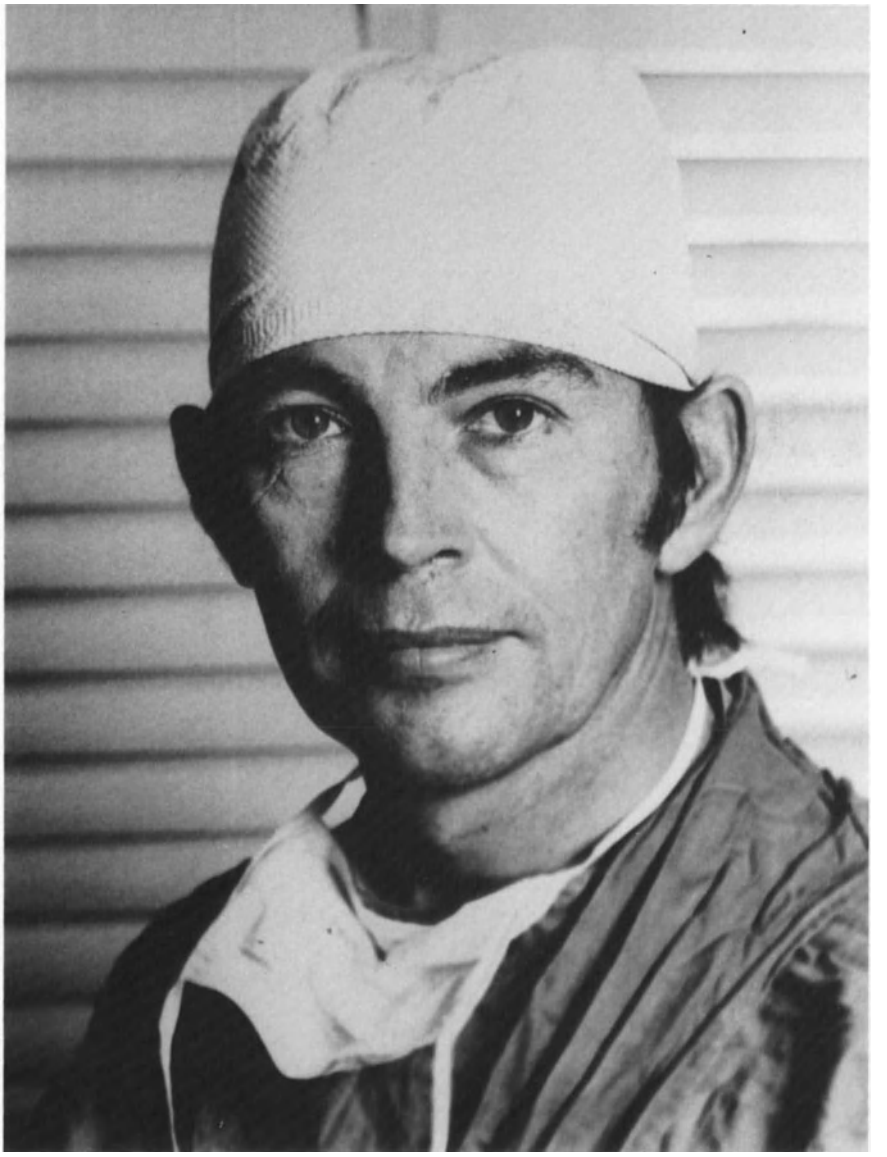
HEART TRANSPLANTATION



PROFESSOR CHRISTIAAN N. BARNARD, who was appointed to the specialist surgical staff of Groote Schuur Hospital and the University of Cape Town Medical School in 1958, became Head of the Department of Cardiac Surgery in 1961, Associate Professor of Surgery in 1962, and Professor of Surgical Science in 1972; he retired from these appointments at the end of 1983. To mark his retirement, the editors and authors offer this book as a tribute to his contributions to cardiac surgery and, in particular, to his pioneering work in the field of heart transplantation.

