptured AAAs remains high and there has been little improvement over the last decade despite advances in surgery and anaesthesia. Postoperative cardiac, respiratory or renal failure are significant causes of death in AAA patients. Due to limitations of the retrospective review of the data, it was not possible to identify risk factors which predispose patients to the above complications and hence affect outcome. A significant proportion of the patients undergoing AAA surgery (35%) have associated ischaemic heart disease and therefore any technique that reduces the aortic clamp time may produce a benefit in aneurysm surgery. The above results show that conventional aneurysm surgery continues to be associated with morbidity and mortality and endovascular techniques may offer some hope of improving the outcome.

CHAPTER SIX

Experimental Animal Work

6.1 Endovascular AAA Repair Using a Single Proximal Stent

Introduction

The animal studies reported so far have shown that endovascular deployment of a graft-stent combination is feasible and can be performed with few complications (Parodi *et al.* 1991; Balko *et al.* 1986; Lawrence *et al.* 1987; Mirich *et al.* 1989; Laborde *et al.* 1992; Chuter *et al.* 1993). However several important questions remain unanswered. A potential disadvantage of endovascular AAA repair is persistent back-bleeding from the lumbar and inferior mesenteric arteries into the aneurysm sac which may lead to continual aneurysmal expansion and eventual rupture. Following conventional aortic aneurysm surgery, this does not occur as these vessels are ligated. Also initially both a single proximal stent and a double (proximal and distal stent) stent technique have been used in clinical practice (Parodi *et al.* 1991). The single proximal stent repair may also allow blood to enter the aneurysm sac from around the distal unstented end with potential risk of rupture.

The aim of this study was:

(1) to design an aneurysm model which allows lumbar back-bleeding to be investigated;

(2) to assess whether a single proximal stent technique allows adequate aneurysm exclusion;

(3) to assess whether the infra-renal aortic stent graft has any deleterious effects on renal function; and

(4) also to assess whether femoral artery blood flow is affected by the endoluminal graft.

Materials and Methods

This study was performed in eight adult Beagle dogs of median weight 10.2 (range 8.8-11.5) kg. The study was divided into 4 phases: (1) creation of a prosthetic AAA; (2) insertion of a graft-stent combination using the single proximal stent technique; (3) measurements of the effects of graft-stent insertion on femoral artery blood flow and renal function; and (4) assessment of graft-stent position and measurement of back-bleeding into the aneurysm sac from the distal unstented end of the graft.

Creation of a prosthetic abdominal aortic aneurysm

General anaesthesia was induced with propofol 1% (0.5ml/kg) and maintained with halothane (1-2%) and oxygen (4l/min). Following endotracheal intubation and administration of intravenous antibiotics (300mg procaine penicillin and 225mg benzathine penicillin), the infrarenal abdominal aorta was exposed through a midline transperitoneal approach, controlled with slings and the distance form the renal arteries to the aortic bifurcation measured. Care was taken not to disturb the lumbar branches of the infra-renal aorta, which contribute to spinal cord blood flow. After systemic heparinisation (50 units/kg) a side-biting Satinsky arterial clamp was applied to the anterior aortic wall. An anterior longitudinal aortotomy was made extending from approximately 3 cm below the renal arteries to 1 cm above the aortic bifurcation and the length of the aortotomy measured. A knitted Dacron patch (Meadox UK Ltd, Caddington, Beds, UK) was sutured onto the arteriotomy so that it bulged anteriorly and laterally to create an aortic aneurysm sac, with continuous 6.0 polypropylene (*Figure 6.1*). This technique was used in preference to excision of a segment of aorta with insertion of a spherical prosthetic aneurysm because the lumbar arteries remain in continuity with the aneurysm, which is more analogous to the human situation (Balko *et al.* 1986). After this, the abdomen was closed and the animals allowed to recover.

Endovascular insertion of the graft-stent combination

Six weeks following creation of a prosthetic aneurysm, each dog underwent insertion of a graft-stent combination. Under general anaesthesia, the left common femoral artery was exposed in the groin and controlled with slings. After systemic heparinisation, a 0.035 inch guide wire (Meadox UK Ltd, Caddington, Beds, UK) was inserted into the femoral artery using a Seldinger technique and passed through the aneurysm into the suprarenal aorta. A 5F arteriography catheter (Meadox UK Ltd, Caddington, Beds, UK) was threaded over the guidewire and baseline arteriograms obtained following injection of contrast medium. This allowed the position of the renal arteries to be marked on the anterior abdominal wall using a radio-opaque marker (*Figure 6.2*). A 1 cm arteriotomy was then made in the femoral artery to allow insertion of the graft-stent combination.

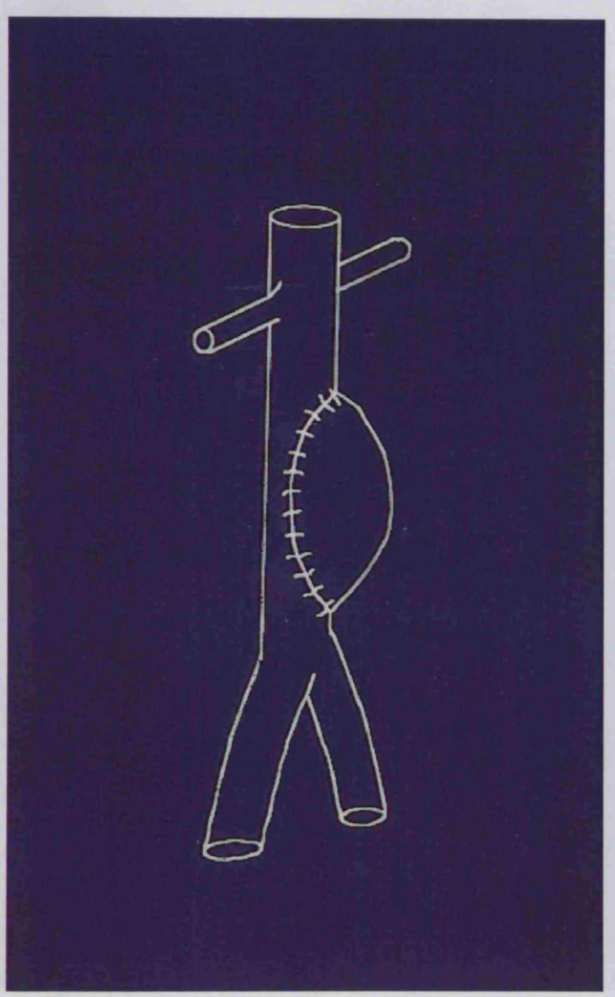


Figure 6.1: *Schematic lateral view of creation of a prosthetic abdominal aortic aneurysm.*

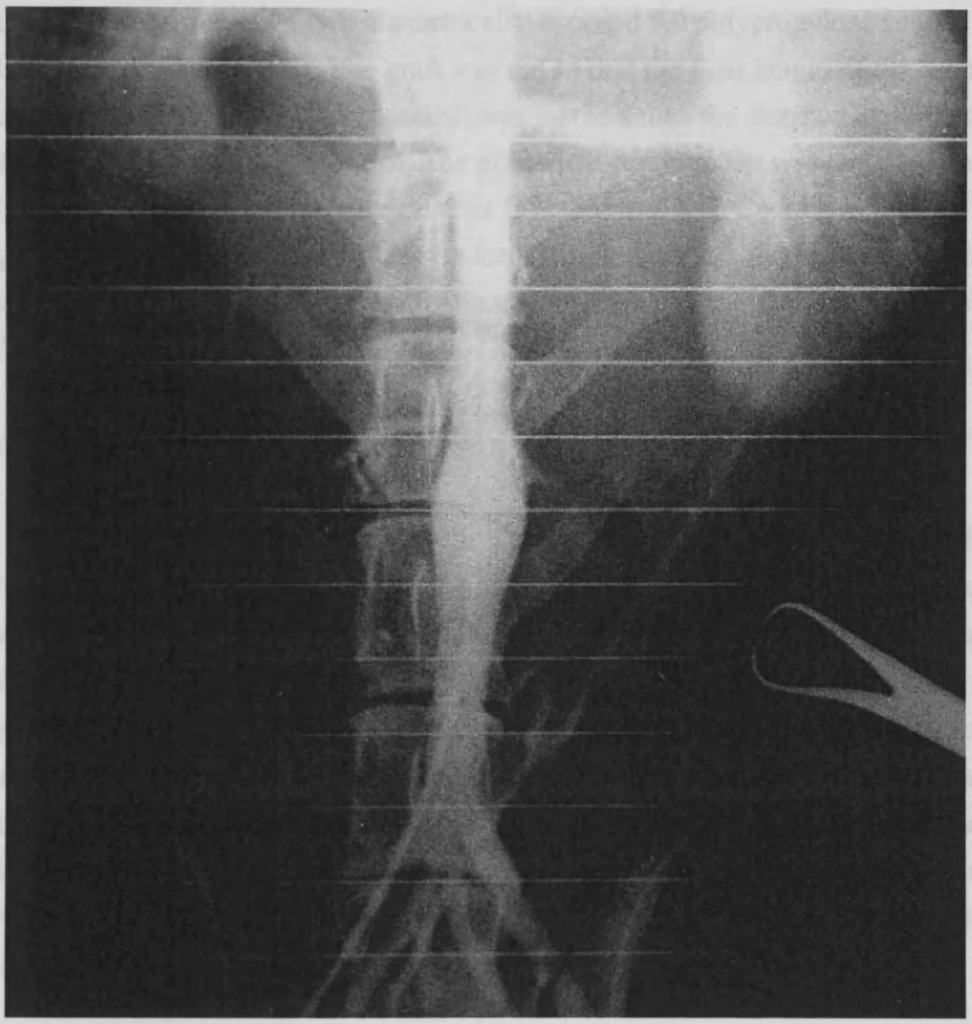


Figure 6.2: *An arteriogram demonstrating the prosthetic aneurysm sac and the renal arteries. Note the marker board lines (1 cm apart) used for obtaining measurements.*

Preparation of the graft-stent combination

A 3.2 mm diameter (unexpanded), 8 mm diameter (expanded), 30 mm long intravascular Palmaz stent (Johnson & Johnson UK Ltd, Berks, UK) was attached to the end of a 6 mm diameter, thin walled poytetrafluoroethylene (PTFE) graft (WL Gore UK Ltd, Livingston, UK) by two diametrically opposed 5.0 polypropylene sutures (Ethicon UK Ltd, Edinburgh, UK). The graft was cut so that the final length of the graft-stent combination (with the stent expanded) was just less than the distance between the renal arteries and the aortic bifurcation. The graft-stent combination was mounted on a 10 mm low profile balloon angioplasty catheter (Meadox UK Ltd, Caddington, Beds, UK). The graft was folded along its long axis to form two wings to allow the insertion of the graft-stent combination and angioplasty catheter into a 30 cm long, 14-French Teflon sheath (Meadox UK Ltd, Caddington, Beds, UK)(*Figure 6.3*).

Graft-stent insertion

Under fluoroscopic control, the Teflon sheath was inserted over the guidewire in the femoral artery and advanced to the aortic bifurcation. The angioplasty balloon catheter and the graft-stent combination were then advanced out of the end of the sheath and into the aneurysm. The radio-opaque stent was accurately positioned in the neck of the aneurysm below the renal arteries. Once satisfactory position was obtained, the angioplasty balloon was inflated (8 atmospheres pressure) to expand the stent and anchor it to the aortic wall. The sheath, angioplasty catheter and guidewire were then withdrawn leaving the graft-stent combination in place. The femoral arteriotomy was closed with interrupted 6.0 polypropylene sutures (Ethicon UK Ltd, Edinburgh, UK) and the animals allowed to recover.

Measurement of femoral artery blood flow and glomerular filtration rate

Mean velocity was measured in the common femoral arteries of awake animals 2 weeks before and 2 weeks after insertion of the graft stent combination using a Diasonics DRF 400 colour duplex scanner (Diasonics UK Ltd). Glomerular filtration rate was measured before and after insertion of the graft-stent combination. Five mega becquerels of 51 Cr-EDTA was injected intravenously into each animal and intravenous blood samples (1 ml) taken at 2, 2.5, 3 and 4 hours post-injection. The blood samples were centrifuged, the radioactivity of the serum was analysed in a gamma counter, and glomerular filtration rate was derived using the method of Chantler *et al.* (1972).

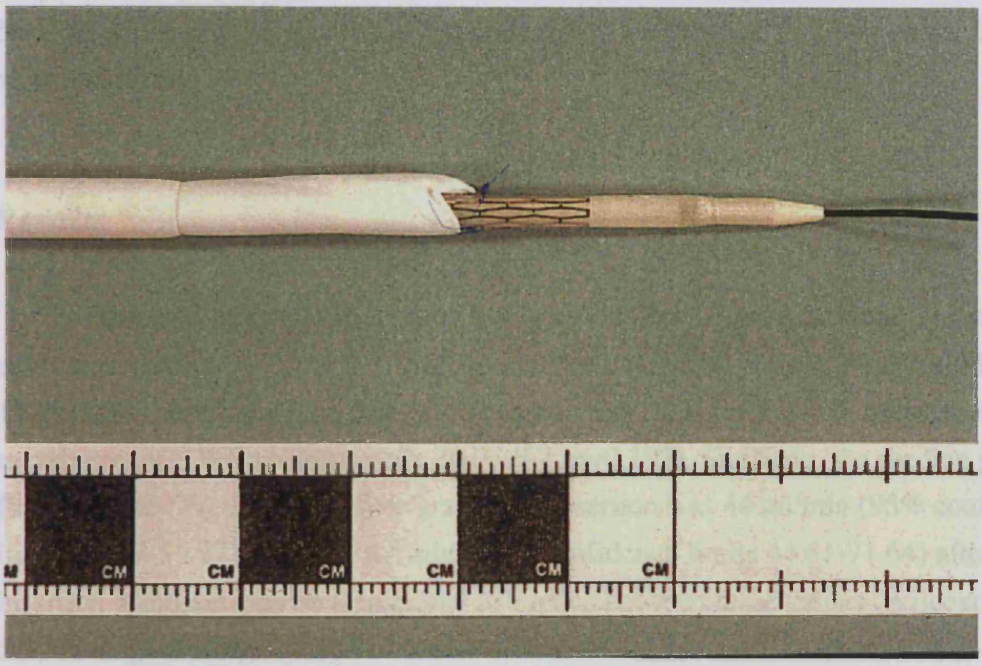


Figure 6.3: *Photograph of the graft-stent combination mounted on an angioplasty balloon emerging from the end of the delivery sheath.*

Assessment of stent position and measurement of backbleeding into the sac from the distal unstented end of the graft

Eight weeks after insertion of the graft-stent combination, a midline laparotomy was performed under general anaesthesia to expose the prosthetic abdominal aortic aneurysm. After systemic heparinisation, a 16G butterfly needle was inserted into the space between the aneurysm sac and the PTFE graft, and blood refluxing from around the distal unstented end of the graft was collected in a measuring cylinder over a period of 1 minute (*Figure 6.4*). The prosthetic aneurysm sac was then opened through an anterior longitudinal incision to allow inspection of its contents, the presence of blood clot and back-bleeding and the position of the graft-stent combination. Following this, the animals were sacrificed.

Results

The median common femoral artery blood flow (*Figure 6.5*) was 27 cm/sec (95% confidence limits 18-31) before graft-stent insertion and 20 cm/sec (95% confidence limits 11-25) after graft-stent insertion. There was no significant difference between these 2 measurements (Wilcoxon statistic 30.0, df 7, p=0.107). Similarly, the median glomerular filtration rate (*Figure 6.6*) before graft-stent insertion was 44 ml/min (95% confidence limits 37.87-56.97) and 63.5 ml/min (95% confidence limits 44.61-71.64) after graft-stent insertion and there was no significant difference between these values (Wilcoxon statistic 6.5, df 7, p=0.123).

Two (25%) of the graft-stent combinations were deployed too low in the aneurysm sac. In 1 case, graft thrombosis occurred with loss of the femoral pulse, because the distal end of the graft was lying in the iliac artery. Six (75%) of the graft-stent combinations were deployed in a satisfactory position with the distal end of the graft located at the aortic bifurcation. The appearance of the stent on a plain abdominal radiograph is shown in *Figure 6.7*. All 6 showed continual reflux of blood from around the distal unstented end of the graft into the aneurysm sac (median blood volume 8 ml/min (95% confidence limits 7-9). In these 6 cases, arteriography prior to opening the sac demonstrated tram-lining in the sac caused by the presence of contrast medium between the graft and sac (*Figure 6.8*).

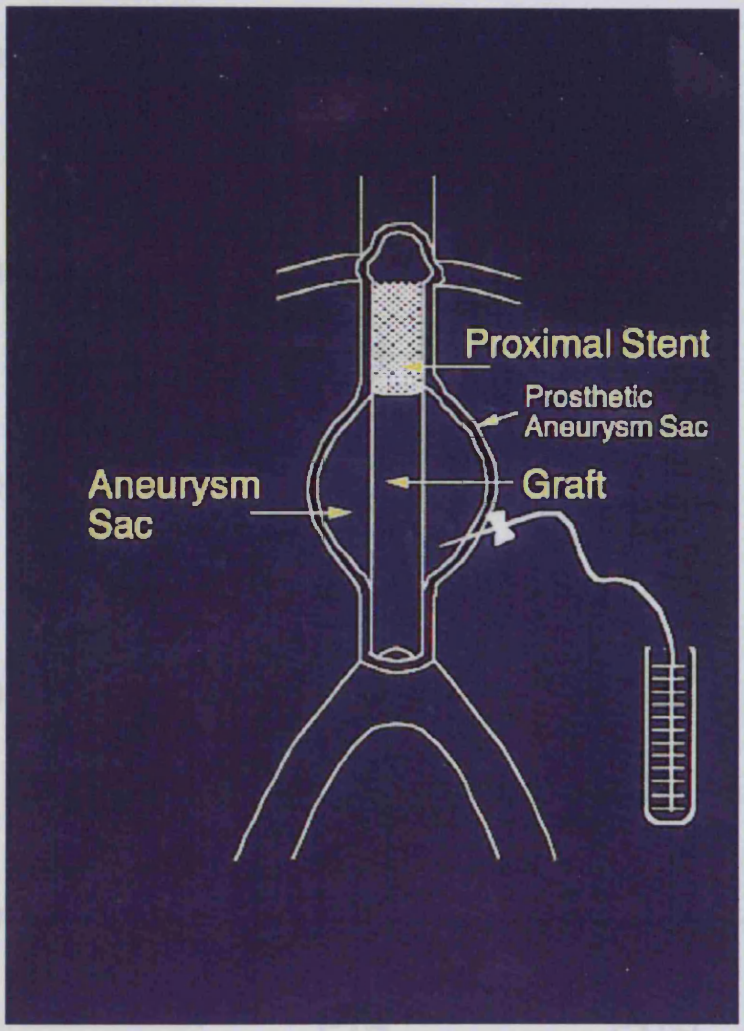


Figure 6.4: *Diagrammatic illustration (lateral view) of measurement of reflux of blood from the distal unstented end of the graft.*

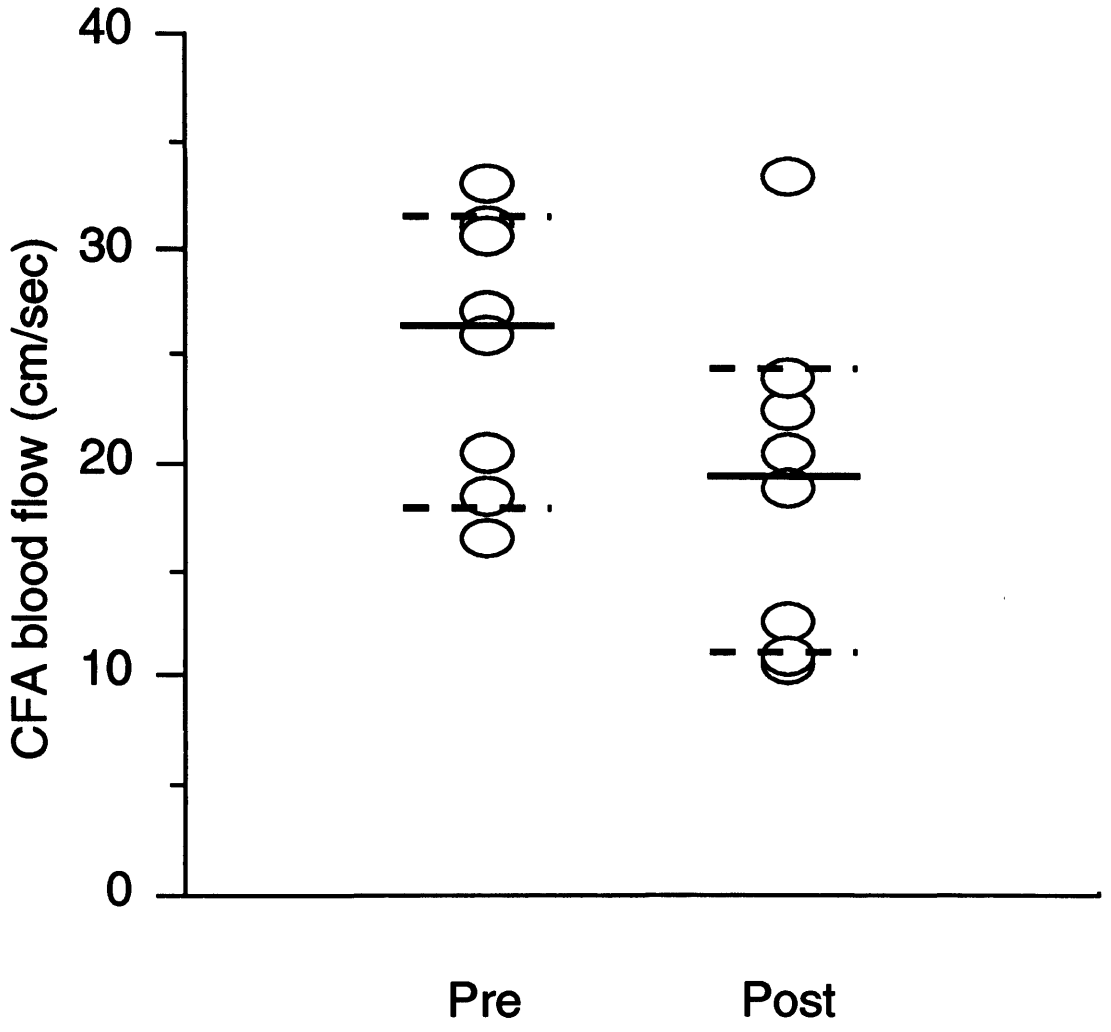


Figure 6.5: *Scatter plot of common femoral artery (CFA) blood flow before and after insertion of the graft-stent combination (solid line=median, dotted lines=95% confidence limits).*

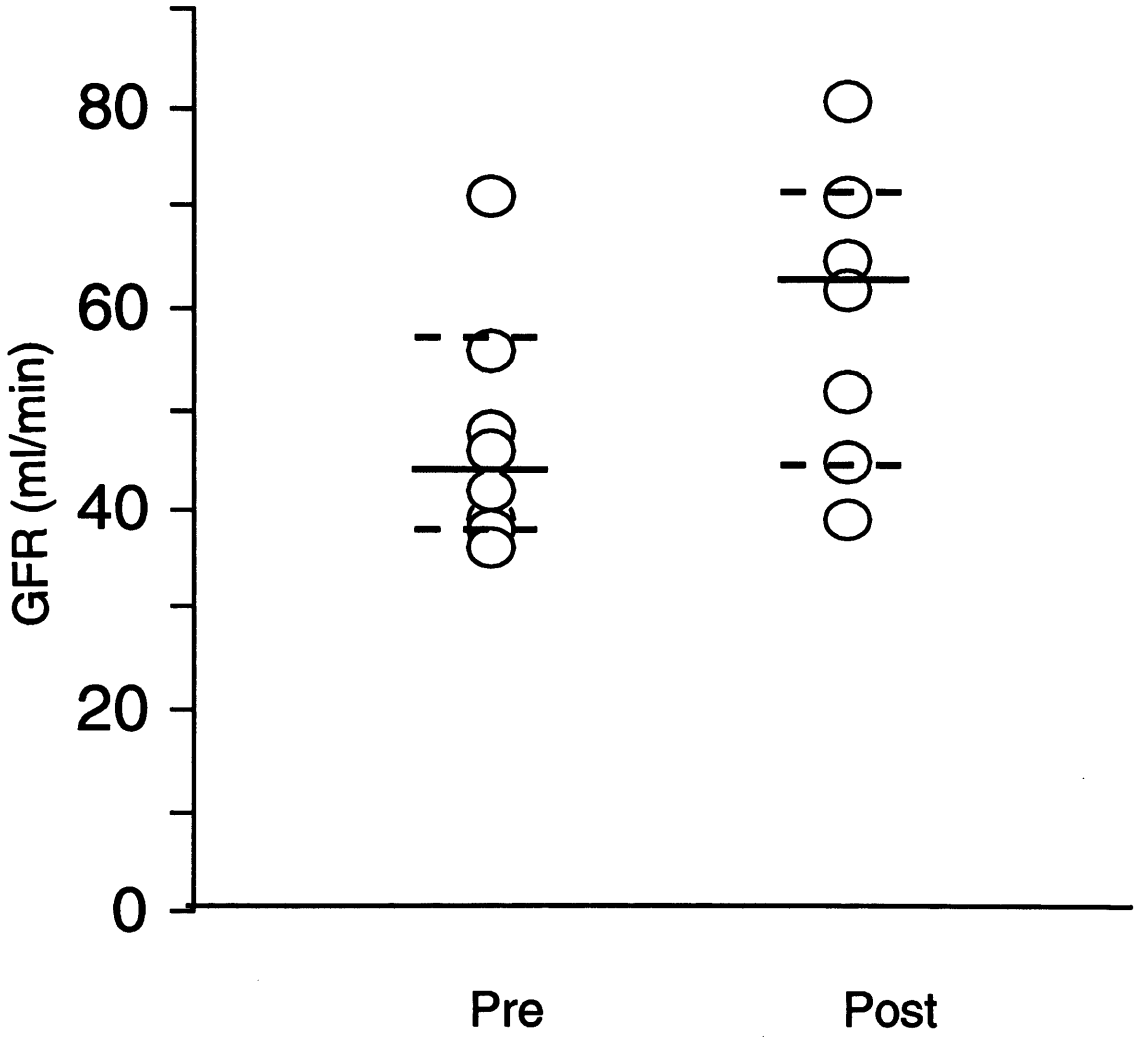


Figure 6.6: *Scatter plot of glomerular filtration rate (GFR) blood flow before and after insertion of the graft-stent combination (solid line=median, dotted lines=95% confidence limits).*

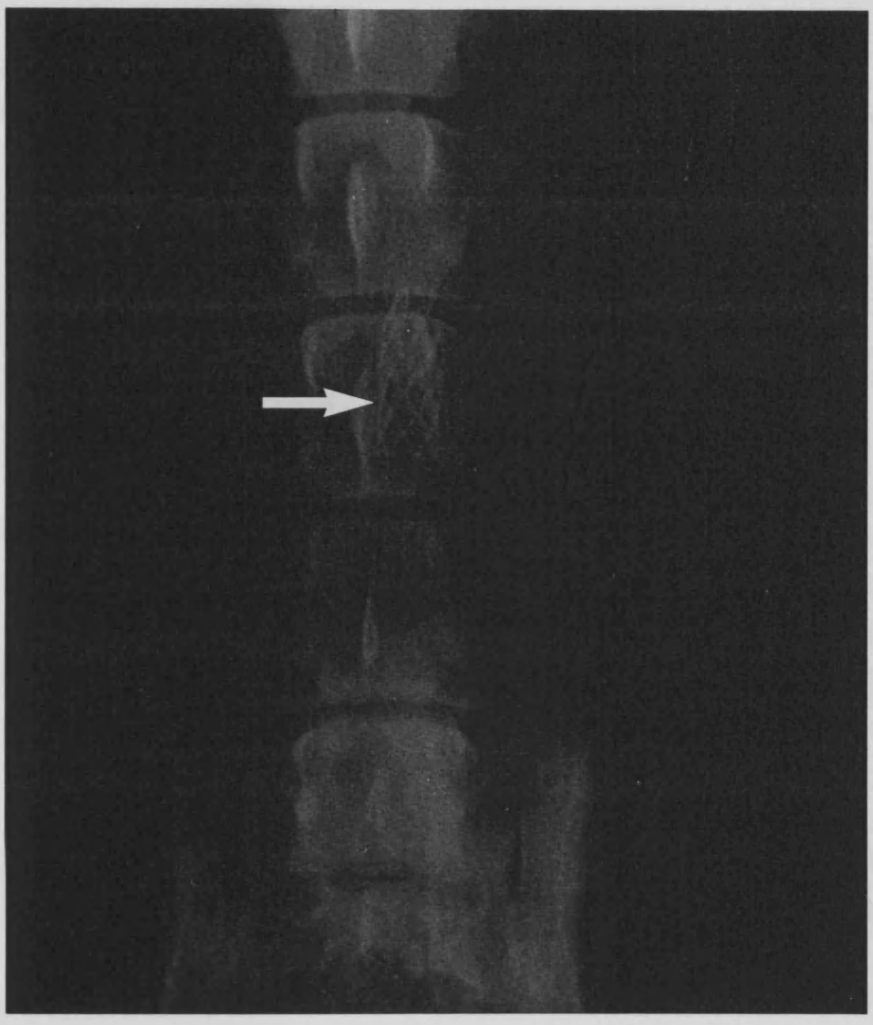


Figure 6.7: *Plain radiograph showing satisfactory expansion of the proximal stent.*

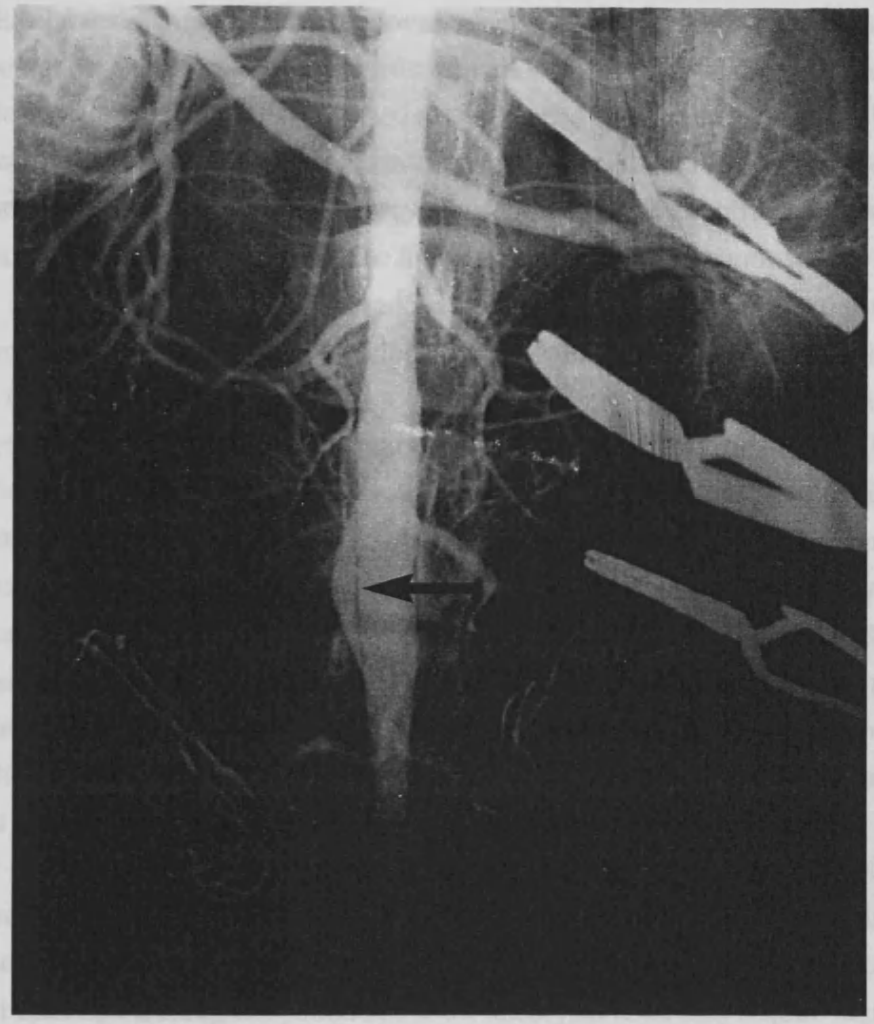


Figure 6.8: *Intra-operative arteriogram showing reflux of blood from the distal unstented end of the graft into the aneurysm sac. Tram-lining caused by presence of contrast medium between the graft and sac can clearly be seen.*

Discussion

Several animal studies, which have differed in the design of the graft-stent combination used, have investigated the feasibility of the technique (Parodi *et al.* 1991; Lawrence *et al.* 1987; Mirich *et al.* 1989; Laborde *et al.* 1992; Chuter *et al.* 1993). These studies have demonstrated that endovascular repair can be performed successfully although complications such as aortic rupture and graft thrombosis have been reported. Initially Parodi *et al.* (1991) reported a small series of patients that had undergone endovascular repair using a single proximal stent technique. However the effects of this technique on femoral and renal artery blood flow, and the occurrence of back-bleeding from the distal end of the graft into the aneurysm sac were unknown.

This study confirms that endovascular repair of abdominal aortic aneurysms is technically feasible and can be performed with minimal morbidity and mortality. However, in 2 cases, the stent was deployed too low in the aneurysm sac resulting in a redundant length of graft at the bifurcation and caused graft thrombosis in one case. This was probably caused by the small diameter of the sheath required for insertion into a 2 mm diameter femoral artery which allowed migration of the graft stent combination on the balloon catheter during deployment due to the increased resistance. Similar problems may occur in patients where the size of the femoral artery will be an important determinant of the size of sheath which can be used to deliver the graft-stent combination to the aortic bifurcation. Patients with small diameter iliac and femoral arteries, and those narrowed by occlusive vascular disease, will be unsuitable for endovascular repair unless pre-dilation with an angioplasty catheter can be performed to allow introduction of the sheath.

Insertion of the graft-stent combination did not significantly affect femoral artery blood flow although loss of the femoral pulse occurred in one case secondary to thrombosis of a malpositioned graft. Similarly renal function was not affected by graft-stent insertion although in patients, a short aneurysm neck may require deployment of the proximal stent close to the renal ostia, which might affect renal blood flow or function.

The most important finding in this study was the presence of back-bleeding from the distal unstented end of the graft into the aneurysm sac. The overall effects of back-bleeding are unknown but it may cause continual aneurysm expansion with the risk of rupture. The single proximal stent technique is therefore inadequate and future attempts at endovascular repair of aortic aneurysms should concentrate on a double (proximal and distal) technique or the development of a bifurcated graft-stent combination.

6.2 Endovascular AAA Repair Using a Double Stent Technique

Introduction

The above study clearly demonstrated that a single proximal stent provided inadequate exclusion of the aneurysm sac from the arterial circulation. Therefore, this study was undertaken to investigate whether use of a proximal and a distal anchoring stent would completely exclude the aneurysm sac. Also if reflux of blood from around the distal end of the graft was abolished, whether lumbar artery back-bleeding would occur into the aneurysm sac and prevent sac thrombosis. We also evaluated the common femoral artery blood velocity, to see whether the double stent had any adverse effects on this.

Materials and Methods

This study was performed in six adult Beagle dogs of median weight 9.8 (range 9.0-10.5) kg. A prosthetic aneurysm was created in a similar way to that described above. Three weeks following creation of a prosthetic aneurysm, each dog underwent insertion of an endoluminal graft. Under general anaesthesia, the left common femoral artery was exposed in the groin and controlled with slings. After systemic heparinisation (50 units/kg), an arteriogram was performed to mark the position of the renal arteries, the aneurysm sac and the aortic bifurcation with the aid of a marker board placed under the animal (*Figure 6.2*).

An 8 mm thin walled Dacron graft was then cut so that the final length of the graft-stent combination with the stent expanded was less than the distance between the renal arteries and the aortic bifurcation. Initially the graft was deployed below the renal arteries using a single proximal stent as described above. The balloon angioplasty catheter was then withdrawn completely, leaving the guidewire and the Teflon sheath in situ. A second Palmaz stent of the same size was then mounted on another 10 mm low-profile balloon angioplasty catheter. This was then introduced over the guidewire into the distal abdominal aorta, and the distal stent deployed inside the distal end of the Dacron graft under fluoroscopic control, taking the previous measurements into account. An angiogram was then performed to assess aneurysm exclusion and graft patency. The sheath and guidewire were then removed, the common femoral artery arteriotomy closed and the animals allowed to recover.

Common femoral artery velocity was assessed on the contralateral undamaged side in awake animals 1 week before and 6 weeks after insertion of the graft-stent combination using a Diasonics DRF 400 colour duplex scanner (Diasonics UK Ltd).

Six months after insertion of the graft-stent combination, a midline laparotomy was

performed under general anaesthesia to expose the prosthetic abdominal aortic aneurysm. The same technique described above was used to assess back-bleeding into the aneurysm sac (*Figure 6.4*). The prosthetic aneurysm sac was then opened through an anterior longitudinal incision to allow inspection of its contents, the presence of blood clot and back-bleeding and the position of the graft-stent combination. After this, the animals were killed with a lethal injection of pentobarbitol.

Results

The procedure was completed successfully in all 6 animals. Arteriography on completion of the procedure showed complete exclusion of the aneurysm sac in 5 out of 6 animals. The median common femoral artery blood flow (*Figure 6.9*) was 19 cm/sec (95% confidence limits 15-25) before graft-stent insertion and 22 cm/sec (95% confidence limits 15-29) after graft-stent insertion. There was no significant difference between these 2 measurements (p=0.4).

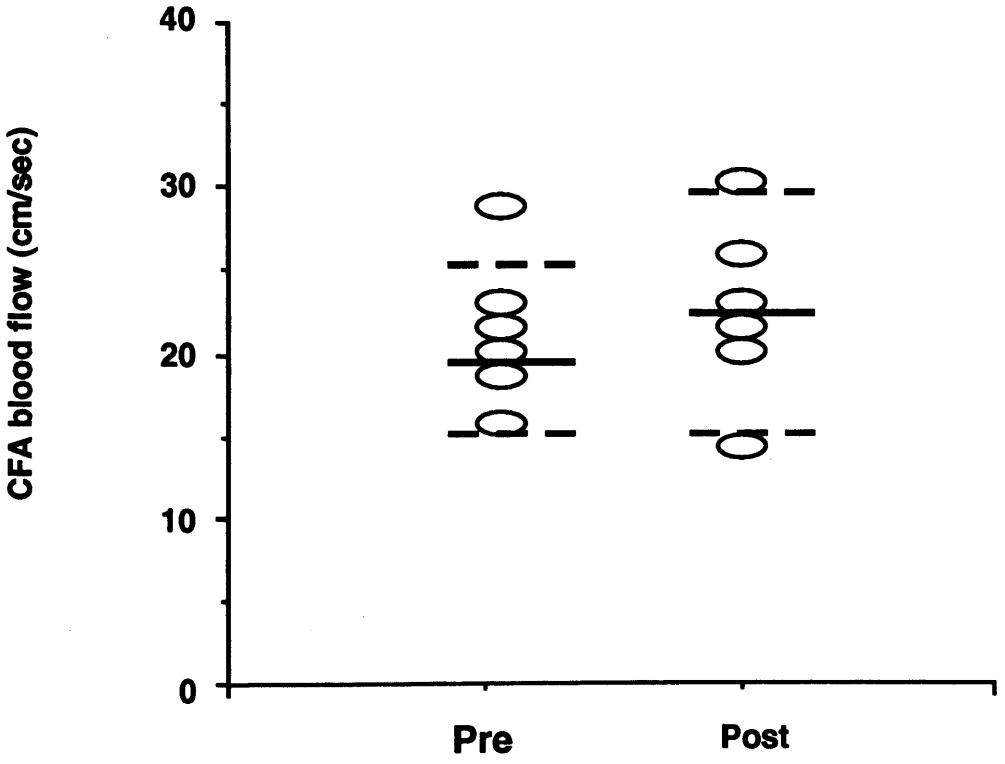


Figure 6.9: *Scatter plot of common femoral artery (CFA) blood flow before and after insertion of the graft-stent combination (solid line=median, dotted lines=95% confidence limits).*

Back-bleeding was only present in one animal (8 ml/min), in which the distal stent was found to be deployed at the origin of the right common iliac artery and the distal end of the graft was not anchored. In the remaining 5 animals, the aneurysm sac was completely excluded and contained well organised thrombus. There was also no lumbar artery back-bleeding. In 3 cases the aortic graft contained longitudinal folds, due to over-sizing of the grafts. This appeared to reduce the lumen in the grafts and there was associated well organised thrombus between the folds. In 2 cases the right common femoral artery was also found to be occluded.

Discussion

The findings of this study suggest that the double stent technique does abolish the lumbar and inferior mesenteric artery back-bleeding and completely excludes the aneurysm sac. The problem of back bleeding in association with a single proximal stent was highlighted by Parodi's initial clinical experience. The first 8 patients he treated, underwent endovascular AAA repair using a single proximal stent. The majority of these patients were noted to have persistent reflux distally into the aneurysm sac on follow-up leading to continued aneurysm expansion and required additional procedures to correct this (Parodi, 1995). Subsequently Parodi has performed all procedures using the double stent technique.

This study also highlights two further problems associated with endovascular AAA repair. Firstly the importance of correct graft sizing. If the graft is oversized, it produces longitudinal folding with compromise of the lumen and risk of graft thrombosis. On the other hand if the graft is small, it may prevent complete exclusion of the aneurysm sac, by restricting the expansion of the stents. The importance of accurate pre-operative assessment of aneurysm morphology will be addressed later in this thesis. The second problem is that of trauma to the femoral or iliac artery caused by insertion of the relatively large diameter sheaths during deployment of the endoluminal grafts. The solution to this problem may lie in better design of prostheses and delivery systems.

6.3 Effects of Stent Deployment Across the Origins of the Renal Arteries.

Introduction

Initial clinical experience has involved insertion of devices where the proximal stent has been deployed below the renal arteries. In some cases accurate positioning of the proximal stent may be difficult particularly if the proximal neck length (distance between the renal arteries and top of the aneurysm sac) is short. The effects of partially or totally covering the renal artery ostia with the proximal stent in such cases are unknown. It has been suggested that covering the origins of the renal arteries will not impede renal artery flow because of the meshed nature of the stent. Alternatively it may cause renal artery thrombosis and impaired renal blood flow or impaired renal function. Also in an effort to broaden the applicability of endovascular AAA repair, it has been proposed that an uncovered segment of the proximal stent could be deployed over the renal arteries when the proximal neck is short.

The aim of this study was to assess ***(1) the effect of stent deployment across the renal arteries on renal function, and (2) to examine the microscopic incorporation and long term effects of the stents on the renal artery ostia.*** A Palmaz balloon expandable stent was chosen, as it is one of the common stents being used in endovascular AAA repair in clinical practice (Johnson and Johnson Interventional systems, Warren, New Jersey, USA).

Materials and Methods

This study was performed in eight adult Beagle dogs of median weight 10.5 (range 9.5-13.5) kg. A prosthetic aneurysm was created in a similar manner to that described above (*Figure 6.1*). The proximal and distal aortic neck distances were recorded. The animals were then allowed to recover. Four weeks later under general anaesthesia, a femoral cut-down was performed and an arteriogram undertaken to accurately determine the position of the renal arteries and the aortic bifurcation. These were marked with the aid of a marker-board placed underneath the animal. A graft-stent combination was then constructed using a 30 mm long Palmaz stent of unexpanded diameter 3.2 mm and expanded diameter 8.0 mm attached to an 8 mm diameter thin walled Dacron graft (Meadox UK Ltd, Caddington, Beds, UK). The graft over-lapped the lower quarter of the stent and was attached by two diametrically opposed sutures of 5/0 proline. The delivery system and the deployment technique was the same as described in the first experiment. Under fluoroscopic control, the proximal uncovered part of the stent was deployed directly

opposite the origins of the renal arteries.