Photo: Don MacKenzie, Cape Town

HEART TRANSPLANTATION

THE PRESENT STATUS OF ORTHOTOPIC AND HETEROTOPIC HEART TRANSPLANTATION

EDITED BY

D. K. C. COOPER, MA, MB, BS, PhD, FRCS
Specialist in Cardiothoracic Surgery,
Groote Schuur Hospital and the
University of Cape Town Medical School, Cape Town, South Africa

and

R. P. LANZA, MD
Chris Barnard Fund Research Fellow,
Cardiac Surgical Research Unit,
Department of Cardiothoracic Surgery,
University of Cape Town Medical School, Cape Town, South Africa

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Contents

Foreword

It is a great pleasure for me to contribute a brief introduction to this volume, to which so many of my colleagues at Groote Schuur Hospital and the University of Cape Town Medical School have contributed.

Though considerable advances have been made in preventing or treating the complications of heart transplantation, even today a transplant programme remains a major undertaking for a hospital team. The acquisition of a sufficient number of donor hearts, the maintenance of viability of those hearts, and the prevention, diagnosis and treatment of acute and chronic rejection and infection remain major challenges to those caring for patients undergoing this operation. A transplant programme draws into it medical, surgical, nursing and paramedical staff from all quarters of the hospital and medical school, and requires sustained interest and dedication if patients are to be brought successfully through the procedure. If relevant experimental research is also to be carried out at such a centre, which in my opinion is essential, then an even greater number of highly skilled and creative people is required.

A few of the authors of this book have been involved with the Groote Schuur heart transplant programme since its inception in December 1967 with the operation on Louis Washkansky. I am sure that none of them (nor I) had any idea of the public interest this operation would attract. The other authors joined us subsequently and have made their own particular contributions to our work in both the clinical and experimental aspects of transplantation.

Over the years, very many others have, of course, been involved in this work in Cape Town. I remember, in particular, the great help I received from my brother, Marius, from immunologist Dr M. C. Botha, and from surgeons 'Bossie' Bosman, Rodney Hewitson, Jacques Losman, Alan Wolpowitz and Jannie Hassoulas. Our early explorations into the problems of heart transplantation were greatly encouraged and facilitated by that outstanding cardiologist, the late Professor Val Schrire, to whom I personally owe a debt of gratitude for his support throughout my early career at Groote Schuur.

The number of transplants performed at our own centre coud have been easily two or three times as large had we been able to acquire sufficient suitable donor hearts. This remains a major limiting factor, suggesting that, in South

Africa at least, the public and the medical profession have not yet fully accepted the donation of organs as a routine which should be considered in every brain-dead patient. A sustained effort in the education of the public will be required to correct the situation, not only in South Africa, but worldwide.

The contributors to this book and, in particular, the editors, David Cooper and Robert Lanza, are to be congratulated in bringing together such a wealth of information on this topic and presenting it in such a balanced and readable way. I believe this book will be essential reading for those considering initiating a heart transplant programme and, indeed, for any interested in progress in this field.

As this is the first year of my retirement from the staff of Groote Schuur Hospital and the University of Cape Town I can take this opportunity of wishing those who continue to work in the field of heart transplantation, not only in Cape Town, but worldwide, every success in their labours.

CHRISTIAAN N. BARNARD

April 1984

Preface

When Professor Christiaan Barnard and his surgical team performed the first human-to-human heart transplant at Groote Schuur Hospital in Cape Town on 2 December 1967, the event not only captured the public interest and imagination but also stimulated many other surgical centres to enter this demanding field of therapy. Interest soon died, however, since some of these groups were ill-prepared to deal with the many major complications of the procedure, and the results were poor.

A very small number of centres, including our own, persisted in their efforts to overcome the problems they faced. Recognition must be given, in particular, to the immense contribution made by the group at Stanford Medical Center, and to the groups at the Medical College of Virginia and La Pitié Hospital in Paris, who continued exploring this area of therapy whilst the enthusiasm of others waned. Now, some 16 years later, the number of centres actively engaged in this field has increased over fivefold, and heart transplantation has progressed from being a clinical research programme to a definitive form of surgical therapy.

It therefore seemed timely to review the present status of heart transplantation. In writing this book, though we have drawn greatly from our own experience at Groote Schuur Hospital and the University of Cape Town, we have endeavoured to review the experience of all of the major groups who have contributed to our knowledge in this area. Though we do not claim that our review has been totally comprehensive, we hope and believe that it provides an informative and balanced account of this form of therapy at the present time.

Professor Barnard retired from the staff of our hospital and medical school at the beginning of this year; this book marks the occasion of his retirement and is offered as a tribute to his pioneering work in the field of heart transplantation.