Renal blood flow was assessed by arteriography using a 5F angiographic catheter, immediately following stent deployment and 9 months later at termination of the experiment. As the distal end of the graft was not stented in these animals, the trans-femoral approach was avoided in case the guidewire or catheter insertion produced a dissection outside the in-situ graft. Therefore the latter arteriograms were performed using a carotid artery cut-down, under brief general anaesthesia, to avoid damage or disturbance to the in situ stent-graft. Renal function was assessed by determining the glomerular filtration rate before deployment of the stent and at 1 and 3 weeks following the procedure, using the technique described previously. In order to avoid excessive use of animals, the animals from the first experiment were used as historic controls in the analysis of renal function.

The animals were sacrificed at 9 months with a lethal dose of intravenous pentobarbitol. The abdomen was opened and the abdominal aorta together with both kidneys were harvested.

Histological examination

The specimens of aorta were fixed for 24 hours under pressure with 4% buffered glutaraldehyde. These were then opened longitudinally and samples taken for histology and electron microscopy to include: the stent, the Dacron graft, junction of the stent and graft, and the origins of both renal arteries. The samples were dehydrated through graded alcohols and those for histology and transmission electron microscopy embedded in resin (methylmethacrylate), and sections cut using a Reichart-Jung Ultracut with a glass knife. Specimens for scanning electron microscopy were critical point dried after dehydration and mounted onto a copper stub using Araldite. The specimens were then sputter coated with gold.

Tissue specimens were taken from the harvested kidneys to include 2 blocks each from upper poles, lower pole and central area of renal parenchyma. A section including renal pelvis and vascular pedicle was also included. The tissue was routinely processed, paraffin embedded and 4 um sections cut for haematoxylin and eosin staining.

Results

In one animal the stent was deployed below the renal arteries by error, and was excluded from further analysis. In the remaining 7 animals the stent was deployed satisfactorily at the level of the renal arteries. Arteriography demonstrated unilateral renal artery occlusion in 1 out of the 7 animals, immediately following deployment of the stent (*Figure 6.9*). One of the animals developed paraplegia post-operatively and was sacrificed after 3 weeks. No further renal artery occlusions were demonstrated in the remaining 6

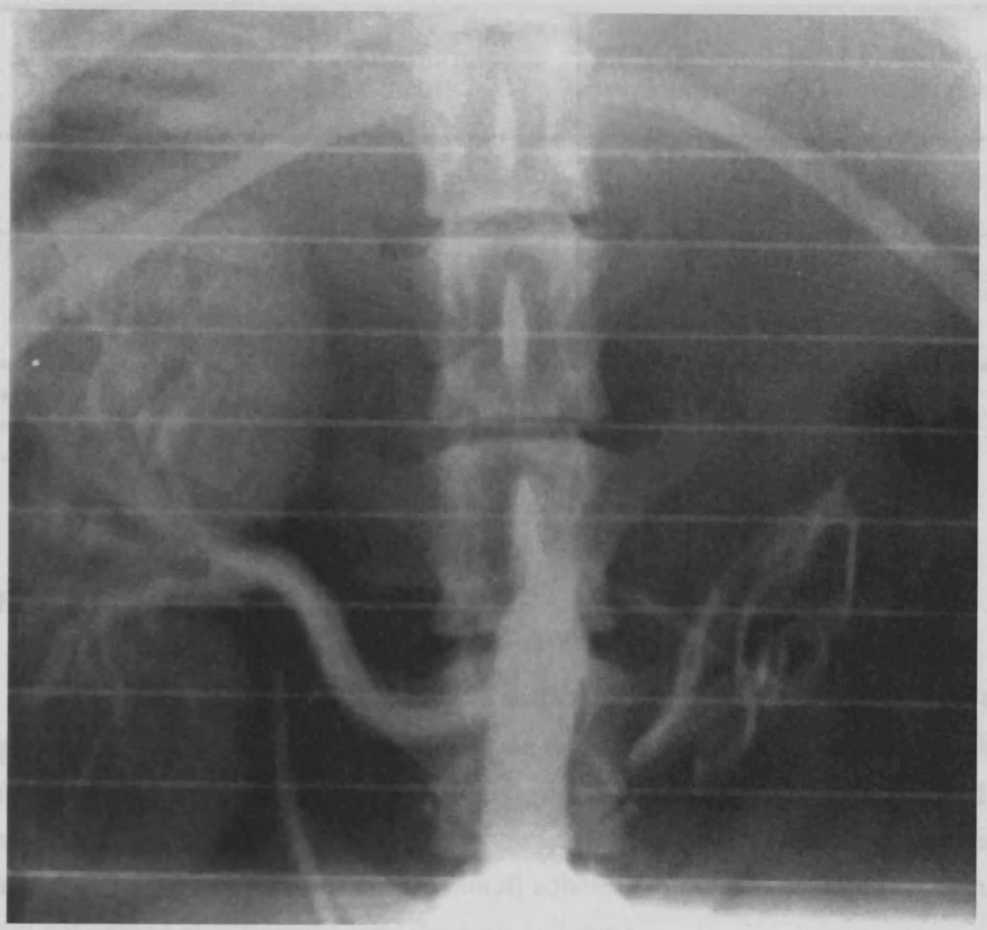


Figure 6.10: *Angiogram demonstrating complete occlusion of the left renal artery. Note the slight bulge in the juxta-renal aorta produced by slight over expansion of the stent.*

animals on arteriography at 9 months. *Table 22* summarises the renal function results in the two groups of animals. The values are given as medians with 95% confidence intervals. There was no statistically significant difference between the two groups pre-operatively, at 1 week and 3 weeks post-stent deployment.

Table 22: *A comparison of the renal function in the two groups.*

Site of stent	GFR (ml/min) Pre-stent	GFR (ml/min) 1 week post-stent	GFR (ml/min) 3 weeks post-stent
Infra-renal (n=8)	44 (38-57)*	64 (45-72)**	48 (41-69)***
Across renal ostia (n=7)	47 (36-62)*	85 (45-111)**	51 (39-71)***

*)
**) (p>0.05, Mann-Whitney U test)
***)

Histology

Macroscopic examination of the aortic specimens showed that in 6 of 7 cases the graft was in the correct place and patent. In one case, there was thrombotic occlusion of the graft throughout its length. The stents were easily defined and were covered by a smooth transparent layer of tissue. In contrast the lining of the Dacron grafts was white and opaque, and there were multiple small adherent thrombi. The lining covering the stent did not extend significantly over the graft (<2 mm).

The unilateral renal artery occlusion was confirmed on scanning electron microscopy , and contained well organised thrombus. The ostia of the renal arteries were bridged by the stent in 7 animals (*Figure 6.10*). Scanning electron microscopy was used to carefully examine the site of the renal artery ostia. In some cases the strut was directly overlying the central lumen of the artery, whereas in others it appeared to occupy the lateral half of the lumen. The latter position was associated with changes in the surface overlying the strut and the endothelial lining of the renal artery. The smooth intact endothelium over the strut was disrupted with exposure of underlying fibrous layer. The adjacent renal artery revealed similar disruption of the endothelial layer and in 2 cases there was associated thrombus formation, causing partial occlusion (*Figure 6.11*). These

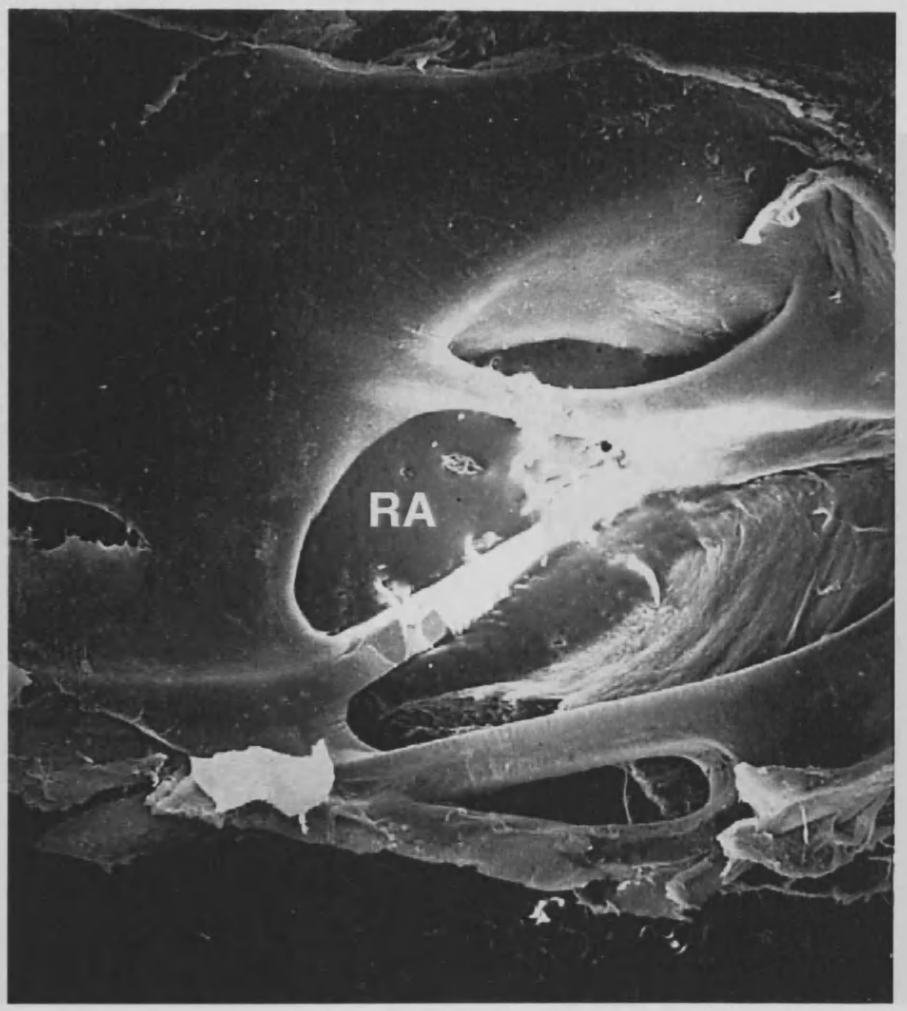


Figure 6.11: *Scanning electron micrograph showing struts of the stent bridging the ostium of a renal artery (RA). There is some 'minor' trauma to endothelium over the stent but no evidence of thrombus in the lumen.*

Figure 6.12: *Scanning electron micrograph showing partially occlusive thrombus within the lumen of the renal artery, bridged by the stent.*

changes appeared to be more marked in those cases in which the strut occupied a greater surface area of the lumen. A number of lumbar arteries bridged by the stent appeared to be totally occluded by well organised thrombus (*Figure 6.12*).

Histologically, the site of the stent could be identified on sections as spaces where the metal strut had been removed. A consistent finding was a marked fibrous reaction around the struts, with dense compact fibrous tissue occupying up to half of the vessel wall thickness (wall thickness 200 um, fibrous reaction 90 um). The surface appeared to consist of a flattened cell layer, but these cells did not stain with immunocytochemical techniques for the human endothelial markers: Factor VIII, Von Willebrand Factor (VWF), CD 31, CD 34 or Q-Bend 10 (the specimen embedded in resin to enable sectioning with the stent in place; antibodies did not work on resin embedded tissue). On scanning EM, however, the stent was found to be covered with an intact endothelial cell layer (*Figure 6.13*). The Dacron grafts were also covered by a relatively thick layer of fibrous tissue and demonstrated variable endothelialisation.

In the animal with the unilateral renal artery occlusion the affected kidney had atrophied. All the other kidneys were of normal size and there was no evidence of scarring or recent infarction. Histologically, there was interstitial calcification (but also seen in controls) but there were no microinfarcts and the glomeruli appeared normal with occasional sclerotic forms. The histological appearances associated with arterial stents in animal models have been well described by other authors (Balko *et al.* 1986; Lawrence *et al.* 1987; Mirich *et al.* 1989) and have not been duplicated in this study. It is not clear as to whether the interstitial calcification observed above is a normal finding in unoperated animals. However, there was no obvious difference in the extent of calcification between controls and animals with stents deployed across the renal arteries.

Discussion

Previous studies in which the renal arteries have been accidentally bridged by stents have shown that these have remained patent and there was no evidence of renal emboli or infarction (Lawrence *et al.* 1987; Whitbread *et al.* 1996).

The exact cause for the unilateral renal artery occlusion in one of the animals immediately following stent deployment is unclear. The struts of the stent did not appear to cover the ostium of the artery and the graft was well away from the lumen. This would lead us to hypothesise that the renal artery occlusion may have been caused by intimal trauma either by guidewire manipulation or the stent, during deployment.

Although the results of renal function and arteriography did not show any long term adverse effects of the stents bridging the renal arteries, the scanning electron microscopy findings are of concern. In a number of animals well organised thrombus was found to be partially occluding the lumen of the renal artery. The exact cause for this

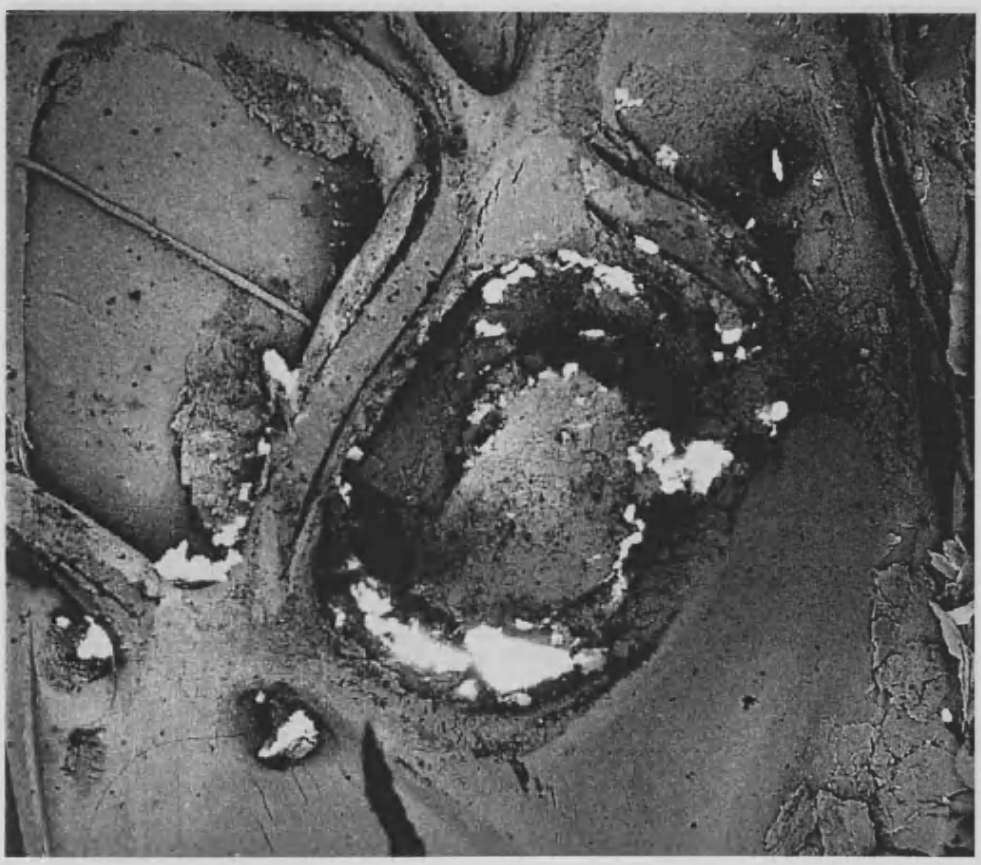


Figure 6.13: *Scanning electron micrograph showing occlusion of a lumbar artery bridged by the stent.*

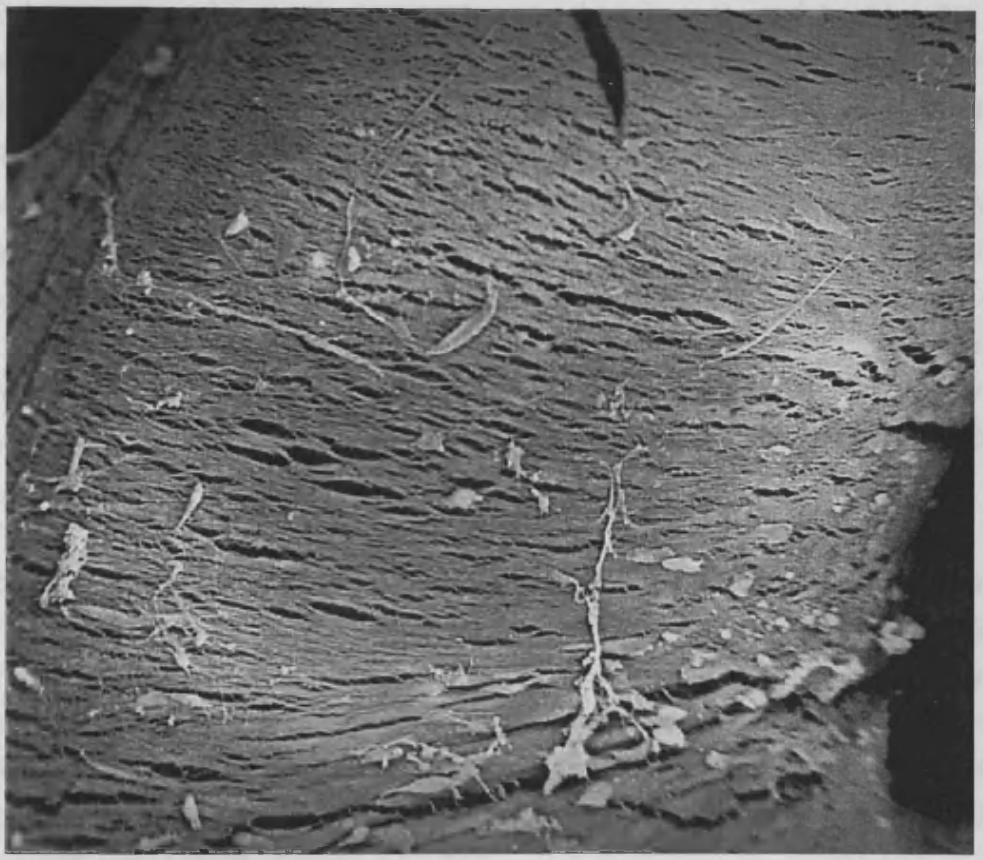


Figure 6.14: *Scanning electron micrograph showing a smooth layer of endothelium covering a strut of the stent.*

thrombus is unclear. The associated disruption in the endothelium over the strut may have acted as a nidus for the thrombus. The fact that these changes appeared to be more marked in those cases in which the strut occupied a greater surface area of the lumen (at least one of the struts passed across the contre of the ostium), leads us to postulate that flow disturbance may also be a possible factor in this process.

Animal studies so far, including our work, suggest that the effects of placing stents across the renal arteries is dependent not only on the method and accuracy of deployment, but also on the shape and composition of different stent struts (Birch *et al.* 1996; Lindh *et al.* 1996; Whitbread *et al.* 1996). Stents constructed from stainless steel alloys, such as the Palmaz stent used in our work, are inherently thrombogenic, and thrombus has been shown to accumulate to some degree on all metallic stents after implantation (Baier *et al.* 1969). Indeed in superficial femoral and coronary arteries, thrombosis occurs in up to 30-40 percent of cases within the first few days after balloon angioplasty and stent implantation (Richter *et al.* 1992; Puel *et al.* 1987a). Similarly the struts of the Memotherm stents, which are constructed from nickel titanium alloy, have a roughened laser-etched surface and are very thrombogenic, causing ostial occlusion in almost all cases when placed across a renal artery ostium in a porcine model (Birch *et al.* 1996). In contrast, the Wallstent which has smooth rounded struts of knitted spring steel wires, appears to have little deleterious effects on ostial patency or renal function in a porcine model (Whitbread *et al.* 1997).

However, the work in animal models has to be interpreted with caution when considering the effects of placing stents across the renal arteries in humans. The arteries in the animal models are relatively free of atherosclerotic disease, whereas a significant proportion of patients with AAA have associated renal occlusive disease (Olin *et al.* 1990). Also the effective functional renal mass decreases with age in humans (Miller *et al.* 1987). These factors may also influence the outcome in clinical practice. Deployment of the stent could theoretically distort the atherosclerotic plaque adjacent to the renal ostia, thereby causing renal emboli or acute occlusion.

In conclusion, the safety of placing stents across the renal arteries remains uncertain. The findings of our study suggest that in the long-term, it may have deleterious effects. However, further evaluation is required if clinical application of this technique is to be considered.

6.3 Summary of Experimental Animal Work

Table 24: *Overall results and complications.*

Type of experiment	**Total no. of animals used**	**No. of failed procedures**	**Overall results**	**Complications**
Single proximal stent *-backbleeding* *-CFA flow* *-GFR*	8	2 (graft deployed too low in aneurysm)	Backbleeding from distal end in 6/6 animals No significant effect on CFA flow or GFR	CFA thrombosis (1)
Double stent *-backbleeding* *-CFA flow*	6	1 (distal stent deployed too low)	aneurysm completely excluded in all 5 cases with no backbleeding	CFA occlusion (2)
Stent across RA *-GFR* *-angiography* *-histology*	8	1 (stent deployed below the renal ostia by error)	1 out of 14 renal arteries occluded No effect on GFR	paraplegia in 1 animal

CFA - common femoral artery *GFR - glomerular filtration rate* *RA - renal artery*

CHAPTER SEVEN

Comparison Of Computed Tomography, Colour Duplex, Arteriography And Magnetic Resonance Angiography In Assessing AAA Prior To Endoluminal Repair

7.1 Introduction

For conventional open repair of abdominal aortic aneurysms, an ultrasound scan alone may be adequate for pre-operative assessment of aneurysm size and morphology. A contrast enhanced computed tomography scan (CT) or an arteriogram may be required if renal artery involvement or associated distal arterial occlusive disease is suspected. Endoluminal AAA repair, however, requires a more detailed assessment of the abdominal aorta for determining patient suitability and accurate sizing of the intraluminal prosthesis (Thompson *et al.* 1995). The best method of pre-operative evaluation in these patients remains to be determined.

Neither CT or arteriography are completely reliable in predicting the proximal or distal extent of AAA (Salaman *et al.* 1994). With conventional CT, the renal artery origins are often not visualised, as they may fall between slices, and have to be inferred from the surrounding anatomy. Tortuosity of the aneurysm sac may also result in oblique images of the aorta, and lead to inaccuracies in assessing proximal and distal aortic involvement. Some of these problems, however, may be addressed using spiral CT, with three dimensional reconstructed images. A major drawback of angiography is that in the presence of mural thrombus, the external extent of the AAA sac is not visualised. This obscures the proximal and distal limits of the sac, and the normal calibre of the lumen may be mistaken for normal aorta, with over estimation of the proximal and distal neck lengths.

Recent studies using magnetic resonance angiography (MRA) suggest that this may be a better tool in assessing AAA morphology than conventional cross sectional imaging (Durham *et al.* 1993; Ecklund *et al.* 1994; Prince *et al.* 1995). Previously spin-echo (SE) magnetic resonance imaging (*Figure 7.1*) only provided limited detail of the aortic branch vessel anatomy. However, the development of MR angiography using gradient echo techniques combined with contrast enhancement (*Figure 7.2*) has overcome many of these limitations (Prince *et al.* 1995; Cherryman *et al.* 1994).

A prospective study was undertaken to assess the ability of CT, MRA, colour duplex (CD), and intra-arterial digital subtraction arteriography (IA-DSA) to visualise AAA morphology. The principal aims of this study were:

(i) What is the best imaging modality for assessing AAAs for endovascular repair?
(ii) Are the femoral and iliac vessels suitable for insertion of the devices?
(iii) Is the proximal neck (the cuff of undilated aorta between the lowermost renal artery and the start of the aneurysm) suitable?

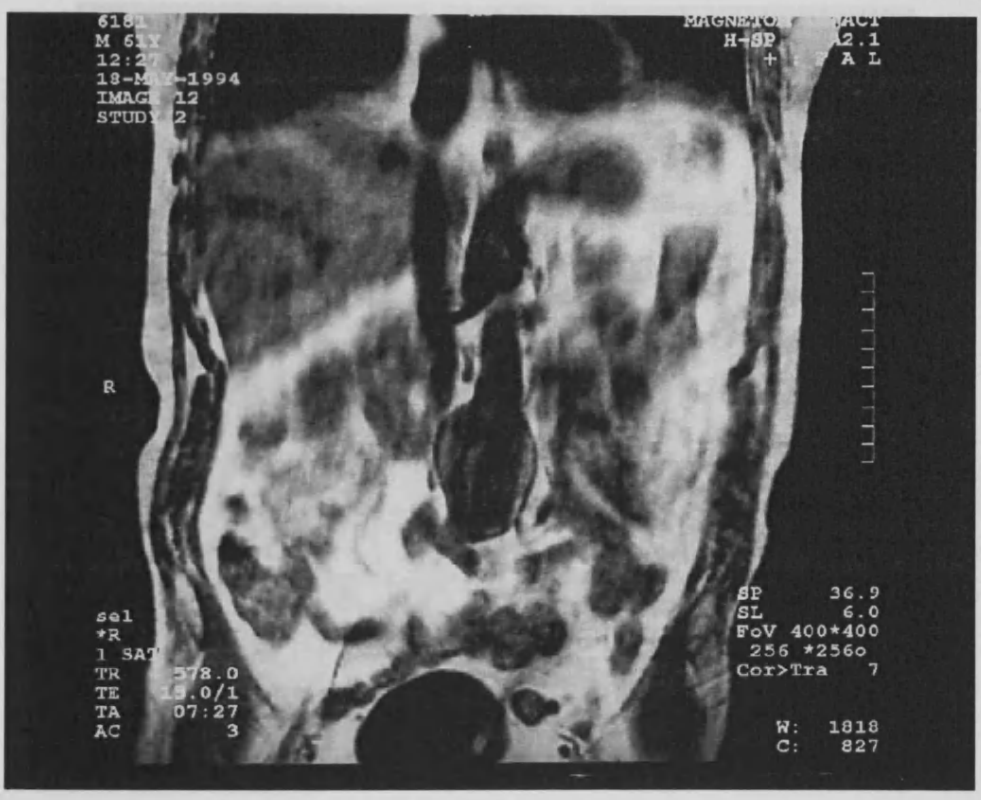


Figure 7.1: *An image of an abdominal aortic aneurysm obtained using conventional MRI (spin echo sequence).*

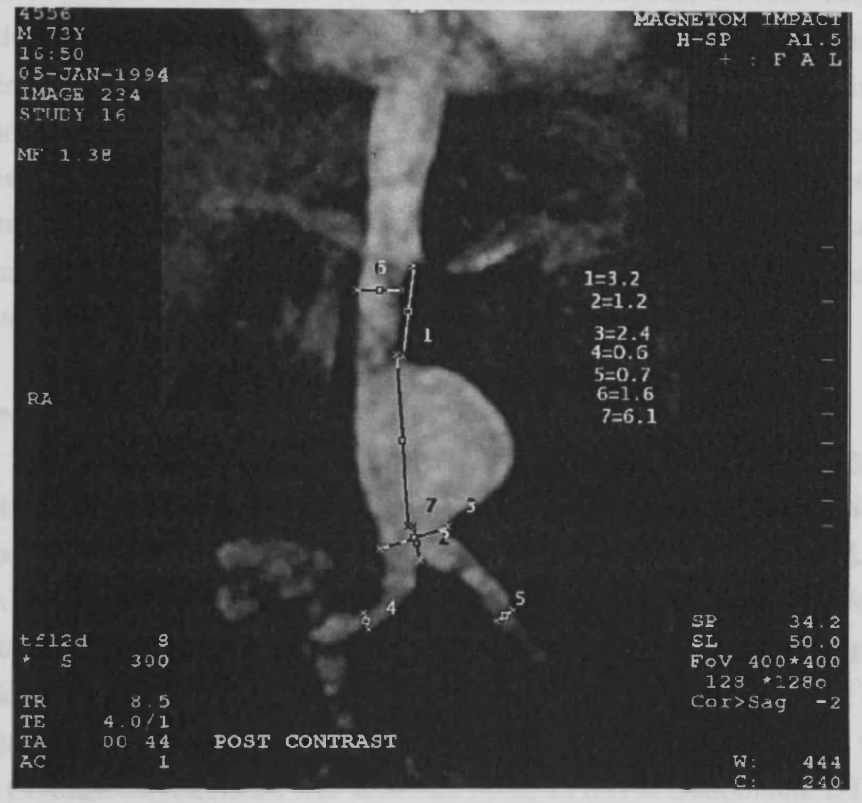


Figure 7.2: *An image of the abdominal aorta obtained using MRA (gradient echo sequence) demonstrating the origin of the renal arteries, the infra-renal AAA, and tortuosity of the iliac arteries.*

(iv) Is the distal neck (segment of normal aorta between the lower end of the aneurysm and the bifurcation) suitable?
(v) What proportion of the aneurysms are suitable for endovascular repair?

7.2 Materials and Methods

Asymptomatic abdominal aortic aneurysms referred to Leicester Royal Infirmary between January 1994 and July 1995 underwent assessment with MRA, contrast enhanced CT scanning and CD. Those patients with favourable anatomy for endoluminal repair on the basis of these 3 non-invasive imaging modalities, underwent further assessment with IA-DSA. The ability of each test to visualise the following parameters was determined: right and left renal artery origin, proximal neck length, maximum antero-posterior diameter, tortuosity of aneurysm sac, distal neck length, tortuosity of iliac arteries and iliac artery diameter. The proximal neck was defined as the non-aneurysmal segment of the aorta (<30 mm) between the origin of the lowest renal artery and start of the aneurysm (aortic diameter > 30 mm) and the distal neck was defined as the length of non-aneurysmal segment before aortic bifurcation. Local ethical committee approval was obtained and all patients gave informed consent.

Magnetic Resonance Angiography

All scans were performed on a Siemens (Siemens AG, Postfach 2348, Fuerth, Germany) 1T scanner employing 10mT/m gradients and a 50 cm body coil. A rapid magnetisation prepared, 2D gradient echo multiplanar sequence (TurboFLASH-TR 8.5, TE 4, TI 300, FA 8, 128x128, FOV 400 x 400, 8 mm thick) was used. Four discrete blocks of slices were positioned to directly acquire images in the coronal plane (11 slices), sagittal plane (7 slices) and obliquely along the line of the renal arteries (7 slices each). Thirty-two slices were obtained per measurement and four measurements were made in total. Contrast enhancement was achieved using 15 mls of Gadolinium DTPA (Magnevist - Schering, West Sussex, UK) diluted to 30 mls with normal saline. A 19 gauge butterfly cannula was sited in an antecubital fossa vein and connected to an extension tube flushed with saline. Timing of the contrast injection was such so as to allow a pre-contrast measurement, one during the arterial phase, one in the venous phase and a final steady state measurement. A hand injection of contrast at approximately 1 ml/second was commenced after acquisition of the twentieth slice during the first measurement. This allowed approximately 15 seconds for the contrast to reach the abdominal aorta prior to the next measurement during which the contrast concentration would be at a peak while the venous enhancement remained small. All scans were obtained during quiet respiration. Total scanning time was 3 minutes.

Images were viewed either from the source images or were post-processed using

maximum intensity projection to create angiographic type images in each of the four planes: coronal, sagittal, and two para-oblique. The definition of the start and the end of the aneurysm was either where an obvious neck could be identified or at the point at which the aorta measured 3.0 cm in diameter. The proximal neck length was taken from the origin of the renal arteries; the distal neck length was taken to the inferior aspect of the aortic bifurcation.

Computed Tomography

CT scans were performed using a Siemens (Siemens AG, Postfach 2348, Fuerth, Germany) HiQ scanner. Contiguous slices of 10 mm thickness were obtained from the diaphragm inferiorly. On reaching the renal vessels 3 mm slices were used, and a similar scanning technique was used through the region of the aortic bifurcation. The intervening aorta was scanned with 10 mm slices. 100 mls of contrast (Omnipaque 320, Nycomed) was hand injected at approximately 2 mls per second when scanning from the level of the renal vessels, which was performed dynamically in quiet respiration and commenced after a 40 second delay.

Colour Duplex

Colour duplex examinations were performed with an Advanced Technology Laboratories Ultramark-9 HDI colour scanner (Advanced Technologies Ltd., Washington, District of Columbia, USA), equipped with a curvilinear-array abdominal transducer. All examinations were performed by an experienced vascular technician using a colour Doppler imaging frequency of 3.0 MHz, and a pulsed Doppler frequency of 2.5 MHz. Examinations were performed with the patient lying supine. The aneurysm was scanned in both transverse and sagittal planes. Colour flow was used to identify the origin of the renal arteries.

Intra-arterial DSA

IA-DSA was performed by percutaneous catheterisation of the femoral artery using the Seldinger technique. A pigtail marker catheter (15 radio-opaque markers at 1 cm intervals) with eight side-holes (6F, 65 cm long: Cordis Corporation, Miami, Florida, USA) was used. Eighty mls of contrast (Omnipaque 300, Nycomed, Sheldon, Birmingham, UK) were injected at 20 mls/s using Medrad Mark V injector (Medrad Inc., Pittsburgh, USA). Anteroposterior and lateral views of the abdominal aorta, and anteroposterior and oblique views of the iliac arteries were obtained with Siemens Multiskop equipped with a Digitron computer system (Siemens AG, Postfach 2348, Fuerth, Germany).

7.3 Results

A total of 82 patients were assessed over the study period. There were 64 males and 18 females (3.5M:1F) and the median age was 74 years (range 59-87). The median AAA diameter, based on MRA, was 5.7 cm (range 3.5-9.7). Five patients did not tolerate CT (1) or MRA (4) examination because of claustrophobia and were excluded from analysis.

Comparison of MRA, CT, CD and IA-DSA.

Seventy-seven patients successfully underwent both CT scanning and MRA. Of these 55 also had a CD scan and 32 proceeded to IA-DSA. The scans were assessed by an independent blinded observer. The results are presented as the percentage of patients in whom the following parameters could be adequately assessed with each investigation:

(i) right renal artery
(ii) left renal artery
(iii) proximal neck length
(iv) maximum AP diameter
(v) AAA sac tortuosity
(vi) distal neck length
(vii) tortuosity of iliacs
(viii) diameter of iliac arteries

The results are presented in *Table 24.* Visualisation was considered to be adequate if 6 or more parameters (out of maximum of 8) were identifiable (including at least one of the renal arteries). Statistical analysis using the Chi-squared test showed MRA to be significantly better ($p<0.01$) at visualising AAA morphology in comparison with CT and Colour Duplex (*Figure 7.3*). There was no statistically significant difference between MRA and arteriography.

Aortic aneurysm morphology

On the basis of the above results, MRA images in 78 patients were used to study AAA morphology and determine suitability for endoluminal repair. Four distinct morphological groups were identified when applying the current criteria for endoluminal repair (*Table 25)*:

(i) *aneurysms with a sufficient proximal and distal neck* (Figure 7.4a),
(ii) *aneurysms with a sufficient proximal neck but insufficient distal neck or iliac involvement* (Figure 7.4b),
(iii) *infra-renal aneurysms with insufficient proximal neck* (Figure 7.4c), and
(iv) *aneurysms with para- or supra-renal extension* (Figure 7.4d).

Detailed aneurysm measurements of each group are summarised in *Table 26.*

TABLE 24: *Comparison of visualisation of aneurysm morphology with each modality. The results are presented as % of patients in whom each parameter was adequately visualised.*

Parameter	CT	MRA	CD	IA-DSA
Right renal artery	63.6	90.9	50.9	100
Left renal artery	77.9	97.4	50.9	100
Proximal neck length	80.5*	94.8	50.9	78.1
Maximum AP diameter	100	100	98.2	6.25
AAA sac tortuosity	0	100	94.5	96.9
Distal neck length	92.2	98.7	94.5	59.4
Tortuosity of iliacs	0	90.9	85.4	100
Diameter of iliac arteries	90.9	84.4	78.2	100

** In some patients this measurement was inferred from visualisation of a single renal artery origin.*

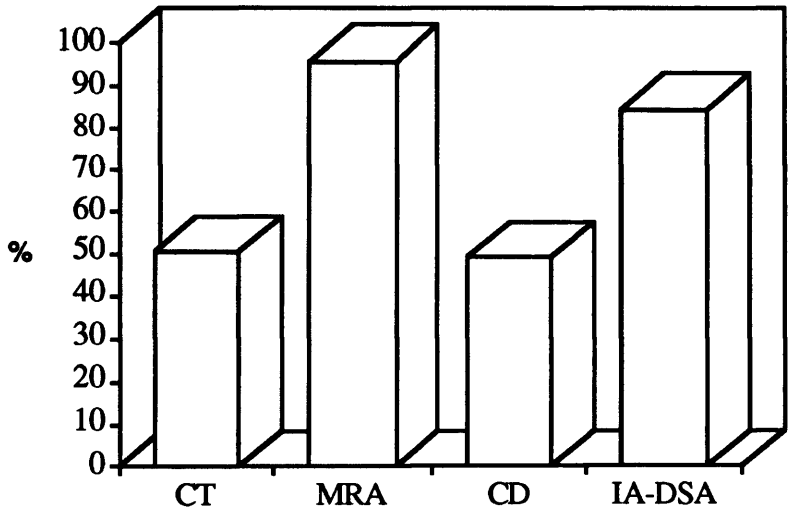


FIGURE 7.3: *Percentage of patients in whom 6 or more parameters were adequately visualised.*

TABLE 25: *The current anatomical criteria used for endoluminal AAA repair, with tube and bifurcated devices.*

	Tube	**Bifurcated**
Proximal neck length (mm)	15	15
Proximal neck diameter (mm)	< 26	< 26
Distal neck length (mm)	10	0
Minimum Iliac artery diameter (mm)	8	8
Maximum Iliac artery diameter (mm)	-	14

**Severe aneurysm and iliac artery tortuosity (change in direction >60°) also contraindicate endoluminal repair.*

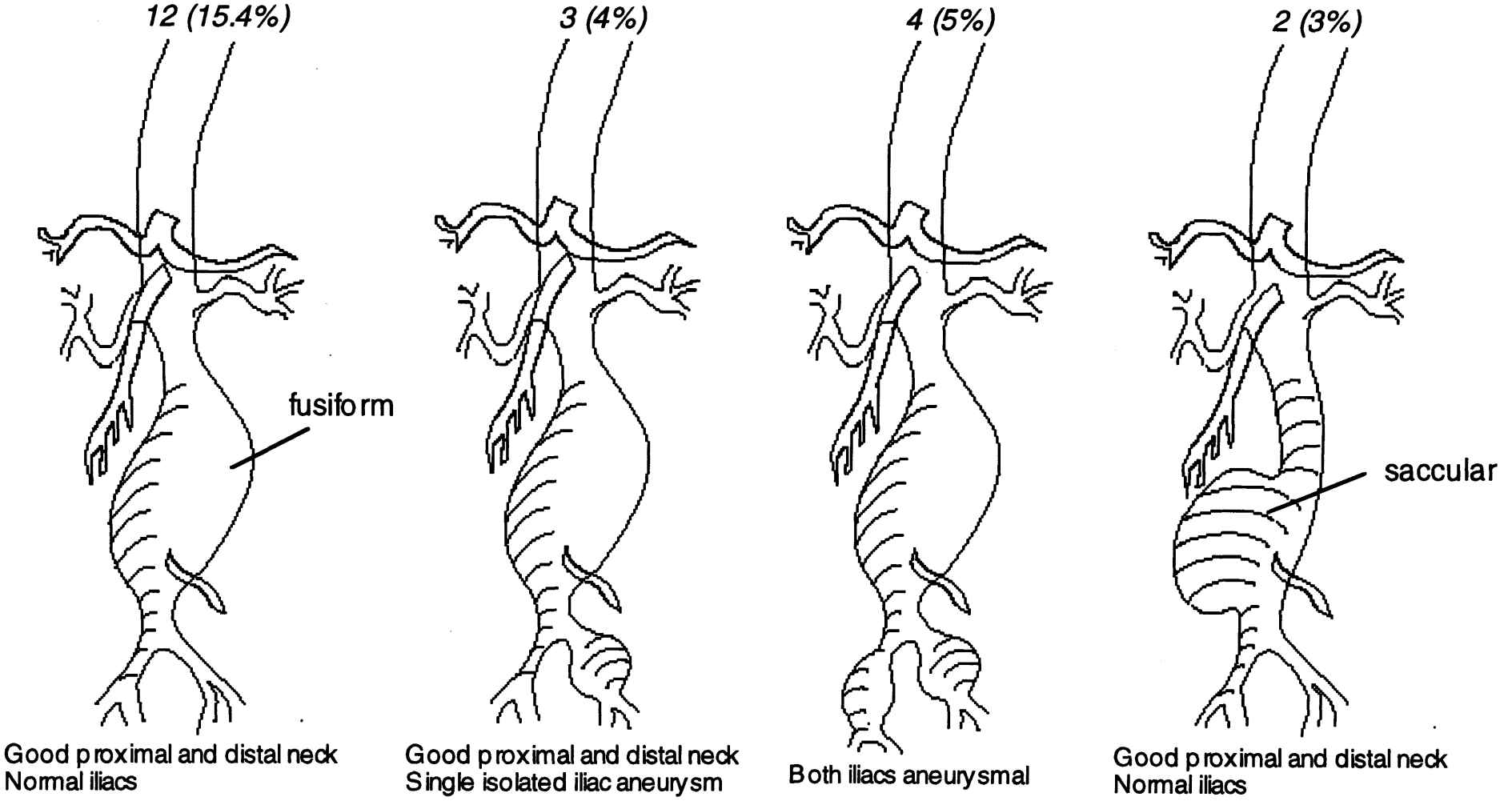


Figure 7.4a) *Aneurysms with a sufficient proximal and distal neck, including those with associated isolated iliac aneurysms. The figures in parenthesis represent the percentage of patients.*

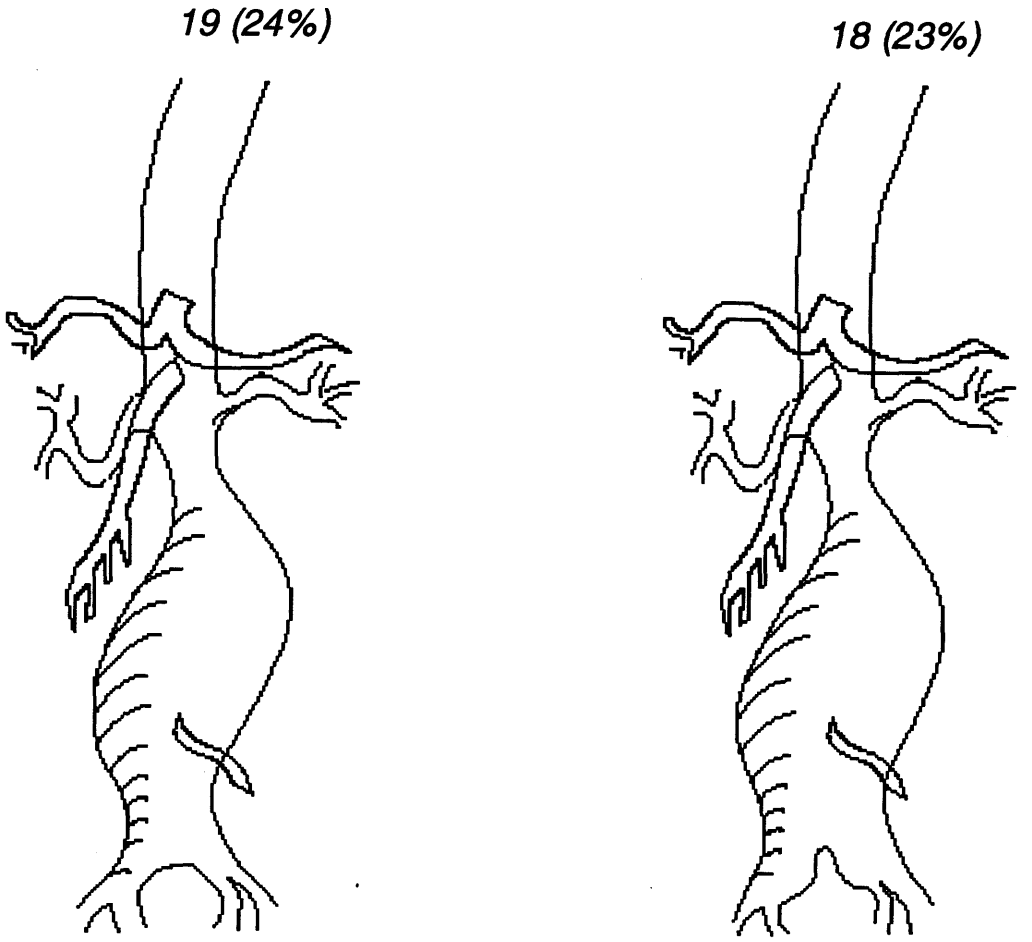


Figure 7.4b) *Aneurysms with a sufficient proximal neck but insufficient distal neck or iliac involvement.*

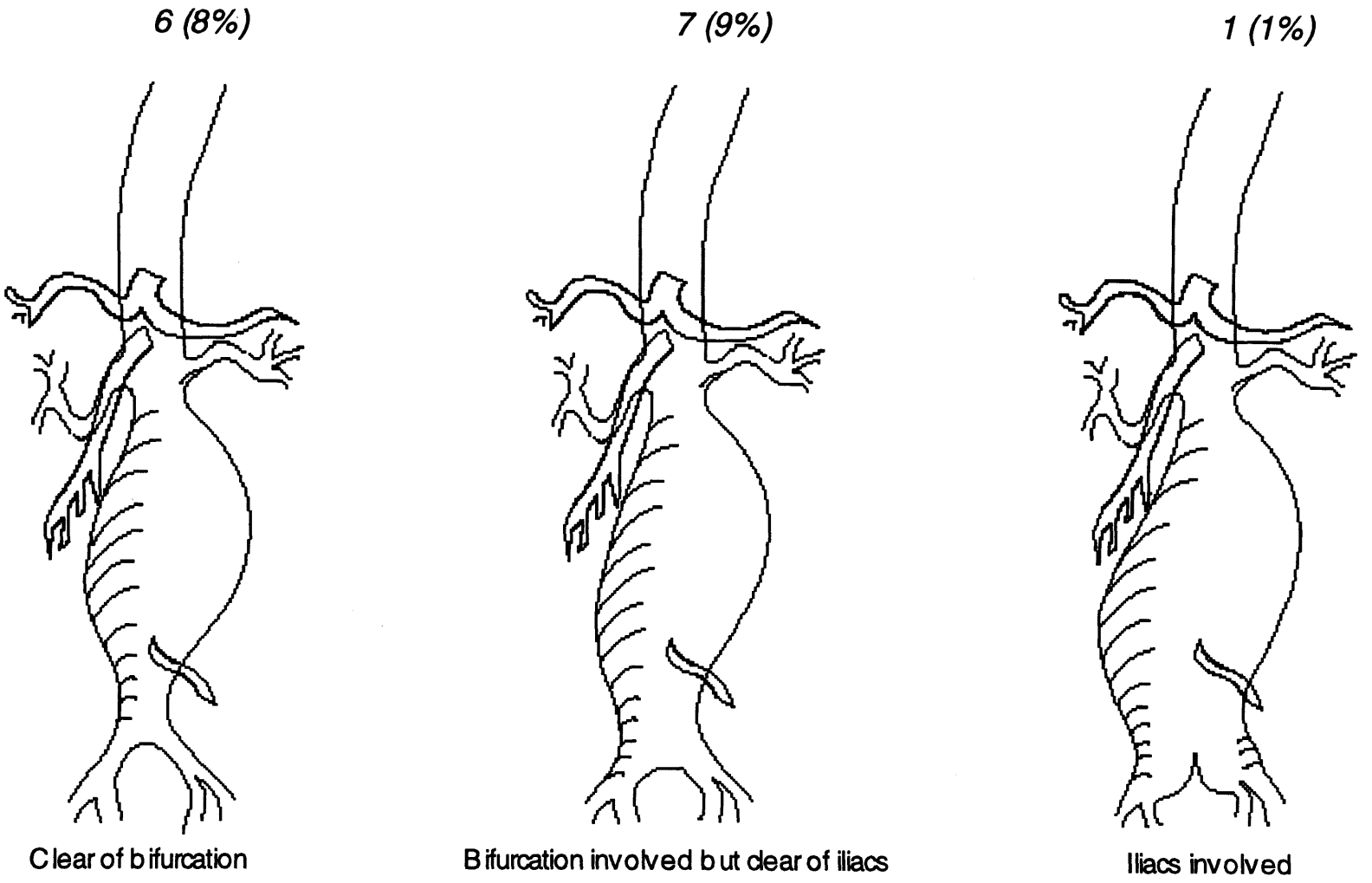


Figure 7.4c) *Infra-renal aneurysms with an insufficient proximal neck (<15mm)*

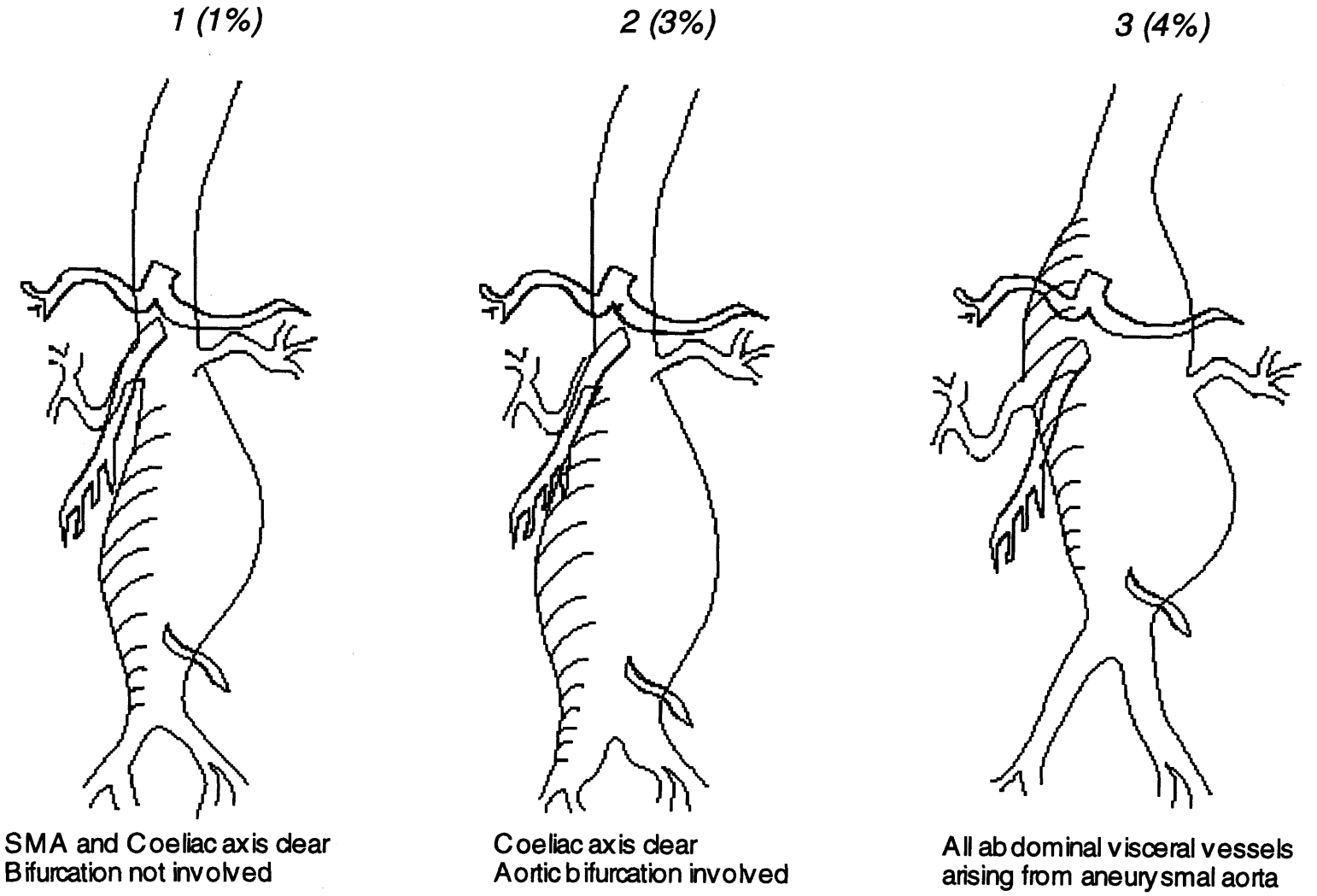


Figure 7. 4d) *Aneurysms with a para- or supra-renal involvement.*

TABLE 27: *Physical characteristics of the 4 morphological groups.*

Parameter	Group I (AAAs with good proximal and distal neck +/- isolated iliac aneurysms)	Group II (AAAs with inadequate distal neck or iliac involvement)	Group III (AAA with very short proximal neck)	Group IV (AAAs with renal artery involvement or extension above)
Proximal neck diameter	19.67 (14.4-27.1)	21 (15.3-30.36)	18.85 (13.63-27)	31.5 (24.5-45.6)
Proximal neck length	33 (15.7-59.13)	33.53 (16-65.06)	9 (4-14.9)	0 (0)
Max AP diameter (AAA)	54.92 (38.84-84)	57.72 (39-96.64)	52.29 (35-77)	61.9 (53-65.4)
AAA sac length	82 (58-125)	86.5 (57-131.5)	111.2 (87.7-147)	121.5 (79-136)
Distal neck diameter	20.64 (13.77-28.77)	29 (17.22-54.18)	22.8 (17.5-38.54)	31.26 (19.2-42)
Distal neck length	16.59 (10-33.89)	0 (0-9)	4 (0-27)	0 (0-30.1)
Left CIA diameter	12.99 (5.75-20.5)	12.48 (7-24)	9.01 (7.6-22.48)	16.8 (13.6-21)
Right CIA diameter	12.92 (7.8-28.7)	13.9 (6-40.46)	11 (9-21.18)	17 (9.7-25)

** all measurements are given in millimetres*

CIA - common iliac artery

Overall only 28 patients (36%) met the criteria for endovascular repair. Of the 21 patients in Group I (*Table 27*) only 12 (15%) were suitable for a straight/tube graft. A further 3 patients from Group I could be treated with a tube graft in combination with endoluminal repair of an isolated common iliac aneurysm. From the 37 patients in Group II, only 16 (21%) met the criteria for a bifurcated endoluminal graft (based on the Mintec Stentor device). *Table 27* lists the reasons which excluded other patients from endoluminal repair. There was no significant correlation between the size of the aneurysm and the length of the proximal and distal necks.

Table 27: *Reasons for unsuitability for endovascular AAA repair.*

	No. of patients
Group I (n = 21)	
Suitable for tube/straight graft	12 (15%)
Unacceptable proximal neck/iliac angulation	4 (5%)
Distal neck stenosis	1 (1%)
Isolated iliac aneurysms	3 (4%)
Proximal neck diameter >28 mm	1 (1%)
Group II (n = 37)	
Suitable for bifurcated graft endoluminal repair	16 (21%)
Proximal neck diameter > 28 mm	2 (3%)
Iliac artery stenosis < 7 mm	2 (3%)
Unacceptable proximal neck/iliac angulation	5 (6%)
Extension of aneurysm to internal iliac artery (> 14 mm) *	12 (15%)
Group III (n = 14)	
Insufficient proximal neck length (< 15 mm)	14 (18%)
Group IV (n = 6)	
Para/Suprarenal aneurysms	6 (8%)
Total	78

** May be treated with aorto-uni-iliac graft in combination with fem-fem crossover bypass.*

7.4 Discussion

Vascular imaging is a vital part of pre-operative evaluation of patients with AAA. For conventional open repair, assessment of the aneurysm size, the proximal and distal extent, involvement of the visceral arteries or adjacent structures, anatomical anomalies and unrecognised intra-abdominal or thoracic conditions, is necessary for decisions such as the timing of the surgical intervention, the operative approach and type of reconstruction required (Ernst, 1993). Endoluminal AAA repair requires a more detailed assessment of the proximal and distal necks, the length and tortuosity of the sac and the state of the iliac arteries (Thompson *et al.* 1995). Conventional imaging modalities such as ultrasonography, angiography and CT are unreliable at providing accurate measurements (Salaman *et al.* 1994; Kandarpa *et al.* 1992).

Although CT remains useful in prediction of AAA size and detection of other retroperitoneal pathology (Vowden *et al.* 1989), it has several drawbacks. The visceral and renal artery origins are often not visualised, as they may fall between slices, and have to be inferred from the surrounding anatomy (Tennant *et al.* 1993). Conventional CT images are obtained along the axial plane of the body which does not conform to the plane of the aortoiliac segment as it is often angulated and tortuous in patients with AAA. This produces oblique images of the aorta making interpretation of visceral artery origins difficult. Thus it is not possible to obtain assessment of the proximal neck length in such cases which is an important factor in determining patient suitability for endoluminal repair. In this study there was inadequate visualisation of both renal artery origins in up to 40% of patients. Visualisation of the renal arteries was only considered adequate if the origin from the aorta was seen clearly on a scanning plane. Adherence to this strict criterion may account for the above poor results. Conventional CT also results in potential inaccuracies in assessment of the aneurysm sac length and tortuosity of the aorto-iliac segment.

Spiral CT is another recent development which allows multiplanar imaging and three-dimensional reconstruction (Rubin *et al.* 1993a). The unique method of the data collection of the spiral scanner has been combined with a dynamic intravenous contrast material bolus to image abdominal vasculartur e. Through various techniques of image processing, including surface renderings and maximum intensity projections, it is possible to obtain excellent anatomical detail of the abdominal aorta and its branches though the post-processing of data involved may be quite labour intensive. This modality is being used by some centres for patient selection prior to endoluminal repair (Yusuf *et al.* 1994; Chuter *et al.* 1994). However, at the present time this facility is not available at Leicester Royal Infirmary and was not included in this study.

Colour Duplex scanning has been proposed previously as the modality of choice for preoperative assessment of AAA for endoluminal repair (Andrews *et al.* 1995).

However in our centre, although colour duplex is regarded as a gold standard for assessment of lower limb arterial lesions (London *et al.* 1995), it has not proven to be equally useful in the full assessment of AAA. It provides excellent assessment of the distal extent of the aneurysm and the iliac artery morphology but in around 50% of patients visualisation of the renal artery origins was obscured by presence of bowel gas or due to obesity. This modality is however very operator dependent and therefore results may vary between different centres (Andrews *et al.* 1995).

Arteriography is very useful in demonstrating visceral artery origins and for assessing the state of the distal vessels (Brewster *et al.* 1975; Gurry *et al.* 1987) which is confirmed by our findings. However in the presence of mural thrombus, the proximal and distal limits of the aneurysm sac are obscured, and the normal calibre of the lumen may be mistaken for normal aorta, with overestimation of the proximal and distal neck lengths. DSA has also been found to be poor at detecting iliac aneurysms (Ecklund *et al.* 1994), although in the present study this was not evaluated. Another important limitation of aortography is that of magnification error. This may partially be overcome by use of a calibrated angiographic catheter (as described above) but accurate assessment of the arterial diameters is still difficult.

Magnetic resonance imaging (MRI) has evolved over the past decade to become an accepted non-invasive method of imaging arterial disease (Polak *et al.* 1992; Kim *et al.* 1990; Owen *et al.* 1992). Recent reports reflect its efficacy in the evaluation of abdominal aortic aneurysms (Durham *et al.* 1993; Ecklund *et al.* 1994; Prince *et al.* 1995; Fox *et al.* 1996). In the study by Fox *et al.* consisting of 20 patients, magnetic resonance imaging accurately predicted aortic dimensions when compared with operative measurements (Fox *et al.* 1996). Magnetic resonance angiography (MRA) uses gradient echo techniques to create angiographic type images which may be acquired using 2-dimensional or 3-dimensional techniques. It is not affected by bowel gas, which can obscure the aorta from view in ultrasonography, and it can outline the size of the lumen as well as the thrombus thickness without the use of iodinated contrast medium. MRA is also useful in evaluating aortic dissections, as it can differentiate between the flow rates in the true and false lumen, and in detecting inflammatory changes by virtue of its high soft tissue contrast resolution (Prince *et al.* 1995; Tennant *et al.* 1993). The disadvantages of MRA are relatively few. A small proportion of patients experience claustrophobic symptoms and may not tolerate the examination (5% in this study). MRA is also contraindicated in those patients with pacemakers or intracranial clips. We found the entire examination could be completed in 20 to 30 minutes. Image quality and scan acquisition times continue to be improved by technical advances such as improved gradient strengths and local coil design allowing rapid image acquisition. In conjunction with bolus technique contrast enhancement, this results in high resolution, high contrast, relatively good angiographic type images. In our study MRA proved the best non-invasive assessment of those AAA parameters which are

relevant to patient selection and graft sizing for endoluminal repair. This study reports the largest series of MRA performed in AAA to date. The classification proposed above also provides a simple guide to ascertaining which aneurysms may be suitable for endoluminal repair.

7.5 Summary

The use of MRA in patient selection for endoluminal repair is recommended, as this can produce the same information as combined CT scanning and aortography but without use of iodinated contrast medium, ionising radiation, or arterial injury. Conventional angiography can, therefore, be reserved for those patients in whom specific questions are not adequately resolved by MRA. However further studies are required to ascertain the optimal application of MRA in vascular disease.

CHAPTER EIGHT

Endovascular AAA Repair: Initial Clinical Experience

8.1 Introduction

Based on the experimental animal experience and having established the best radiological modality for patient assessment and selection, endovascular AAA repair was attempted in a series of patients. In this chapter the initial experience with tube (aorto-aortic), aorto-uni-iliac and bifurcated endoluminal AAA repair is described.

The aims of the clinical work presented in this thesis are to investigate:

(1) ***whether pre-operative radiological assessment provides adequate visualisation of the aneurysm morphology for endovascular repair,***
(2) ***an endoluminal device which can be applied to a greater proportion of the patients,***
(3) ***the technical problems associated with this technique,***
(4) ***the incidence of peripheral embolisation during deployment of the devices,***
(5) ***the early complications associated with this technique***, and
(6) ***the early changes in aneurysm morphology following endovascular repair.***

8.2 Patients and Methods

At present in Leicester, patients with asymptomatic AAA greater than 5 cm in diameter, undergo detailed assessment with magnetic resonance angiography (MRA), contrast enhanced computed tomography (CT) and colour duplex to determine their suitability for endoluminal repair. Those patients considered to have favourable anatomy undergo further assessment with arteriography using a graduated 6F marker catheter (Cordis UK Ltd, Brentford, Middlesex, UK) prior to endovascular repair. Local ethical committee approval was obtained and all patients gave written consent.

8.3 Endoluminal Devices

Tube (aorto-aortic) graft

The initial few patients were treated with the EVT tube graft (Endovascular Technologies Inc., Menlo Park, CA, USA). This device has been described in detail in Chapter 3, comprises of a woven polyester graft with metal attachment systems affixed to both ends. The catheter delivery system of this device comprises a co-axial unit that consists of a capsule containing the compressed graft, a retractable capsule jacket that permits graft delivery and a movable balloon catheter which is used to fix the stent hooks

at the proximal and distal ends of the graft into the aortic wall. This catheter-based delivery system is introduced via a 28-Fr sheath placed in the common femoral or iliac artery over a guidewire. However, the use of this device was limited to those patients with a proximal neck length of >1.5 cm and a distal neck length of >1.0 cm, who comprised only 16 % (12 out of 77) of patients assessed for endovascular repair (Chapter 7).

Tapered aorto-uni-iliac graft

In order to extend the application of endovascular AAA repair to a larger proportion of patients, I have developed an aorto-uni-iliac device, from commercially available components. This device is constructed in the operating theatre under sterile conditions from a commercially available thin-walled 8-mm polytetrafluoroethylene (ePTFE) (Impra, Droitwich, UK) graft. The graft is prepared by stretching the ePTFE to predetermined dimensions using a graded series of angioplasty balloons (Richter *et al.* 1994) (*Figure 8.1*). The W L Gore PTFE graft used in the animal work could not be stretched in this manner. The ePTFE graft can be stretched safely to 3.5 times its original diameter without losing its strength. Hence a thin walled, large diameter graft can be created that can be crimped and introduced through a small sheath. The proximal 7 cm of the graft is dilated over a 60 minute period to 35 mm in diameter using progressively larger angioplasty balloons and finally a 35-mm achalasia balloon (Boston Scientific, St Albans, UK). The graft is then tapered from 35mm proximally to 12 mm at the distal extent (*Figure 8.2*) and secured to a 5 cm long, 4.6 mm diameter Palmaz stent (Johnson and Johnson Interventional Systems, Bracknell, UK) with two diametrically opposed 2/0 polypropylene sutures (*Figure 8.3*). The graft-stent combination is then mounted on a 30 mm balloon angioplasty catheter (Gambro, Sidcup, UK) and the entire device is then back loaded into a 21-Fr (William Cook Europe, Letchworth, UK) packaging sheath before use (*Figure 8.4 and Figure 8.5*). To avoid damage to the endoprosthesis, the package device is delivered into the aorta through a 25-Fr introducer sheath. The design of this device was adopted from the method initially described by Parodi *et al.* (1991).

This device is introduced into the arterial circulation via a temporary iliac conduit, and used to perform an aorto-uni-iliac reconstruction as previously described by May *et al.* (1994a). A diagrammatic illustration of this technique is shown in *Figure 8.6*. In this method, an extraperitoneal approach is used to perform an anastomosis between the external iliac artery and a straight Dacron graft that acts as a temporary conduit for the sheath (*Figure 8.7*). The ipsilateral internal iliac artery is ligated at the start of the procedure. On successful attachment of the proximal end of the graft in the infra-renal aorta, the sheaths are removed and the distal end brought out via the Dacron conduit (*Figures 8.8, Figure 8.9* and *Figure 8.10*). The ends are then sutured together to obliterate the space between the conduit and the endoluminal graft. The resulting double layer end is

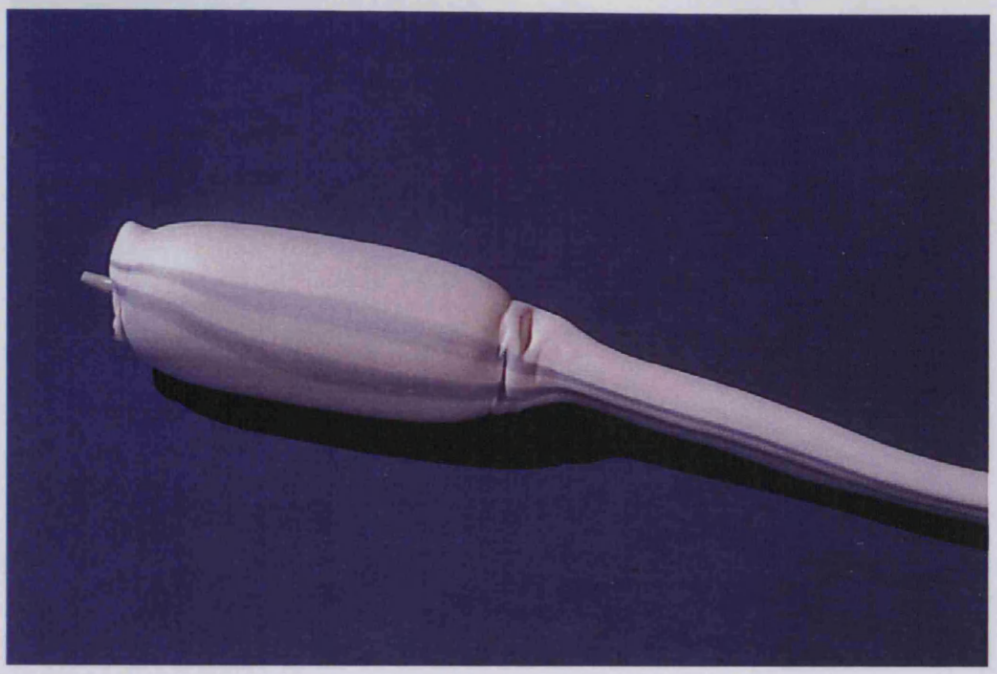


Figure 8.1: *An 8 mm thin walled ePTFE graft being gradually stretched with a 30 mm balloon angioplasty catheter.*

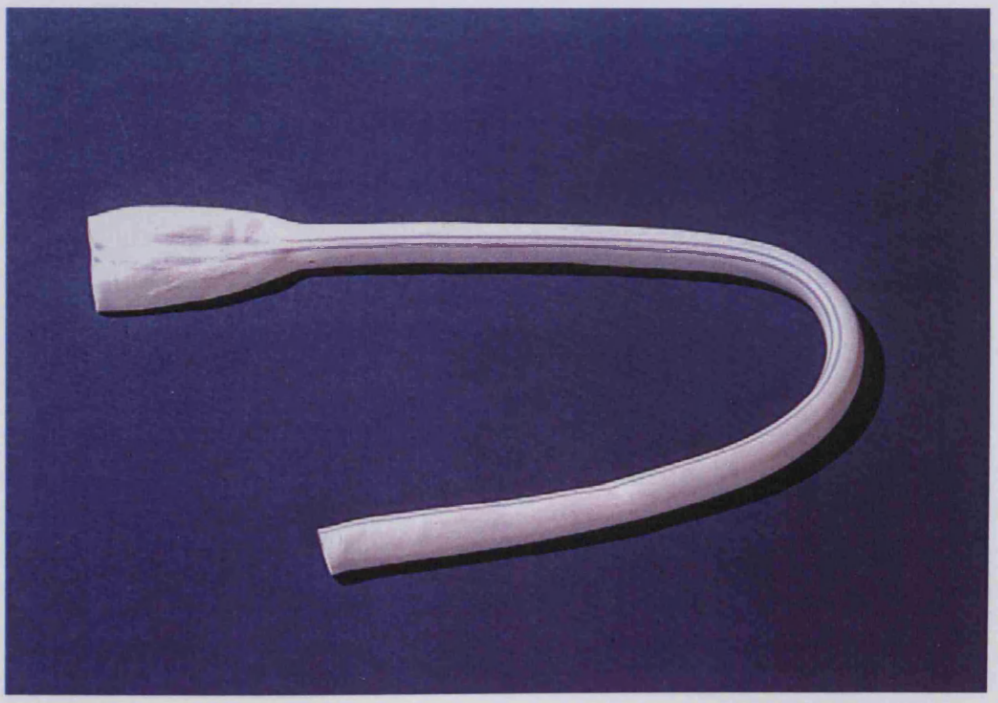


Figure 8.2: *A tapered ePTFE graft, ready for attachment to a stent and further assembly.*

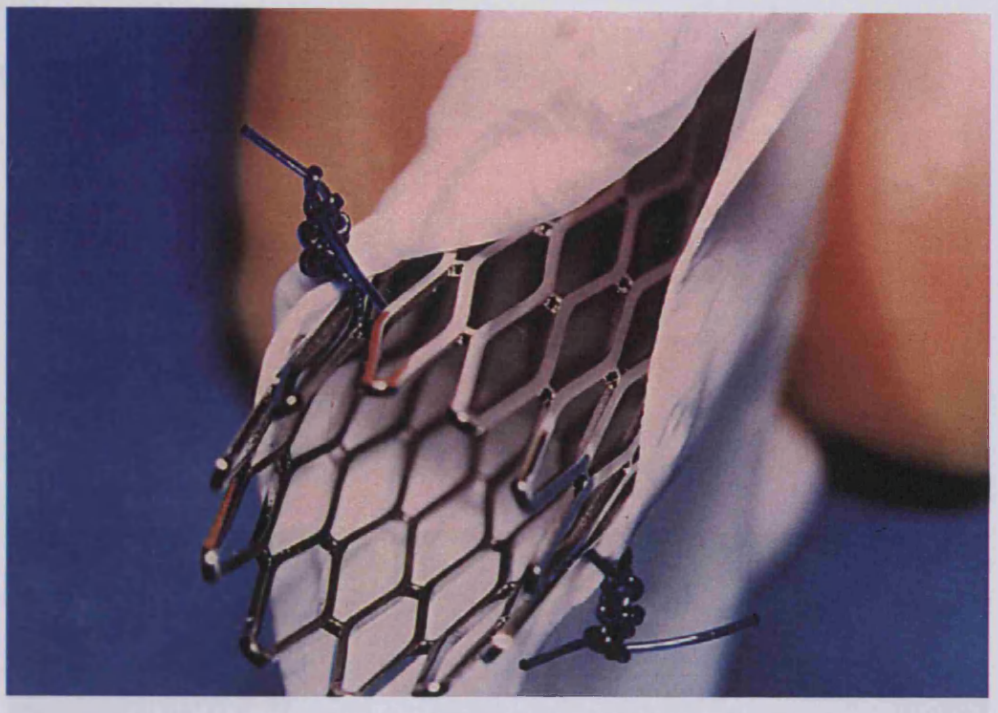


Figure 8.3: *Photograph illustrating the 5 cm long Palmaz stent secured to the PTFE graft with two diametrically opposed 2/0 polypropylene sutures*

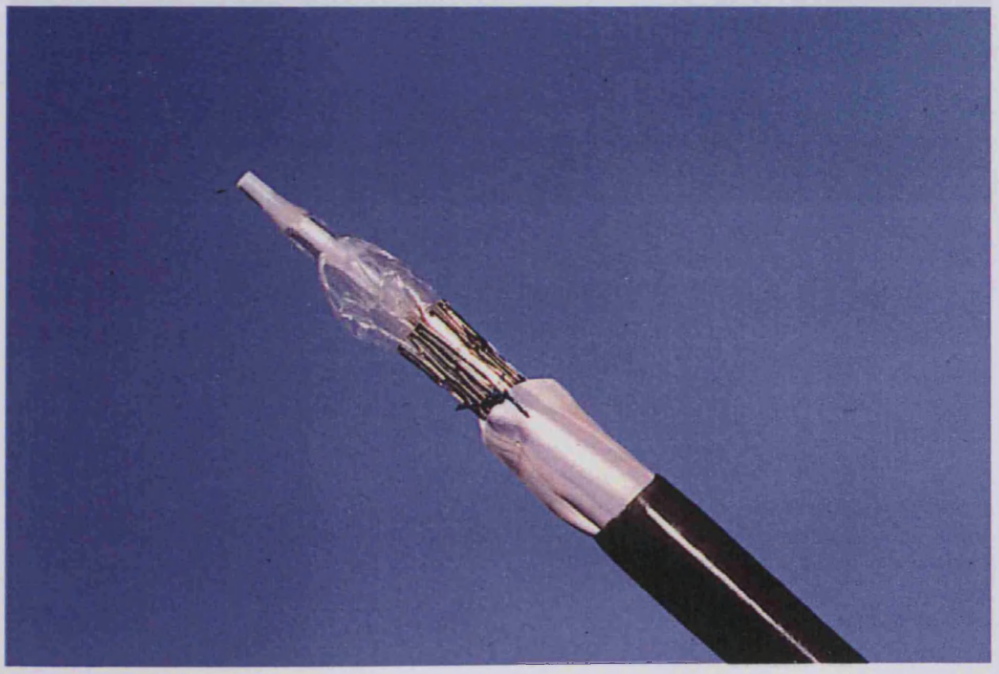


Figure 8.4: *A close-up view showing the graft-stent combination mounted on a 30 mm diameter angioplasty balloon.*

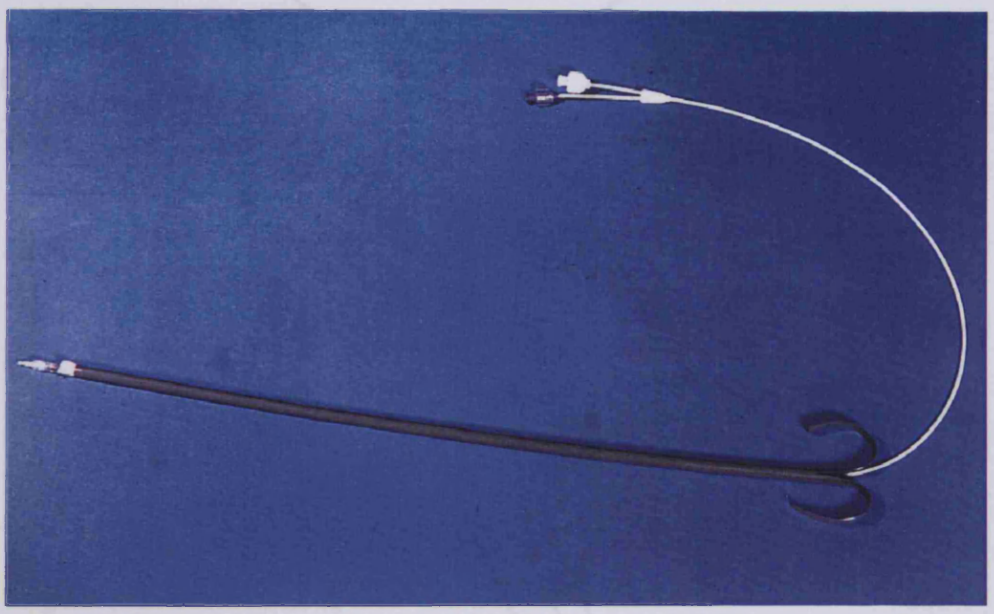
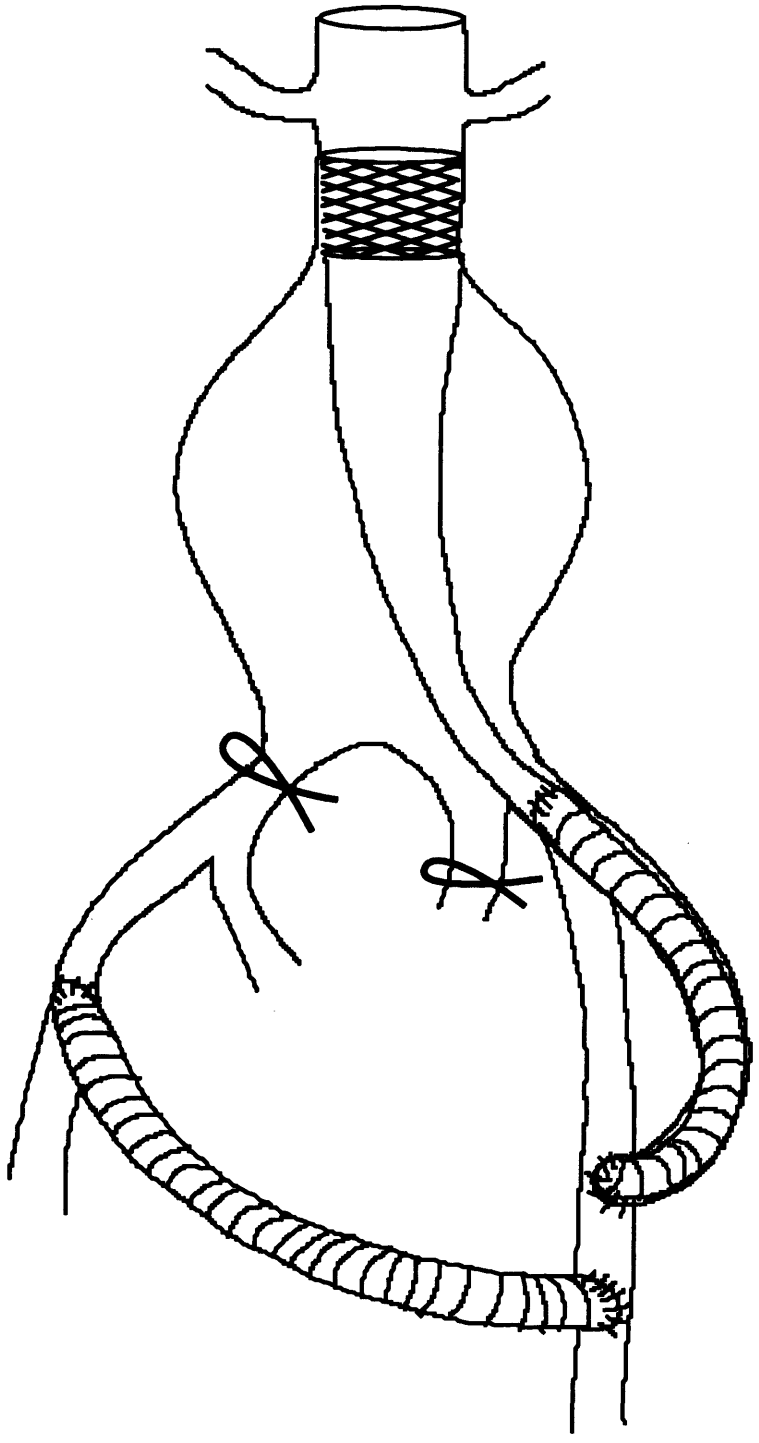


Figure 8.5: *Completed endoprosthesis packaged inside a 21-Fr Teflon peel-away sheath.*

Figure 8.6: *Diagrammatic illustration of a tapered aorto-uni-iliac graft. The graft is secured at the proximal end by means of a single balloon-expandable stent. The endoprosthesis is then passed through the temporary iliac conduit and anastomosed to the ipsilateral common femoral artery. The procedure is completed by a femorofemoral crossover graft combined with occlusion of the contralateral common iliac artery.*



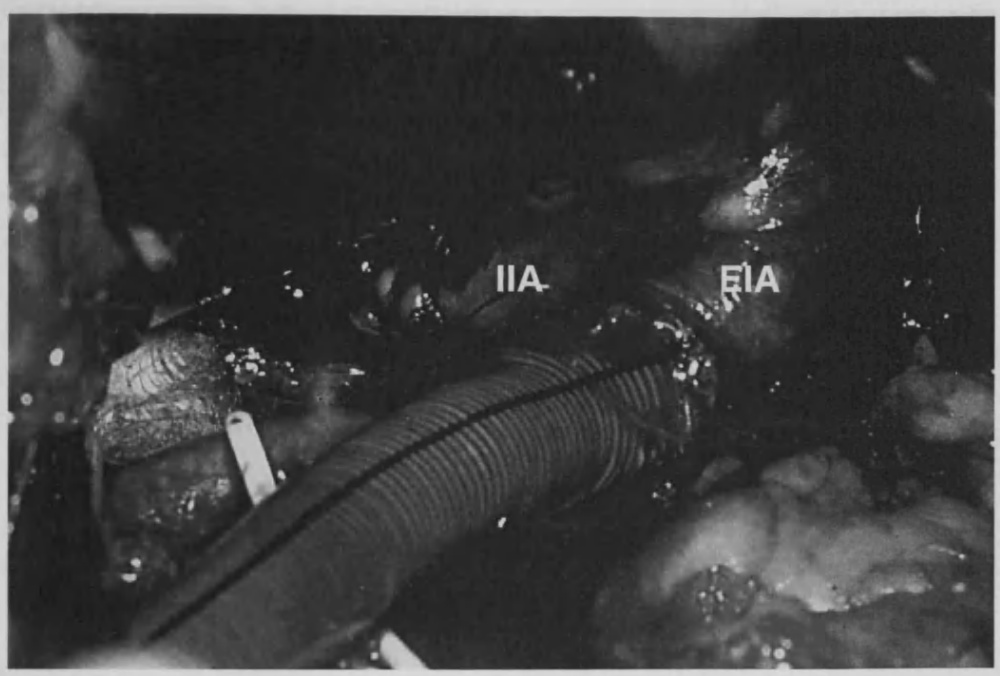


Figure 8.7: *Operative photograph showing a temporary Dacron conduit, constructed by anastmosing 10 mm Dacron graft to the external iliac artery via an extraperitoneal approach.*

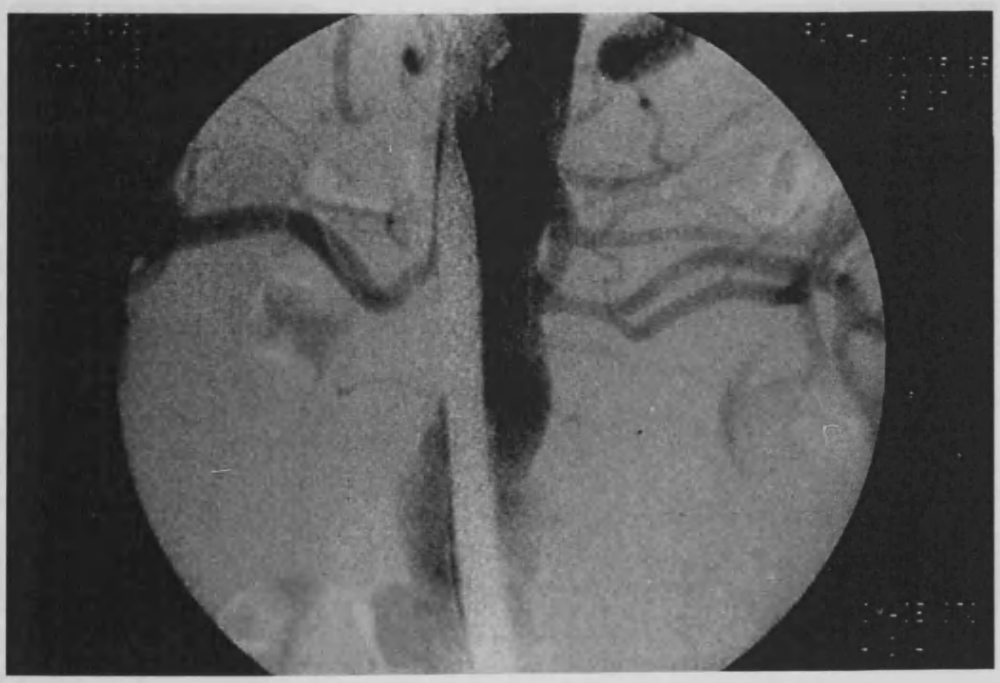


Figure 8.8: *A 25-Fr introducer sheath positioned within the abdominal aorta, and angiogram showing the position of the renal arteries.*

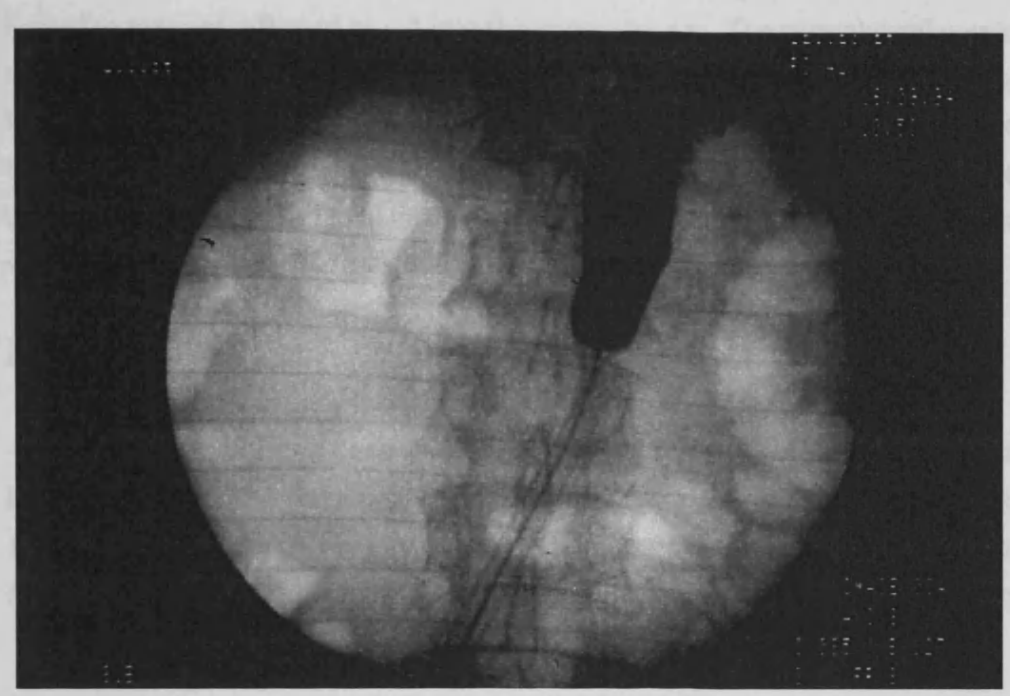


Figure 8.9: *A fully inflated balloon, during deployment of the stent just below the renal artery origins.*

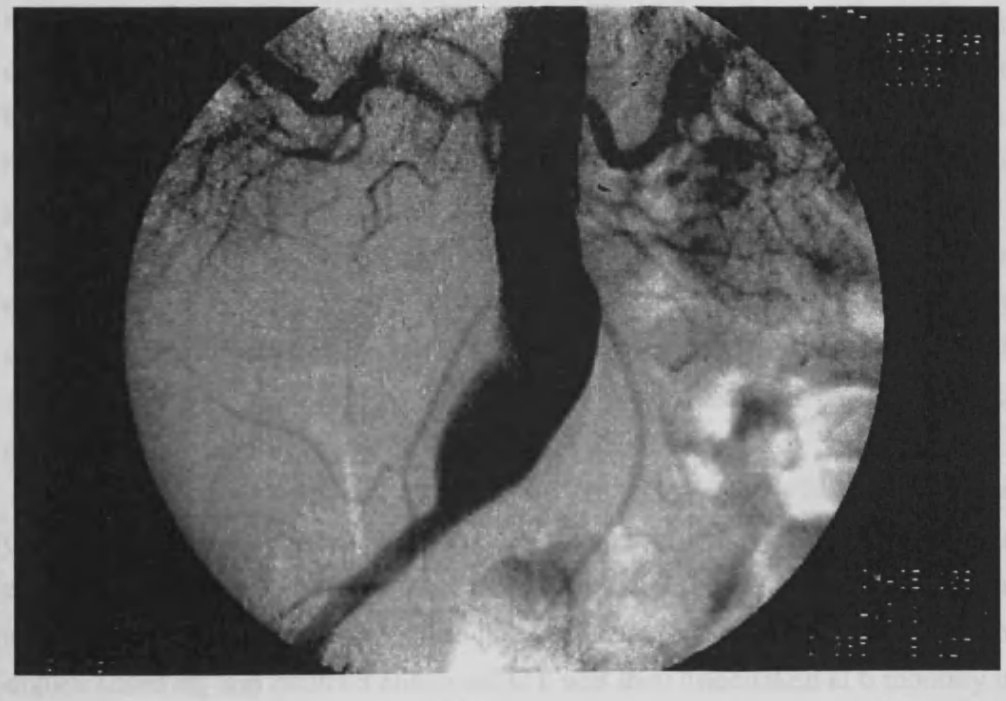


Figure 8.10: *A completion arteriogram illustrating patent renal arteries and the tapered endograft.*

anastomosed to the common femoral artery distally. The ipsilateral external iliac artery is ligated to prevent reflux of blood into the aneurysm sac. The contralateral common iliac artery is occluded by use of either a detachable silicone balloon (Merck Radiology Division, Alton, Hampshire, UK) (*Figure 8.11*), stainless steel coil embolisation (Cook UK Ltd., Letchworth, Herts, UK) or surgical ligation via an extraperitoneal approach using an additional small incision. Finally the contralateral lower limb is revascularised with a 10 mm Dacron femoro-femoral crossover graft.