D. K. C. Cooper
R. P. Lanza
Department of Cardiothoracic Surgery
Groote Schuur Hospital and the
University of Cape Town Medical School

April 1984

List of Contributors

(All members of the staff of Groote Schuur Hospital and/or the University of Cape Town Medical School)

C. N. Barnard, MD, MMed, MS, PhD, FACS, FACC, DSc (Hon Causa)
Formerly Professor of Surgical Science and Head
Department of Cardiac Surgery

E. D. Bateman, MB, ChB, DCH, MRCP
Senior Specialist
Respiratory Clinic
Department of Medicine

P. J. Commerford, MB, ChB, FCP(SA), FACC
Senior Specialist
Cardiac Clinic
Department of Medicine

D. K. C. Cooper, MA, MB, BS, PhD, FRCS
Specialist
Department of Cardiothoracic Surgery

J. C. de Villiers, MD, FRCS(Eng), FRCS(Edin)
Helen and Morris Mauerberger Professor and Head
Department of Neurosurgery

E. D. du Toit, MD
Head
Laboratory for Tissue Immunology
Cape Provincial Administration

A. A. Forder, MB, ChB, MMed(Path)
Wernher and Beit Professor and Head
Department of Medical Microbiology

A. R. Horak, MB, ChB, FCP(SA)
Specialist
Cardiac Clinic
Department of Medicine

R. P. Lanza, MD
Chris Barnard Fund Research Fellow
Cardiac Surgical Research Unit
Department of Cardiothoracic Surgery

E. S. Nash, MB, ChB, FRCP, DPM, FFPsych(SA)
Senior Specialist
Department of Psychiatry

D. Novitzky, MD, FCS(SA)
Specialist
Department of Cardiothoracic Surgery

J. Ozinsky, MB, ChB, DA, FFARCS
Chief Specialist
Department of Anaesthetics

A. G. Rose, MB, ChB, MMed(Path), MRCPath, FACC
Associate Professor
Department of Pathology

L. S. Smith, MB, BCh, DPH, DBact, FRCPath
Professor and Head
Department of Forensic Medicine and Toxicology

C. J. Uys, MD, DClin Path, FRCPath
Wernher and Beit Professor and Head
Department of Pathology

J. van Heerden
Chief Technologist
Department of Cardiothoracic Surgery

W. N. Wicomb, PhD
Chris Barnard Fund Research Fellow
Cardiac Surgical Research Unit
Department of Cardiothoracic Surgery

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We wish to express our appreciation to the contributing authors, who have expertly presented their information in a clear and concise manner. Our surgical colleague, Dimitri Novitzky, reviewed several of the chapters and gave us the benefit of his expertise and experience; his comments proved most helpful. Other colleagues—Jack Jacobson, Machteld Oudshoorn, Gwen Sayers and John Stevens—also read and commented on several chapters at various stages of their preparation. We thank all of them.

Mrs Desirée Fray proved untiring in producing a carefully typed manuscript and is deserving of our sincere gratitude; her contribution greatly facilitated the preparation of this book. Her secretarial colleagues, Mrs Doreen Lambie and Mrs Doris Walker, gave her valuable support.

The excellent illustrations are the work of Miss Jenny Bosman, medical artist in the Department of Clinical Photography at Groote Schuur Hospital. We are most grateful to her and to her departmental colleagues for the photographic work which appears in the book.

We gratefully acknowledge permission to reproduce tables and illustrations previously published in the following journals: Figure 5.1 from *Transplantation*, **34**, 247, 1982; Figure 5.2 from *S. Afr. Med. J.*, **60**, 246, 1981; Figure 6.1 from *Heart Transplant.*, **3**, 89, 1983; Figures 6.2 and 6.3 op. cit. p. 90; Figures 8.10 and 8.11 from *Ann. Thoracic Surg.*, **36**, 477, 1983; Figures 8.12 and 8.13 op. cit. p. 478; Figure 8.20 op. cit. p. 481; Figure 8.22 from *Br. J. Clin. Pract.*, **36**, 340, 1982; Figure 11.15 from *Arch. Path. Lab. Med.*, **107**, 368, 1983; Figure 17.3 from *Heart Transplant.*, **3**, 258, 1984; Figures 19.7 and 19.8 from *Heart Transplant.*, **3**, 88, 1983; Figure 20.1 from *Ann. Thoracic Surg.*, **37**, 246, 1984; Figure 20.2 from *Br. J. Clin. Pract.*, **36**, 331, 1982; Table 13.2 from *Thorax*, **38**, 823, 1983; Table 13.3 op. cit. p. 825; Table 14.2 from *J. Am. Med. Assoc.*, **249**, 1747, 1983; Tables 19.2 and 19.3 from *Heart Transplant.*, **3**, 89, 1983; Table 19.4 from *Heart Transplant.*, **3**, 249, 1984.

One of us (R.P.L.) is indebted to Dr Eliot Stellar and the University Scholars' Program of the University of Pennsylvania, and to Scott Randall, and Barbara and Eugene O'Donnell for their valuable support.

Since the inception of the heart transplant programme in 1967 many members of the medical, nursing and paramedical staff of Groote Schuur

Hospital and the University of Cape Town Medical School have contributed towards the care of our patients and to our research activities; to all of them we give our thanks. We also take this opportunity of expressing our gratitude to the generous and continuing support given to our research programmes by the Cape Provincial Administration, the University of Cape Town, and the Chris Barnard Fund.

Finally, we wish to record our gratitude to Dr H-Reeve Sanders, the present Chief Medical Superintendent of Groote Schuur Hospital, for the support and encouragement she has given to both the clinical and experimental work on heart transplantation in our department.

D. K. C. COOPER
R. P. LANZA
Groote Schuur Hospital and the
University of Cape Town Medical School

April 1984

1
Experimental Development and Early Clinical Experience

INTRODUCTION

Clinical heart transplantation was made possible by the considerable experimental work carried out earlier this century which embraced mainly the technical, physiological and immunological aspects of the procedure. This chapter endeavours to review briefly the evolution and results of experimental surgical techniques utilized by cardiac transplant research workers; a comprehensive review appears elsewhere[1].

Experimental work on cardiac transplantation evolved through several overlapping phases. In the earliest experiments animals were given a second, often parasitic, heart which enabled certain physiological, pharmacological and pathological studies to be made. Initially the neck was chosen as the locus, though the abdomen and inguinal regions were occasionally used. The subsequent evolution of surgical techniques permitted the insertion of the donor heart into the chest as an auxiliary pump in circuit with the recipient organ. With the advent of hypothermia and the pump oxygenator, total excision and replacement of the recipient heart became more feasible. Finally, after technical and physiological problems had been studied and minimized, efforts were made to combat the immune response with immunosuppressive agents.

TRANSPLANTATION OF AN ACCESSORY HEART

The first reported attempts at experimental heart transplantation were by Carrel and Guthrie in 1905[2,3]. The principal technique they used is inadequately described as 'anastomosing the cut ends of the jugular vein and the carotid artery to the aorta, the pulmonary artery, one of the vena cava and a pulmonary vein'. This procedure took approximately 75 minutes. Although

contractions of the donor atria appeared immediately after the operation, effective contractions of the ventricles did not begin for approximately 1 hour. The operation was performed without aseptic technique; the experiment was interrupted after a further 2 hours when coagulation occurred in the cavities of the heart. Carrel also attempted transplantation of the heart and both lungs into the neck of a cat, but the lungs became oedematous with subsequent distension of the right chambers of the heart[3].

The crucial factor of donor coronary perfusion (viviperfusion) was simplified in 1933 when Mann and his colleagues developed a technique of cervical transplantation[4] (Figure 1.1). The donor coronary system was perfused by anastomosing the recipient common carotid artery to the donor aorta. Coronary sinus blood returned to the recipient jugular vein via the right atrium, right ventricle and pulmonary artery. Immediately after the coronary circulation was established the heart usually began to contract at a heart rate of approximately 100–130 beats per minute. This rate increased further if the animal