Bifurcated device

More recently we have also started using the Stentor™ bifurcated system (Mintec Inc., Freeport, Grand Bahamas, Bahamas), in aneurysms with a proximal neck length > 1.5 cm but with a deficient distal aortic cuff without involvement of the iliac arteries (diameter <12 mm). This device has been described previously in detail in Chapter 3.

8.4 Implantation Technique

With all 3 devices, the operation was performed under standard general anaesthesia in a fully equipped vascular operating theatre. All patients were given 5000 units of heparin intravenously at the start of the procedure. Through a groin incision a longitudinal common femoral arteriotomy was used for deployment of the device. In patients with tortuous or narrow common femoral arteries, a temporary Dacron conduit anastomosed to the external iliac artery was used (*Figure 8.7*). Accurate positioning of the endoluminal graft was obtained using digital fluoroscopic control (Philips BVM 29, Phillips Medical Systems, Best, The Netherlands). Stent deployment was aided by balloon inflation for 1 minute at 2 atmospheres (approximately 202 kPa) intraluminal pressure. During deployment of the devices the mean arterial pressure was maintained at 80 mmHg. Angiography was performed on completion of the procedure to confirm successful exclusion of the aneurysm sac from the circulation.

After operation all patients were monitored for 24 hours in the intensive care unit. A colour duplex scan and contrast enhanced CT were performed to assess the endoluminal graft prior to discharge from hospital. All patients were reviewed at 6 weeks and underwent physical examination and colour duplex scanning. Assessment with colour duplex scanning and contrast enhanced CT was then undertaken at 6 monthly intervals. Patients treated with the EVT device also underwent plain abdominal radiography at each follow-up visit to assess the attachment system hooks.

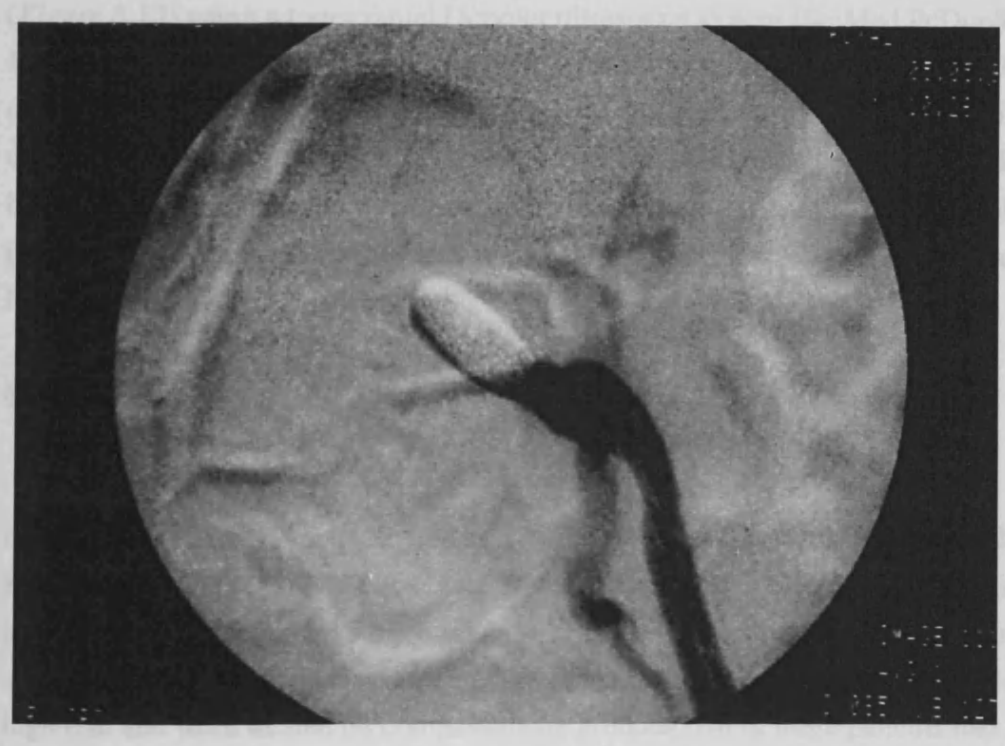


Figure 8.11: *Occlusion of the contralateral common iliac artery using a detachable silicone balloon to prevent reflux into the aneurysm sac.*

8.5 Detection of Emboli

During the initial experience, a number of patients were noted to have "trash" foot following endovascular AAA repair. In light of this observation, embolisation was monitored in subsequent patients. A comparison was made with patients undergoing conventional AAA repair during the same period.

Both superficial femoral arteries were pre-operatively imaged by duplex scanning, and the artery with the optimal signal was chosen for monitoring. During endovascular procedures, the femoral artery contra-lateral to the endograft insertion site was monitored. The methodology for emboli detection and characterisation is described in detail elsewhere (Smith *et al.* 1995). Briefly, the superficial femoral artery in mid thigh was insonated (*Figure 8.12*) using a transcranial Doppler ultrasound system (SciMed PcDop842, Bristol, UK) with a 2-MHz transducer operating at the maximum power output due to the absence of any bone between the transducer and the insonated artery. Lower limb emboli were detected as unidirectional high-intensity transient signals within the background Doppler blood signal. To accurately determine the number and composition of the embolic particles (gaseous or particulate), the Doppler signal was recorded onto digital audio tape for off-line analysis.

8.6 Results

Over a 26 month period from March 1994 to April 1996, we attempted endoluminal AAA repair in 29 patients (28 male, 1 female). Median age was 72 (range 57-82) years and the median AAA diameter was 5.5 cm (4.3-7.9). Only 1 patient in our series had an aneurysm less than 5 cm in diameter, and this was a patient with a 4.3 cm symptomatic inflammatory aneurysm. Twelve patients (41 per cent) were considered to be high risk and were treated on compassionate grounds. All of these patients had severe co-existent cardiorespiratory disease (ASA grade 4 or 5). The ASA grading system used is outlined in Appendix A. In addition, 2 had inflammatory aneurysms, 1 suffered from hereditary haemorrhagic telangiectasia and 1 patient was considered to have a hostile abdomen due to previous para-aortic node radiotherapy for non-Hodgkin's lymphoma. *Table 28* shows a comparison of the patient demographics and the results achieved in the "normal" risk (ASA grade 3 or better) and the "high" risk patients (ASA grade 4 or 5).

The aorto-uni-iliac device was used in 19 patients, the EVT tube Endograft^{R} in 7 and the Stentor^{TM} bifurcated system in 3. The individual results for the 3 devices are summarised in *Table 29*. Overall 24 procedures (83 per cent) were completed successfully. There were 5 conversions due to iliac artery perforation (n=1), inadequate stent fixation (n=1), low stent deployment (n=2) and balloon malfunction during stent

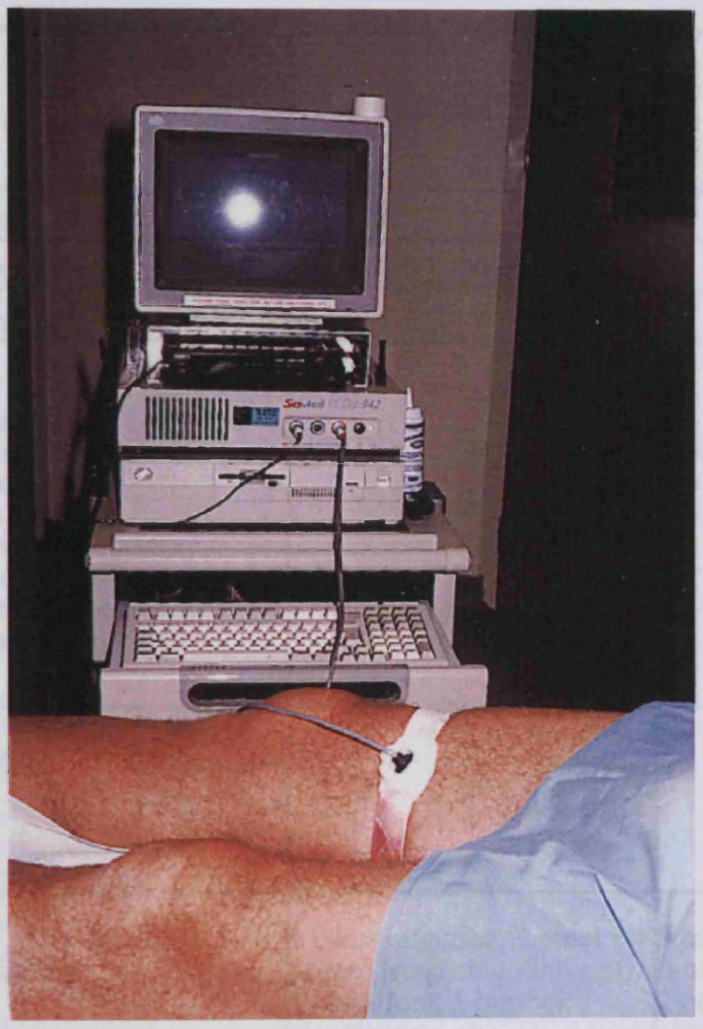


***Figure 8.12**: The method deployed for monitoring peripheral embolisation during endovascular AAA repair.*

Table 28: *A comparison of the patient demographics and the results obtained in "normal" risk and "high" risk patients.*

	"Normal" risk	"High" risk
No. of patients	17	12
Age (years)	71 (60-82)	71 (57-79)
AAA size (cm)	5.5 (5-7.9)	5.4 (4.3-6.9)
Risk factors:		
Ischaemic heart disease	3	11
Hypertension	5	3
Diabetes mellitus	0	2
Cerebrovascular disease	0	1
Respiratory disease	1	1
Past pulmonary embolism	0	1
Smoking (current : ex)	4 : 6	5 : 3
Conversions: Immediate+	2	2
Early++	2	0
Late+++	1	0
Complications	1 chest infection, 1 renal failure (requiring dialysis), 1 trash foot, 1 buttock claudication	2 microembolisation and multi-organ failure*, 2 buttock claudication, 1 chest infection
Hospital stay (days)	7 (4-21)	9 (6-13)
Mortality	0	2*

The values are given as medians with the range in parenthesis

\+ Immediate = converted at the time of the procedure ('on table conversions')

++ Early = converted prior to hospital discharge (within a 30 day period)

+++ Late = beyond the 30 day period

Table 29: *A comparison of the results obtained with each of the 3 endoluminal devices.*

	EGS^{R} (EVT device)	**Aorto-uni-iliac and crossover**	**Stentor^{TM} (Bifurcated)**
No. attempted	7	19	3
Conversions: Immediate+ Early++ Late+++	 0 0 2	 4 1 0	 0 0 0
Age (years)	74 (64-82)	70 (57-79)	78 (66-79)
AAA size (cm)	5.6 (5-6.0)	5.5 (4.3-7.9)	5.1(5-6.3)
Operation time (mins)	150 (95-262)	188 (128-270)	218 (145-240)
Blood loss (mls)	1200 (800-2000)	2500 (500-5000)	600 (600-2500)
Hospital stay (days)	9 (5-13)	7 (6-21)	6 (4-8)
Complications	1 chest infection	3 buttock claudication, 3 trash foot, 1 acute tubular necrosis, 1 chest infection	0
Perigraft leaks: Early++ Late+++	 3 1	 0 0	 0 0
Mortality: Early++ Late+++	 1 0	 1 0	 0 0
Follow-up (months)	23 (22-27)	6 (1-21)	10 (3-15)
Overall mortality (%)	14	5	0

The values are given as medians with the range in parenthesis

+ Immediate = at the time of the procedure ('on table')

++ Early = prior to hospital discharge (within a 30 day period)

+++ Late = beyond the 30 day period

deployment (n=1). The contralateral CIA was occluded using coil embolisation in one case, detachable silicone balloon in 2 cases and surgical ligation in 12 cases. The use of coil embolisation and detachable balloons (maximum diameter 10mm) was limited to common iliac arteries with a diameter of <10mm, and this precluded their use in the majority of cases. The median operative time was 187 minutes (range 95-270). The patient with the procedure time of 270 minutes also required a femorodistal vein bypass graft for rest pain and repair of isolated bilateral femoral artery aneurysms. The median blood loss was 1500ml (range 500-4000). The median hospital stay was 7 days (range 4-21).

We have encountered a number of early complications. These have included 2 deaths due to multi-organ failure (day 3 and day 12 post-op), thought to be due to microembolisation. Two patients developed chest infection and required prolonged hospitalisation. One patient developed acute tubular necrosis requiring renal dialysis for 3 weeks. Post-operative CT scan in this patient confirmed stent deployment well below the renal arteries. Three patients were noted to have trash foot but none required any intervention or suffered tissue loss.

On follow-up 3 patients treated with the aorto-uni-iliac device were noted to have buttock claudication causing mild disability. Perigraft leaks were noted in 4 patients (3 proximal, 1 distal), all of whom were treated with the EVT tube Endograft^{R} (*Figure 3.8*) The 3 proximal leaks were detected on the completion angiogram and confirmed on colour duplex (*Figure 8.13*) and the initial post-operative contrast enhanced CT scan. One of the proximal leaks resolved spontaneously within 6 weeks. The other 2 were still present at 6 months follow-up. The graft was explanted in 1 patient and conventional repair undertaken successfully. The other patient was considered to be unfit for conversion and has been followed up closely. The distal leak was detected at the one year follow-up on colour duplex (*Figure 8.14*) in a patient in whom all previous scans had confirmed successful aneurysm sac exclusion (*Figure 8.15*). Further evaluation with contrast-enhanced CT and intra-arterial DSA confirmed a posterior leak at the distal attachment site (*Figure 8.16 and Figure 8.17*) with antegrade perfusion of a lumbar artery. During the explant procedure, the aneurysm was pulsatile and dilatation of the aortic bifurcation and the left common iliac artery was noted. Partial thrombosis of the aneurysm sac and a distal leak were confirmed on opening the aneurysm sac. Histological evaluation of the explanted graft showed healing pannus composed of loosely organised neointima. However, this was only present focally at the distal end of the graft and was completely absent at the proximal end. No evidence of endothelialisation was observed at the proximal, mid or distal portions of the graft. Similar histological findings were observed in the other explant specimen. Both patients in whom the graft was explanted also had a single hook fracture at the opposite end to the perigraft leak. The median follow-up in the remaining 20 patients with endoluminal grafts is 9 months (range 1-27 months). There have been no long-term aneurysm ruptures or deaths from any other causes.

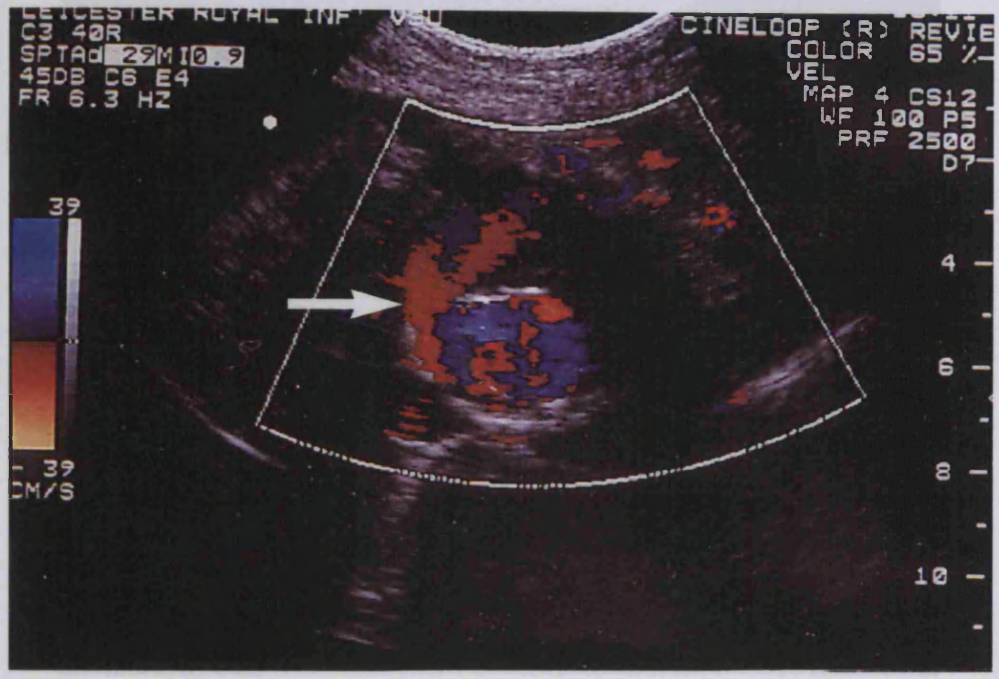


Figure 8.13: *A colour duplex scan showing a proximal perigraft leak.*

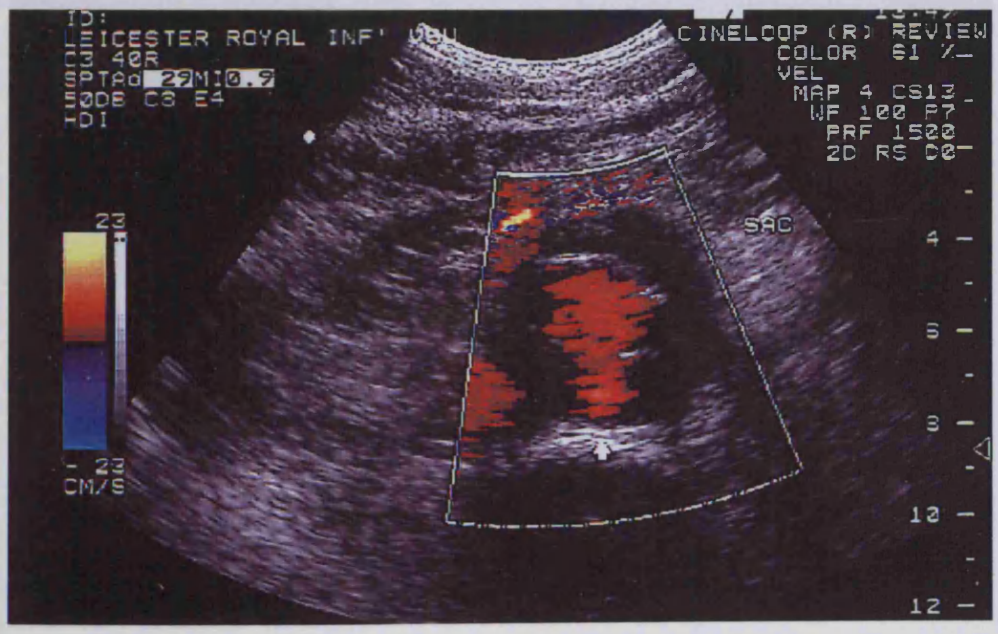


Figure 8.14: *A posterior perigraft leak demonstrated on colour duplex at one year follow-up.*

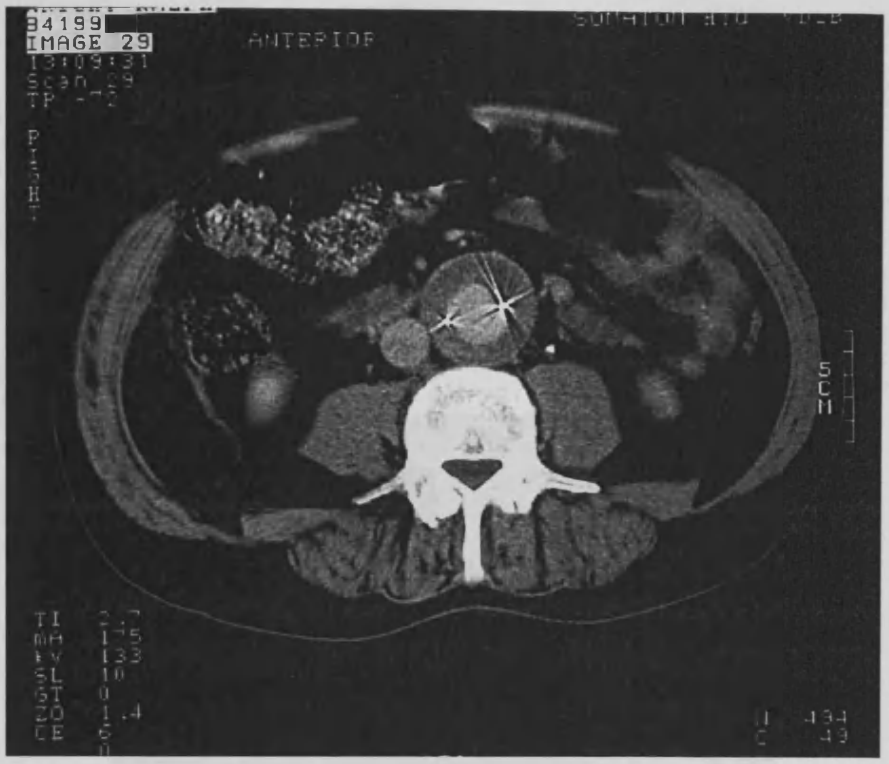


Figure 8.15: *Contrast-enhanced CT image obtained at 6 weeks after operation showing no evidence of perigraft leak*

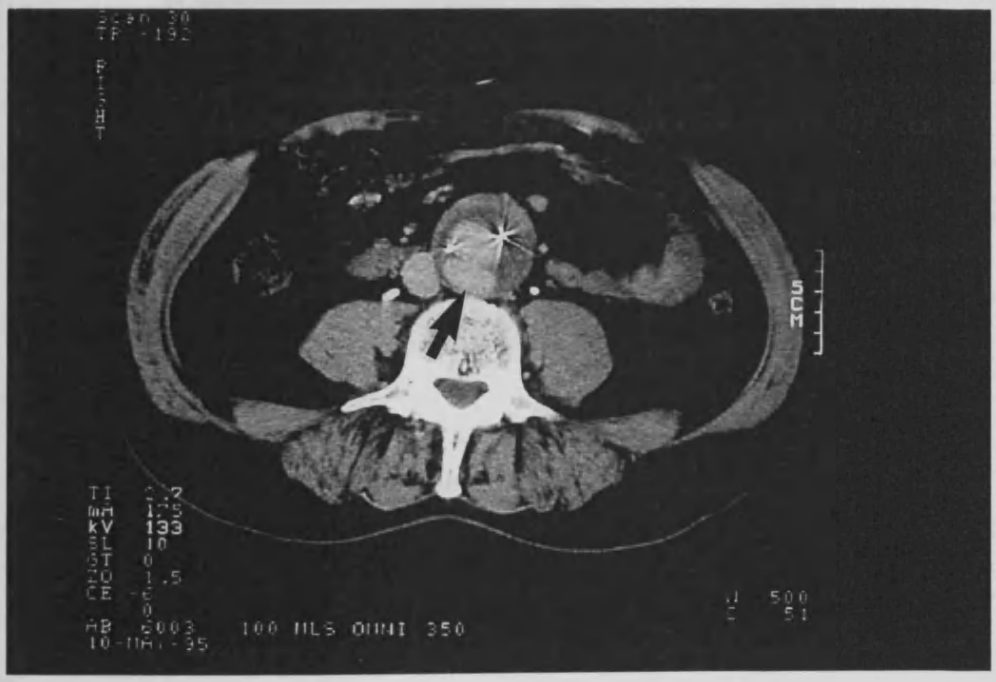


Figure 8.16: *A contrast enhanced CT at 12 months showing a posterior perigraft leak at the distal end*

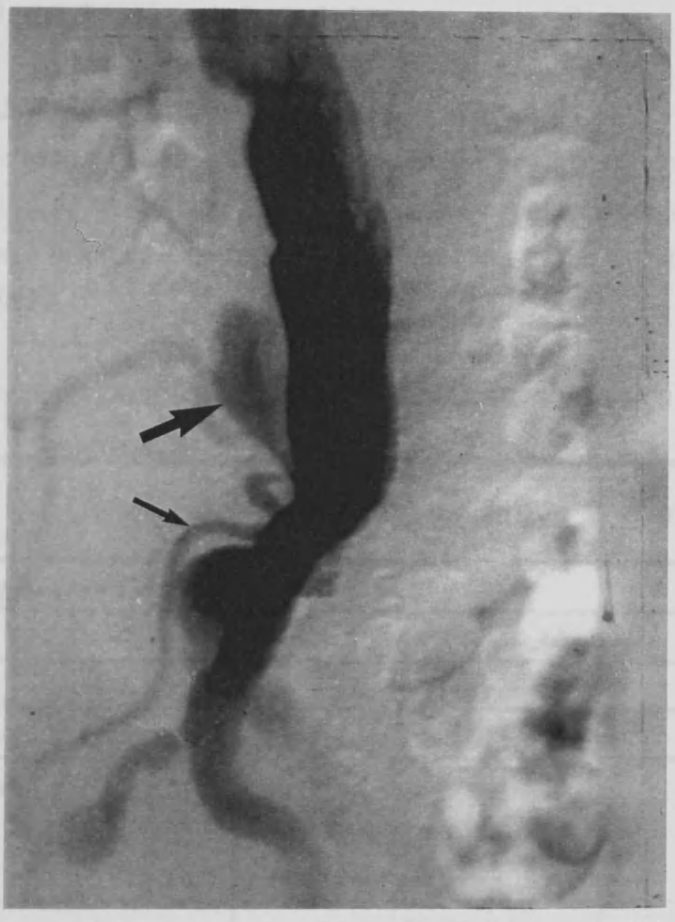


Figure 8.17: *Intra-arterial digital subtraction angiogram demonstrating a posterior leak at the distal attachment site (large arrow). Note the antegrade perfusion of a lumbar artery (small arrow).*

The morphological changes observed in the aneurysm sac on follow-up with contrast enhanced CT scan in the EVT tube Endograft^{R} treated group are illustrated in *Figure 8.18.* All 3 patients with persistent perigraft leaks (patients A, B and C) showed a progressive increase in aneurysm size. In contrast, those patients without any evidence of extra-graft flow (patients D, E and F) showed a progressive diminution in the size of the aneurysm following endoluminal repair. At present the intermediate follow-up data in patients treated with the aorto-uni-iliac and the Stentor^{TM} device is not sufficient to enable a similar analysis of the morphological changes.

Lower Limb Embolisation

Lower limb microemboli were quantified in 7 patients undergoing endovascular repair (6 aorto-iliac and 1 aorto-aortic grafts) and 8 patients undergoing conventional repair (5 straight and 3 bifurcated grafts). The demographics of the two groups of patients are given in *Table 30.*

Table 30: *The demographics of patients in the microembolisation study.*

	Endovascular group	**Conventional group**
No. of patients	7	8
Age (years)	74 (65-83)*	71 (60-83)*
Sex	7 male	6 male, 1 female
AAA size (cm)	5.6 (5.2-6.9)*	5.4 (4.5-5.8)*
Reconstruction	6 aorto-uni-iliac 1 aorto-aortic	5 tube 3 bifurcated
Procedure duration (mins)	210 (150-270)*	110 (72-186)*

*Median (range)

The numbers of emboli in the conventional and endovascular groups are illustrated in *Table 31.* The results are presented as medians with inter quartile ranges. There were significantly greater emboli in the endovascular group than in patients undergoing conventional aneurysm repair. Three patients with > 100 particulate emboli developed self-limiting trash feet post-operatively. There were no cases of massive microembolisation in either group. Although there was quite a wide variation in the length of procedure amongst the endovascular group, this did not appear to influence the emboli count.

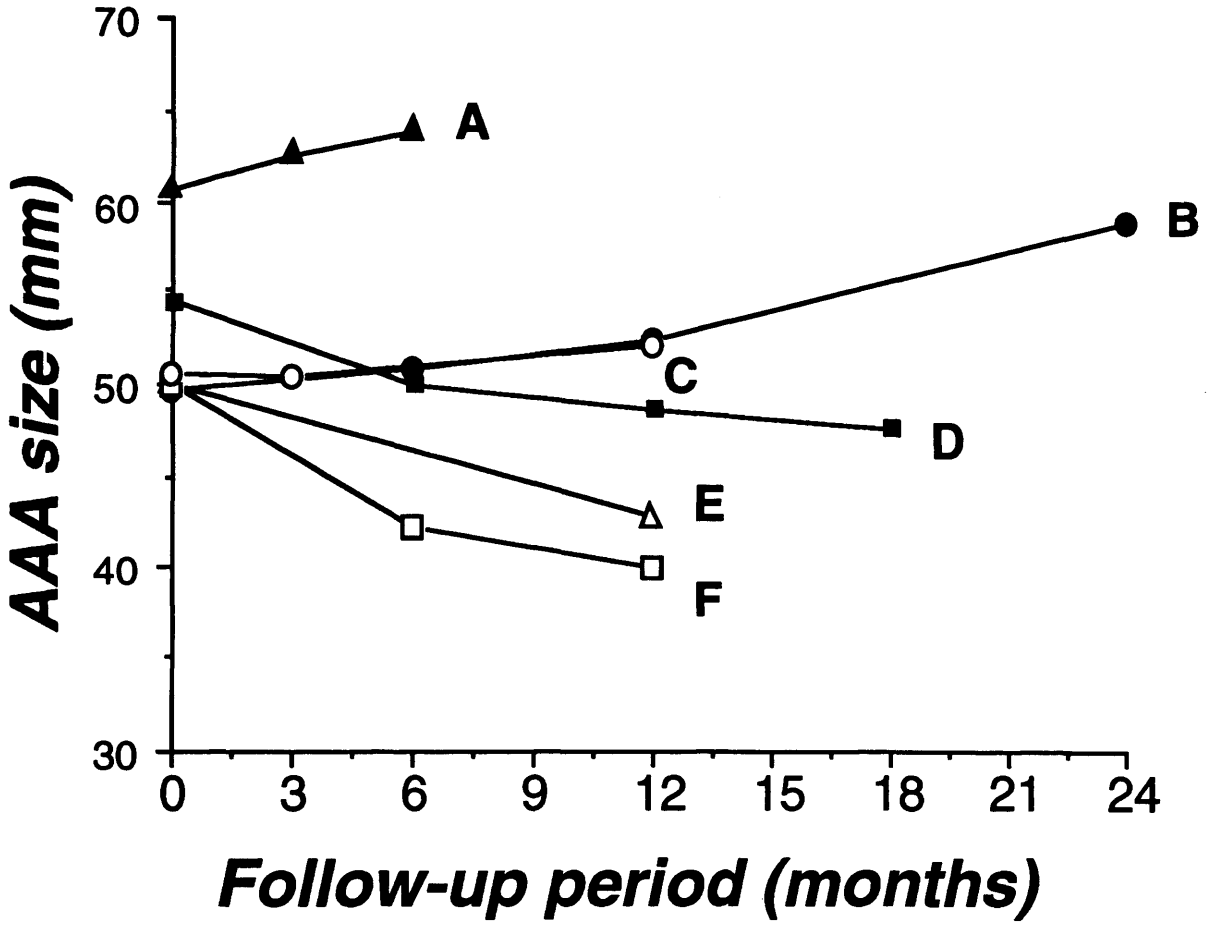


Figure 8.18: *The changes in maximum aneurysm diameter observed on contrast enhanced CT in patients following treatment with EGS^R (Endovascular Technologies Inc., Menlo Park, CA, USA). Perigraft leaks were present in patients A, B (noted on completion angiogram) and C (detected at 1 year follow-up).*

Table 31: *The number of particulate (PE) and air emboli (AE) during conventional and endovascular aneurysm repair.*

	PE during graft insertion **	Total PE ***	Total AE	Total emboli
Endovascular	84 (42-182)*	127 (101-182)	244 (90-361)	371 (195-489)*
Conventional	15 (2-36)	41 (18-183)	81 (29-124)	163 (110-252)

*$p<0.05$ - Mann Whitney test

** *In the endovascular group this part of the procedure includes insertion of the deployment catheter over the guide wire, deployment of the graft-stent combination and retrieval of the deployment system.*

*** *This calculation included emboli during the insertion of the guide wire and the marker catheter, while performing the peri-operative angiogram to determine the position of the renal arteries and measurement of other relevant aneurysm dimensions.*

8.7 Discussion

Initial experience from several centres including ours has confirmed the feasibility of endoluminal AAA repair (Parodi, 1995; Moore *et al.* 1996; Yusuf *et al.* 1994; May *et al.* 1994b; Chuter *et al.* 1997; Blum *et al.* 1996). However a number problems including the long term durability of this technique need further evaluation prior to its widespread use.

In our centre, pre-operative magnetic resonance angiography (MRA) has been a valuable modality in patient selection for endoluminal repair. This combined with intra-arterial DSA using a marker catheter, appears to provide adequate information for endoluminal AAA repair. However during patient selection we have encountered considerable anatomical constraints which limit the application of endoluminal techniques. Previous studies suggest that aneurysms of infra-renal aorta without involvement of the iliac arteries or a functional inferior mesenteric artery constitute more than 50% of AAAs (Gordon-Smith *et al.* 1978; Orr *et al.* 1974; Evans *et al.* 1988). Such aneurysms can be repaired with a tube-type graft during conventional open repair. However, the initial morphological studies prior to endovascular repair, including the work in this thesis, suggest that less than 50% of AAAs can be repaired endoluminally using a combination of tube, bifurcated and tapered aortoiliac devices (Chuter *et al.* 1994; Moore *et al. 1994*; Armon *et al.* 1997; Schumacher *et al.* 1997). Moore and Vescera (1994) assessed 69 AAAs for endovascular grafting. Of these only 10 patients (14%) were found to be suitable endovascular repair using a tube graft. Recently Schumacher *et al.* (1997) have published their findings in 242 consecutive AAA patients. Overall, 51.7% were considered to be suitable for endovascular repair on the basis of morphology. However, after taking into consideration relevant concomitant vascular diseases, proximal iliac kinking, and iliac, renal, or visceral occlusive disease, only 30.2% of the AAA population were potential candidates for an effective endovascular repair using the currently available devices. These findings are consistent with the work in this thesis described in Chapter 7. The diameter of the iliac arteries is also a major limiting factor. Many of the common iliac arteries exceed the upper limit for the diameter of the graft limbs (Chuter *et al.* 1997). The data published recently by Armon *et al.* (1997) and that presented in this thesis suggests that the aorto-uni-iliac device has the widest applicability of the currently available endovascular systems (Boyle *et al.* 1997). However, the aorto-uni-iliac system and some of the bifurcated devices (Chuter *et al.* 1997, Mialhe *et al.* 1995), seek to treat patients with large common iliac arteries by extending the stent-graft down to the external iliac artery. This assumes that the internal iliac artery can be bypassed without risk of retrograde aneurysm perfusion or ischaemia of the pelvis, colon, or buttocks. Buttock claudication was a significant problem (3/14) in patients treated with the aorto-uni-iliac device, in whom the internal iliac artery was occluded.

The systems used at present are large and stiff and inappropriate for use in tortuous iliac arteries. The large diameter of some of these may cause local damage to the artery at the site of access. We encountered iliac artery perforation in one of our patients, which required conversion to conventional repair. In some cases there may be traumatic endarterectomy of the femoral and external iliac arteries as described by May *et al.* (1994c). This problem of narrow and tortuous iliac arteries can in some patients be overcome by using a temporary conduit (Figure 8.7), as described by Parodi (1993). Future developments such as devices which can be inserted percutaneously and prostheses which can deployed suprarenally and have side branches that can be stented into the major aortic branches may extend the indications for endoluminal repair.

Initial reports from early clinical trials have suggested that massive microembolisation and peripheral embolisation may be a significant problem affecting endovascular aneurysm repair. Both deaths in our series were attributed to this phenomenon which has been reported by other authors (Veith, 1994; Parodi, 1995). This study has demonstrated that the numbers of particulate emboli were significantly greater in patients undergoing endovascular aneurysm repair. However, these findings relate to lower limb emboli only. It has been suggested that such embolic events may be prevented by occluding the common femoral arteries during graft insertion. However, this manoeuvre would negate one of the advantages of endoluminal procedures, that is, the reduction in the duration of limb ischaemia. Moreover, it would be unlikely to prevent massive microembolisation because this appears to be a widespread phenomenon rather than an isolated event in the lower limbs. The mechanism of embolisation during endovascular repair is thought to be related to manipulation large endoluminal devices within the aneurysm sac (Parodi, 1995; Norgren *et al.* 1996). Further studies are required to ascertain whether there is some intrinsic property of the aneurysm which predisposes to this complication, in order to predict cases at high risk.

The early changes in aneurysm morphology have been reported from several centres (May *et al.* 1995a; Balm *et al.* 1995; Malina *et al.* 1997). Balm *et al.* (1995) reported follow-up of 9 patients (median follow-up of 6 months) treated with EVT tube Endograft^{R}, using spiral CT-angiography. They observed a significant increase in the distal aortic diameter and no change in the proximal aortic diameter. A decrease in the maximum aneurysm diameter was only observed in 5 patients, and the remaining 4 remain unchanged. May *et al.* (1995a) reported follow-up in 41 patients and concluded that aneurysms which showed a decrease in size remained isolated from the general circulation whereas those with a perigraft leak showed an increase in size. They also observed a significant increase in the diameter of the proximal neck in both groups (May, 1997). These findings have been observed by Malina *et al.* (1997). The follow-up at present is insufficient to know whether these changes may lead to late leaks. However it is clear from the above observations that the changes in the proximal neck are observed with both

self expanding and balloon expandable stents. Only with long term follow-up will the significance of these changes become clear.

The morphological changes observed in our patients treated with the EVT tube Endograft^R confirm the above findings. All patients with perigraft leaks showed a progressive increase in the diameter of aneurysm. This emphasises the importance of regular follow-up in all patients following endoluminal repair. The presence of a perigraft leak represents failure of treatment and may result in aneurysm rupture (Lumsden *et al.* 1995). Therefore if possible these patients should be considered for conversion to open repair. The increase in the diameter of the proximal and distal necks observed on follow-up by the above authors is of greater concern. This may account for the late failure seen in one of our cases (patient C). The findings at operation in this patient confirmed that the aneurysmal process had not been retarded by endoluminal repair. This may have important implications for the long term durability of endoluminal AAA repair, in particular the aorto-aortic (tube) devices. The EVT tube Endograft^R used in our patients has been redesigned to eradicate the problem of hook fractures seen in some patients. The clinical trials were suspended temporarily but have now recommenced with the new modified prosthesis. The use of the EVT tube Endograft^R was suspended after 7 grafts had been implanted in our centre. This accounts for the 5 patients who were identified to be suitable for a tube graft but were not treated during this period. However it was uncertain as to whether the hook fractures detected in 2 of our patients had contributed to development of the perigraft leak.

At present there is also very limited information on the histological incorporation of endoluminal grafts in humans. McGahan *et al.* (1995) reported some encouraging results from a post-mortem examination in a patient who died of unrelated causes 7 months following endoluminal repair. Scanning electron microscopy of their explant showed a well developed neo-intima surrounding the metallic struts. This was composed of fibrous strands with entrapped erythrocytes and endothelial cells. However similar findings have not been observed by Moore (presentation on emerging technologies at the Society for Vascular Surgery/North American Chapter of the International Society for Cardiovascular Surgery Joint Annual Meeting, New Orleans, LA, June 11-14, 1995) or in our patient. One possible explanation for the different findings may be that the latter 2 patients exhibited either graft migration or a perigraft leak which may have prevented graft incorporation.

A comparison of the "normal" and "high" risk patients suggests that the mortality is higher in the latter group. However the numbers in this study are very small to draw any definite conclusions. The hospital stay in our patients was longer in comparison with other series (Parodi, 1995; Moore *et al.* 1996). This was due to the post-operative assessment of patients with colour duplex and contrast enhanced computed tomography to detect graft related complications. A prompt CT scan was not always possible due to a busy schedule

in the radiology department. In our centre all 3 devices are being used concurrently to evaluate the long term outcome. The learning curve for this procedure is formidable and this may account for the high early conversion rate with the aorto-uni-iliac device. All the conversions occurred in the early part of our experience with the aorto-uni-iliac device and some refinements have been made subsequently to reduce the 'on table' conversion rate. Errors in the deployment of the proximal stent have been overcome by inflating the balloon with saline instead of contrast (which obscured visualisation of the Palmaz stent). Several modification have also been made to reduce the operative blood loss. We have also started using cell saver system to minimise the homologous blood transfusions. The aorto-uni-iliac device can be used when the iliac vessels are wide (>14 mm) or aneurysmal and is therefore applicable in a higher proportion of patients. Also an accurate length of graft is not required with this device and can potentially be used in patients with a contained rupture (Yusuf *et al.* 1995).