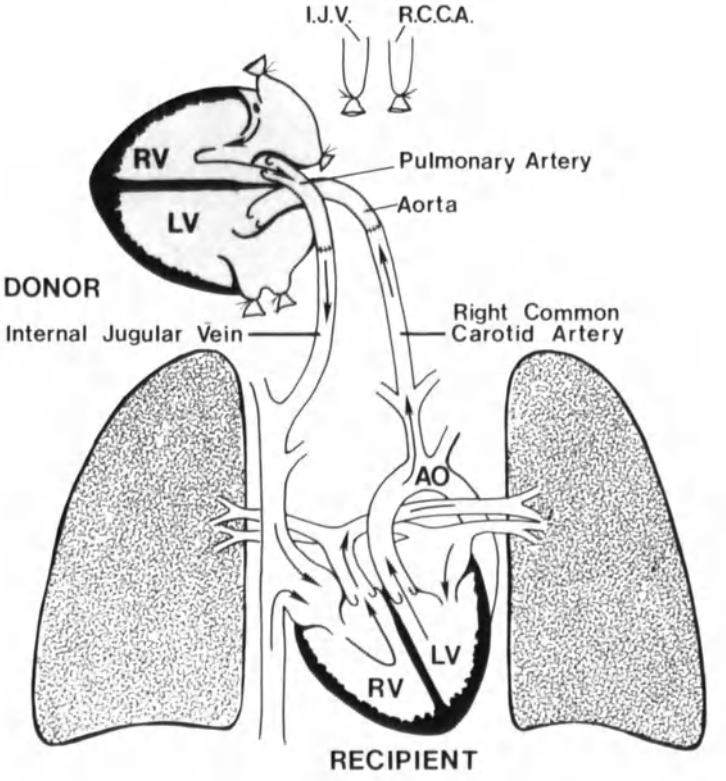

Figure 1.1 Technique of experimental heterotopic heart transplantation in the neck (Mann *et al.*, 1933)[4]. I.J.V. = Internal jugular vein; R.C.C.A. = Right common carotid artery

Figure 1.1 Technique of experimental heterotopic heart transplantation in the neck (Mann *et al.*, 1933)[4]. I.J.V. = Internal jugular vein; R.C.C.A. = Right common carotid artery

Electrocardiographic (ECG) tracings were 'surprisingly normal'. Numerous investigators have subsequently used modifications of the Mann technique to study problems of heart transplantation and the response of the denervated heart to pharmacological agents and physiological stresses[1]. One such modification remains a standard model in many laboratories, including our own, for experimental animal studies on acute rejection and immunosuppression (Figure 1.2).

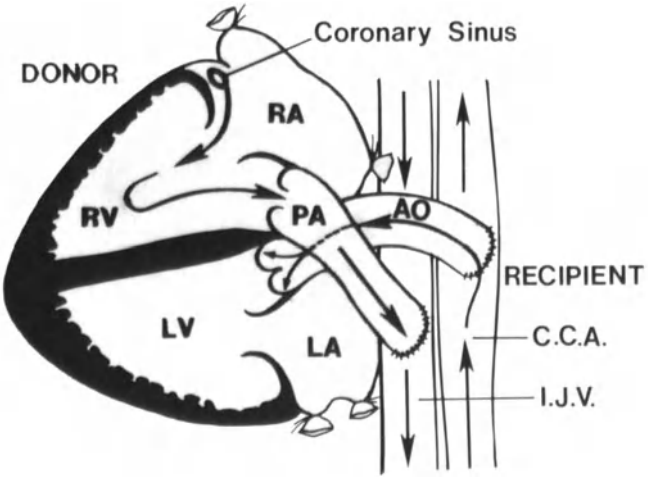

Figure 1.2 Modification of the Mann experimental cervical heterotopic heart transplantation technique as used in our own laboratory

Mann and his colleagues reported irregularities in the pulse rate of the transplanted heart after an average of 4 days; these were soon followed by fibrillation or absence of pulsation. When the heart was excised just prior to becoming quiescent, the left atrium was found to be filled with clot, both the right atrium and ventricle were distended, the surface of the heart was mottled, and the myocardium friable on section. Histologically, the heart was completely infiltrated with lymphocytes, large mononuclear cells, and polymorphonuclear leukocytes. From these results the investigators concluded that a functioning cardiac allograft was no less 'resistant' than a renal allograft, the graft failing to survive due to the same 'biologic factor' which also prevented survival of other homotransplanted tissues and organs.

With regard to short experiments performed within 24 hours of transplantation, the same research team had no hesitation, however, in concluding that the transplanted heart should be a valuable test object for the investigation of various physiological problems. For example, they investigated the effect of the intravenous administration of thyroxine to the host animal. Although the pulse rate of the transplanted organ increased significantly

within 18 hours, the rate of the host's heart remained unchanged. This experiment demonstrated that thyroxine-induced tachycardia was independent of the central nervous system (CNS), and that the denervated heart was more sensitive to the accelerating influence of the drug since CNS influence was inhibitory.

In more recent years, techniques for transplanting the auxiliary donor heart into the abdomen of the recipient have been described (Figure 1.3). Anastomoses are made between the recipient abdominal aorta and the donor ascending aorta to allow perfusion of the myocardium through the coronary arteries.

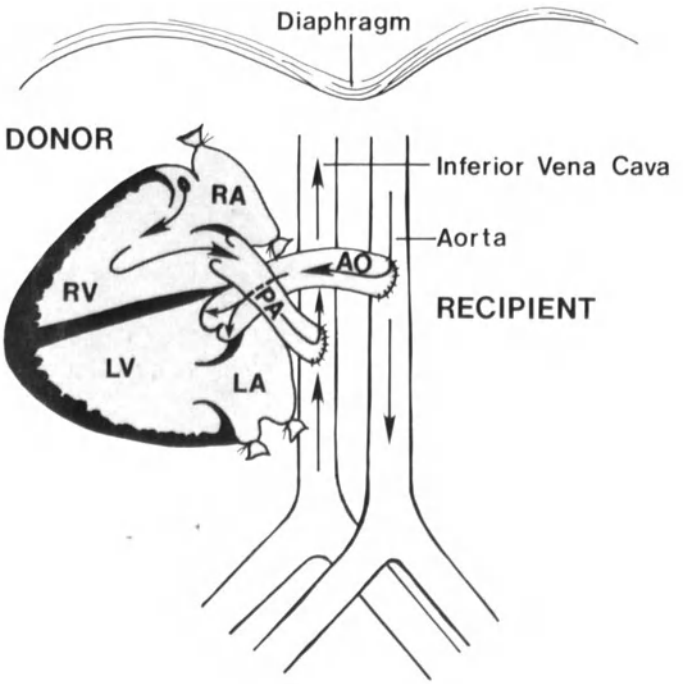

Figure 1.3 Technique of experimental heterotopic heart transplantation in the abdomen (Abbott *et al.*, 1964)

Coronary venous return drains through the right heart and pulmonary artery to the recipient inferior vena cava. This technique has also been used principally for the study of the immune response and its modification by therapeutic agents, particularly using microsurgical techniques in rats[5,6] where it remains an important model.

THE TRANSPLANTED HEART AS AN AUXILIARY INTRATHORACIC PUMP

In 1946, Demikhov began extensive studies on transplantation of the heart into the thorax. These involved the addition of a second heart (occasionally with an attached lobe of a lung) as an auxiliary pump, as well as orthotopic transplantation of the heart with and without both lungs[7]. The ambitious nature of Demikhov's attempts can be appreciated best when it is remembered that supportive techniques, such as hypothermia and cardiopulmonary bypass, had not yet been developed.