8.8 Summary

The initial results suggest that endovascular AAA repair is feasible. However, number of problems including, size of prosthesis, phenomenon of microembolisation, perigraft leaks and the durability of endografts need further evaluation prior to widespread use of this technique.

CHAPTER NINE

Ischaemia Reperfusion Injury

9.1 Introduction

Abdominal aortic aneurysm repair is a good model of ischaemia-reperfusion injury (Ward *et al.* 1994; Baigrie *et al.* 1993; Roumen *et al.* 1993). During aortic clamping, the lower limbs and the gut may become ischaemic and initiate a series of biochemical and cellular events which can lead to local and systemic organ damage (Welbourn *et al.* 1991a).

There is now increasing evidence to suggest that tissue injury occurs upon reperfusion. This was shown dramatically by Parks and Granger (1986) in a feline model of intestinal ischaemia. They found that the histological changes of injury after 3 hours of ischaemia followed by 1 hour of reperfusion were far worse than the changes observed after 4 hours of ischaemia without reperfusion. During ischaemia, xanthine dehydrogenase is converted to xanthine oxidase with subsequent build up of hypoxanthine in the tissues. On reperfusion, this enzyme catalyses the formation of xanthine from hypoxanthine, with the formation of reactive oxygen free radicals in the process (McCord, 1985). This process probably occurs in organ parenchymal cells and in the endothelium. The other important event in early reperfusion is the inflow of neutrophils, which are avidly sequestered in the small vessels of the post-ischaemic organ. This is an effect attributed to expression of adhesion molecules on both endothelium {(intercellular adhesion molecule-1 (1CAM-1)} and neutrophils (L-selectin, and CD11b/CD18) (Lefer *et al.* 1996). Adherence and activation of neutrophils is considered to be a critical contributor to reperfusion injury mediated by further release of oxidants accompanied by proteases and elastases, by activation of phospholipases, and by release of platelet activating factor (PAF) and leucotrienes (Conger *et al.* 1995). It has been postulated that oxygen free radicals may generate chemotactive activity leading to this directed migration of activated neutrophils into the reperfused tissue (McCord, 1987; Repine *et al.* 1987). Increased levels of cytokines interleukin -I beta (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) have been observed following elective AAA repair (Roumen *et al.* 1993). These inflammatory mediators may initiate local and systemic organ damage (lung, kidneys and myocardium) and account for the multiorgan failure seen in some patients following AAA repair (Soreide *et al.* 1982a; Gefke *et al.* 1994).

Endovascular AAA repair avoids intra-abdominal manipulation and aortic clamping. There may be a temporary occlusion of the aorta during deployment of some of the intraluminal prostheses (Thompson *et al.* 1995), but this is considerably less than the aortic occlusion during conventional open aneurysm surgery. Endovascular techniques, therefore have the potential to diminish the severity of ischaemia-reperfusion injury. **The aim of this study was to assess whether the metabolic response during surgery differs between conventional and endovascular AAA repair. This has been investigated by quantifying oxygen free radical and cytokine production in a non-randomised cohort of patients.**

9.2 Patients and Methods

This study comprised a cohort of 12 patients undergoing abdominal aortic aneurysm repair, six by conventional transperitoneal inlay replacement (Crawford *et al.* 1985), and six by endovascular techniques. Patient details are recorded in *Table 32.* All operations were performed under general anaesthesia, without epidural opiates or local anaesthetic agents. Intra-venous thiopentone was used for induction and anaesthesia was maintained with a combination of nitrous oxide, oxygen, isoflurane and morphine. Sodium nitroprusside was used to control the cardiac after load during the procedure. Substances with known anti-oxidative properties (Crozier *et al.* 1994) were avoided during the peri-operative period.

Table 32: *Demographic data of the study patients. Continuous variables are given as medians with ranges in parentheses.*

	Endovascular group (n=6)	**Conventional group (n=6)**
Age (range)	72.5 (64-76)	71 (64-85)
Sex (M/F)	6/0	3/3
Hypertension	3	1
IHD	4	0
PVD	3	1
Current smokers	1	3
AAA diameter (cm)	5.5 (5-6.2)	5.8 (4.4-7.6)
Aortic clamp time (mins)	4*	35 (20-60)

IHD = Ischaemic Heart Disease

PVD = Peripheral Vascular Disease.

**Total balloon inflation time during stent deployment*

All patients underwent tube graft repair. Endovascular repair was undertaken using the Endovascular Grafting System™ (EndoVascular Technologies Inc., California, USA), described in the earlier chapters. Stent deployment was aided by balloon inflation for one minute at two atmospheres intraluminal pressure. Two inflations were used both at the proximal and distal stent sites. Deployment of the device was undertaken via the common femoral artery in two cases and via a temporary iliac conduit in the remaining four cases.

Blood samples were collected from the common femoral vein by intermittent venepuncture prior to aortic clamping or balloon occlusion, during completion of the proximal and distal anastomosis (sutured or stented), and at 5 and 30 minutes post reperfusion. The samples were centrifuged immediately at 3000 rpm for 5 minutes and the serum separated. The serum samples were snap frozen and stored in liquid nitrogen until prior to analysis. In the endovascular group, samples were obtained from the common femoral vein contralateral to the device insertion site.

Determination of Oxygen Free Radical and Cytokine production

Generation of oxygen free radicals (OFR's) was measured indirectly by determination of IgG oxidation in plasma using the method of Lunec *et al.* (1985), a method previously used to determine IgG oxidation in rheumatoid sera and synovial fluid. Interleukin -I beta (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) were measured using commercially available radio immunoassays (Amersham International plc., Bucks, UK). The sensitivity of these assays was given as 38pg/ml, 22pg/ml and 90pg/ml respectively. The exact methodology for these assays is described in Appendix B and Appendix C.

9.3 Results

All metabolites, with the exception of IL-6 showed an increase during the ischaemic and reperfusion periods. The absolute values for cytokine and free radical generation are tabulated in *Table 33*. The proportional change from baseline values for both cytokines and OFR activity is illustrated in *Figures 9.1-9.4.* The changes in IL-1β, TNF-α, and OFR activity were reduced by endovascular aneurysm repair when compared to conventional procedures. The peak change from baseline values for OFR activity, IL-1β, and TNF-α is given in *Table 34*. The reduction in IL-1β and TNF-α was significant at the 95% confidence level using two way analysis of variance. The fall in OFR activity did not reach statistical significance.

Table 33: *Table illustrating cytokine and free radical results. Values are medians with interquartile*

	Baseline	Proximal Anastomosis	Distal Anastomosis	5 mi Reperfu
OFR-EV	0.45 (0.38-0.88)	0.64 (0.52-1.1)	0.67 (0.48-1.43)	0.71 (0.5
OFR-Con	0.6 (0.48-1.0)	0.96 (0.51-1.25)	1.06 (0.51-1.38)	1.14 (0.89
IL-1β-EV	2.4 (2.37-3.25)	2.56 (1.3-3.52)	2.65 (1.9-3.3)	2.1 (1.35
IL-1β-Con	1.7 (1.27-2.5)	1.45 (1.2-1.83)	2.1 (1.65-3.4)	1.82 (0.69
IL-6-EV	0.32 (0.26-1.15)	0.44 (0.21-0.97)	1.12 (0.1-2.38)	1.2 (0.14
IL-6-Con	0.12 (0.1-0.25)	0.16 (0.12-0.52)	0.12 (0.1-1.36)	0.15 (0.1
TNF-α-EV	10.3 (4.5-14.1)	5.8 (3.8-13.1)	3.9 (2.1-10.4)	4.4 (1.5
TNF-α-Con	3.35 (2.1-4.7)	5.05 (3.4-8.6)	4.75 (3.3-10.9)	4.3 (1.8

OFR - oxygen free radicals *IL - interleukin TNF - tumour necrosis factor*

EV - endovascular repair *Con - conventional repair*

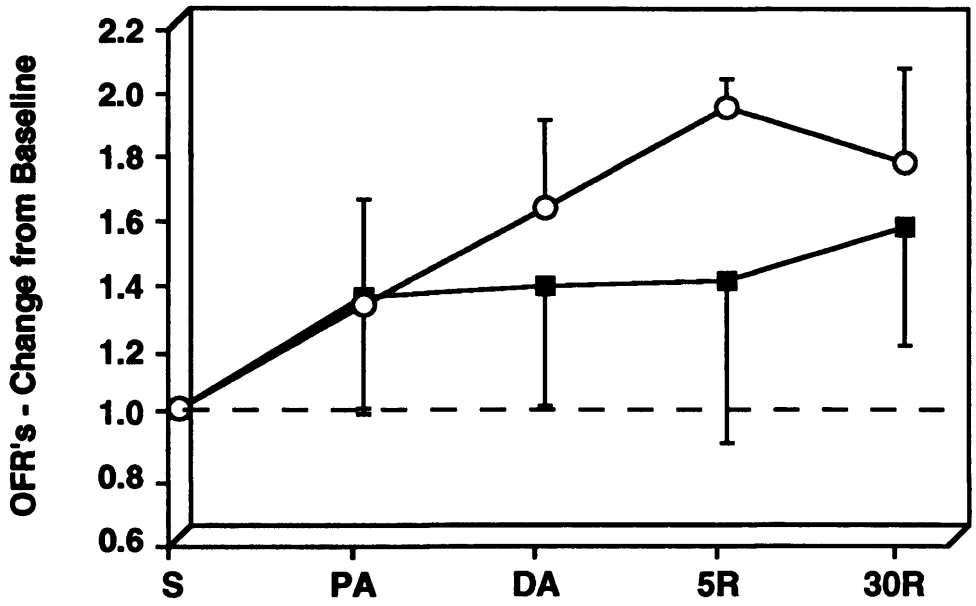


Figure 9.1: *Graph illustrating the changes in oxygen free radical (OFR) generation during endovascular (■) and conventional (O) repair. Time points: S = baseline sample; PA = completion of proximal anastomosis; DA = completion of distal anastomosis; 5R = 5 min post reperfusion; 30R = 30 min post reperfusion. Values are presented as medians with interquartile ranges.*

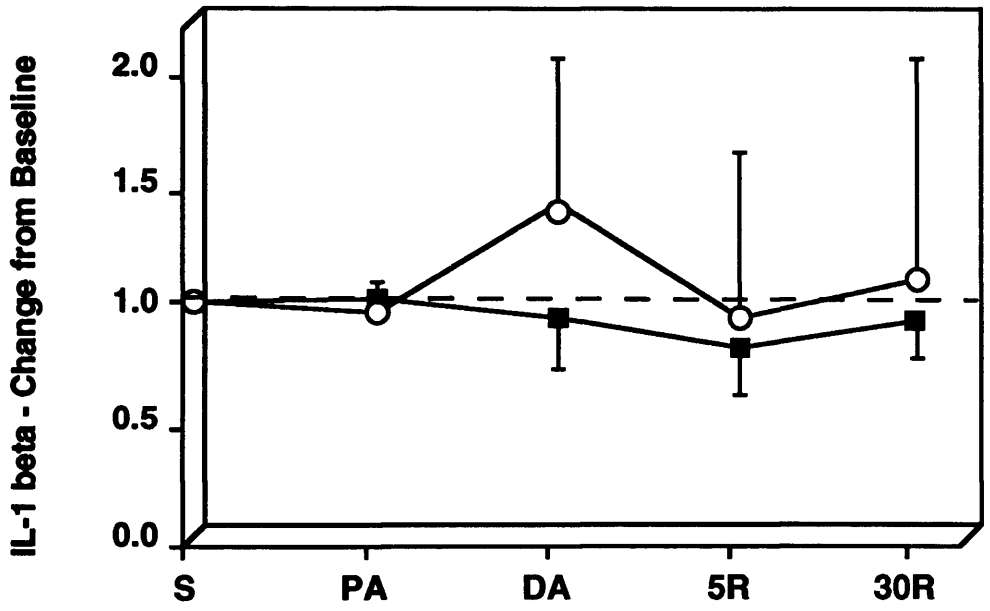


Figure 9.2: *Graph illustrating the changes in IL-1β generation during endovascular (■) and conventional (O) repair. Time points: S = baseline sample; PA = completion of proximal anastomosis; DA = completion of distal anastomosis; 5R = 5 min post reperfusion; 30R = 30 min post reperfusion. Values are presented as medians with interquartile ranges.*

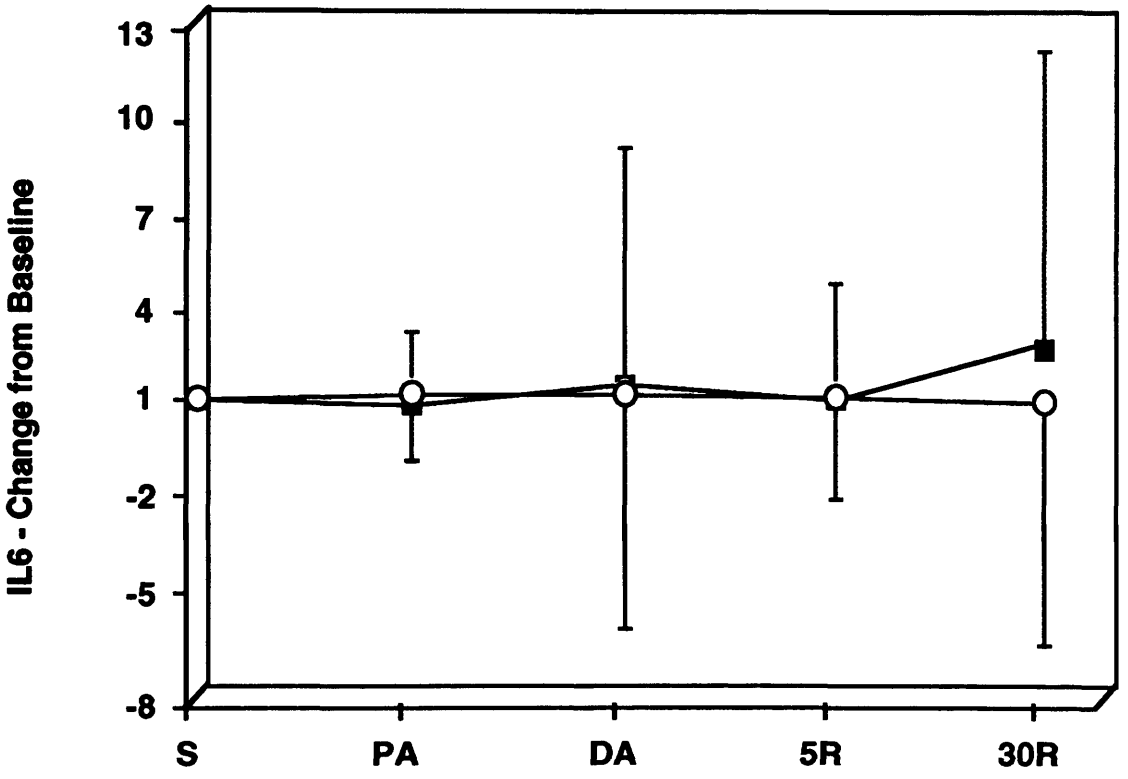


Figure 9.3: *Graph illustrating the changes in IL-6 generation during endovascular (■) and conventional (O) repair. Time points: S = baseline sample; PA = completion of proximal anastomosis; DA = completion of distal anastomosis; 5R = 5 min post reperfusion; 30R = 30 min post reperfusion. Values are presented as medians with interquartile ranges.*

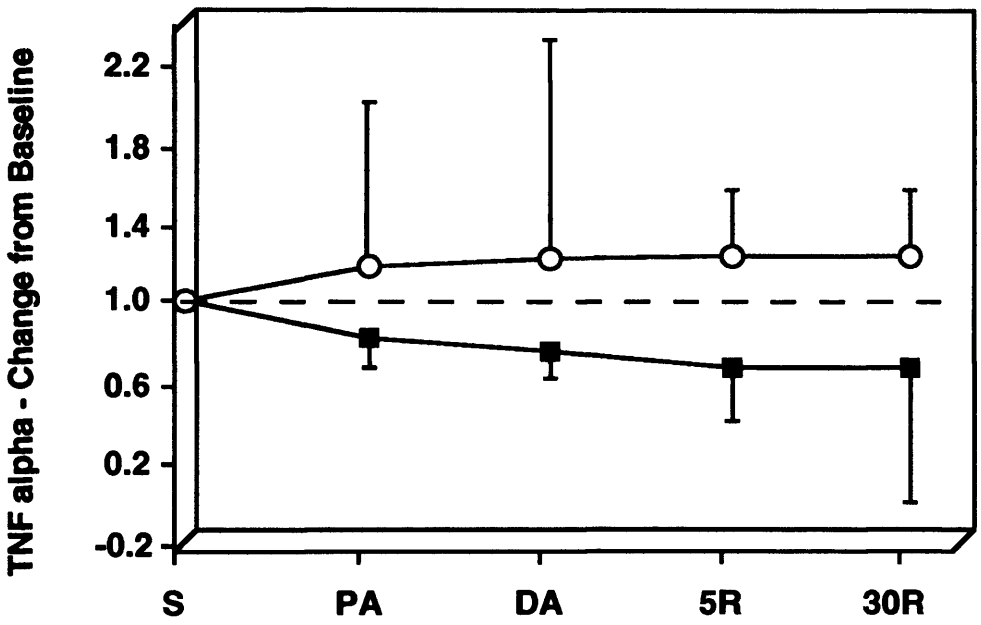


Figure 9.4: *Graph illustrating the changes in TNF-α generation during endovascular (■) and conventional (O) repair. Time points: S = baseline sample; PA = completion of proximal anastomosis; DA = completion of distal anastomosis; 5R = 5 min post reperfusion; 30R = 30 min post reperfusion. Values are presented as medians with interquartile ranges.*

Table 34: *The change in OFR, IL-1β and TNF-α levels during conventional open and endovascular AAA repair. The values are given as medians with interquartile ranges:*

	Peak levels (Change from baseline)		
	OFR	**IL-1β**	**TNF-α**
Conventional repair	1.93 (1.4-2.0)	1.42 (0.74-2.03)	1.23 (0.39-1.34)
Endovascular repair	1.55 (1.33-1.92)	1.02 (0.56-1.1)*	0.81 (0.66-0.96)*

**p<0.05 - two way analysis of variance*

9.4 Discussion

The cell damage following ischaemia is now recognised as a biphasic phenomenon, with injury being initiated during ischaemia and exacerbated during reperfusion. During ischaemia, the cell is deprived of the energy needed to maintain ionic gradients and homoeostasis, and failure of enzyme systems leads to cell death. Reperfusion injury is thought to be mediated by an interaction of free radicals, endothelial factors and neutrophils. The resulting injury is similar in most states of tissue hypoperfusion, including abdominal aortic aneurysm surgery, limb ischaemia, organ transplantation, stroke and hypovolaemic shock.

The mechanisms underlying ischaemia-reperfusion injury have been reviewed extensively by several authors (Welbourn *et al.* 1991a; Grace, 1994). The enzyme xanthine oxidase is a major source of free radicals in post-ischaemic tissue (McCord, 1985). During ischaemia, xanthine oxidase, produced by the conversion of xanthine dehydrogenase accumulates in the tissues. As a consequence the tissue levels of hypoxanthine, a substrate for xanthine oxidase, increase. During reperfusion, xanthine oxidase uses molecular oxygen to convert hypoxanthine to xanthine, resulting in the production of highly reactive oxygen free radicals (Sinclair *et al.* 1990). The most damaging effect of oxygen free radicals is lipid peroxidation, which results in structural and functional cell damage (Kellog, 1975). However, oxygen metabolites produced through plasmalemmal and intracellular sources in ischaemic tissues are unlikely to be responsible for the systemic organ damage, as they are very reactive and short lived (Pryor, 1986). It has been proposed that oxygen free radicals may react with endothelial cells to promote formation of inflammatory mediators such as platelet-activating factor (PAF) (Lewis *et al.* 1988) and Leukotriene (LT) B4 (Plamblad *et al.* 1981), which may be responsible for neutrophil activation and adhesion observed in non-ischaemic areas of tissue following ischaemia-reperfusion (Ferrante *et al.* 1996). Therefore, activated neutrophils are thought play a pivotal role in cellular injury in organs and tissues that are some distance from the reperfused tissue through release of OFRs, proteolytic enzymes (collagenase, elastase, cathepsin G) and peroxidase (Welbourn *et al.* 1991a; Windsor *et al.* 1993). The interaction between neutrophils and the endothelial cell is regulated by cell adhesion molecules (CAMs) such as L-selectin and CD11b/CD18 (present in neutrophils), and intercellular adhesion molecule-1 (ICAM-1) which is the major counter-receptor on endothelial cells (Lefer *et al.* 1996). ICAM-1 is constitutively present on the surface of endothelial cells to a moderate degree, and can be strongly upregulated over a period of 2-4 hours by cytokines including IL-1β, IL-8, and TNF-α (Lefer *et al.* 1996).

The organs which commonly reflect the global injury seen following reperfusion in AAA surgery are lung, myocardium and kidney. Lung injury is characterised by non-cardiogenic pulmonary oedema, an early manifestation of the adult respiratory distress syndrome (ARDS). This pulmonary injury is characterised by increased microvascular

permeability and accumulation of neutrophils (Labbe *et al.* 1987; Anner *et al.* 1987) that have migrated to the lung following activation by agents released from ischaemic reperfused tissue (Anner *et al.* 1988; Klausner *et al.* 1988; Klausner *et al.* 1989; Welbourn *et al.* 1991b). Lindsay *et al.* (1992) have suggested that the increased pulmonary permeability is complement dependent and were able to reduce muscle and lung permeability following lower torso ischaemia with specific complement inhibitor soluble human complement receptor type 1. Activation of neutrophils and their subsequent sequestration in the lungs and other organs is an important step in the development of multisystem organ failure (Deitch, 1992).

In this study, the largest rise in OFR activity was observed during the revascularisation phase which is in agreement with other human revascularisation models (Ward *et al.* 1994; Rabl *et al.* 1992; Murphy *et al.* 1992). During infra-renal aortic clamping all structures supplied by the inferior mesenteric, iliac and femoral arteries are predisposed to the ischaemia-reperfusion insult (Smeets *et al.* 1995). Murphy *et al.* (1992), measured anti-oxidant compounds (α-tocopherol, ascorbic acid, and protein thiols), oxidation products (α-tocopherol quinone), and lipid peroxidation products (lipid-derived malondialdehyde) in patients undergoing thoracoabdominal aneurysm repair. They found that during ischaemia, anti-oxidant compounds decreased, whereas α-tocopheryl quinone doubled. On reperfusion, the anti-oxidant activity remained low whilst lipid peroxidation products increased significantly. These findings suggest that oxidative stress occurred during aortic clamping, and also during the reperfusion phase. Our results show a slight rise in OFR activity during aortic clamping which was also observed by Ward *et al.* (1994). This may be due to the collateral blood flow via lumbar arteries to the lower limbs whilst the aorta is clamped (Ward *et al.* 1994).

Cytokines are polypeptides produced by cells of the immune system that act as mediators of both the immune response and the response of other tissues in the body to injury. TNF-a and IL-1β are considered to be primarily responsible for the non-hepatic manifestations of the acute-phase response such as fever, elevated prostaglandins, tachycardia and accelerated catabolism (Dinarello, 1984). IL-6 is primarily responsible for the hepatic component of the acute-phase response, resulting in synthesis of acute-phase proteins (Castell *et al.* 1989; Gauldie *et al.* 1987). There is some evidence to suggest that high levels of IL-1β, IL-6 and TNF-a are associated with increased incidence of adult respiratory distress syndrome (ARDS) and multiorgan failure, and a higher mortality in patients after major trauma and AAA surgery (Roumen *et al.* 1993; Cruikshank *et al.* 1990; Baigrie *et al.* 1992). Previous studies have shown colon to be a major source of IL-6 response in AAA surgery (Baigrie *et al.* 1993). Baigrie *et al.* (1993) undertook portal and systemic cytokine analysis and found IL-1 levels to be similar in the two compartments but the portal IL-6 levels greatly exceeded the systemic levels. Our study has quantified cytokine production from the lower limbs which may account for the lack of IL-6 response

observed. Also the systemic IL-6 levels have been found to peak between 4 and 48 hours after abdominal incision (Baigrie *et al.* 1992), which is considerably later than our sampling times. IL-6 levels in portal blood may reflect occult cellular injury in the colon, arising during surgery and further studies including use of intraluminal tonometry to assess colonic ischaemia are required to determine whether exaggerated IL-6 responses are associated with subsequent development of major post-operative complications (Soong *et al.* 1993).

Interleukin-1β and TNF-α are produced primarily by blood monocytes and tissue macrophages, although other cells may produce them in smaller quantities under certain circumstances (Dinarello, 1989). In this study, conventional AAA repair was associated with an increase in levels of IL-1β and TNF-α, which is consistent with findings of other investigators (Roumen *et al.* 1993). The levels of these cytokines have been found to peak within 1 to 4 hours of the abdominal incision which precedes the peak in IL-6 levels (Roumen *et al.* 1993; Parry-Billings *et al.* 1992). Their levels remained diminished in the endovascular group throughout the procedure. Norgren *et al.* (1996) have also undertaken a similar study in a small series of patients and found TNF-α levels to be significantly higher in the endovascular group. They concluded that the catheter manoeuvres into the aneurysmal thrombotic content may cause extensive cellular activation in the endovascular group. However, further studies are required to evaluate whether there are any differences in patients undergoing tube or bifurcated graft endoluminal repair, as the latter involve greater guide wire and catheter manipulation.

This study has concentrated on contralateral limb ischaemia which is only rendered ischaemic during aortic balloon inflation, as a simplified model of reperfusion injury. However the same cannot be said for the limb ipsilateral to device insertion, that may have been intermittently ischaemic for much longer. The total ischaemia time in the ipsilateral limb was more difficult to define and hence blood samples were collected from the contralateral common femoral vein only. Thus the overall magnitude of the reperfusion injury may have been underestimated by this study. Also this study was undertaken in patients undergoing aorto-aortic grafting. The reperfusion injury may be greater in patients undergoing aorto-uni-iliac reconstruction combined with a femoro-femoral crossover. The additional ischaemic time may be avoided by performing the crossover at the start of the procedure. Therefore the ischaemia-reperfusion response may vary depending on the device used.

9.5 Summary

The findings in this study suggest that the ischaemia-reperfusion response associated with conventional aneurysm surgery may be largely negated by endovascular techniques. This may have the potential to decrease the remote organ failure following aneurysm repair, and this idea is worthy of further evaluation.

CHAPTER TEN

Final Discussion, Conclusions and Future work

Abdominal aortic aneurysms are a relatively common cause of death in the elderly. In England and Wales, with a total population of about 47 000 000, it is estimated that between 6000 and 10 000 people die each year from rupture of an abdominal aortic aneurysm and that around 3000 undergo successful elective or emergency surgical treatment (Powell *et al.* 1990). The incidence of abdominal aortic aneurysms in western countries has risen dramatically during the second half of this century (Fowkes *et al.* 1989). This increase has been confirmed by data presented in this thesis (Chapter 5). The increase may partly be due to a change in the age structure of the population, as reflected by increase in the median age of patients in our data (69.5 years in 1979 to 74 years in 1991), better diagnostic methods and greater clinical awareness. However, the trends observed by us and by others (Samy *et al.* 1993; Fowkes *et al.* 1989; Budd *et al.* 1989) suggest that there is also a true increase in the age specific prevalence of this condition.

The data in Chapter 5 also shows that against a background of increased prevalence, there has been very little change in the operative mortality following both elective and emergency aneurysm surgery in the last decade (Figure 5.2), despite improvements in operative techniques and anaesthesia. Although elective open aneurysm repair (using inlay graft replacement) is a very successful operation in fit patients, the risks associated with this condition increase in the elderly patients, obese patients and those with co-existing cardiorespiratory disease. In these patients the operative mortality may approach 60% (McCombs *et al.* 1979) and they may be denied surgery as the risks of operative intervention exceed the benefits. This prompted a search for less traumatic ways to overcome the drawbacks of major open surgery. The concept of endovascular aneurysm repair was conceived in order to reduce the operative trauma, the need for postoperative intensive care and to speed recovery, with the aim of reducing the mortality in high risk patients (Parodi, 1997).

Although the potential benefits of endovascular AAA repair are immense, scientific evidence must be accumulated carefully and thoroughly before advocating its widespread use. The experimental work presented in this thesis (Chapter 6) attempted to investigate a number of aspects of this technique which may affect the outcome. The animal experience presented confirms that endovascular repair of abdominal aortic aneurysms is feasible and can be performed with minimal morbidity and mortality. The work in this thesis has demonstrated that the single proximal stent technique is associated with backbleeding from the distal unstented end and that this can be abolished by the double stent technique. However, the safety of placing stents across the renal arteries remains uncertain. Previous studies have shown that renal arteries accidentally bridged by stents remain patent. The results presented in this thesis suggest that although there was no disturbance of renal function, the finding of organised thrombus and endothelial disruption seen on electron

microscopy do cast a doubt on the long term safety of such a manoeuvre. Further work is required in this area before applying this technique in humans.

A detailed radiological assessment of the aneurysm is an important prerequisite for planning an endovascular repair. For endovascular aneurysm repair to be successful, the morphology of the aorta and iliac arteries must be shown to be suitable for the device to be used and the size of the prosthesis must be correct in every detail. This problem has been addressed in Chapter seven. The work presented in this thesis shows that colour duplex scanning, although regarded as a gold standard in our centre for assessment of lower limb arterial lesions, appears to be poor at visualising the renal arteries and hence provides unreliable assessment of the proximal aneurysm neck. The presence of thrombus in the aneurysm sac obscures the proximal and distal limits of the aneurysm sac on intra-arterial DSA and therefore limits its usefulness in patient selection. Conventional CT also has a limited role due to inadequate visualisation of renal artery origins in up to 40% of patients. This is due to a combination of factors including the obliquity of image slices due to tortuosity of the aorta, and the intervals between images which fail to demonstrate the structures falling between the slices. Our results suggest that magnetic resonance angiography (MRA) provides the best non-invasive assessment of those aneurysm parameters relevant to patient selection and graft sizing for endovascular repair. Spiral CT scanning with three dimensional reconstruction was not included in our comparison, as this modality is not currently available at Leicester Royal Infirmary. Other centres have found this modality to be equally good at assessing aneurysm morphology prior to endovascular repair (Low *et al.* 1993; Rozenblit *et al.* 1995). The present policy in our centre (and also in other centres evaluating endovascular AAA repair) is that all patients declared suitable for endovascular repair on the basis of MRA or spiral CT findings should also undergo calibrated, marker catheter angiography for confirmation of measurements and to provide an anatomical road-map. Future hardware and software developments in MRA and CT image acquisition and processing may reduce the need for angiography in the future.

The data on aneurysm morphology (detailed in Chapter 7) also highlights the considerable anatomical constraints that exist with the currently available endoluminal prostheses. At present the most restrictive criteria apply to the iliac arteries. Many common iliac arteries exceed the upper limit of the diameter of the bifurcated graft limbs. Some of the systems, in particular the aorto-uni-iliac device, seek to treat the patients with large common iliac arteries by extending the stent-graft combination down to the external iliac artery. This assumes that the internal iliac artery can be bypassed without risk of retrograde aneurysm perfusion or ischaemia of the pelvis, colon and buttocks. Three patients treated on this basis in our centre have experienced buttock claudication, which suggests that the above strategy may not be safe in all patients. Indeed colonic ischaemia has been reported as a complication of endovascular repair from 2 centres (Dereume *et al.*

1997; Sandison *et al.* 1997). Preliminary work using balloon tonometry to measure sigmoid intramucosal pH suggests that exclusion of the inferior mesenteric artery, either alone or in combination with the internal iliac artery during endovascular AAA repair, did not affect the level of sigmoid pH nor did it cause the development of clinically apparent colonic ischaemia, provided that the superior mesenteric artery was patent (Elmarasy *et al.* 1997). However, the numbers in this study were small (n=16) and further research is necessary before ignoring this possible complication.

The initial clinical experience presented in Chapter 8 confirms that endoluminal graft placement is feasible. However, a number of early problems have been encountered which require further evaluation. The fundamental difference between conventional surgery and endovascular procedures as far as the aneurysm is concerned is that, in the former case, the aneurysm is opened and all its side branches are ligated, whereas in the latter procedure, the aneurysm remains intact, and is merely excluded from the aortic blood flow and pressure. Therefore any leak at the stent sites, or collateral perfusion may then exert continuous pressure on the aneurysm wall. Incomplete seal at the proximal or distal sites was encountered in 4 out of 7 patients treated with the tube endograft and has also been reported with other devices. The early follow up data presented in this thesis suggests that patients with perigraft leaks exhibit a progressive increase in the diameter of aneurysm. Therefore the presence of a perigraft leak must be considered as failure of treatment. Future research is needed to investigate whether perigraft leaks are related to the characteristics of the native aorta (such as degree of calcification or presence of thrombus) or the type of stent used for endograft attachment. Also, although animal studies have shown incorporation of the stent into the aortic wall, at present there is very little evidence on whether a similar response occurs in the atheromatous human aorta.

The results of conventional aneurysm surgery presented in Chapter 5 suggest that perioperative mortality is primarily cardiac in origin. However both deaths encountered in patients treated with endovascular technique during our initial experience have resulted from microembolisation. This complication has also been encountered in other centres and has proven fatal in over 90% of affected patients (Parodi, 1995; Mialhe *et al.* 1995; Marin *et al.* 1995). In direct contrast, death from massive microembolisation is a comparatively rare event following conventional aneurysm surgery (Starr *et al.* 1979). The emboli data presented in this thesis (Chapter 8) confirmed that the numbers of particulate emboli were significantly greater in patients undergoing endovascular aneurysm repair compared with those undergoing conventional repair. The potential mechanism of massive microembolisation during endovascular aneurysm repair may be related to repeated, difficult and prolonged manipulation of large endoluminal devices within an aneurysm, which may dislodge the laminated thrombus that lines the aneurysm wall. The thrombus may then be dispersed into visceral, renal, and lower limb arteries by turbulent flow within the aneurysm sac (Asbury *et al.* 1995; Lautstsen *et al.* 1995; Low *et al.* 1993). Further

work is also required in this area to identify patients at high risk for developing this complication and to develop therapeutic strategies which may reduce the likelihood of this fatal complication.

The other major area where future research is needed is the long term durability of endoluminal grafts. The aortas of healthy individuals appear to dilate through out life. This process may be accentuated in vessel segments adjacent to an aneurysm. Whether this process is reversed or halted by endoluminal grafts is at present not known. There is concern about the late failure seen in one of our patients, and the dilatation of the aorta surrounding the proximal graft-anchoring stent on intermediate term follow up reported by other authors (Balm *et al.* 1995; Malina *et al.* 1997; May, 1997). Hypothetically, it is possible that the stress exerted by the expanded stent may start the dilatation process. However, this stress is necessary to keep the stent in place and prevent persistent leakage. On the other hand, the force of the expanding stent must not damage the aortic wall at the neck, thus causing further dilatation. Excessive over sizing of stent-grafts may therefore be harmful in this context. If the aortic dilatation at the stent site is part of the patient's aneurysmal disease rather than a consequence of stent action, then the long term durability remains uncertain. Under these circumstances whether self-expanding stents confer advantage over balloon expandable stents is also not known. There is some preliminary experimental evidence to suggest that balloon expandable stents detach from dilating vessels in growing animals (Mangell *et al.* 1996). Further research is clearly needed to establish the long term durability before recommending the widespread use of this technique.

The dose of radiation and the volume of contrast used during stent-graft treatment have also been subjects of concern . A radiation dose to the skin in the order of 2 to 4 Gy and 300 ml of contrast material are frequently used; this is in addition to the amounts delivered during pre-operative angiography and CT examinations performed on follow up. The use of alternative methods for visualisation such as magnetic resonance imaging, intravascular ultrasound and colour duplex needs to be explored.

Considerable progress has been made since Parodi's first description of endovascular grafting for AAA exclusion (Parodi *et al.* 1991). What is now required is the development of a system small enough to be used percutaneously. This would eliminate the need for open arterial access and would reduce stress, discomfort and blood loss associated with stent-graft placement, all of which can be important in patients with poor cardiac reserve. Also, although dozens of endograft designs are under investigation, the ideal attachment system and graft material are still to be established. It is still early to draw conclusions regarding the morbidity and mortality based on our small clinical series. However early results from other centres suggest that the recovery time is more rapid and pain free after endografting, and the perioperative morbidity and mortality are low (Chuter *et al.* 1996; White *et al.* 1996; Blum, 1997; Moore *et al.* 1996; May *et al.* 1995b). The

work presented in Chapter 9 suggests that the ischaemia-reperfusion response associated with conventional aneurysm surgery may be attenuated by endovascular techniques. This may have the potential to decrease the remote organ failure seen in some patients following conventional AAA repair. The prospect of further improvements in graft technology and delivery system design will make endovascular an important tool in AAA management in the near future. The potential benefits render endoluminal grafts extremely attractive to vascular surgeons and patients alike, which generates strong pressures to use them before they have been proven safe and effective. However, whether endovascular procedures will be associated with lower mortality and morbidity rates can be demonstrated only by a large scale randomised comparative trial between endovascular and open surgical technique.

Appendix A

American Society of Anaesthesiologists Classification

Status	Disease State
ASA Class 1	No organic, physiologic, biochemical, or psychiatric disturbance
ASA Class 2	Mild to moderate systemic disturbance that may or may not be related to the reason for surgery
ASA Class 3	Severe systemic disturbance that may or may not be related to the reason for surgery
ASA Class 4	Severe systemic disturbance that is life-threatening with or without surgery
ASA Class 5	Moribund patient who has little chance of survival but is submitted to surgery as a last resort (resuscitative effort)
Emergency Operation (E)	Any patient in whom an emergency operation is required

From information in the American Society of Anesthesiologists: New classification of physical status. Anesthesiology 24:111,1963.

Appendix B

Interleukin-6 (IL-6) Assay System

The assay is based on the competition between unlabelled IL-6 and a fixed quantity of ^{125}I-labelled IL-6 (human, recombinant) for a limited number of binding sites on an IL-6-specific antibody. With fixed amounts of antibody and radioactive ligand, the amount of radioactive ligand bound by the antibody will be inversely proportional to the concentration of added non-radioactive ligand.

The antibody bound IL-6 is then reacted with the Amerlex-M second antibody reagent (Amersham International plc., Bucks, UK) which contains second antibody that is bound to magnetisable polymer particles. Separation of the antibody bound fraction is effected by either magnetic separation or centrifugation of the Amarlex-M suspension and decantation of the supernatant.

Measurement of the radioactivity in the pellet enables the amount of labelled IL-6 in the bound fraction to be calculated. The concentration of unlabelled IL-6 in the sample is then determined by interpolation from a standard curve.

Assay Methodology

This pack contains sufficient material for 100 assay tubes.

Contents of the assay system

Assay buffer
Assay buffer concentrate 5ml. On dilution to 50 ml this gives a 0.02M borate buffer pH7.4 containing 0.1% sodium azide.

Standard
Recombinant human IL-6, lyophilised. On reconstitution this bottle contains 320fmol/ml IL-6.

Antiserum
Rabbit anti-IL-6 serum, lyophilised.

Tracer
[^{125}I] IL-6 (human, recombinant) ~41kBq, 1.1uCi, lyophilised.

Amerlex-M second antibody reagent

Donkey anti-rabbit serum coated on to magnetisable polymer particles, colour coded blue green. This solution contains 0.06% w/v sodium azide, 30 ml ready to use.

Results plotting sheet

Radioimmunoassay procedure

The assay was performed with a 4 hour room temperature pre-incubation followed by an overnight incubation at room temperature after tracer addition. On day two, magnetic separation was performed and pellet count established with a gamma counter.

Assay buffer

The contents of the bottle containing the assay buffer, with washings, were transferred to a 50ml measuring cylinder and diluted to 50 ml with distilled water. This was mixed well and then used to redissolve all other components.

Standard

2.0ml of the assay buffer was added to the standard solution. This was mixed well by inversion and swirling, taking care to avoid foaming. The final solution contained human recombinant IL-6 at a concentration of 320fmol/ml in 0.02M borate buffer pH7.4 containing 0.1% sodium azide.

Antiserum

11.0ml of assay buffer was carefully added to the antiserum. The contents of the bottle were mixed by inversion and swirling, taking care to avoid foaming. The final solution contained anti-IL-6 serum in 0.02M borate buffer pH7.4 containing 0.1% sodium azide.

Tracer

11.0 ml of assay buffer was added to the tracer. The contents of the bottle were mixed by inversion and swirling, taking care to avoid foaming. The final solution contained [125I] human recombinant IL-6 in 0.02M borate buffer pH7.4 containing 0.1% sodium azide.

Preparation of working standards

1) 7 polystyrene tubes were labelled: 0.25, 0.5, 1, 2, 4, 8 and 16.
2) 500ul of assay buffer was pipetted into all tubes

3) Into the 16 tube 500ul of the assay standard (320fmol/ml) was pipetted and mixed in vortex thoroughly.
4) 500ul from the 16 tube was transferred to the 8 tube and mixed thoroughly in vortex.
5) This doubling dilution was repeated successively with the remaining tubes.
6) 100ul aliquots from each serial dilution gave rise to 7 standard levels of IL-6 ranging from 0.25 to 16fmol (5.5 to 352pg).

Assay Protocol

1) All reagents were equilibrated to room temperature.
2) The reagents and assay standards were prepared as describe above.
3) Polystyrene tubes were labelled in duplicate for: total counts (TC), non-specific binding (NSB), zero standard (B_0), standards and samples.
4) 200ul of the assay buffer was pipetted into the non-specific binding (NSB) tubes.
5) 100ul of assay buffer was pipetted into the zero standard (B_0)tubes.
6) Starting with the most dilute, 100ul of each standard were pipetted into the appropriately labelled tubes.
7) 100ul of the unknown sample was pipetted into appropriately labelled tubes.
8) 100ul of antiserum was pipetted into all tubes except NSB and TC.
9) All tubes were mixed thoroughly with vortex. The tubes were covered with plastic film and incubated for 4 hours at room temperature.
10) 100ul of [^{125}I] IL-6 was pipetted into all tubes. The TC tubes were stoppered and put aside for counting.
11) All the tubes were mixed thoroughly with vortex. The tubes were covered and incubated for 24 hours at room temperature.
12) The bottle containing Amerlex-M second antibody reagent was gentled swirled to ensure a homogeneous suspension. 150ul were added to each tube except the TC. These were then incubated at room temperature for 10 minutes.
13) The antibody bound fraction was then separated using magnetic separation as described below.

Magnetic separation

The rack containing the tubes was attached to the Amerlex-M Separator base, ensuring that all the tubes were in contact with the base plate, and left at room temperature for 15 minutes. After separation the rack was left on the separator base, and the supernatant poured off and discarded. Keeping the separator inverted, the tubes were placed on a pad of absorbent tissues and allowed to drain for 5 minutes.

14) On completion of magnetic separation, the rims of the tubes were firmly blotted with

tissue pad to remove any adherent liquid.

15) The radioactivity present in each tube was determined by counting for 60 seconds in a gamma scintillation counter.

Calculation of results

1) The average counts per minute (cpm) were calculated for each set of replicate tubes.