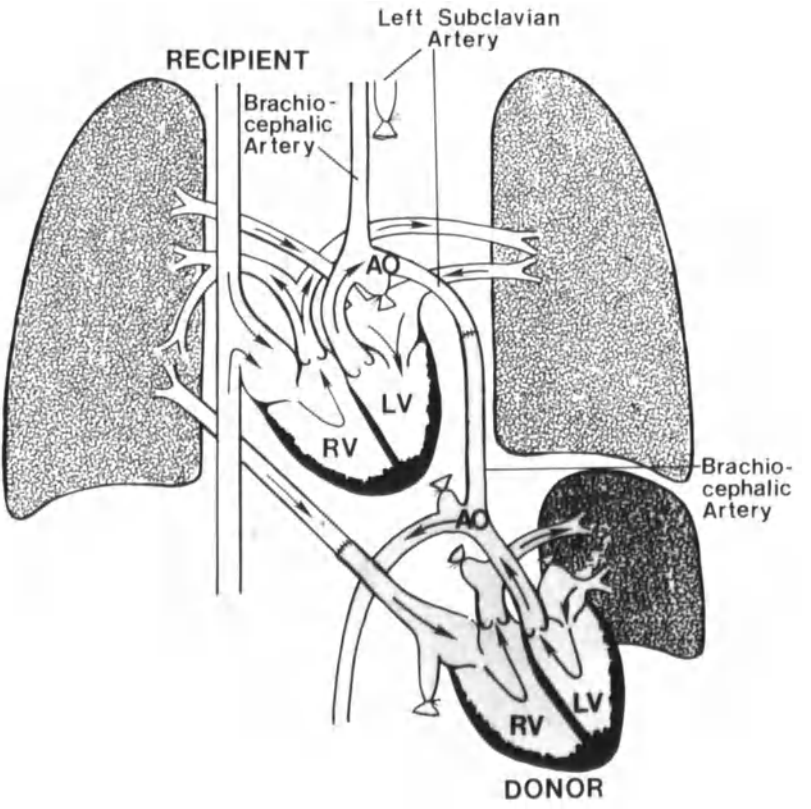

Figure 1.4 Technique of insertion of the heterotopic heart in the chest as an auxiliary pump (Demikhov, 1962)[7]

In all, Demikhov described 24 variants of his technique to place an additional heart within the thorax. He performed 250 operations on dogs utilizing most of the major vessels within the chest cavity; 43 animals died on the operating table, 87 during the first 2 days, 110 between the 2nd and 19th day, and one on day 32. Most of the early deaths were associated with

technical problems. The best results with regard to functional activity of the transplanted heart and preservation of its structure were obtained after operations using the technique illustrated in Figure 1.4.

Physiologically the transplanted heart was distinguished by the comparative constancy of its rhythm and by its greater resistance to the action of toxic doses of various cardiac glycosides. Marked bradycardia of the dog's own heart occurred after injection of large doses of strophanthin, although no changes took place in the rhythm of the transplanted heart. When lethal doses of cardiac glycosides were administered, the transplanted heart continued to function for 10–15 minutes after the animal's own heart had arrested. It was also observed that when a dog died from haemorrhage or peritonitis the coordinated activity of the animal's own heart ceased long before that of the transplanted heart. The physiological and pharmacological responses of the denervated, transplanted heart are discussed more fully in Chapter 10.

Several years later, Reemtsma[8] described a method of inserting an additional intrathoracic heart as an auxiliary pump, which was similar in principle to that later developed and used clinically in our own heterotopic heart transplant programme in Cape Town[9,10]. The donor inferior vena cava was anastomosed to the recipient's right atrial appendage, followed by anastomosis of the two left atrial appendages, and end-to-side anastomoses of the two pulmonary arteries and aorta. Function as an auxiliary pump was maintained for a maximum period of 72 hours.

Sen and his colleagues described a further technique in which the transplanted heart supported only the systemic circulation of the recipient[11]. This auxiliary heart functioned in one animal for 48 hours, when it was surgically excised and the animal supported solely by its own heart once again, thus demonstrating the heterotopic heart transplant as a temporary left ventricular assist device.

ORTHOTOPIC TRANSPLANTATION OF THE HEART

Between 1946 and 1955, Demikhov used an ingenious method in 67 attempts to transplant the heart and both lungs in dogs, with survival up to the 6th day[7] (Chapter 21). Deaths resulted primarily from thrombosis at the sites of blood vessel anastomosis, or from bronchopneumonia in the lower lobes.

On 25 December 1951—a date which surely tells us a great deal about this surgeon—Demikhov made the first recorded attempt to replace the heart alone. Without the availability of hypothermia or pump oxygenator support the technique was necessarily complicated. The procedure consisted of end-to-side anastomoses between the corresponding thoracic aortae, superior and inferior venae cavae, and pulmonary arteries. The two inferior pulmonary veins of the donor were joined together and connected to the recipient's left atrial appendage. After these anastomoses, the ascending parts of the recipient's

thoracic aorta and pulmonary artery were ligated, and the recipient's left atrium was indrawn at its border with the ventricle by means of a purse-string suture. The entire segment of the recipient's heart thus excluded from the circulation was then excised.

Demikhov performed this procedure on 22 occasions, and in 1955 was successful in obtaining good cardiac function in two cases for periods of $11\frac{1}{2}$ and $15\frac{1}{2}$ hours respectively. In the former case, death was due to thrombosis at the superior vena caval anastomosis, whereas in all other cases death resulted from technical problems. These were amongst the first reported experiments, however, where animals survived for a few hours solely on the activity of the transplanted heart.