2) The percent NSB/TC was calculated using the following equation:

$$\%NSB/TC = \frac{\text{NSB cpm}}{\text{TC cpm}} \times 100$$

3) The percent B_0/TC was calculated using the following equation:

$$\%B_0/TC = \frac{(B_0 \text{ cpm} - \text{NSB cpm})}{\text{TC cpm}} \times 100$$

4) The percent bound/B_0 for each standard and sample was calculated using the following equation:

$$\%B/B_0 = \frac{(\text{Standard or sample cpm} - \text{NSB cpm})}{(B_0 \text{ cpm} - \text{NSB cpm})} \times 100$$

5) A standard curve was generated by plotting the percent B/B_0 as a function of the log IL-6 concentration. The $\%B/B_0$ (y-axis) was plotted against fmol standard per tube (x-axis). The fmol per tube was then read directly from the graph.

The assay for IL-1β used exactly the same technique but employed recombinant human IL-1β as a standard, rabbit anti-IL-1β serum as antiserum and [^{125}I] IL-1β (human recombinant) as tracer.

Appendix C

Tumour necrosis factor-alpha (TNF-α) Assay System

The assay is based on the competition between unlabelled TNFα and a fixed quantity of [^{125}I]-labelled TNFα (human, recombinant) for a limited number of binding sites on a TNFα-specific antibody. With fixed amounts of antibody and radioactive ligand, the amount of radioactive ligand bound by the antibody will be inversely proportional to the concentration of added non-radioactive ligand.

The antibody bound TNFα is then reacted with the Amerlex-M second antibody reagent which contains second antibody that is bound to the magnetisable polymer particles. separation of the antibody bound fraction is effected by magnetic separation of the Amerlex-M suspension and decantation of the supernatant.

Measurement of the radioactivity in the pellet enables the amount of labelled TNFα in the bound fraction to be calculated. The concentration of the unlabelled TNFα in the sample is then determined by interpolation from a standard curve.

Assay methodology

Contents of the assay system

The pack contains sufficient material for 100 assay tubes.

Assay buffer

Assay buffer concentrate 5ml. On dilution to 50ml this will give 0.025M phosphate buffer pH7.4 containing sodium azide.

Tracer

[^{125}I] TNFα (human, recombinant) ~41kBq, 1.1uCi, lyophilised.

Standard

Recombinant human TNFα, lyophilised. On reconstitution this bottle contains 2500fmol/ml TNFα.

Antiserum

Sheep anti-TNFα serum, lyophilised.

Amerlex-M second antibody reagent

Donkey anti-sheep serum coated on to magnetisable polymer particles containing sodium azide, colour coded yellow, 30 ml ready to use.

Results plotting sheet.

Radioimmunoassay procedure

The assay was performed with a 4 hour, room temperature pre-incubation followed by an overnight incubation at 2-8°C.

Reagent preparation

Assay buffer

The contents of the bottle, with washings, were transferred to a 50ml measuring cylinder and diluted to 50ml with distilled water. This solution was warmed to 40°C while stirring continuously for 10 minutes. This was then allowed to cool before use. The assay buffer consisted of 0.025M phosphate pH7.4 containing sodium azide, and was used to redissolve all other components.

Standard

2.0ml of the assay buffer was added to the antiserum and the contents of the bottle were mixed by inversion and swirling, taking care to avoid foaming. The final solution contained human recombinant TNFα at a concentration of 2500fmol/ml.

Antiserum

11.0 ml of the assay buffer was added to the antiserum and the contents of the bottle were mixed by inversion and swirling, taking care to avoid foaming. The final solution contained anti-TNFα serum in 0.025M phosphate buffer pH7.4 containing 0.1% azide.

Tracer

11.0 ml of the buffer was added to the tracer and the contents of the bottle were mixed by inversion and swirling, taking care to avoid foaming. The final solution contained [^{125}I] human recombinant TNFα in 0.025M phosphate buffer pH7.4 containing 0.1% azide.

Preparation of working standards

1) Eight polystyrene tubes were labelled 1, 2, 3.9, 7.8, 15.6, 31.2, 62.5, and 125..
2) 500ul of the assay buffer was pipetted into all tubes.
3) Into the 125 tube, 500ul of assay standard (2500fmol/ml) was pipetted and mixed thoroughly with vortex.
4) 500ul from the 125 tube was then transferred to the 62.5 tube and mixed thoroughly with vortex.
5) This doubling dilution was repeated successively with the remaining tubes.

6) 100ul aliquots from each serial dilution gave rise to 8 standard levels of TNFα ranging from 1 to 125 fmol (17 to 2125pg).

Assay Protocol

1) All reagents were equilibrated to room temperature.
2) The reagents and assay standards were prepared as describe above.
3) Polystyrene tubes were labelled in duplicate for: total counts (TC), non-specific binding (NSB), zero standard (B_0), standards and samples.
4) 200ul of the assay buffer was pipetted into the non-specific binding (NSB) tubes.
5) 100ul of assay buffer was pipetted into the zero standard (B_0)tubes.
6) Starting with the most dilute, 100ul of each standard were pipetted into the appropriately labelled tubes.
7) 100ul of the unknown sample was pipetted into appropriately labelled tubes.
8) 100ul of antiserum was pipetted into all tubes except NSB and TC.
9) All tubes were mixed thoroughly with vortex. The tubes were covered with plastic film and incubated for 4 hours at room temperature.
10) 100ul of [^{125}I] TNFα was pipetted into all tubes. The TC tubes were stoppered and put aside for counting.
11) All the tubes were mixed thoroughly with vortex. The tubes were covered and incubated for 24 hours at 2-8°C.
12) The tubes were removed from 2-8°C.
13) The bottle containing Amerlex-M second antibody reagent was gently swirled to ensure a homogeneous suspension. 250ul were added to each tube except the TC. These were then incubated at room temperature for 10 minutes.
14) The antibody bound fraction was then separated using magnetic separation as described below.

Magnetic separation

The rack containing the tubes was attached to the Amerlex-M Separator base, ensuring that all the tubes were in contact with the base plate, and left at room temperature for 15 minutes. After separation the rack was left on the separator base, and the supernatant poured off and discarded. Keeping the separator inverted, the tubes were placed on a pad of absorbent tissues and allowed to drain for 5 minutes.

15) On completion of magnetic separation, the rims of the tubes were firmly blotted with tissue pad to remove any adherent liquid.
16) The radioactivity present in each tube was determined by counting for 60 seconds in a gamma scintillation counter.

Calculation of results

1) The average counts per minute (cpm) were calculated for each set of replicate tubes.
2) The percent NSB/TC was calculated using the following equation:

$$\%NSB/TC = \frac{NSB\ cpm}{TC\ cpm} \times 100$$

3) The percent B_0/TC was calculated using the following equation:

$$\%B_0/TC = \frac{(B_0\ cpm - NSB\ cpm)}{TC\ cpm} \times 100$$

4) The percent bound/B_0 for each standard and sample was calculated using the following equation:

$$\%B/B_0 = \frac{(Standard\ or\ sample\ cpm - NSB\ cpm)}{(B_0\ cpm - NSB\ cpm)} \times 100$$

5) A standard curve was generated by plotting the percent B/B_0 as a function of the log TNFα concentration. The $\%B/B_0$ (y-axis) was plotted against fmol standard per tube (x-axis). The fmol per tube was then read directly from the graph.

BIBLIOGRAPHY

Abbe, R. The surgery of the hand. *NY Med J* 33-40, 1894.

Abbott, W.M., Abel, R.M., Beck, C.H.,Jr. and Fischer, J.E. Renal failure after ruptured aneurysm. *Archives of Surgery* **110**:1110-1112, 1975.

Abernathy, J. *Surgical Observations*, London: Longman and O'Rees, 1804. pp. 209-231.

Akersdijk, G., Puylaert, J. and de Vries, A. Abdominal aortic aneurysm as an incidental finding in abdominal ultrasonography. *Br J Surg* **78**:1261-1263, 1991.

Akkersdijk, G.J., van der Graaf, Y., van Bockel, J.H., de Vries, A.C. and Eikelboom, B.C. Mortality rates associated with operative treatment of infrarenal abdominal aortic aneurysm in The Netherlands. *Br J Surg* **81**:706-709, 1994.

Albaza, S.G.G., Ghosh, S.C. and Grana, V.P. Use of a ringed intraluminal graft in the surgical treatment of dissecting aneurysms of the thoracic aorta. *J Thorac Cardiovasc Surg* **76**:390-396, 1978.

Allardice, J.T., Allwright, G.J., Wafula, J.M. and Wyatt, A.P. High prevalence of abdominal aortic aneurysm in men with peripheral vascular disease: screening by ultrasonography. *Br J Surg* **75**:240-242, 1988.

Allen, P., Gourevitch, D., McKinley, J., Tudway, D. and Goldman, M. Population screening for aortic aneurysms. *Lancet* **2**:736-737, 1987.

Allen, R.C., Schneider, B.S., Longenecker, L., Smith, R.B. and Lumsden, A.B. Paraanastomotic aneurysms of the abdominal aorta. *J Vasc Surg* **18**:424-432, 1993.

Amundsen, S., Skjaerven, R., Trippestad, A. and Soreide, O. Abdominal aortic aneurysms - a study of factors influencing post-operative mortality. *Eur J Vasc Surg* **3**:405-409, 1989.

Anderson, J. and Kron, I.L. Treatment of *Aspergillus* infection of the proximal aortic prosthetic graft with associated vertebral osteomyelitis. *J Vasc Surg* **1**:579-581, 1984.

Anderson, J.C., Sjolin, S.U. and Holstein, P. Ligation of the renal vein during resection of abdominal aortic aneurysm. *J Cardiovasc Surg* **27**:454, 1986.

Andrews, S.M., Cuming, R., MacSweeney, S.T., Barrett, N.K., Greenhalgh, R.M. and Nott, D.M. Assessment of feasibility for endovascular prosthetic tube correction of aortic aneurysm. *Br J Surg* **82**:917-919, 1995.

Anidjar, S., Salzmann, J.L., Gentric, D. and *et al.* Elastase induced experimental aneurysms in rats. *Circulation* **82**:973-981, 1990.

Anner, H., Kaufman, R.P., Kobzik, L., Valeri, C.R., Shepro, D. and Hechtman, H.B. Pulmonary leukosequestration induced by hind limb ischaemia. *Ann Surg* **206**:162-167, 1987.

Anner, H., Kaufman, R.P., Valeri, C.R., Shepro, D. and Hechtman, H.B. Reperfusion of ischaemic lower limbs increases pulmonary microvascular permeability. *J Trauma* **28**:607-610, 1988.

Anton, G.E., Hertzer, N.R., Beven, E.G., *et al.* Surgical management of popliteal aneurysms: Trends in presentation, treatment, and results from 1952 to 1984. *J Vasc Surg* **3**:125-131, 1986.

Appleberg, M., Coupland, G.A.E. and Reeve, T.S. Ruptured abdominal aortic aneurysm: Long-term survival after operation. *Aust N Z J Surg* **50**:28-33, 1980.

Armon, M.P., Yusuf, S.W., Latief, K., *et al.* Anatomical suitability of abdominal aortic aneurysms for endovascular repair. *Br J Surg* **84**:178-180, 1997.

Asbury, C.L., Ruberti, J.W., Bluth, E., *et al.* Experimental investigation of steady flow in rigid models of abdominal aortic aneurysms. *Ann Biomed Eng* **23**:29-39, 1995.

Bacharach, J.M., Olin, J.W., Sullivan, T.M. *et al.* Renal artery stents: early patency and clinical follow-up (abstract). *Circulation* **92**:128, 1995.

Bahnson, H.T. Considerations in the excision of aortic aneurysms. *Ann Surg* **97**:257-250, 1953.

Baier, R.E. and Dutton, R.C. Initial events in interactions of blood with foreign surface. *J Biomed Mater Res* **3**:191-206, 1969.

Baigrie, R.J., Lamont, P.M., Kwiatkowski, D., Dallman, M.J. and Morris, P.M. The cytokine response to major surgery. *Br J Surg* **79**:757-760, 1992.

Baigrie, R.J., Lamont, P.M., Whiting, S. and Morris, P.J. Portal endotoxin and cytokine responses during abdominal aortic surgery. *Am J Surg* **166**:248-251, 1993.

Bailey, I.S., Bundred, N.J., Pearson, H.J. and Bell, P.R. Successful treatment of an infected vascular graft with gentamicin beads. *Eur J Vasc Surg* **1**:143-144, 1987.

Baker, M.S., Fisher, J.H., Van Der Reis, L. and Baker, B.H. Endoscopic diagnosis of an aorto-duodenal fistula. *Arch Surg* **111**:304, 1976.

Balko, A., Piasecki, G.J., Shah, D.M., Carney, W.I., Hopkins, R.W. and Jackson, B.T. Transfemoral placement of intraluminal polyurethane prosthesis for abdominal aortic aneurysm. *J Surg Res* **40**:305-309, 1986.

Balm, R., Kaatee, R., Mali, W. and Eikelboom, B. Vanishing aortic aneurysms following transfemoral endovascular aneurysm management with tube graft: measurements with spiral CT angiography. *European Society for Vascular Surgery* Annual Meeting, Antwerp, Belgium, 1995. (Abstract)

Bandyk, D.F., Berni, G.A., Thiele, B.L. *et al.* Aortofemoral graft infection due to *Staphylococcus epidermidis*. *Arch Surg* **119**:102-108, 1984.

Banerjee, A. Atypical manifestations of ruptured abdominal aortic aneurysms. *Postgraduate Medical Journal* **69**:6-11, 1993.

Banerjee, A.K., Bhutiani, R.P. and Lewis, J.D. Irreducible inguinal hernia as a presentation of ruptured abdominal aortic aneurysm. *J. R. Coll. Surg Edinb.* **34**:281, 1989.

Bartle, E.J., Pearce, W.H., Sun, J.H., *et al.* Infrarenal venous anomalies and aortic surgery: avoiding vascular injury. *J Vasc Surg* **6**:590-593, 1987.

Baskerville, P.A., Blakeney, C.G., Young, A.E. and Browse, N.L. The diagnosis and treatment of peri-aortic fibrosis ('inflammatory' aneurysms). *Br J Surg* **70**:381-385, 1983.

Bast, T.J., van der Biezen, J.J., Scherpenisse, J. and Eikelboom, B.C. Ischaemic disease of the colon and rectum after surgery for abdominal aortic aneurysm: a prospective study of the incidence and risk factors. *Eur J Vasc Surg* **4**:253-257, 1990.

Baxter, B., McGee, G., Shively, V., *et al.* Elastin content, cross-links, and mRNA in normal and aneurysmal human aorta. *J Vasc Surg* **16**:192-200,1992.

Baxter, B.T., Davis, V.A., Minion, D.J., Wang, Y.P., Lynch, T.G. and McManus, B.M. Abdominal aortic aneurysms are associated with altered matrix proteins of the nonaneurysmal segments. *J Vasc Surg* **19**:797-803, 1994.

Beall, C.W., Simpson, C.F., Pritchard, W.R. and Harms, R.H. Aortic rupture in turkeys induced by diethylstilbestrol. *Proc Soc Exp Biol Med* **113**:442, 1963.

Beckman, E.N. Plasma cell infiltrates in atherosclerotic abdominal aortic aneurysms. *American Journal of Clinical Pathology* **85**:21-24, 1986.

Bengtsson, H., Bergqvist, D., Jendteg, S., Lindgren, B. and Persson, U. Ultrasonographic screening for abdominal aortic aneurysm: analysis of surgical decisions for cost-effectiveness. *World J Surg* **13**:266-271, 1989.

Bengtsson, H., Bergqvist, D. and Sternby, N.H. Increasing prevalence of abdominal aortic aneurysm: a necropsy study. *Eur J Surg* **158**:19-23, 1992.

Bergamini, T.M., Bandyk, D.F., Govostis, D., *et al.* Infection of vascular prostheses caused by bacterial biofilms. *J Vasc Surg* **7**:21-30, 1988.

Bernhard, V.M. Management of graft infections following abdominal aortic aneurysm replacement. *World Journal of Surgery* **4**:679-686, 1980.

Bernhard, V.M. and Towne, J.B. Complications in vascular surgery. In: *Vascular Surgery: A Comprehensive Review*, edited by Moore, W.S. New York: Grune & Stratton, 1983, p. 737-776.

Bernstein, E.F., Dilley, R.B., Goldberger, L.E., Gosink, B.B. and Leopold, G.R. Growth rates of small abdominal aortic aneurysms. *Surgery* 80:765-773, 1976.

Bernstein, E.F. and Chan, E.L. Abdominal aortic aneurysm in high-risk patients; outcome of selective management based on size and expansion rate. *Annals of Surgery* **200**:255-263, 1984.

Bickel, W.H. Intravenous fluid administration and uncontrolled haemorrhage (editorial). *J Trauma* **29**:409, 1989.

Bickerstaff, L.K., Hollier, L.H., Van Peenen, H.J., Melton, L.J., Pairolero, P.C. and Cherry, K.J. Abdominal aortic aneurysms: the changing natural history. *J Vasc Surg* **1**:6-12, 1984.

Birch, P.C., Whitbread, T., Rogers, S., Start, R., Beard, J. and Gaines, P. Comparative study of the effects of covering porcine renal artery origins with stents differing in size of strut and interstices. *Br J Surg* **83**:561-562,1996.

Birkedal-Hansen, H., Moore, W.G.I. and Bodden, M.K. Matrix metalloproteinases: a review. *Crit Rev Oral Biol Med* **4**:197-250, 1993.

Blaisdell, F.W. and Hall, A.D. Axillary-femoral artery bypass for lower extremity ischemia. *Surgery* **54**:563-568, 1963.

Blaisdell, F.W., Hall, A.D. and Thomas, A.N. Ligation treatment of abdominal aortic aneurysms. *Am J Surg* **109**:560-564, 1965.

Blakemore, A. Vitallium tube for arterial reconstruction. *Surgery* **12**:488-508, 1942.

Blakemore, A.H. Progressive constrictive occlusion of the abdominal aorta with wiring and electrothermic coagulation. *Ann Surg* **133**:447-462, 1951.

Blamey, R.W. and Hardcastle, J.D. The early detection of cancer. In: *Recent advances in surgery*, edited by Russell, R.C.G. Edinburgh: Churchill Livingstone, 1986, p. 29.

Blau, S.A., Kerstein, M.A. and Deterling, R.A.Jr. Abdominal Aortic Aneurysms. In: *Aneurysms,* edited by Kerstein, M.A., Moulder, P.V. and Webb, W.R. Baltimore: Willams & Wilkins, 1983, p. 127-196.

Blum, U., Langer, M., Spillner, G., *et al.* Abdominal aortic aneurysms: preliminary technical and clinical results with transfemoral placement of endovascular self-expanding stent-grafts. *Radiology* **198**:25-31, 1996.

Blum, U. The Min Tec system. In: *Endovascular Surgery for Aortic Aneurysms,* edited by Hopkinson, B., Yusuf, W., Whitaker, S. and Veith, F. London: W.B. Saunders, 1997, p. 72-87.

Blum, U., Voshage, G., Lammer, J., *et al.* Endoluminal stent-grafts for infra-renal abdominal aortic aneurysms. *N Engl J Med* **336**:13-20, 1997.

Bodily, K.C. and Buttorff, J.D. Ruptured abdominal aortic aneurysm: the Tacoma experience. *Am J Surg* **149**:580-582, 1985.

Boontje, A.H., van der Dungen, J. and Blanksma, C. Inflammatory abdominal aortic aneurysms. *J Cardiovasc Surg* **31**:611-616, 1990.

Boucek, R.J., Gunia-Smith, Z., Noble, N.L. and Simpson, C.F. Modulation by propranolol of the lysyl cross-links in aortic elastin and collagen of the aneurysm-prone turkey. *Biochem Pharmacol* **32**:275-280, 1983.

Boucher, C.A., Brewster, D.C., Darling, R.C., *et al.* Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med* **312**:389-394, 1985.

Boyle, J.R., Thompson, M.M., Sayers, R.D., *et al.* Development of an endovascular aorto-uni-iliac graft: difficult solutions for difficult aneurysms. *Br J Surg* **84**:568-569,1997.

Breckwoldt, W.L., Mackey, W.C. and O'Donnell, T.F. The economic implications of high-risk abdominal aortic aneurysms. *J Vasc Surg* **13**:798-804, 1991.

Brener, B.J., Darling, R.C. and Frederick, P.L. Major venous anomalies complicating abdominal aortic surgery. *Arch Surg* **108**:159-165, 1974.

Brewster, D.C., Retana, A., Waltman, A.C. and Darling, R.C. Angiography in the management of aneurysms of the abdominal aorta; its value and safety. *New England Journal of Medicine* **292**:822-825, 1975.

Brewster, D.C., Okada, R.D., Strauss, W., *et al.* Selection of patients for preoperative coronary angiography: use of dypyridamole-stress-thallium myocardial imaging. *J Vasc Surg* **2**:504-510, 1985.

Briggs, R.M., Jarstfer, B.S. and Collins, G.J.Jr. Anastomotic aneurysms. *American Journal of Surgery* **146**:770-773, 1983.

Brock, R.C., Rob, C.G. and Forty, F. Reconstructive arterial surgery. *Proc R Soc Med* **46**:115-110, 1953.

Brophy, C.M., Tilson, J.E. and Tilson, M.D. Propranolol delays the formation of aneurysms in the male Blotchy mouse. *J Surg Res* **44**:687-691, 1988.

Brophy, C.M., Tilson, J.E. and Tilson, M.D. Propranolol stimulates the crosslinking of matrix components in skin from the aneurysm-prone Blotchy mouse. *J Surg Res* **46**:330-332, 1989.

Brown, O.W., Hollier, L.H., Pairolero, P.C., Kazmier, F.J. and McCready, R.A. Abdominal aortic aneurysm and coronary artery disease. *Archives of Surgery* **116**:1484-1488, 1981.

Brown, P.M., Pattenden, R. and Gutelius, J.R. The selective management of small abdominal aortic aneurysms: the Kingston study. *J Vasc Surg* **15**:21-27, 1992.

Buck, N., Devlin, H.B. and Lunn, J.N. *The report of a confidential enquiry into perioperative deaths*, London: Nuffield Provincial Hospitals Trust/Kings Fund, 1987.

Buckels, J.A., Fielding, J.W., Black, J., Ashton, F. and Slaney, G. Significance of positive bacterial cultures from aortic aneurysm contents. *Br J Surg* **72**:440-442, 1985.

Budd, J.S., Finch, D.R. and Carter, P.G. A study of the mortality from ruptured abdominal aortic aneurysms in a district community. *Eur J Vasc Surg* **3**:351-354, 1989.

Bulkley, B.H. and Roberts, W.C. Steroid therapy during acute myocardial infarction: a cause of delayed healing and of ventricular aneurysm. *Am J Med* **56**:244, 1974.

Bunt, T.J. Synthetic vascular graft infections I: Graft infections. *Surgery* **93**:733-746, 1983.

Burton, A.C. Relation of structure to function of the tissues of the wall of blood vessels. *Physiol Rev* **34**:619-642, 1954.

Bush, H.L.,Jr., LoGerfo, F.W., Weisel, R.D., Mannick, J.A. and Hechtman, H.B. Assessment of myocardial performance and optimal volume loading during elective abdominal aortic aneurysm resection. *Archives of Surgery* **112**:1301-1305, 1977.

Busuttil, R.W., Rees, W., Baker, J.D. and Wilson, S.E. Pathogenesis of aortoduodenal fistula: experimental and clinical correlates. *Surgery* **85**:1-13, 1979.

Busuttil, R.W., Abou-Zamzam, A.M. and Machleder, H.I. Collagenase activity of the human aorta. A comparison of patients with and without abdominal aortic aneurysms. *Archives of Surgery* **115**:1373-1378, 1980.

Cabellon, S.,Jr., Moncrief, C.L., Pierre, D.R. and Cavanaugh, D.G. Incidence of abdominal aortic aneurysms in patients with atheromatous arterial disease. *American Journal of Surgery* **146**:575-576, 1983.

Calligaro, K.D., Azurin, D.J., Dougherty, M.J., *et al.* Pulmonary risk factors of elective abdominal aortic surgery. *J Vasc Surg* **18**:914-921, 1993.

Cambria, R.P., Brewster, D.C., Abbott, W.M., *et al.* Transperitoneal versus retroperitoneal approach for aortic reconstruction: a randomised prospective study. *J Vasc Surg* **11**:314-325, 1990.

Campa, J., Greenhalgh, R. and Powell, J. Elastin degradation in abdominal aortic aneurysms. *Atherosclerosis* **65**:13-21, 1987.

Campbell, W.B., Collin, J. and Morris, P.J. The mortality of abdominal aortic aneurysm. *Annals of the Royal College of Surgeons of England* **68**:275-278, 1986.

Campbell, W.B. Mortality statistics for elective aortic aneurysms. *Eur J Vasc Surg* **5**:111-113, 1991.

Cannon, D.J. and Read, R.C. Blood elastolytic activity in patients with aortic aneurysm. *Annals of Thoracic Surgery* **34**:10-15, 1982.

Caro, C.G., Pedley, T.J., Schroter, R.C. and Seed, W.A. Solid mechanics and the properties of blood vessel walls. In: *The Mechanics of the Circulation*, Oxford: Oxford University Press, 1978, p. 86-105.

Carrell, R.W. Alpha-1-antitrypsin: molecular pathology, leucocytes, and tissue damage. *J Clin Invest* **78**:1427-1431, 1986.

Carty, G.A., Nachtigal, T., Magyar, R., Herzler, G. and Bays, R. Abdominal duplex ultrasound screening for occult aortic aneurysm during carotid arterial evaluation. *J Vasc Surg* **17**:696-702, 1993.

Casali, R.E., Tucker, W.E., Thompson, B.W. and Read, R.C. Infected prosthetic grafts. *Arch Surg* **115**:577-580, 1980.

Castell, J.V., Andus, T., Kunz, D. and Heinrich, P.C. Interleukin-6: the major regulator of acute-phase protein synthesis in man and rat. *Ann N Y Acad Sci* **557**:87-99, 1989.

Castleden, W.M. and Mercer, J.C. Abdominal aortic aneurysms in Western Australia: descriptive epidemiology and patterns of rupture. *Br J Surg* **72**:109-112, 1985.

Champion, M.C., Sullivan, S.N., Coles, J.C., *et al.* Aortoenteric fistula: incidence, presentation, recognition, and management. *Ann Surg* **195**:314-317, 1982.

Chang, B.B., Paty, P.K., Shah, D.M. and Leather, R.P. Selective use of retroperitoneal aortic exposure in the emergency treatment of ruptured and symptomatic abdominal aortic aneurysms. *Am J Surg* **156**:108-110, 1988.

Chantler, C. and Barrett, T.M. Estimation of glomerular filtration rate from plasma clearance of 51-chromium edetic acid. *Arch Dis Child* **47**:613-617, 1972.

Cherryman, G.R., Moody, A.R. and Rodgers, P. New imaging techniques and arterial disease. *Vascular Medicine Review* **5**:107-120, 1994.

Chuter, T., Risberg, B., Hopkinson, B., *et al.* Clinical experience with a bifurcated endovascular graft for abdominal aortic aneurysm repair. *J Vasc Surg* **24**:655-666, 1996.

Chuter, T.A., Green, R.M., Ouriel, K., Fiore, W.M. and DeWeese, J.A. Transfemoral endovascular aortic graft replacement. *J Vasc Surg* **18**:185-195, 1993.

Chuter, T.A.M., Green, R.M., Ouriel, K. and DeWeese, J.A. Infrarenal aortic aneurysm structure: implications for transfemoral repair. *J Vasc Surg* **20**:44-49, 1994.

Chuter, T.A.M., Wendt, G., Hopkinson, B.R., *et al.* European experience with a system for bifurcated stent graft insertion. *J Endovasc Surg* **4**:13-22, 1997.

Clark, J.M. and Glagov, S. Transmural organisation of the arterial media. The lamellar unit revisited. *Arteriosclerosis* **5**:19-34, 1985.

Clifton, M.A. Familial abdominal aortic aneurysms. *Br J Surg* **64**:765-766, 1977.

Clyne, C.A. and Abercrombie, G.F. Perianeurysmal retroperitoneal fibrosis: two cases responding to steroids. *British Journal of Urology* **49**:463-467, 1977.

Cohen, J., Sarfati, I., Danna, D. and Wise, L. Smooth muscle cell elastase, atherosclerosis, and abdominal aortic aneurysms. *Ann Surg* **216**:327-332, 1992.

Cohen, J.R., Mandell, C., Chang, J.B. and Wise, L. Elastin metabolism of the infrarenal aorta. *J Vasc Surg* **7**:210-214, 1988.

Cole, W., Barber, G. and Bouchard, A. Abdominal aortic aneurysms: consequences of positive family history. *Can J Surg* **32**:117-120, 1989.

Collin, J. Elective surgery for small abdominal aortic aneurysms. *Lancet* 1:909, 1987.

Collin, J. The epidemiology of abdominal aortic aneurysm. *British Journal of Hospital Medicine* **40**:64-67, 1988.

Collin, J., Araujo, L., Walton, J. and Lindsell, D. Oxford screening programme for abdominal aortic aneurysm in men aged 65 to 74 years. *Lancet* **2**:613-615, 1988.

Collin, J. The value of screening for abdominal aortic aneurysm by ultrasound. In: *The cause and management of aneurysms*, edited by Greenhalgh, R.M. and Mannick, J.A. London: W.B. Saunders, 1990a, p. 447-456.

Collin, J. Screening for abdominal aortic aneurysm. *Br J Surg* **80**:1363-1364, 1993.

Conger, J.D. and Weil, J.V. Abnormal vascular function following ischaemia-reperfusion injury. *Journal of Investigative Medicine* **43** (5):431-442, 1995.

Conn, J.H., Hardy, J.D., Chavez, C.M. and Fain, W.R. Infected arterial grafts: experience in 22 cases with emphasis on unusual bacteria and technics. *Ann Surg* **171**:704-714, 1970.

Connolly, J.E., Kwaan, J.H., McCart, P.M., Brownell, D.A. and Levine, E.F. Aortoenteric fistula. *Annals of Surgery* **194**:402-412, 1981.

Cook, T.A., Jones, A.J., Webb, A.J. and Baird, R.N. Traumatic abdominal aortic aneurysm. *Eur J Vasc Surg* **8**:364-365, 1994.

Cooper, A.P. *Lectures on the Principles and Practice of Surgery*, London:F.C.Westley, 1830. Ed. 2nd

Cormier, J.M., Ward, A.S., Lagneau, P. and Janneau, D. Infection complicating aortoiliac surgery. *J Cardiovasc Surg* **21**:303-314, 1980.

Counts, D.F., Shull, S. and Cutroneo, K.R. Skin lysyl oxidase activity is not rate limiting for collagen crosslinking in the glucocorticoid-treated rat. *Conn Tiss Res* **14**:237, 1986.

Cragg, A., Lund, G., Rysavy, J., Castaneda, F., Castaneda-Zuniga, W.R. and Amplatz, K. Nonsurgical placement of arterial endoprostheses: a new technique using nitinol wire. *Radiology* **147**:261-263, 1983.

Craig, S.R., Wilson, R.G., Walker, A.J. and Murie, J.A. Abdominal aortic aneurysm: still missing the message. *Br J Surg* **80**:450-452, 1993.

Crawford, E.S., Morris, G.C., Howell, J.F., *et al.* Operative risk in patients with previous coronary artery bypass. *Ann Thorac Surg* **26**:215-221, 1978.

Crawford, E.S., Saleh, S.A., Babb, J.W., Glaeser, D.H., Vaccaro, P.S. and Silvers, A. Infrarenal abdominal aortic aneurysm: factors influencing survival after operation performed over a 25-year period. *Annals of Surgery* **193**:699-709, 1981.

Crawford, E.S. and Crawford, J.L. *Diseases of the aorta: including an atlas of angiographic and surgical technique*, Baltimore,USA.:Williams and Williams, 1985.

Crawford, E.S. Ruptured abdominal aortic aneurysm [editorial]. *J Vasc Surg* **13**:348-350, 1991.

Crawford, J.L., Stowe, C.L., Safi, H.J., Hallman, C.H. and Crawford, E.S. Inflammatory aneurysms of the aorta. *J Vasc Surg* **2**:113-124, 1985.

Creech, O.,Jr. Endo-aneurysmorrhaphy and treatment of aortic aneurysm. *Annals of Surgery* **164**:935-946, 1966.

Cronenweit, J.L., Sargent, S.K., Wall, M.H., *et al.* Variables that effect expasion rate and outcome of small aortic aneurysms. *Proceedings of the Society for Vascular Surgery* **43**:38, 1989.

Cronenwett, J., Sargent, S., Wall, M., *et al.* Variables that affect the expansion rate and outcome of small abdominal aortic aneurysms. *J Vasc Surg* **11**:260-269, 1990.

Cronenwett, J.L., Murphy, T.F. and Zelenock, G.B. Actuarial analysis of variables associated with rupture of small abdominal aortic aneurysms. *Surgery* **98**:472-483, 1985.

Crozier, T.A., Muller, J.E., Quittkat, D., Sydow, M., Wuttke, W. and Ketter, D. Effect of anaesthesia on the cytokine responses to abdominal surgery. *Br J Anaesth* **72**:280-285, 1994.

Cruikshank, A.M., Fraser, W.D., Burns, H.J.G., van Damme, J. and Shenkin, A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci* **79**:161-165, 1990.

Cullenward, M.J., Scanlan, K.A., Pozniak, M.A. and Archer, C.A. Inflammatory aortic aneurysm (periaortic fibrosis): radiologic imaging. *Radiology* **159**:75-82, 1986.

Curl, G.R., Faggioli, G.L., Stella, A., D'Addato, M. and Ricotta, J.J. Aneurysmal change at or above the proximal anastomosis after infrarenal aortic grafting. *J Vasc Surg* **16**:855-9; 1992.

Cutler, B.S., Wheeler, H.B., Paraskos, J.A. and Cardullo, P.A. Applicability and interpretation of electrocardiographic stress testing in patients with peripheral vascular disease. *Am J Surg* **141**:501-506, 1981.

Cutler, B.S. and Leppo, J.A. Dipyridamole thallium 201 scintigraphy to detect coronary artery disease before abdominal aortic surgery. *J Vasc Surg* **5**:91-100, 1987.

Cutroneo, K.R., Rokoswki, R. and Counts, D.F. Glucocorticoids and collagen synthesis: comparison of in vivo and cell culture studies. *Col Rel Res* **1**:557, 1981.

Darke, S.G. and Eadie, D.D. Abdominal aortic aneurysmectomy: a review of 60 consecutive cases contrasting elective and emergency surgery. *Journal of Cardiovascular Surgery* **14**:484-491, 1973.

Darling III, R., Brewster, D. and Darling, R. Are familial abdominal aortic aneurysms different? *J Vasc Surg* **10**:39-43, 1989.

Darling, R.C. Ruptured arteriosclerotic abdominal aortic aneurysms. A pathologic and clinical study. *American Journal of Surgery* **119**:397-401, 1970.

Darling, R.C., Messina, C.R., Brewster, D.C. and Ottinger, L.W. Autopsy study of unoperated abdominal aortic aneurysms. The case for early resection. *Circulation* **56**:II161-II164, 1977.

Davies, M.J., Murphy, W.G., Murie, J.A., *et al.* Preoperative coagulopathy in ruptured abdominal aortic aneurysm predicts poor outcome. *Br J Surg* **80**:974-976, 1993.

Deak, S.B., Ricotta, J.J., Mariani, T.J., *et al.* Abnormalities in the biosynthesis of type III procollagen in cultured skin fibroblasts from two patients with multiple aneurysms. *Matrix* **12**:92-100, 1991.

Dean, R.H., Keyser, J.E., Dupont, W.D., Nadeau, J.H. and Meacham, P.W. Aortic and renal vascular disease. Factors affecting the value of combined procedures. *Annals of Surgery* **200**:336-344, 1984.

DeBakey, M.E. and Cooley, D.A. Surgical treatment of aneurysm of abdominal aorta by resection of continuity with homograft. *Surg Gynecol Obstet* **97**:257-250, 1953.

DeBakey, M.E., Cooley, D.A., Morris, G.C.J. and Collins, M. Arteriovenous fistula involving the abdominal aorta. Report of 4 cases with successful repair. *Ann Surg* **147**:646-657, 1958.

DeBakey, M.E., Crawford, E.S., Cooley, D.A., *et al.* Aneurysm of abdominal aorta: analysis of results of graft replacement therapy one to 11 years after operation. *Ann Surg* **160**:622-639, 1984.

Deitch, E.A. Multiorgan failure. *Ann Surg* **216**:117-134, 1992.

Delin, A., Ohlsen, H. and Swedenborg, J. Growth rate of abdominal aortic aneurysms as measured by computed tomography. *Br J Surg* **72**:530-532, 1985.

Dennis, J.W., Littooy, F.N., Greisler, H.P. and Baker, W.H. Anastomotic pseudoaneurysms. A continuing late complication of vascular reconstructive procedures. *Archives of Surgery* **121**:314-317, 1986.

Depalma, R.G. Impotence in vascular disease: relationship to vascular surgery. [Review]. *Br J Surg* **69** Suppl:S14-S16, 1982.

Dereume, J. and Ferreira, J. The Corvita system. In: *Endovascular Surgery for Aortic Aneurysms*, edited by Hopkinson, B., Yusuf, W., Whitaker, S. and Veith, F. London: W.B. Saunders, 1997, p. 122-139.

Diehl, J.T., Cali, R.F., Hertzer, N.R. and Beven, E.G. Complications of abdominal aortic reconstruction. An analysis of perioperative risk factors in 557 patients. *Annals of Surgery* **197**:49-56, 1983.

Diethrich, E.B., Ndiaye, M. and Reid, D.B. Stenting in the carotid artery: initial experience in 110 patients. *J Endovasc Surg* **3**:42-62, 1996.

DiGiovanni, R., Nicholas, G., Volpetti, G., Berkowitz, H., Barker, C. and Roberts, B. Twenty-one years' experience with ruptured abdominal aortic aneurysms. *Surgery,Gynecology & Obstetrics* **141**:859-862, 1975.

Dinarello, C.A. Interleukin-1. *Rev Infect Dis* **6**:51-95, 1984.

Dinarello, C.A. Interleukin-1 and its biologically related cytokines. *Adv Immunol* **44**:153-205, 1989.

Dobrin, P.B. Mechanics of normal and diseased blood vessels. *Ann Vasc Surg* **2**:283-294, 1988.

Doll, R. and Peto, R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J* **ii**:1525-1536, 1976.

Doppman, J.L. Paraplegia after surgery for thoracoabdominal aneurysms: Russian roulette for the vascular surgeon [editorial]. *Radiology* **189**:27-28, 1993.

Dotter, C.T. Transluminally placed coilspring endarterial tube grafts: long term patency in canine popliteal artery. *Invest Radiol* **4**:327-332, 1969.

Dotter, C.T., Buschmann, R.W., McKinney, M.K. and Rosch, J. Transluminally expandable nitinol coil stent grafting: preliminary report. *Radiology* **147**:259-260, 1983.

Downs, A.R., Lye, C.R. and MacKean, G. Graft infections in aortoiliac arterial reconstructions. *Can J Surg* **26**:328-329, 1983.

Drott, C., Arfvidsson, P., Ortenwall, P. and Lundholm, K. Age-standardised incidence of ruptured aortic aneurysm in a defined Swedish population between 1952 and 1988: mortality rate and operative results. *Br J Surg* **79**:175-179, 1992.

Dubost, C., Allory, M. and Oeconomos, N. Resection of an aneurysm of the abdominal aorta. Re-establishment of the continuity by a preserved human arterial graft, with result after five months. *Arch Surg* **64**:405-408, 1952.

Dureau, G., Villard, J., George, M., Deliry, P., Froment, J.C. and Clermont, A. New surgical technique for the operative management of acute dissections of the ascending aorta. Report of two cases. *Journal of Thoracic & Cardiovascular Surgery* **76**:385-389, 1978.

Durham, J.R., Hackworth, C.A., Tober, J.C., *et al.* Magnetic resonance angiography in the pre-operative evaluation of abdominal aortic aneurysms. *Am J Surg* 166:173-177, 1993.

Eagle, K.A., Coley, C.M., Newwell, J.B., *et al.* Combining clinical and thallium data optimises preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med* **110**:859-866, 1989.

Earnshaw, J.J. Infection after vascular reconstruction - hard graft for surgeons. *Surg Infect* **3**:4-6, 1991.

Ecklund, K., Hartnell, G.G., Hughes, L.A., Stokes, K.R. and Finn, J.P. MR angiography as the sole method in evaluating abdominal aortic aneurysms: correlation with conventional techniques and surgery. *Radiology* **192**:345-350, 1994.

Editorial. Special series on endovascular abdominal aortic aneurysm exclusion: Part 1. *J Endovasc Surg* **4**:1-2, 1997.

Edwards, J.M., Teeffey, F.A., Zierler, R.E. and Kohler, T.R. Intraabdominal paraanastomotic aneurysms after aortic bypass grafting. *J Vasc Surg* **15**:344-353, 1992.

Elmarasy, N.M. and Yusuf, W. Colonic perfusion. In: *Endovascular Surgery for Aortic Aneurysms*, edited by Hopkinson, B., Yusuf, W., Whitaker, S. and Veith, F. London: W.B.Saunders, 1997, p. 279-288.

Erichsen, J.E. *Observations on Aneurism*, London:C & J Allard, 1844. pp. 183.

Eriksson, I., Forsberg, O., Lundqvist, B. and Schwan, A. Significance of positive bacterial cultures from aortic aneurysms. *Acta Chirurgica Scandinavica* **149**:33-35, 1983.

Ernst, C.B., Hagihara, P.F., Daughtery, M.E., Sachatello, C.R. and Griffen, W.O.,Jr. Ischaemic colitis incidence following abdominal aortic reconstruction: a prospective study. *Surgery* **80**:417-421, 1976.

Ernst, C.B., Hagihara, P.F., Daugherty, M.E. and Griffen, W.O.,Jr. Inferior mesenteric artery stump pressure: a reliable index for safe IMA ligation during abdominal aortic aneurysmectomy. *Annals of Surgery* **187**:641-646, 1978.

Ernst, C.B. Prevention of intestinal ischaemia following abdominal aortic reconstruction. *Surgery* **93**:102-106, 1983.

Ernst, C.B. Abdominal aortic aneurysm. *N Engl J Med* **328**:1167-1172, 1993.

Estes, J.E.J. Abdominal aortic aneurysm: a study of one hundred and two cases. *Circulation* **2**:258-264, 1950.

Evans, W.E. and Hayes, J.P. Tube graft replacement of abdominal aortic aneurysm. *American Journal of Surgery* **156**:119-121, 1988.

Faggioli, G.L., Stella, A., Gargiulo, M., Tarantini, S., D'Addato, M. and Ricotta, J.J. Morphology of small aneurysms: definition and impact on risk of rupture. *Am J Surg* **168**:131-135, 1994.

Farkas, J.C., Fichelle, J.M., Laurian, C., *et al.* Long-term follow-up of positive cultures in 500 abdominal aortic aneurysms. [Review]. *Arch Surg* **128**:284-288, 1993.

Ferrante, R.J., Hobson, R.W., Miyasaka, M., Granger D.N., Duran W.N. Inhibition of white blood cell adhesion at reperfusion decreases tissue damage in postischaemic striated muscle. *J Vasc Surg* **24(2)**:187-193,1996.

Fielding, J.W., Black, J., Ashton, F., Slaney, G. and Campbell, D.J. Diagnosis and management of 528 abdominal aortic aneurysms. *British Medical Journal Clinical Research Ed.* **283**:355-359, 1981.

Fitzgerald, J.F., Stillman, R.M. and Powers, J.C. A suggested classification and reappraisal of mortality statistics for ruptured atherosclerotic infrarenal aortic aneurysms. *Surgery,Gynecology & Obstetrics* **146**:344-346, 1978.

Flanigan, D.P., Schuler, J.J., Keifer, T., Schwartz, J.A. and Lim, L.T. Elimination of iatrogenic impotence and improvement of sexual function after aortoiliac revascularization. *Archives of Surgery* **117**:544-550, 1982.

Fletcher, J.P., Antico, V.F., Gruenwald, S. and Kershan, L.Z. Dipyridamole-thallium imaging for screening of coronary artery disease prior to vascular surgery. *J Cardiovasc Surg* **29**:666-669, 1988.

Foster, J.H., Bolasny, B.L., Gobbel, W.G.,Jr. and Scott, H.W.,Jr. Comparative study of elective resection and expectant treatment of abdomianl aortic aneurysm. *Surgery,Gynecology & Obstetrics* **129**:1-9, 1969.

Fowkes, F., Macintyre, C. and Ruckley, C. Increasing incidence of aortic aneurysms in England and Wales. *Br Med J* **298**:33-35, 1989.

Fox, A.D., Whiteley, M.S., Murphy, P., Budd, J.S. and Horrocks, M. Comparison of magnetic resonance imaging measurements of abdominal aortic aneurysms with measurements obtained by other imaging techniques and intraoperative measurements: possible implications for endovascular grafting. *J Vasc Surg* **24**:632-638, 1996.

Franco, C.D., Goldsmith, J., Veith, F.J., *et al.* Resting gated pool ejection fraction a poor predictor of perioperative myocardial infarction in patients undergoing vascular surgery for infrainguinal bypass grafting. *J Vasc Surg* **10**:656-561, 1989.

Frenkel, J.K., Rasmussen, P. and Smith, O.D. Synergism of cortisol and desoxycorticosterone in the production of dissecting aneurysms in hamsters. *Fed Proc* **18**:477, 1959.

Friedman, S.G. and Krishnasastry, K.V. Ruptured abdominal aortic aneurysm: an editorial. *J Vasc Surg* **15**:456, 1992.

Fujita, J., Abboud, R.T., Richter, A. and Johal, S.H.S. Evaluation of elastase and antielastase balance in patients with chronic bronchitis and pulmonary emphysema. *Am Rev Respir Dis* **142**:57-61, 1990.

Gadowski, G.R., Pilcher, D.B. and Ricci, M.A. Abdominal aortic aneurysm expansion rate: effect of size and beta-adrenergic blockade. *J Vasc Surg* **19**:727-731, 1994.

Galis, Z., Muszynski, M., Sukhova, G.K., *et al.* Cytokine-stimulated human smooth muscle cells synthesize a complement of enzymes required for extracellular matrix digestion. *Circulation Research* **75**:181-189, 1994.

Gandhi, R.H., Irizarry, E., Cantor, J.O., *et al.* Analysis of elastin cross-linking and the connective tissue matrix of abdominal aortic aneurysms. *Surgery* **115**:617-620, 1994.

Gans, R.O., Hoorntje, S.J., Rauwerda, J.A., *et al.* The inflammatory abdominal aortic aneurysm; prevalence, clinical features and diagnostic evaluation. *Netherlands J Med* **43**:105-115, 1993.

Gauldie, J., Richards, C., Harnish, D., Lansdorp, P. and Baumann, H. Interferon B2/B cell stimulatory factor 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. *Proc Natl Acad Sci USA* **84**:7251-7255, 1987.

Gautier, C., Borie, H. and Lagneau, P. Aortic false aneurysms after prosthetic reconstruction of the infrarenal aorta. *Ann Vasc Surg* **6**:413-417, 1992.

Gaylis, H. Pathogenesis of anastomotic aneurysms. *Surgery* **90**:509-515, 1981.

Gefke, K., Schroeder, T.V., Thisted, B., *et al.* Abdominal aortic aneurysm surgery: survival and quality of life in patients requiring prolonged postoperative intensive therapy. *Ann Vasc Surg* **8**:137-143, 1994.

George, P.M., Travis, J., Vissers, M.C.M., Winterbourn, C.C. and Carrell, R.W. A genetically engineered mutant of alpha 1-antitrypsin protects connective tissue from neutrophil damage and may be useful in lung disease. *Lancet* **ii**:1426-1428, 1984.

Gertz, S., Kurgan, A. and Eisenberg, D. Aneurysm of the rabbit common carotid artery induced by periarterial application of calcium chloride in vivo. *J Clin Invest* **81**:649-656, 1988.

Glagov, S., Zarins, C., Giddens, D.P. and Ku, D.N. Haemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med* **112**:1018-1031, 1988.

Glickman, M.H., Julian, C.C., Kimmins, S. and Evans, W.E. Aortic aneurysm: to tube or not to tube. *Surgery* **91**:603-605, 1982.

Gliedman, M.L., Ayers, W.B. and Vestal, B.L. Aneurysms of the abdominal aorta and its branches. A study of untreated patients. *Ann Surg* **146**:207-214, 1957.

Glimaker, H., Holmberg, L., Elvin, A., *et al.* Natural history of patients with abdominal aortic aneurysm. *Eur J Vasc Surg* **5**:125-130, 1991.

Gloviczki, P., Pairolero, P.C., Mucha, P.J., *et al.* Ruptured abdominal aortic aneurysms: repair should not be denied. *J Vasc Surg* **15**:851, 1992.

Goddard, M.B., Lucas, A.R., Curletti, E.L., Cohn, M.S. and Sadighi, P.J. Sutureless intraluminal graft for repair of abdominal aortic aneurysm. *Archives of Surgery* **120**:791-793, 1985.

Golden, M.A., Whittemore, A.D., Donaldson, M.C. and Mannick, J.A. Selective evaluation and management of coronary artery disease in patients undergoing repair of abdominal aortic aneurysms. A 16-year experience. *Ann Surg* **212**:415-420, 1990.

Goldman, L., Cook, E.F., Mitchel, N., *et al.* Incremental value of the exercise test for diagnosing the presence or absence of coronary artery disease. *Circulation* **69**:945-953, 1984.

Goldstone, J. and Moore, W.S. Infection in vascular prostheses: clinical manifestations and surgical management. *Am J Surg* **128**:255, 1974.

Goldstone, J., Malone, J.M. and Moore, W.S. Inflammatory aneurysms of the abdominal aorta. *Surgery* **83**:425-430, 1978.

Goldstone, J. The infected infra-renal aortic graft. *Acta Chir Scand Suppl* **538**:72-86, 1987.

Goldstone, J. *Aneurysms of the Aorta and Iliac Arteries.* In: Vascular Surgery, edited by Moore, W. Philadelphia: Saunders, 1991, p. 304-323.

Golub, L.M., Lee, H.M., Lehrer, G., *et al.* Minocycline reduces gingival collagenolytic activity during diabetes: preliminary observations and a proposed new mechanism of action. *J Periodontal Res* **18**:516-526, 1983.

Gooding, G.A., Effeney, D.J. and Goldstone, J. The aortofemoral graft: detection and identification of healing complications by ultrasonography. *Surgery* **89**:94-101, 1981.

Gordon-Smith, I.C., Taylor, E.W., Nicolaides, A.N., Golcman, L., Kenyon, J.R. and Eastcott, H.H. Management of abdominal aortic aneurysm. *Br J Surg* 65:834-838, 1978.

Grace, P.A. Ischaemia-reperfusion injury. *Br J Surg* **81**:637-647, 1994.

Graham, M. and Chan, A. Ultrasound screening for clinically occult abdominal aortic aneurysm. *Canadian Medical Association Journal* **138**:627-629, 1988.

Greenhalgh, R.M. Prognosis of abdominal aortic aneurysm. *BMJ.* 301:136, 1990.

Greenwald, R.A., Simonson, B.G., Moak, S.A., *et al.* Inhibition of epiphyseal cartilage collagenase by tetracyclines in low phosphate rickets in rats. *J Orthop Res* **6**:695-703, 1988.

Greenwald, R.A. Treatment of destructive arthritic disorders with MMP inhibitors: potential role of tetracyclines. *Ann NY Acad Sci* **732**:181-198, 1994.

Gurry, J.F., Doyle, J.C. and Vidovich, J.D. Pre-operative aortography in the assessment of abdominal aortic aneurysms. *Aust N Z J Surg* **57**:831-835, 1987.

Haeger, K. *The Illustrated History of Surgery*, New York:Bell Publishing, 1988.

Hallbrook, T. and Holmquist, B. Sexual disturbances following dissection of the aorta and the common iliac arteries. *J Cardiovasc Surg* **11**:255-260, 1970.

Hallett, J.W. Abdominal aortic aneurysm: natural history and treatment. *Heart Disease and Stroke* 303-308, 1992.

Hallett, J.W.,Jr., Naessens, J.M. and Ballard, D.J. Early and late outcome of surgical repair for small abdominal aortic aneurysms: a population-based analysis. *J Vasc Surg* **18**:684-691, 1993.

Hallett, J.W.J., Fowl, R., O'Brien, P.C., *et al.* Renovascular operations in patients with chronic renal insufficiency: do the benefits justify the risks? *J Vasc Surg* **5**:622-627, 1987.

Halloran, B.G. and Baxter, B.T. Pathogenesis of Aneurysms. *Seminars in Vascular Surgery* **8(2)**:85-92, 1995.

Hammond, E.C. and Garfinkel, L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Archives of Environmental Health* **19**:167-182, 1969.

Hands, L.J., Collin, J. and Lamont, P. Observed incidence of paraplegia after infrarenal aortic aneurysm repair. *Br J Surg* **78**:999, 1991.

Harris, J.D. and Jepson, R.P. Aorto-iliac stenosis: a comparison of two procedures. *Aust NZ J Surg* **34**:211-214, 1965.

Harris, L.M., Faggioli, G.L., Fiedler, R., Curl, G.R. and Ricotta, J.J. Ruptured abdominal aortic aneurysms: factors affecting mortality rates. *J Vasc Surg* **14**:812-818, 1991.

Harris, P.L. Reducing the mortality from abdominal aortic aneurysms: need for a national screening programme. *Br Med J* **305**:697-699, 1992.

He, C.M. and Roach, M.R. The composition and mechanical properties of abdominal aortic aneurysms. *J Vasc Surg* **20**:6-13, 1994.

Hedges, A.R. and Bentley, P.G. Resection of inflammatory aneurysm after steroid therapy. *Br J Surg* **73**:374, 1986.

Helsby, R. and Moossa, A.R. Aorto-iliac reconstruction with special reference to the extraperitoneal approach. *Br J Surg* **62**:596-600, 1975.

Henney, A, Adiseshiah, M., Poulter, N., MacSweeney, S.T.R., Greenhalgh, R.M. and Powell, J.T. Abdominal aortic aneurysm. *Lancet* **341**:215-220, 1993.

Henry, L.G. and Bernhard, V.M. Ureteral pathology associated with aortic injury: a report of 3 unusual cases. *Surgery* **83**:464-469, 1978.

Hermreck, A.S. Prevention and management of surgical complications during repair of abdominal aortic aneurysms. *Surg Clin North Am* **69**:869-894, 1989.

Herron, G., Unemori, E., Wong, M., Rapp, J., Hibbs, M. and Stoney, R. Connective tissue proteinases and inhibitors in abdominal aortic aneurysms: involvement of the vasa vasorum in the pathogenesis of aortic aneurysms. *Arterioscler Thromb* **11**:1667-1677, 1991.

Hertzer, N.R., Beven, E.G., Young, J.R., *et al.* Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Annals of Surgery* **199**:223-233, 1984.

Hickey, N.C., Downing, R., Hamer, J.D., Ashton, F. and Slaney, G. Abdominal aortic aneurysms complicated by spontaneous iliocaval or duodenal fistula. *J Cardiovasc Surg* **32**:181-185, 1991.

Hicks, G.L., Eastland, M.W., DeWeese, J.A., May, A.G. and Rob, C.G. Survival improvement following aortic aneurysm resection. *Annals of Surgery* **181**:863-869, 1975.

Hildebrand, H.D. and Fry, P.D. Ruptured abdominal aortic aneurysm. *Surgery* **77**:540-544, 1975.

Hilton, S., Megibow, A.J., Naidich, D.P. and Bosniak, M.A. Computed tomography of the postoperative abdominal aorta. *Radiology* **145**:403-407, 1982.

Hoffert, P.W., Gensler, S. and Haimovici, H. Infection complicating arterial grafts. *Arch Surg* **90**:427-435, 1965.

Hoffman, M., Avellone, J.C., Plecha, F.R., *et al.* Operation for ruptured abdominal aortic aneurysms: a community-wide experience. *Surgery* **91**:597-602, 1982.

Hojer, J. Diagnosis of acute symptomatic aortic aneurysm - ultrasonography an important tool. *Journal of Internal Medicine* **232**:427-431, 1992.

Hollier, L.H., Plate, G., O'Brien, P.C., *et al.* Late survival after abdominal aortic aneurysm repair: influence of coronary artery disease. *J Vasc Surg* **1**:290-299, 1984.

Hollier, L.H., Taylor, L.M. and Ochsner, J. Recommended indications for operative treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. *J Vasc Surg* **15**:1046-1056, 1992.

Hunt, D.M. Primary defect in copper transport underlies mottled mutants in the mouse. *Nature* **249**:852-853, 1974.

Hunter, G.C., Long, S.C., Yu, G.S.M., McIntyre, K.E. and Bernhard, V.W. Aortic blebs: possible site of aneurysm rupture. *J Vasc Surg* **10**:93-99, 1989.

Ilgenfritz, F.M. and Jordan, F.T. Microbiological monitoring of aortic aneurysm wall and contents during aneurysmectomy. *Archives of Surgery* **123**:506-508, 1988.

Iliopoulos, J.I., Howanitz, P.E., Pierce, G.E., *et al.* The critical hypogastric circulation. *Am J Surg* **154**:670-675, 1987.

Imparato, A.M. Abdominal aortic surgery: prevention of lower limb ischemia. *Surgery* **93**:112-116, 1983.

Ingoldby, C.J.H., Wujanto, R. and Mitchell, J.E. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. *Br J Surg* **73**:551-550, 1986.

Irizarry, E., Newman, K.M., Gandhi, R.H., *et al.* Demonstration of interstitial collagenase in abdominal aortic aneurysm disease. *J Surg Res* **54**:571-579, 1993.

Iskandrian, A.S., Hero, J., Askenase, A., Segal, B.L. and Auerbach, N. Dipyridamole cardiac imaging. *Am Heart J* **115**:432-443, 1988.

Jacobs, M.J., Reul, G.J., Gregoric, I. and Cooley, D.A. In-situ replacement and extra-anatomic bypass for the treatment of infected abdominal aortic grafts. *Eur J Vasc Surg* **5**:83-86, 1991.

Jamieson, G.G., DeWheese, J.A. and Rob, C.G. Infected arterial grafts. *Ann Surg* **181**:850-852, 1975.

Jarrett, F. Ischaemic foot following aneurysm repair. In: *Common Problems in Vascular Surgery*, edited by Brewster, D.C. Chicago: Year Book Medical, 1989, p. 135-139.

Joffre, F., Puel, J., Imbart, C., *et al.* Use of a new type of self expanding vascular stent prosthesis: early clinical results. Presented at the 72nd Scientific Assembly and *Annual Meeting of the Radiological Society of North America*, Chicago, Nov 30-December 5: 1986.

Johansen, K. and Koepsell, T. Familial tendency for abdominal aortic aneurysms. *JAMA* **256**:1934-1936, 1986.

Johansen, K., Kohler, T.R., Nicholls, S.C., Zierler, R.E., Clowes, A.W. and Kazmers, A. Ruptured abdominal aortic aneurysm: the Harborview experience. *J Vasc Surg* **13**:240-5; 1991.

Johansson, G. and Swedenborg, J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. *Br J Surg* **73**:101-103, 1986.

Johansson, G., Nydahl, S., Olofsson, P. and Swedenborg, J. Survival in patients with abdominal aortic aneurysms. Comparison between operative and nonoperative management. *Eur J Vasc Surg* **4**:497-502, 1990.

Johansson, G. and Swedenborg, J. Little impact of elective surgery on the incidence and mortality of ruptured aortic aneurysms. *Eur J Vasc Surg* **8**:489-493, 1994.

Johnson, G.,Jr., Avery, A., McDougal, E.G., Burnham, S.J. and Keagy, B.A. Aneurysms of the abdominal aorta. Incidence in blacks and whites in North Carolina. *Archives of Surgery* **120**:1138-1140, 1985.

Johnson, J.M., Gaspar, M.R., Movius, H.J. and Rosental, J.J. Sudden complete thrombosis of aortic and iliac aneurysms. *Archives of Surgery* **108**:792-794, 1974.

Johnson, T. *The Workes of That Famous Chrurgeon Ambrose Pare*, London:Coates & Dugard, 1649.

Johnson, W.C., Gale, M.E., Gerzof, S.G., Robbin, A.H. and Nabseth, D.C. The role of computed tomography in symptomatic aortic aneurysms. *Surgery,Gynecology & Obstetrics* **162**:49-53, 1986.

Johnston, K.W. and Scobie, T.K. Multicenter prospective study of nonruptured abdominal aortic aneurysms. I. Population and operative management. *J Vasc Surg* **7**:69-81, 1988.

Johnston, K.W. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. *J Vasc Surg* **9**:437-447, 1989.

Johnston, K.W., Rutherford, R.B., Tilson, M.D., Shah, D.M., Hollier, L. and Stanley, J.C. Suggested standards for reporting on arterial aneurysms. *J Vasc Surg* **13**:444-450, 1991.

Johnston, K.W. Nonruptured abdominal aortic aneurysm: six-year follow-up results from the multicenter prospective Canadian aneurysm study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg* **20**:163-170, 1994a.

Johnston, K.W. Ruptured abdominal aortic aneurysm: six-year follow-up results of a multicenter prospective study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg* **19**:888-900, 1994b.

Julian, O.C., Grove, W.J. and Dye, W.S. Direct surgery of atherosclerosis. Resection of abdominal aorta with homologous aortic graft replacement. *Ann Surg* **138**:387-380, 1953.

Kahn, H. The Dorn study of smoking and mortality among US veterans: report on 8.5 years of observation. *National Cancer Institute Monographs* **19**:1-125, 1966.

Kandarpa, K., Piwinica-Worms, D., Paramjit, S.C., *et al.* Prospective double-blinded comparison of MR imaging and aortography in the preoperative evaluation of abdominal aortic aneurysms. *JVIR* **3**:83-89, 1992.

Karanjia, P.N., Madden, K.P. and Lobner, S. Co-existence of abdominal aortic aneurysm in patients with carotid stenosis. *Stroke* **24**:627-630, 1994.

Kato, H., Koike, S. and Yokayama, T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics* **63**:175, 1979.

Katsuda, S., Okada, Y., Imai, K. and Nakanishi, I. Matrix metalloprotenase-9 (92-kd gelatinase) can degrade arterial elastin. *Am J Path* **145**:1208-1218, 1994.

Katz, D.A., Littenberg, B. and Cronenwett, J.L. Management of small abdominal aortic aneurysms. Early surgery vs watchful waiting. *JAMA* **268**:2678-2686, 1992.

Katz, D.J., Stanley, J.C. and Zelenock, G.B. Operative mortality rates for intact and ruptured abdominal aortic aneurysms in Michigan: an eleven-year statewide experience. *J Vasc Surg* **19**:804-15; 1994.

Kellog, E.W. Superoxide, hydrogen peroxide and singlet oxygen in lipid peroxidation by xanthine oxidase system. *J Biol Chem* **250**:8812-8817, 1975.

Kiell, C.S. and Ernst, C. Advances in managementof abdominal aortic aneurysm. *Advances in Surgery* **26**:73-98, 1993.

Kim, D., Edelman, R.R., Kent, K.C., Porter, D.H. and Skillman, J.J. Abdominal aorta and renal artery stenosis: evaluation with MR angiography. *Radiology* **174**:727-731, 1990.

Klausner, J.M., Paterson, I.S., Valeri, C.R., Shepro, D. and Hechtman, H.B. Limb ischaemia-induced increase in permeability is mediated by leukocytes and leukotrienes. *Ann Surg* **208**:755-760, 1988.

Klausner, J.M., Patereson, I.S., Mannick, J.A., Valeri, C.R., Shepro, D. and Hechtman, H.B. Reperfusion pulmonary oedema. *JAMA* **261**:1030-1035, 1989.

Kleinhans, G., Leusmann, D. and Ruhland, D. Urologic complications following vascular prosthetic interventions in the aortofemoral area. *Chirurg* **56**:95-99, 1985.

Kleinman, L.H., Towne, J.B. and Bernhard, V.M. A diagnostic and therapeutic approach to aortoenteric fistulas: clinical experience with twenty patients. *Surgery* **86**:868-880, 1979.

Koch, A., Haines, G., Rizzo, R., *et al.* Human abdominal aortic aneurysms: immunophenotypic analysis suggesting an immune-mediated response. *Am J Path* **137**:1199-1213, 1990.

Kontusaari, S., Tromp, G., Kuivaniemi, H., Romanic, A. and Prockop, D. A mutation in the gene for type III procollagen in a family with aortic aneurysm. *J Clin Invest* **86**:1465-1473, 1990.

Krohg-Sorensen, K. and Kvernebo, K. Laser flowmetry in evaluation of colonic blood flow during aortic reconstruction. *Eur J Vasc Surg* **3**:37-41, 1989.

Krupski, W.C. *Arterial aneurysms.* In: Vascular Surgery, edited by Rutherford, R.B. Philadelphia, PA.: Saunders, 1994, p. 1028-1029.

Labbe, R., Lindsay, T. and Walker, P.M. The extent and distribution of skeletal muscle necrosis after graded periods of complete ischaemia. *J Vasc Surg* **6**:152-157, 1987.

Laborde, J.C., Parodi, J.C., Clem, M.F., *et al.* Intraluminal bypass of abdominal aortic aneurysm: feasibility study. *Radiology* **184**:185-190, 1992.

Lachapelle, K., Graham, A.M. and Symes, J.F. Does the clinical evaluation of the cardiac status predict outcome in patients with abdominal aortic aneurysms? *J Vasc Surg* **15**:964-971, 1992.

Lambardini, M.M. and Ratliff, R.K. The abdominal aortic aneurysm and the ureter. *J Urol* **89**:590-601, 1967.

Lanne, T. and Bergqvist, D. Aortocaval fistulas associated with ruptured abdominal aortic aneurysms. *Eur J Surg* **158**:457-465, 1992.

Laurell, C.B. and Erikson, E. The electrophoretic alpha-1-globulin pattern of serum in alpha-1-antitrypsin deficiency. *Scan J Clin Lab Invest* **15**:132-140, 1963.

Lautstsen, J., Paaske, W.P., Oyre, S., *et al.* Dynamic quantification, visualisation and animation of blood velocities and flows in infrarenal aortic aneurysms in vivo by three dimensional MR phase velocity encoding. *Eur J Vasc Endovasc Surg* **9**:383-388, 1995.

Lawrence, D.D., Charnsangavej, C., Wright, K.C., Gianturco, C. and Wallace, S. Percutaneous endovascular graft: experimental evaluation. *Radiology* **163**:357-360, 1987.

Lawrie, G.M., Morris, G.C.J., Crawford, E.S., *et al.* Improved results of operation for ruptured abdominal aortic aneurysms. *Surgery* **85**:483-488, 1979.

Lazarus, H.M. Intraluminal graft device, system, and method. US Patent No. 4: 787899, 1988.

Lazarus, H.M. Endovascular grafting for the treatment of abdominal aortic aneurysms. *Surg Clin North Am* **72**:959-968, 1992.

Lea Thomas, M. Arteriomegaly. *Br J Surg* **58**:690-694, 1971.

Leach, S.D., Toole, A.L., Stern, H., DeNatale, R.W. and Tilson, M.D. Effect of beta-adrenergic blockade on the growth rate of abdominal aortic aneurysms. *Archives of Surgery* **123**:606-609, 1988.

Leather, R.P., Shah, D., Goldman, M., Rosenberg, M. and Karmody, A.M. Nonresective treatment of abdominal aortic aneurysms. Use of acute thrombosis and axillofemoral bypass. *Archives of Surgery* **114**:1402-1408, 1979.

Leather, R.P., Shah, D.M., *et al.* Comparative analysis of retroperitoneal and transperitoneal aortic replacement of aneurysm. *Surg Gynecol Obstet* 158:156-158, 1989.

Lefer, A.M. and Lefer, D.J. The role of nitric oxide and cell adhesion molecules on the microcirculation in ischaemia-reperfusion. *Cardiovascular Research* **32**:743-751, 1996.

Lemole, G.M., Spagna, P.M., Strong, M.D. and Karmilowicz, N.P. Rigid intraluminal prosthesis for replacement of thoracic and abdominal aorta. *J Vasc Surg* **1**:22-26, 1984.

Leopold, G.R., Goldberger, L.E. and Bernstein, E.F. Ultrasonic detection and evaluation of abdominal aortic aneurysms. *Surgery* **72**:939-945, 1972.

Leung, D.Y.M., Glagov, S. and Mathews, M.B. Cyclic stretching stimulates synthesis of matrix components by arterial smooth muscle cells in vitro. *Science* **191**:475-477, 1976.

Lewis, M.S., Whatley, R.E., Cain, P., McIntyre, T.M., Presott, S.M. and Zimmerman, G.A. Hydrogen peroxide stimulates the synthesis of platelet activating factor by endothelium and induces endothelial cell dependent neutrophil adhesion. *J Clin Invest* **82**:2045-2055, 1988.

Liekweg, W.J. and Greenfield, L.J. Vascular prosthetic infections: collected experience and results of treatment. *Surgery* **81**:335-342, 1977.

Lilienfield, C.E., Gunderson, P.D., Sprafka, J.M. and Vargas, C. Epidemiology of aortic aneurysms: 1. Mortality trends in the United States, 1951-1981. *Arteriosclerosis* **7**:637-643, 1987.

Limet, R., Sakalihassan, N. and Albert, A. Determination of the expansion rate and incidence of rupture of abdominal aortic aneurysms. *J Vasc Surg* **14**:540-548, 1991.

Lindh, M., Malina, M., Ivancev, K., Brunkwall, J. and Lindbald, B. Endovascular stent-anchored aortic grafts: a comparison between self-expanding and balloon-expandable stents in minipigs. *J Endovasc Surg* **3**:284-289, 1996.(Abstract)

Lindholm, L., Ejlertsson, G., Forsberg, L. and Norgren, L. Low prevalence of abdominal aortic aneurysm in hypertensive patients. A population-based study. *Acta Medica Scandinavica* **218**:305-310, 1985.

Lindsay, T.F., Hill, J., Ortiz, F., *et al.* Blockade of complement activation prevents local and pulmonary albumin leak after torso ischaemia-reperfusion. *Ann Surg* **216**:677-683, 1992.

Littooy, F.N., Steffan, G., Greisler, H.P., *et al.* Use of sequential b-mode ultrasonography to manage abdominal aneurysms. *Arch Surg* **124**:419-421, 1989.

London, N.J.M., Nydahl, S., Hartshorne, T., Bolia, A., Bell, P.R.F. and Fishwick, G. Colour-coded doppler ultrasonography to diagnose and guide angioplasty of lower limb arterial lesions. *Br J Surg* **82**:557-550, 1995.

Lord, R.S.A., Crozier, J.A., Snell, J. and Meek, A.C. Transverse abdominal incisions compared with midline incisions for elective infra-renal aortic reconstruction: predisposition to incisional hernia in patients with increased intraoperative blood loss. *J Vasc Surg* **20**:27-33, 1994.

Lorentzen, J.E., Nielsen, O.M., Arendrup, H., *et al.* Vascular graft infection: an analysis of sixty-two graft infections in 2411 consecutively implanted synthetic vascular grafts. *Surgery* **98**:81-86, 1985.

Louw, J.H. Splenic-to-femoral and axillary-to-femoral bypass grafts in diffuse atherosclerotic occlusive disease. *Lancet* **1**:1401-1402, 1963.

Low, M., Perktold, K. and Raunig, R. Haemodnamics in rigid and distensible saccular aneurysms: a numerical study of pulsatile flow characteristics. *Biorheology* **30**:287-298, 1993.

Lucarotti, M., Shaw, E., Poskitt, K. and Heather, B. The Gloucestershire aneurysm screening programme: the first 2 years experience. *Eur J Vasc Surg* **7**:397-401, 1993.

Lumsden, A.B., Allen, R.C., Chaikof, E.L., *et al.* Delayed rupture of aortic aneurysms following endovascular stent grafting. *Am J Surg* **10**:174-178, 1995.

Lunec, J., Blake, D.R., McCleary, S.J. and Bacon, P.J. Self-perpetuating mechanisms of immunoglobulin G aggregation in rheumatoid inflammation. *Journal of Clinical Investigation* **76**:2084-2090, 1985.

Maass, D., Kropf, L., Egloff, L., Demierre, D., Turina, M. and Senning, A. Transluminal implantation of intravascular "double helix" spiral prostheses: technical and biological considerations. *ESAO Proc* **9**:252-256, 1982.

Maass, D., Demierre, D., Deaton, D., Largiader, F. and Senning, A. Transluminal implantation of self-adjusting expandable prosthesis: principles, techniques, and results. *Prog Artif Org* 979-987, 1983.

Maass, D., Zollikofer, C.H.L., Largiader, F. and Senning, A. Radiological follow-up of transluminally inserted vascular endoprostheses: An experimental study using expanding spirals. *Radiology* **152**:659-663, 1984.

Machleder, H.I. and Weinstein, M. Sexual dysfunction following surgical therapy for aorto-iliac disease. *Vascular Surgery* **9**:283-287, 1975.

MacSweeney, S.T., O'Meara, M., Alexander, C., O'Malley, M.K., Powell, J.T. and Greenhalgh, R.M. High prevalence of unsuspected abdominal aortic aneurysm in patients with confirmed symptomatic peripheral or cerebral arterial disease. *Br J Surg* **80**:582-584, 1993.

MacSweeney, S.T., Ellis, M., Worrell, P.C., Greenhalgh, R.M. and Powell, J.T. Smoking and growth rate of small abdominal aortic aneurysms. *Lancet* **344**:651-652, 1994a.

MacSweeney, S.T.R., Powell, J.T. and Greenhalgh, R. Pathogenesis of abdominal aortic aneurysm. *Br J Surg* **81**:935-941, 1994b.

Magee, T.R., Scott, D.J.A., Dunkley, A., *et al.* Quality of life following surgery for abdominal aortic aneurysm. *Br J Surg* **79**:1014-1016, 1992.

Makherjee, D., Mayberry, J., Inahara, T. and Greig, J. The relationship of the abdominal aortic aneurysm to the tortuous internal carotid artery. *Arch Surg* **124**:955-956, 1989.

Malina, M., Ivancev, K., Chuter, T., *et al.* Changing aneurysmal morphology after endovascular grafting. *J Endovasc Surg* **4**:23-30, 1997.

Malone, J.M., Moore, W.S., Campagna, G., *et al.* Bacteremic infectability of vascular grafts: The influence of pseudointimal integrity and duration of graft function. *Surgery* **78**:211-216, 1975.

Manachi, S., Campa, J.S., Greenhalgh, R.M. and Powell, J.T. Collagen in abdominal aortic aneurysm: typing, content, and degradation. *J Vasc Surg* **6**:578-582, 1987.

Mangell, P., Malina, M., Vogt, K., *et al.* Are Self-expanding stents superior to balloon expanded in dilating aortas? An experimental study in pigs. *Eur J Vasc Endovasc Surg* **12(3)**:287-294,1996

Marin, M.L, Veith, F.J., Cynamon, J., *et al.* Initial experience with transluminally placed endovascular grafts for the treatment of complex vascular lesions. *Ann Surg* **222**:449-469, 1995.

Mark, A., Moss, A.A., Lusby, R. and Kaiser, J.A. CT evaluation of complications of abdominal aortic surgery. *Radiology* **145**:409-414, 1982.

Mark, M.S., McCarthy, S.M., Moss, A.A., *et al.* Detection of abdominal aortic graft infection: comparison of CT and indium-labelled white blood cell scans. *AJR* **144**:315-318, 1985.

Martin, P. On abdominal aortic aneurysms. *Journal of Cardiovascular Surgery* **19**:597-598, 1978.

Matas, R. An operation for the radical cure of aneurism based on arteriorrhaphy. *Ann Surg* **37**:161, 1903.

Matas, R. The radical cure of aneurism. *JAMA* **47**:990, 1906.

Matas, R. Ligation of the abdominal aorta. *Ann Surg* **457**:457-450, 1925.

Matsumae, M., Uchida, H. and Teramoto, S. An experimental study of a new sutureless intra-luminal graft with an elastic ring that can attach itself to the vessel wall. A preliminary report. *J Vasc Surg* **8**:38-44, 1988.

Matsumura, J.S., Pearce, W.H., McCarthy, W.J. and Yao, J.S.T. Reduction in aortic aneurysm size: early results after endovascular graft placement. *J Vasc Surg* **25**:113-123, 1997.

May, A.G., DeWeese, J.A. and Rob, C.G. Changes in sexual function following operation on the abdominal aorta. *Surgery* **65**:41-47, 1969.

May, J., White, G., Waugh, R., Yu, W. and Harris, J. Treatment of complex abdominal aortic aneurysms by a combination of endoluminal and extraluminal aorto-femoral grafts. *J Vasc Surg* **19**:24-33, 1994a.

May, J., White, G.H., Waugh, R.C., Yu, W., Stephen, M.S. and Harris, J.P. Endoluminal repair of abdominal aortic aneurysms. *Med J Aust* **161**:541-543, 1994b.

May, J., White, G.H., Yu, W., *et al.* Endoluminal grafting of abdominal aortic aneurysms: causes of failure and their prevention. *J Endovasc Surg* **1**:44-52, 1994c.

May, J., White, G.H., Waugh, R, Stephen, M.S. and Harris, J.P. A prospective study of changes in morphology and dimensions of abdominal aortic aneurysms following endoluminal repair. *J Endovasc Surg* **2**:343-347, 1995a.

May, J., White, G.H., Yu, W., *et al.* Early experience with the Sydney and EVT prosthesis for endoluminal treatment of abdominal aortic aneurysms. *J Endovasc Surg* **2**:240-247, 1995b.

May, J. The ins and outs of the excluded abdominal aortic aneurysm: decreasing diameters and dilating necks. *J Endovasc Surg* **4**:31-32, 1997.

McAuley, C.E., Steed, D.L. and Webster, M.W. Bacterial presence in aortic thrombus at elective aneurysm resection: is it clinically significant? *Am J Surg* **147**:332, 1984.

McCabe, C.J., Coleman, W.S. and Brewster, D.C. The advantage of early operation for abdominal aortic aneurysm. *Archives of Surgery* **116**:1025-1029, 1981.

McCann, R.L., Schwartz, L.B. and Georgiade, G.S. Management of abdominal aortic graft complications. *Ann Surg* **217**:729-734, 1993.

McCombs, P.R. and Roberts, B. Acute renal failure following resection of abdominal aortic aneurysm. *Surgery,Gynecology & Obstetrics* **148**:175-178, 1979.

McCord, J.M. Oxygen-derived free radicals in post-ischaemic tissue injury. *N Engl J Med* **312**:159-163, 1985.

McCord, J.M. Oxygen-derived radicals: a link between reperfusion injury and inflammation. *Fed Proc* **46**:2402-2406, 1987.

McCready, R.A., Siderys, H., Pittman, J.N., *et al.* Ruptured abdominal aortic aneurysms in a private hospital: a decade's experience (1980-1989). *Ann Vasc Surg* **7**:225-228, 1993.

McEnroe, C.S., O'Donnell, T.F.J., Yeager, A., Konstam, M. and Mackey, W.C. Comparison of ejection fraction and Goldman risk factor analysis to dipyridamole-thallium 201 studies in the evaluation of cardiac morbidity after aortic aneurysm surgery. *J Vasc Surg* **11**:497-504, 1990.

McGahan, T.J., Berry, G.A., McGahan, S.L., White, G.H., Yu, W. and May, J. Results of autopsy 7 months after successful endoluminal treatment of an infra-renal abdominal aortic aneurysm. *J Endovasc Surg* **2**:348-355, 1995.

McGee, G., Baxter, B., Shively, V., *et al.* Aneurysm or occlusive disease - factors determining the clinical course of atherosclerosis of the infrarenal aorta. *Surgery* **110**:370-376, 1991.

McPhail, N., Calvin, J.E., Shariatmadar, A., Barber, G.G. and Scobie, T.K. The use of preoperative exercise testing to predict cardiac complications after arterial reconstruction. *J Vasc Surg* **7**:60-68, 1988.

Mealy, K. and Salman, A. The true incidence of ruptured abdominal aortic aneurysms. *Eur J Vasc Surg* **2**:405-408, 1988.

Mehigan, D.H., Fitzpatrick, B., Browna, H.I. and Boucher-Hayes, D.J. Is compliance mismatch the major cause of anastomotic arterial aneurysms? *J Cardiovasc Surg* **26**:147-150, 1985.

Melton, L.J., Bickerstaff, L.K., Hollier, L.H., *et al.* . Changing incidence of abdominal aortic aneurysms: a population-based study. *American Journal of Epidemiology* **120**:379-386, 1984.

Menashi, S., Campa, J.S., Greenhalgh, R.M. and Powell, J.T. Collagen in abdominal aortic aneurysm: typing, content, and degradation. *J Vasc Surg* **6**:578-582, 1987.

Merchant, R.F.,Jr., Cafferata, H.T. and Depalma, R.G. Pitfalls in the diagnosis of abdominal aortic aneurysm. *American Journal of Surgery* **142**:756-758, 1981.

Mesh, C.L., Baxter, B.T., Pearce, W.H., Chisholm, R.L., McGee, G.S. and Yao, J.S.T. Collagen and elastin gene expression in aortic aneurysms. *Surgery* **112**:256-262, 1992.

Metz, P. and Mathieson, F.R. Retroperitoneal approach for implantation of aorto-iliac and aortofemoral vascular prosthesis. *Acta Chir Scand* **144**:471-473, 1978.

Mialhe, C. and Amicable, C. Experience with the Stentor system for AAA treatment. *J Endovasc Surg* **2**:405-406, 1995.

Mianni, S., Giorgetti, P.L., Arpesani, A., Giuffrida, G.F., Biasi, G.M. and Ruberti, U. Spontaneous aorto-caval fistulas from ruptured abdominal aortic aneurysms. *Eur J Vasc Surg* **8**:36-40, 1994.

Mikati, A., Marache, P., Watel, A., *et al.* End-to-side aortoprosthetic anastomoses: long-term computed tomography assessment. *Ann Vasc Surg* **4**:584-591, 1990.

Miles, J.R.,Jr., Miles, D.G. and Johnson, G.,Jr. Aortoiliac operations and sexual dysfunction. *Archives of Surgery* **117**:1177-1181, 1982.

Miller, D.C. and Meyers, B.D. Pathophysiology and prevention of acute renal failure associated with thoracoabdominal and abdominal aortic aneurysm surgery. *J Vasc Surg* **5**:518, 1987.

Milne, A.A., Murphy, W.G., Bradbury, A.W. and Ruckley, C.V. Postoperative haemorrhage following aortic aneurysm repair. *Eur J Vasc Surg* **8**:622-626, 1994.

Minion, D.J., Davis, V.A., Nejezchleb, P.A., Wang, Y., McManus, B.M. and Baxter, B.T. Elastin is increased in abdominal aortic aneurysms. *J Surg Res* **57**:443-446, 1994.

Mir-Majdlessi, S.H., Sullivan, R.H., Farmer, R.J. and Beven, E.G. Endoscopic diagnosis of an aorto-duodenal fistula. *Gastrointestinal Endoscopy* **19**:187-188, 1973.

Mirich, D., Wright, K.C., Wallace, S., *et al.* Percutaneously placed endovascular grafts for aortic aneurysms: feasibility study. *Radiology* **170**:1033-1037, 1989.

Moher, D., Cole, C.W. and Hill, G.B. Epidemiology of abdominal aortic aneurysm: the effect of differing definitions. *Eur J Vasc Surg* **6**:647-650, 1992.

Moore, W.S. Thrombosis of aortofemoral, axillofemoral, or femorofemoral grafts. In: *Critical Problems in Vascular Surgery*, edited by Veith, F.J. New York: Appleton-Century-Crofts., 1982, p. 445-461.

Moore, W.S. and Vescera, C.L. Repair of abdominal aortic aneurysm by transfemoral endovascular graft placement. *Ann Surg* **220**:331-9,1994.

Moore, W.S. and Rutherford, R.B. Transfemoral endovascular repair of abdominal aortic aneurysm: results of the North American EVT phase 1 trial. EVT Investigators. *J Vasc Surg* **23**:543-553, 1996.

Moran, C.G., Edwards, A.T. and Griffith, G.H. Ruptured abdominal aortic aneurysm presenting with ureteric colic. *Br Med J* **294**:1279, 1987.

Moriyama, Y., Toyohira, H., Saigenji, H., Shimokawa, S. and Taira, A. A review of 103 cases with elective repair for abdominal aortic aneurysm: an analysis of the risk factors based on postoperative complications and long-term follow-up. *Surgery Today* **24**:591-595, 1994.

Morris, G.E., Friend, P.J., Vassallo, D.J., Farrington, M., Leapman, S. and Quick, C.R. Antibiotic irrigation and conservative surgery for major aortic graft infection. *J Vasc Surg* **20**:88-95, 1994.

Mortality statistics cause: *Review of the Registrar General on deaths by cause, sex and age in England and Wales 1983.* Series DH2 No.10, Her Majesty's Stationary Office. 1983.

Moulton, S., Adams, S. and Johanson, K. Aortoenteric fistula: a 7-year urban experience. *Am J Surg* **151**:607-611, 1986.

Muluk, S.C., Gertler, J.P., Brewster, D.C., *et al.* Presentation and patterns of aortic aneurysms in young patients. *J Vasc Surg* **20**:880-888, 1994.

Murley, R. John Hunter, velvet and vascular surgery. *Annals of the Royal College of Surgeons of England* **66**:214, 1984.

Murphy, M.E., Kolvenbach, R., Aleksis, M., Hansen, R. and Sies, H. Antioxidant depletion in aortic cross clamping ischaemia: increase of the plasma alpha-tocopheryl quinone/alphatocopherol ratio. *Free Radic Biol Med* **13**:95-100, 1992.

Naylor, A.R., Webb, J., Fowkes, F.G. and Ruckley, C.V. Trends in abdominal aortic aneurysm surgery in Scotland (1971-1984). *Eur J Vasc Surg* **2**:217-221, 1988.

Naylor, A.R., Clark, S., London, N.J.M., *et al.* . Treatment of major aortic graft infection: preliminary experience with total graft excision and *in situ* replacement with a rifampicin bonded prosthesis. *Eur J Vasc Endovasc Surg* **9**:252-256, 1995.

Nevitt, M.P., Ballard, D.J. and Hallett, J.W. Prognosis of abdominal aortic aneurysms. *N Engl J Med* **321**:1009-1014, 1989.

Newman, K.M., Jean-Claude, J., Li, H., Ramey, W.G. and Tilson, M.D. Cytokines that activate proteolysis are increased in abdominal aortic aneurysms. *Circulation* **90** (part 2):224-227, 1994a.

Newman, K.M., Malon, A.M., Shin, R.D., Scholes, J.V., Ramey, W.G. and Tilson, M.D. Matrix metalloproteinases in abdominal aortic aneurysm: characterisation, purification, and their possible sources. *Conn Tissue Res* **30**:265-276, 1994b.

Newman, K.M., Ogata, Y., Malon, A.M., *et al.* . Identification of matrix metalloprotenase-3 (stromelysin-1) and 9 (gelatinase-B) in abdominal aortic aneurysms. *Arteriscler Thromb* **14**:1315-1320, 1994c.