ADVENT OF SUPPORTIVE TECHNIQUES

With the advent of methods of supporting the recipient during the operative procedure, workers in this field became more ambitious. Neptune and his colleagues used hypothermia in three attempts at transplantation of the heart and both lungs, with survival for up to 6 hours[12]. Webb and Howard performed cardiopulmonary replacement on an animal maintained on mechanical pump-oxygenator support, with survival to 22 hours[13,14]; they studied cardiac and unilateral pulmonary transplants, autotransplants of the heart and lungs and of the heart alone.

In 1958, Goldberg and Berman used a technique which differed from that of Webb in that a left atrial cuff was preserved in the recipient, thus nullifying the need to anastomose the pulmonary veins. They reported three experiments, with survival for only 21, 117 and 86 minutes; in two of these cases pacemakers had to be inserted to maintain an adequate heart rate[15,16].

Cass and Brock reported six attempts at autotransplantation and homotransplantation using a modification of Goldberg's technique, where both atria were left intact in the recipient, thus simplifying the procedure even further[17]. Anastomoses of the atria, aorta and pulmonary artery were now all that were required. This procedure was described again 1 year later at Stanford Medical School by Lower and Shumway, who obtained the first consistently successful results[18]. With a further modification made by Barnard[19], the technique is now used in the clinical operation of orthotopic heart transplantation and is described in detail in Chapter 8.

It was, therefore, not until 1960 that the major experimental advance was made, when Lower and Shumway reported that five out of eight consecutive dogs undergoing transplantation had lived for 6–21 days[18]. During convalescence the dogs ate and exercised normally, the pulse rate was variable and increased moderately with exercise, and only a few hours before death the ECG remained virtually normal, showing no evidence of arrhythmia or conduction defects. The terminal course was usually rapid, occurring within

approximately 24 hours, during which time the animal became lethargic and progressively tachypnoeic. Postmortem examination of the heart showed it to be ecchymotic and oedematous with a fibrinoid pericarditis and generalized dilatation. Microscopical examination of sections demonstrated severe myocarditis, with massive round-cell infiltration, patchy necrosis, interstitial haemorrhage, and oedema. The authors concluded that in all likelihood the graft would have continued to function for the normal life span of the animal if the immunologic mechanisms of the host had been suppressed.

In the following year, Lower *et al.* reported complete homograft replacement of the heart and both lungs, with survival of up to 5 days; deaths were from respiratory insufficiency, which was apparently secondary to infiltration of mononuclear cells into the lung parenchyma[20].

These investigators and their colleagues subsequently confined their studies to autotransplantation[21,22] and allotransplantation[23–25] of the heart alone, achieving long-term survival, and contributing extensively to our knowledge of this subject[26–28]. In the experimental animal the transplanted heart was found to have the capacity to increase cardiac output, primarily by increasing stroke volume, under a variety of physiological stresses, including hypoxia and exercise; a normal cardiac output was demonstrated 1 year after allotransplantation and $5\frac{1}{2}$ years after autotransplantation; evidence of autonomic reinnervation of the heart after autotransplantation was obtained.

In 1962, Willman and his colleagues produced the first of several papers on the subject of myocardial structure and function following autotransplantation of the heart[29]. Their technique differed from those of previous workers in being a piecemeal division and resuture in turn of each of the vessels connecting the heart to the rest of the body. Twenty-seven out of 40 animals died within 2 days, primarily from technical causes; 13 survived longer than 2 days. All survivors appeared critically ill during the first week, though a few long-term survivors were obtained. They concluded that there was a specific adverse effect of severing the heart from the body and suggested that this resulted from severance of the extrinsic innervation and/or the lymphatic drainage. The specific mechanism of adaptation by which long-term survival was achieved remained unclear. Shumway's group later disputed these pessimistic findings, having obtained autotransplants in dogs which survived for over 18 months[21]. The disparity between these results has never been explained. Willman and his associates subsequently used their technique to carry out extensive studies of the physiology[30–33], histology[34,35], metabolism[36–38], and pharmacology[39] of the autografted heart, including autotransplantation in the primate[40].

USE OF PROFOUND HYPOTHERMIA

Kondo and his colleagues performed orthotopic transplantation in puppies under profound hypothermia rather than with a pump oxygenator[41]. Total