Ng, R.L.H., Davies, A.H., Magee, T.R., Tennant, W., Horrocks, M. and Baird, R.N. Early reoperation after arterial surgery. *Eur J Vasc Surg* **8**:78-82, 1994.

Nitecki, S.S., Hallett, J.W., Stanson, A.W., *et al.* Inflammatory abdominal aortic aneurysms: new clinical implications from a case control study. *J Vasc Surg* **23**:860-869, 1996.

Nolte, J.E., Rutherford, R.B., Nawaz, S., Rosenberger, A., Speers, W.C. and Krupski, W.C. Arterial dissections associated with pregnancy. [Review]. *J Vasc Surg* **21**:515-520, 1995.

Norgren, L., Albrechtsson, U. and Swartbol, P. Side-effects of endovascular grafting to treat aortic aneurysm. *Br J Surg* **83**:520-521, 1996.

Norrgard, O., Rais, O. and Angquist, K.A. Familial occurrence of abdominal aortic aneurysms. *Surgery* **95**:650-656, 1984.

O'Donnell, T.F.,Jr., Scott, G., Shepard, A., Mackey, W., Deterling, R.A. and Callow, A.D. Improvements in the diagnosis and management of aortoenteric fistula. *American Journal of Surgery* **149**:481-486, 1985.

O'Hara, P.J., Hertzer, N.R., Beven, E.G. and Krajewski, L.P. Surgical management of infected abdominal aortic grafts: review of a 25-year experience. *J Vasc Surg* **3**:725-731, 1986.

O'Kelly, J. and Heather, P. General practice-based population screening for abdominal aortic aneurysms. *Br J Surg* **76**:479-480, 1989.

O'Mara, C. and Imbembo, A.L. Paraprosthetic-enteric fistula. *Surgery* **81**:556-566, 1977.

Olin, J.W., Melia, M., Young, J.R., Graor, R.A. and Risius, B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med* **88**:46N-51N, 1990.

Orr, W.M. and Davies, M. Simplified repair of abdominal aortic aneurysms using non-bifurcated (straight) inlay prostheses. *Br J Surg* **61**:847-849, 1974.

Osler, W. Aneurysm of the abdominal aorta. *Lancet* **2**:1089-1080, 1905.

Osler, W. Remarks on arterio-venous aneurysm. *Lancet* **2**:949-940, 1915.

Oudot, J. La greffe vasculaire dans les thromboses du carrefour aortique. *Press Med* **59**:234-230, 1951.

Ouriel, K., Geary, K., Green, R.M., Fiore, W., Geary, J.E. and DeWeese, J.A. Factors determining survival after ruptured aortic aneurysm: the hospital, the surgeon, and the patient. *J Vasc Surg* **11**:493-496, 1990.

Ouriel, K., Green, J.R.M., Donayre, C., *et al.* An evaluation of new methods of expressing aortic aneurysm size; relationship to rupture. *J Vasc Surg* **15**:12-20, 1992.

Owen, R.S., Carpenter, J.P., Baum, R.A., Perloff, L.J. and Cope, C. Magnetic resonance imaging of angiographically occult runoff vessels in peripheral arterial occlusive disease. *N Engl J Med* **326**:1577-1581, 1992.

Oz, H.C., Ashton, R.C.J., Oz, M.C., *et al.* Replacement of the abdominal aorta with a sutureless intraluminal ringed prosthesis. *Am J Surg* **158**:121-126, 1989.

Pairolero, P.C. Repair of abdominal aortic aneurysms in high-risk patients. *Surg Clin North Am* **69**:755-763, 1989.

Palmaz, J.C., Sibbitt, R.R., Reuter, S.T.R., Tio, F.O. and Rice, W.J. Expandable intraluminal graft: a preliminary study. *Radiology* **156**:73-77, 1985.

Palmaz, J.C., Windeler, S.A., Garcia, F., Tio, F.O., Sibbitt, R.R. and Reuter, S.R. Atherosclerotic rabbit aortas: expandable intraluminal grafting. *Radiology* **160**:723-726, 1986.

Palmaz, J.C., Laborde, J.C., Rivera, F.J., *et al.* Stenting of the iliac arteries with the Palmaz stent: experience from a multicenter trial. *Cardiovasc Intervent Radiol* **15**:291-297, 1992.

Parks, D.A. and Granger, D.N. Contributions of ischaemia and reperfusion to mucosal lesion formation. *Am J Physiol* **250**:G749-753, 1986.

Parodi, J.C., Palmaz, J.C. and Barone, H.D. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* **5**:491-499, 1991.

Parodi, J.C. Endovascular repair of abdominal aortic aneurysms. *Advances in Vascular Surgery* **1**:85-106, 1993.

Parodi, J.C. Endovascular repair of abdominal aortic aneurysms and other arterial lesions. *J Vasc Surg* **21**:549-557, 1995.

Parodi, J.C. Endoluminal treatment of arterial diseases using a stent-graft combination: reflections 20 years after the initial concept. *J Endovasc Surg* **4**:3-4, 1997.

Parodi, J.C., Schonholz, C. and La Mura, R. The Parodi system. In: *Endovascular Surgery for Aortic Aneurysms*, edited by Hopkinson, B., Yusuf, W., Whitaker, S. and Veith, F. London: W.B. Saunders, 1997, p. 164-179.

Parry-Billings, M., Baigrie, R.J., Lamont, P.M., Morris, P.J. and Newsholme, E.A. Effects of major and minor surgery on plasma glutamine and cytokine levels. *Arch Surg* **127**:1237-1240, 1992.

Pasic, M., Carrel, T., Vogt, M., von Segesser, L. and Turina, M. Treatment of mycotic aneurysm of the aorta and its branches: the location determines the operative technique. *Eur J Vasc Surg* **6**:419-423, 1992.

Pasquinelli, G., Preda, P., Gargiulo, M., *et al.* An immunohistochemical study of inflammatory abdominal aortic aneurysms. *J Submicrosc Cytol Pathol* **25**:103-112, 1993.

Pasternack, P.F., Imparato, A.M., Bear, G., *et al.* The value of radionuclide angiography as a predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysm resection. *J Vasc Surg* **1**:320-325, 1984.

Patt, A., McCroskey, B.L. and Moore, E.E. Hypothermia induced coagulopathies in trauma. *Surg Clin North Am* **68**:775-785, 1988.

Payne, D.F., Rosenthal, D., Lamis, P.A., *et al.* Infrarenal aortic aneurysms: asymptomatic versus symptomatic. *Am Surgeon* **2**:94, 1985.

Pearce, W.H., Sweis, I., Yao, J.S.T., McCarthy, W.J. and Koch, A. Interleukin-1 beta and tumour necrosis factor-alpha release in normal and diseased human infra-renal aortas. *J Vasc Surg* **16**:784-789, 1992.

Peck, J.J. and Eidemiller, L.R. Aortoenteric fistulas. *Arch Surg* **127**:1191-3; 1992.

Pennell, R.C., Hollier, L.H., Lie, J.T., *et al.* Inflammatory abdominal aortic aneurysms: a thirty-year review. *J Vasc Surg* **2**:859-869, 1985.

Perdue, G.D.,Jr., Smith, R.B., Ansley, J.D. and Costantino, M.J. Impending aortoenteric hemorrhage: the effect of early recognition on improved outcome. *Annals of Surgery* **192**:237-243, 1980.

Petrinec, D., Liao, S., Holmes, D.R., Reilly, J.M., Parks, W.C. and Thompson, R.W. Doxycycline inhibition of aneurysmal degeneration in an elastase-induced rat model of abdominal aortic aneurysm: preservation of aortic elastin associated with suppressed production of 92 kD gelatinase. *J Vasc Surg* **23**:336-346, 1995.

Picone, A.L., Green, R.M., Ricotta, J.R., *et al.* Spinal cord ischaemia following operations on the abdominal aorta. *J Vasc Surg* **3**:94, 1986.

Pilcher, D.B., Davis, J.H., Ashikaga, T., *et al.* Treatment of abdominal aortic aneurysm in an entire state over 7 1/2 years. *American Journal of Surgery* **139**:487-494, 1980.

Plamblad, J., Malmstein, C.L., Uden, A.M., Radmark, O., Engstedt, L. and Samuelsson, B. Leukotriene B4 is a potent and stereospecific stimulator of neutrophil chemotaxis and adherence. *Blood* **58**:658-661, 1981.

Plate, G., Hollier, L.A., O'Brien, P., Pairolero, P.C., Cherry, K.J. and Kazmier, F.J. Recurrent aneurysms and late vascular complications following repair of abdominal aortic aneurysms. *Archives of Surgery 120*:590-594, 1985.

Pleumeekers, H.J., Hoes, A.W., van der Does, E., van Urk, H. and Grobbee, D.E. Epidemiology of abdominal aortic aneurysms. *Eur J Vasc Surg* **8**:119-128, 1994.

Polak, J.F., Bajakian, R.L., O'Leary, D.H., Anderson, M.R., Donaldson, M.C. and Jolesz, F.A. Detection of internal carotid artery stenosis: comparison of MR angiography, colour Doppler sonography, and arteriography. *Radiology* **182**:35-40, 1992.

Ponraj, P. and Pepper, J. Aortic dissection. *BJCP* **46**:127-131, 1992.

Porter, J.M., McGregor, F.,Jr., Acinapura, A.J. and Silver, D. Renal function following abdominal aortic aneurysmectomy. *Surgery,Gynecology & Obstetrics* **123**:819-825, 1966.

Potkin, B.N. and Roberts, W.C. Effects of percutaneous transluminal angioplasty in atherosclerotic plaques and relation of plaque composition and arterial size to outcome. *Am J Cardiol* **62**:41, 1988.

Pott, P. *Remarks of the Necessity and Propriety of the Operation of Amputation in Certain Cases*, London:J Johnson, 1779.

Powell, J. and Greenhalgh, R. Cellular, enzymatic, and genetic factors in the pathogenesis of abdominal aortic aneurysms. *J Vasc Surg* **9**:297-304, 1989.

Powell, J., Bashir, A., Dawson, S., *et al.* Genetic variation on chromosome 16 is associated with abdominal aortic aneurysm. *Clin Science* **78**:13-16, 1990.

Powell, J.T., Greenhalgh, R.M., Ruckley, C.V. and Fowkes, F.G.R. Prologue to a surgical trial. *Lancet* **342**:1473-1474, 1993.

Prince, M.R., Narasimham, D.L., Stanley, J.C., *et al.* Gadolinium-enhanced magnetic resonance angiography of abdominal aortic aneurysms. *J Vasc Surg* **21**:656-669, 1995.

Provan, J.L., Fialkov, J., Ameli, F.M. and St Louis, E.L. Is tube repair of aortic aneurysm followed by aneurysmal change in the common iliac arteries? *Can.J Surg* **33**:394-397, 1990.

Pryor, W.A. Oxy-radicals and related species: their formation, life times and reactions. *Annu Rev Physiol* **48**:657-667, 1986.

Puel, J., Rosseau, H., Joffre, F., *et al.* Intervascular stents to prevent restenosis after transluminal coronary angioplasty. *Circulation* **76** (suppl IV):V-27, 1987a.

Puel, J., Rosseau, H., Joffre, F., Hatem, S., Fauvel, J.M. and Bounhoure, J.P. Intravascular stents to prevent restenosis after transluminal coronary angioplasty. *Circulation* **76 (IV)**:27, 1987b.

Pyeritz, R.E. Propranolol retards aortic root dilation in Marfan syndrome. *Circulation* **68** (suppl 3):365, 1983.

Queral, L.A., Whitehouse, W.M., Flinn, W.R., *et al.* Pelvic hemodynamics after aortoiliac reconstruction. *Surgery* **36**:799-809, 1979.

Quinones, B.W., Hernandez, J.J. and Moore, W.S. Long-term results following surgical management of aortic graft infection. *Arch Surg* **126**:507-511, 1991.

Rabl, H., Khoschsorur, G., Colombo, T., Tatzber, F. and Esterbauer, H. Human plasma lipid peroxide levels show a strong transient increase after successful revascularisation operations. *Free Radical Biology and Medicine* **13**:281-288, 1992.

Ramirez, F., Periera, L., Zhang, H. and Lee, B. The fibrillin-Marfan syndrome connection. *Bioessays* **15**:589-594, 1993.

Raptopoulos, V., Cummings, T. and Smith, E.H. Computed tomography of life-threatening complications of abdominal aortic aneurysm. The disrupted aortic wall. *Invest.Radiol.* **22**:372-376, 1987.

Rastad, J., Almgren, B., Bowald, S., *et al.* Renal complications to the left renal vein ligation in abdominal aortic surgery. *J Cardiovasc Surg* **25**:432-436, 1984.

Reed, D., Reed, C., Stemmermann, G. and Hayashi, T. Are aortic aneurysms caused by atherosclerosis? *Circulation* **85**:205-211, 1992.

Reilly, D.T., Grigg, M.J. and Mansfield, A.O. Intraperitoneal placement of gentamicin beads in the management of prosthetic graft sepsis. *J R Coll Surg Edinb* **34**:314-315, 1989.

Reilly, J.M., Savage, E.B., Brophy, C.M. and Tilson, M.D. Hydrocortisone rapidly induces rupture of aortic aneurysms in a genetically susceptible mouse. *Arch Surg* : 1995.

Reilly, L.M., Altman, H., Lusby, R.J., Kersh, R.A., Ehrenfeld, W.K. and Stoney, R.J. Late results following surgical management of vascular graft infection. *J Vasc Surg* **1**:36-44, 1984.

Reilly, L.M., Ehrenfeld, W.K., Goldstone, J., *et al.* Gastrointestinal tract involvement by prosthetic graft infection: the significance of gastrointestinal hemorrhage. *Ann Surg* **202**:342-348, 1985.

Reilly, L.M., Stoney, R.J., Goldstone, J. and Ehrenfeld, W.K. Improved management of aortic graft infection: the influence of operation sequence and staging. *J Vasc Surg* **5**:421-431, 1987.

Reiz, S., Peter, T. and Rais, O. Hemodynamic and cardiometabolic effects of infrarenal aortic and common iliac artery declamping in man--an approach to optimal volume loading. *Acta Anaesthesiologica Scandinavica* **23**:579-586, 1979.

Repine, J.E., Cheronis, J.C., Rodell, T.C., Linas, S.L. and Patt, A. Pulmonary oxygen toxicity and ischaemia reperfusion injury: a mechanism in common involving xanthine oxidase and neutrophils. *Am Rev Respir Dis* **136**:483-485, 1987.

Richter, G.M., Roeren, T., Noeldge, G., *et al.* Initial long-term results of a randomised 5-year study: iliac stent implantation versus PTA. *Vasa (Suppl)* **35**:192-193, 1992.

Richter, G.M., Palmaz, J.C., Allenberg, J.R. and Kauffmann, G.W. Transluminal stent prosthesis in aneurysm of the abdominal aorta. Initial experiences with a new procedure. (German). *Radiologe* **34**:511-518, 1994.

Ricotta, J.J., Faggioli, G.L., Stella, A., *et al.* Total excision and extra-anatomic bypass for aortic graft infection. *Am J Surg* **162**:145-149, 1991.

Rijbroek, A., Moll, F.L., van Dijk, H.A., Meijer, R. and Jansen, J. Inflammation of the abdominal aortic aneurysm wall. *Eur J Vasc Surg* **8**:41-46, 1994.

Risberg, B., Seeman, T. and Ortenwall, P. A new incision for retroperitoneal approach to the aorta. *Acta Chir Scand* **155**:89-91, 1989.

Rizzo, R.J., McCarthy, W.J., Dixit, S.N., *et al.* Collagen types and matrix protein content in human abdominal aortic aneurysms. *J Vasc Surg* **10**:365-373, 1989.

Rob, C.G. Extraperitoneal approach to the abdominal aorta. *Surgery* 53:87-89, 1963.

Roberts, W.C. Aortic dissection: anatomy, consequences, and causes. [Review]. *American Heart Journal* **101**:195-214, 1981.

Roger, V., Ballard, D., Hallett, J., Osmundson, P., Puetz, P. and Gersh, B. Influence of coronary artery disease on morbidity and mortality after abdominal aortic aneurysmectomy: a population based study. *J Am Coll Cardiol* **14**:1245-1252, 1989.

Rohrer, M.J., Cutler, B.S. and Wheeler, H.B. Long-term survival and quality of life following ruptured abdominal aortic aneurysm. *Archives of Surgery* 123:1213-1217, 1988.

Rose, A.G. and Dent, D.M. Inflammatory variant of abdominal aortic atherosclerotic aneurysm. *Arch Pathol Lab Med* **105**:409-413, 1981.

Ross, R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* **362**:801-809, 1993.

Roumen, R.M., Hendriks, T., van der Ven-Jongekrijg, J., *et al.* Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Ann Surg* **218**:769-776, 1993.

Rousseau, H., Puel, J., Joffre, F., *et al.* Self-expanding endovascular prostheses: an experimental study. *Radiology* **164**:709-714, 1987.

Rowe, D.W., McGoodwin, E.B., Martin, G.R. and Grahn, D. Decreased lysyl oxidase activity in the aneurysm prone, mottled mouse. *J Biol Chem* **132**:939-942, 1977.

Rozenblit, A., Marin, M.L., Veith, F.J., Cynamon, J., Wahl, S.I. and Bakal, C.W. Endovascular repair of abdominal aortic aneurysm: value of postoperative follow-up with helical CT. *Am J Roentgenol* **165**:1473-1479, 1995.

Rubin, G.D., Dake, M.D., Napel, S.A., McDonnell, C.H. and Jeffrey, R.B.,Jr. Three-dimensional spiral CT angiography of the abdomen: initial clinical experience. *Radiology* **186**:147-152, 1993a.

Rubin, G.D., Walker, P.J., Dake, M.D., *et al.* Three-dimensional spiral computed tomographic angiography: an alternative imaging modality for the abdominal aorta and its branches. *J Vasc Surg* **18**:656-665, 1993b.

Rutherford, R.B. Infra-renal aortic aneurysms. In: *Vascular Surgery*, edited by Rutherford, R.B. Philadelphia, USA.: WB Saunders Co., 1984, p. 755-777.

Rutherford, R.B. and McCroskey, B.L. Ruptured abdominal aortic aneurysms: special considerations. *Surg Clin North Am* **69**:859-868, 1989.

Sabri, S. and Cotton, L.T. Sexual dysfunction following aortoiliac reconstruction. *Lancet* **2**:1218-1219, 1971.

Sacks, D. and Miller, J. Ureteral leak around an aortic bifurcation graft: complication of ureteral stenting. *Journal of Urology* **140**:1526-1528, 1988.

Sakalihasan, N., Heyeres, A., Nusgens, B.V., Limet, R. and Lapiere, C.M. Modifications of the extracellular matrix of aneurysmal abdominal aortas as a function of their size. *Eur J Vasc Surg* **7**:633-637, 1993.

Salaman, R.A., Shandall, A., Morgan, R.H., Fligelstone, L., Davies, W.T. and Lane, I.F. Intravenous digital subtraction angiography versus computed tomography in the assessment of abdominal aortic aneurysm. *Br J Surg* **81**:661-663, 1994.

Samy, A.K. and MacBain, G. Abdominal aortic aneurysm: ten years' hospital population study in the city of Glasgow. *Eur J Vasc Surg* **7**:561-566, 1993.

Samy, A.K., Whyte, B. and MacBain, G. Abdominal aortic aneurysm in Scotland. *Br J Surg* **81**:1104-1106, 1994.

Sandison, A.J.P., Edmondson, R.A., Panayiotopoulos, Y.P., Reidy, J.F., Adam, A. and Taylor, P.R. Fatal colonic ischaemia after stent graft for aortic aneurysm. *Eur J Vasc Endovasc Surg* **13**:219-220, 1997.

Schafer, P.W. and Hardin, C.A. The use of temporary polythene shunts to permit occlusion, resection, and frozen homologous graft replacement of vital vessel segments. *Surgery* **31(2)**:186-199, 1952.

Schatz, R.A., Palmaz, J.C., Tio, F.O., Garcia, O. and Reuter, S.R. Balloon-expandable intracoronary stents in the adult dog. *Circulation* **76**:450-457, 1987.

Schmitt, D.D., Bandyk, D.F., Pequet, A.J., *et al.* Mucin production by *Staphylococcus epidermidis*: A virulence factor promoting adherence to vascular grafts. *Arch Surg* **121**:89-95, 1986.

Schroeder, T., Christofferson, J.K., Anderson, J., *et al.* Ischaemic colitis complicating reconstruction of the abdominal aorta. *Surg Gynecol Obstet* **160**:299-303, 1985.

Schubart, P., Fortner, G., Cummings, D., *et al.* The significance of hydronephrosis after aortofemoral reconstruction. *Archives of Surgery* **120**:377-381, 1985.

Schumacher, H., Eckstein, H.H., Kallinowski, F. and Allenberg, J.R. Morphometry and classification in abdominal aortic aneurysms: patient selection for endovascular and open surgery. *J Endovasc Surg* **4**:39-44, 1997.

Schwartz, J.A., Powell, T.W., Burnham, S.J. and Johnson, G.J. Culture of abdominal aortic aneurysm contents. An additional series. *Arch.Surg* **122**:777-780, 1987.

Schwend, R., Wolf, Y., Torruella, A., *et al.* The validity of abdominal aortic evaluation during lower extremity arterial examination. *J Vasc Tech* **18**:121-123, 1994.

Scott, D.J.A., Farmilo, R.W., McMahon, J.N. Nicholson, M. and Horrocks, M. Inflammatory aneurysms: are they all the same? *J Cardiovasc Surg* **29**:7, 1988a.

Scott, R.A., Ashton, H.A. and Kay, D.N. Routine ultrasound screening in management of abdominal aortic aneurysm. *British Medical Journal* (Clinical Research Edition). **296**:1709-1710, 1988b.

Scott, R.A.P., Gudgeon, A.M., Ashton, H.A., Allen, D.R. and Wilson, N.M. Surgical workload as a consequence of screening for abdominal aortic aneurysm. *Br J Surg* **81**:1440-1442, 1994.

Selwyn, S. and Ellis, H. Skin bacteria and skin disinfection reconsidered. *Br Med J* **1**:136-140, 1972.

Senapati, A., Hurst, P.A., Thomas, M.L., Browse, N.L. and Burnard, K.G. Differentiation of ruptured aortic aneurysm from acute expansion by computerised tomography. *Journal of Cardiovascular Surgery* **27**:719-722, 1986.

Senior, R., Griffin, G., Fliszar, C., Shapiro, S., Goldberg, G. and Welgus, H. Human 92- and 72-kilodalton Type IV collagenases are elastases. *J Biol Chem* **266**:7870-7875, 1991.

Sharp, W.V. and Donovan, D.L. Retroperitoneal approach to the abdominal aorta: revisited. *J Cardiovasc Surg* **28**:270-273, 1987.

Shepard, A.D., Scott, G.R., Mackey, W.C., O'Donnell, T.F.,Jr., Bush, H.L. and Callow, A.D. Retroperitoneal approach to high-risk abdominal aortic aneurysms. *Archives of Surgery* **121**:444-449, 1986.

Shumaker, H.B.J. Midline extraperitoneal exposure of the abdominal aorta and iliac arteries. *Surg Gynecol Obstet* **135**:791-792, 1972.

Sicard, G.A., Freeman, M.B., VanderWoude, J.C. and Anderson, C.B. Comparison between the transabdominal and retroperitoneal approach for reconstruction of the infrarenal abdominal aorta. *J Vasc Surg* **5**:19-27, 1987.

Sicard, G.A., Allen, B.T., Munn, J.S. and Anderson, C.B. Retroperitoneal versus transperitoneal approach for repair of abdominal aortic aneurysm. *Surg Clin North Am* **69**:795-806, 1989.

Sicard, G.A., Reilly, J.M., Rubin, B.G., *et al.* Transabdominal versus retroperitoneal incision for abdominal aortic surgery: report of a prospective randomized trial. *J Vasc Surg* **21**:174-81, 1995.

Siegel, C.L. and Cohan, R.H. CT of abdominal aortic aneurysms. *Am J Rad* **163**:17-29, 1994.

Simpson, C.F., Kling, J.M. and Palmer, R.F. The use of propranolol for the protection of turkeys from the development of beta-aminopropionitrile-induced aortic ruptures. *Angiology* **19**:414-418, 1968.

Simpson, C.F. and Boucek, R.J. The beta-aminopropionitrile fed turkey; a model for detecting potential drug action on arterial tissue. *Cardiovasc Res* **17**:26-32, 1983.

Sinclair, A.J., Barnett, A.H. and Lunec, J. Free radicals and antioxidant systems in health and disease. *British Journal of Hospital Medicine* **43**:334-344, 1990.

Sladen, J.G., Gerein, A.S. and Miyagishima, R.T. Late rupture of prosthetic aortic grafts. *Am J Surg* **153**:453-458, 1987.

Slootmans, F.C., van der Vliet, J.A., Reinaerts, H.H., van Roye, S.F. and Buskens, F.G. Relaparotomies after ruptured abdominal aortic aneurysm repair. *Eur J Vasc Surg* **8**:342-345, 1994.

Smeets, H.J., Camps, J., van Milligen de Witt, A.W.M., *et al.* Influence of low dose allopurinol on ischaemia-reperfusion injury during abdominal aortic surgery. *Eur J Vasc Endovasc Surg* **9**:162-169, 1995.

Smith, G. Anaesthesia for vascular surgery. In: *Surgical mannagement of vascular disease*, edited by Bell, P.R.F., Jamieson, C.W. and Ruckley, C.V. London: W.B.Saunders, 1992, p. 291-308.

Smith, J.L., Evans, D.H., Fan, L., *et al.* Interpretation of embolic phenomena during carotid endarterectomy. *Stroke* **26**:2281-2284, 1995.

Sonesson, B., Lanne, T., Vernersson, E. and Hansen, F. Sex differences in the mechanical properties of the abdominal aorta in human beings. *J Vasc Surg* **20**:959-969, 1994.

Soong, C.V., Blair, P.H., Halliday, M.I., *et al.* Endotoxaemia, the generation of the cytokines and their relationship to intramucosal acidosis of the sigmoid colon in elective abdominal aortic aneurysm repair. *Eur J Vasc Surg* **7**:534-539, 1993.

Soreide, O., Grimsgaard, C., Myhre, H.O., Solheim, K. and Trippestad, A. Time and cause of death for 301 patients operated on for abdominal aortic aneurysms. *Age & Ageing* **11**:256-260, 1982a.

Soreide, O., Lillestol, J., Christensen, O., *et al.* Abdominal aortic aneurysms: survival analysis of four hundred thirty-four patients. *Surgery* **91**:188-193, 1982b.

Spanos, P.K., Gilsdorf, R.B., Sako, Y. and Najarian, J.S. The management of infected abdominal aortic grafts and graft-enteric fistulas. *Annals of Surgery* **183**:397-400, 1976.

Speziale, F., De Santis, F., Giannoni, M.F., *et al.* Familial incidence of abdominal aortic aneurysms. *Vasc Surg* **28**:261-266, 1994.

Spiro, M. and Cotton, L.T. Aorto-iliac thrombo-endarterectomy. *Br J Surg* **57**:161-168, 1979.

Stanley, J.C., Wakefield, T.W., Graham, L.M. and Whitehouse, W.M. Clinical importance and management of splanchnic artery aneurysms. *J Vasc Surg* **3**:836, 1986.

Starr, D.S., Lawrie, G.M. and Morris, G.C.,Jr. Prevention of distal embolism during arterial reconstruction. *American Journal of Surgery* **138**:764-769, 1979.

Stella, A., Gargiulo, M., Faggioli, G.L., *et al.* Postoperative course of inflammatory abdominal aortic aneurysms. *Ann Vasc Surg* **7**:229-238, 1993.

Sterpetti, A.V., Schultz, R.D., Feldhaus, R.J., Peetz, D.J.,Jr., Fasciano, A.J. and McGill, J.E. Abdominal aortic aneurysm in elderly patients. Selective management based on clinical status and aneurysmal expansion rate. *American Journal of Surgery* **150**:772-776, 1985.

Sterpetti, A.V., Schultz, R.D., Feldhaus, R.J., Cheng, S.E. and Peetz, D.J. Factors influencing enlargement rate of small abdominal aortic aneurysms. *J Surg Res* **43**:211-219, 1987.

Sterpetti, A.V., Hunter, W.J., Feldhaus, R.J., *et al.* Inflammatory aneurysms of the abdominal aorta: incidence, pathologic, and etiologic considerations. *J Vasc Surg* **9**:643-649, 1989.

Stevens, K. The incidence of abdominal aortic aneurysms. *BJCP* **47**:208-210, 1993.

Stockly, R.A. Alpha-1-antitrypsin and the pathogenesis of emphysema. *Lung* **65**:61-67, 1987.

Strachan, C.J.L., Newsom, S.W.B. and Ashton, T.R. The clinical use of an antibiotic bonded graft. *Eur J Vasc Surg* **5**:627-632, 1991.

Strachan, D. Predictors of death from aortic aneurysm among middle-aged men: the Whitehall study. *Br J Surg* **78**:401-404, 1991.

Strecker, E.P., Berg, C., Weber, H., Bohl, M. and Dietrich, B. Experimentelle Untersuchung mit einer neuen perkutan einfurbaren und aufdehnbaren Gefassendoprosthese. *Fortschr Rontgenstr* **147**:669-672, 1987.

String, S.T. Cholelithiasis and aortic reconstruction. *J Vasc Surg* **1**:664, 1984.

Strom, J.A., Bernhard, V.M. and Towne, J.B. Acute limb ischemia following aortic reconstruction. A preventable cause of increased mortality. *Archives of Surgery* **119**:470-473, 1984.

Sumner, D.S., Hokanson, D.E. and Strandness, D.E.,Jr. Stress-strain characteristics and collagen-elastin content of abdominal aortic aneurysms. *Surgery,Gynecology & Obstetrics* **130**:459-466, 1970.

Szilagyi, D.E., Smith, R.F., DeRusso, F.J., Elliott, J.P. and Sherrin, F.W. Contribution of abdominal aortic aneurysmectomy to prolongation of life. *Annals of Surgery* **164**:678-699, 1966.

Szilagyi, D.E., Elliott, J.P. and Berguer, R. Coincidental malignancy and abdominal aortic aneurysm. Problems of management. *Archives of Surgery* **95**:402-412, 1967.

Szilagyi, D.E., Elliott, J.P. and Smith, R.F. Clinical fate of the patient with asymptomatic abdominal aortic aneurysm and unfit for surgical treatment. *Archives of Surgery* **104**:600-606, 1972a.

Szilagyi, D.E., Smith, R.F., Elliot, J.P. and Vrandecic, M.P. Infection in arterial reconstruction with synthetic grafts. *Ann Surg* **176**:321-333, 1972b.

Szilagyi, D.E., Hageman, J.H., Smith, R.F. and Elliott, J.P. Spinal cord damage in surgery of the abdominal aorta. *Surgery* **83**:38-56, 1978.

Taheri, S.A., Gawronski, S. and Smith, D. Paramedian retroperitoneal approach to the abdominal aorta. *J Cardiovasc Surg* **24**:529-531, 1983.

Tarazi, R.Y., Hertzer, N.R., Beven, E.G., *et al.* Simultaneous aortic reconstruction and renal revascularisation: risk factors and late results in eighty-nine patients. *J Vasc Surg* **5**:707-714, 1987.

Taylor, L.M.Jr. and Porter, J.M. Abdominal aortic aneurysms. *Ann Vasc Surg* **1**:502-504, 1987.

Tchirkow, G. and Beven, E.G. Leg ischemia following surgery for abdominal aortic aneurysm. *Annals of Surgery* **188**:166-170, 1978.

Tennant, W.G., Hartnell, G.G., Baird, R.N. and Horrocks, M. Radiologic investigation of abdominal aortic aneurysm disease: comparison of three modalities in staging and the detection of inflammatory change. *J Vasc Surg* **17**:703-709, 1993.

The UK Small Aneurysm Trial Participants. The U.K. small aneurysm trial: design, methods, and progress. *Eur J Vasc Endovasc Surg* **9**:42-48, 1995.

Thomas, P.R. and Stewart, R.D. Abdominal aortic aneurysm. *Br J Surg* **75**:733-736, 1988.

Thompson, J.E., Hollier, L.H., Patman, R.D. and Persson, A.V. Surgical management of abdominal aortic aneurysms: factors influencing mortality and morbidity--a 20-year experience. *Annals of Surgery* **181**:654-661, 1975.

Thompson, M.M., Sayers, R.D., Nasim, A. and Bell, P.R.F. Endovascular aortic aneurysm repair. *Current Practice in Surgery* **7**:21-27, 1995.

Tilson, M. Atherosclerosis and aneurysm disease. *J Vasc Surg* **12**:371-372, 1990.

Tilson, M.D. and Dang, C. Generalized arteriomegaly. A possible predisposition to the formation of abdominal aortic aneurysms. *Archives of Surgery* **116**:1030-1032, 1981.

Tilson, M.D. and Seashore, M.R. Human genetics of the abdominal aortic aneurysm. *Surgery,Gynecology & Obstetrics* **158**:129-132, 1984a.

Tilson, M.D. and Seashore, M.R. Fifty families with abdominal aortic aneurysms in two or more first-order relatives. *American Journal of Surgery* **147**:551-553, 1984b.

Tilson, M.D. Editorial comment: Aortic aneurysms and atherosclerosis. *Circulation* **85**:205-211, 1992.

Todd, G., Nowygrod, R., Benvenisty, A., Buda, J. and Reemtsma, K. The accuracy of CT scanning in the diagnosis of abdominal and thoracoabdominal aortic aneurysms. *J Vasc Surg* **13**:302-310, 1991.

Torsello, G., Sandmann, W., Gehrt, A. and Jungblut, R.M. In-situ replacement of infected vascular prostheses with rifampicin soaked vascular grafts: early results. *J Vasc Surg* **17**:768-773, 1993.

Treiman, G.S., Weaver, F.A., Cossman, D.V., *et al.* Anastomotic false aneurysms of the abdominal aorta and the iliac arteries. *J Vasc Surg* **8**:268-273, 1988.

Treiman, R.L., Levine, K.A., Cohen, J.L., Cossman, D.V., Foran, R.F. and Levin, P.M. Aneurysmectomy in the octogenarian. A study of morbidity and quality of survival. *American Journal of Surgery* **144**:194-197, 1982.

Trout, H.H., Kozloff, L. and Giordano, J.M. Priority of revascularisation in patients with graft enteric fistulas, infected arteries, or infected arterial prostheses. *Ann Surg* **199**:669-683, 1984.

Turnispeed, W.D., Acher, C.W., Detmer, D.E., *et al.* Digital subtraction angiography and B-mode ultrasonography for abdominal and peripheral aneurysms. *Surgery* **92**:619-626, 1982.

Valeri, E.D., Feingold, H., Cassidy, G., *et al.* Hypothermia-induced reversible platelet dysfunction. *Ann Surg* **205**:175-181, 1987.

van Laarhoven, C., Borstlap, A., van Berge Henegouwen, D., Palmen, F., Verpalen, M. and Schoemaker, M. Chronic obstructive pulmonary disease and abdominal aortic aneurysms. *Eur J Vasc Surg* **7**:386-390, 1993.

van Ramshorst, B., van der Griend, R. and Eikelboom, B.C. Survival and life quality after surgery for ruptured abdominal aortic aneurysm. In: *The Cause and Management of Aneurysms*, edited by Greenhalgh, R.M. and Mannick, J.A. London: W.B. Saunders, 1990, p. 433-440.

Veith, F.J. Transluminally placed endovascular stented grafts and their impact on vascular surgery. *J Vasc Surg* **20**:855-860, 1994.

Vine, N. and Powell, J. Metalloproteinases in degenerative aortic disease. *Clin Science* **81**:233-239, 1991.

Vollmar, J., Paes, E., Pauschinger, P., Henze, E. and Friesch, A. Aortic aneurysms as late sequelae of above-knee amputation. *Lancet* **ii**:834-835, 1989.

Voorhees, A., Jaretzki, A. and Blakemore, A.H. The use of tubes constructed from ninyon "N" cloth in bridging arterial defects. *Am Surg* **135**:332-330, 1952.

Vowden, P., Wilkinson, D., Ausobsky, J.R. and Kester, R.C. A comparison of three imaging techniques in the assessment of an abdominal aortic aneurysm. *J Cardiovasc.Surg* **30**:891-896, 1989.

Walker, D.I., Bloor, K., Williams, G. and Gillie, I. Inflammatory aneurysms of the abdominal aorta. *Br J Surg* **59**:609-614, 1972.

Walker, E.M., Hopkinson, B.R. and Makin, G.S. Unoperated abdominal aortic aneurysm: presentation and natural history. *Annals of the Royal College of Surgeons of England* **65**:311-313, 1983.

Walker, W.E., Cooley, D.A., Duncan, J.M., Hallman, G.J., Ott, D.A. and Reul, G.J. The management of aortoduodenal fistula by in situ replacement of the infected abdominal aortic graft. *Ann Surg* **205**:727-732, 1987.

Ward, A., McBurney, A. and Lunec, J. Evidence for involvement of oxygen-derived free radicals in ischaemia-reperfusion injury. *Free Rad Res* **20**:21-28, 1994.

Ward, A.S. Aortic aneurysmal disease: a generalised dilating diathesis? *Arch Surg* **127**:990-991, 1992.

Webb, L.X., Myers, R.T., Cordell, R., *et al.* Inhibition of bacterial adhesion by antibacterial surface pretreatment of vascular prostheses. *J Vasc Surg* **4**:16-21, 1986.

Webster, M. The inheritance and screening program in aortic aneurysm. In: *Aneurysms: New Findings and Treatments*, edited by Yao, J. and Pearce, W. Norwalk: Appleton and Lange, 1994, p. 63-70.

Webster, M.W., Ferrell, R.E., St.Jean, P.L., Majumder, P.P., Fogel, S.R. and Steed, D.L. Ultrasound screening of first-degree relatives of patients with an abdominal aortic aneurysm. *J Vasc Surg* **13**:9-13; discuss, 1991a.

Webster, M.W., St.Jean, P.L., Steed, D.L., Ferrell, R.E. and Majumder, P.P. Abdominal aortic aneurysm: results of a family study. *J Vasc Surg* **13**:366-372, 1991b.

Weinbaum, F.I., Dubner, S., Turner, J.W. and Pardes, J.G. The accuracy of computed tomography in the diagnosis of retroperitoneal blood in the presence of abdominal aortic aneurysm. *J Vasc Surg* **6**:11-16, 1987.

Weinstein, M.H. and Machleder, H.I. Sexual function after aortoiliac surgery. *Ann Surg* **181**:787, 1975.

Weissler, J.C. Pulmonary emphysema: current concepts in pathogenesis. Southwest Internal Medicine conference. *Am J Med Sci* **293**:125-138, 1987.

Welbourn, C.R.B., Goldma, G., Paterson, I.S., Valeri, C.R., Shepro, D. and Hechtman, H.B. Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil. *Br J Surg* **78**:651-655, 1991a.

Welbourn, R., Goldman, G., O'Riordain, M., *et al.* Role of tumour necrosis factor as mediator of lung injury following lower torso ischaemia. *J Appl Physiol* **70**:2645-2649, 1991b.

Welgus, H., Campbell, E., Cury, J., *et al.* Neutral metalloproteinases produced by human mononuclear phagocytes: enzyme profile, regulation, and expression during cellular development. *J Clin Invest* **86**:1496-1502, 1990.

Welling, R.E., Roedersheimer, L.R., Arbaugh, J.J. and Cranley, J.J. Ischemic colitis following repair of ruptured abdominal aortic aneurysm. *Archives of Surgery* **120**:1368-1370, 1985.

Wheat, M.W,Jr. Acute dissecting aneurysms of the aorta: diagnosis and treatment. *Am Heart J* **99**:373-387, 1988.

Whitbread, T., Birch, P., Majeed, A., Rochester, J., Beard, J.D. and Gaines, P. A new model for abdominal aortic aneurysms: initial results using a multiple-wire stent. *Eur J Vasc Endovasc Surg* **11**:90-97, 1996.

Whitbread, T., Birch, T., Rogers, S., Beard, J.D. and Gaines, P.A. The effect of placing an aortic wallstent across the renal artery origins in an animal model. *Eur J Vasc Endovasc Surg* **13**:154-158, 1997.

White, G.H., May, J., McGahan, T., *et al.* Historic control comparison of outcome for matched groups of patients undergoing endoluminal versus open repair of abdominal aortic aneurysms. *J Vasc Surg* **223**:201-212, 1996.

White, J.V., Haas, K., Phillips, S. and Comerota, A.J. Adventitial elastilysis is a primary event in aneurysm formation. *J Vasc Surg* **17**:371-381, 1993.

Whittemore, A.D., Clowes, A.W., Hechtman, H.B. and Mannick, J.A. Aortic aneurysm repair: reduced operative mortality associated with maintenance of optimal cardiac performance. *Annals of Surgery* **192**:414-421, 1980.

Wilberger, J.E.,Jr. Lumbosacral radiculopathy secondary to abdominal aortic aneurysms. Report of three cases. *Journal of Neurosurgery* **58**:965-967, 1983.

Williams, G.M., Ricotta, J., Zinner, M. and Burdick, J. The extended retroperitoneal approach for treatment of extensive atherosclerosis of the aorta and renal vessels. *Surgery* **88**:846-855, 1980.

Windsor, A.C.J., Mullen, P.G., Fowler, A.A. and Sugerman, H.J. Role of neutrophil in adult respiratory distress syndrome. *Br J Surg* **80**:10-17, 1993.

Woessner, J. Matrix metalloproteinases and their inhibitors in connective tissue remodelling. *FASEB J* **5**:2145-2154, 1991.

Wolinsky, H. and Glagov, S. A lamellar unit of aortic medial structure and function in mammals. *Circ Res* **20**:99-111, 1967a.

Wolinsky, H. and Glagov, S. Nature of species differences in the medial distribution of aortic vasa vasorum in mammals. *Circ Res* **20**:409-421, 1967b.

Wright, I.S., Urdaneta, E. and Wright, B. Re-opening the case of the abdominal aortic aneurysm. *Circulation* **13**:754-759, 1956.

Wright, K.C., Wallace, S., Charnsanggaveg, C., Carrasco, C.H. and Gianturco, C. Percutaneous endovascular stents: an experimental evaluation. *Radiology* **156**:69-72, 1985.

Wright, R.R. Elastic tissue of normal and emphysematous lungs. A three-dimensional histologic study. *Am J Pathol.* **39**:355-363, 1961.

Yeager, R.A., McConnell, D.B., Sasaki, T.M. and Vetto, R.M. Aortic and peripheral prosthetic graft infection: differential management and causes of mortality. *American Journal of Surgery* **150**:36-43, 1985.

Young, J.R., Hertzer, N.R., Beven, E.G., *et al.* Coronary artery disease in patients with aortic aneurysm: a classification of 302 coronary angiograms and results of surgical management. *Annals of Vascular Surgery* **1**:36-42, 1986.

Yusuf, S.W., Baker, D.M., Chuter, T.A., Whitaker, S.C., Wenham, P.W. and Hopkinson, B.R. Transfemoral endoluminal repair of abdominal aortic aneurysm with bifurcated graft. *Lancet* **344**:650-651, 1994.

Yusuf, S.W., Baker, D.M., Hind, R.E., *et al.* Endoluminal transfemoral abdominal aortic aneurysm repair with aorto-uni-iliac graft and femorofemoral bypass. *Br J Surg* **82**:916, 1995.

Zarins, C., Glagov, S., Vesselinovitch, D. and Wissler, R. Aneurysm formation in experimental atherosclerosis: relationship to plaque evolution. *J Vasc Surg* **12**:246-256, 1990.