A GIFT OF LIFE

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OBSERVATIONS ON ORGAN TRANSPLANTATION

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TO

SIR PETER MEDAWAR

WHO KINDLED MY INTEREST

IN TRANSPLANTATION

AND HAS CONTRIBUTED

SO MUCH TO THIS SUBJECT

PREFACE

In the past few years the transplantation of organs in man has received publicity unprecedented in medical history. The first heart grafts were covered by press, radio, and television on a scale equivalent to the news of the outbreak of a major war. Unwarranted and extravagant optimism has been followed by bitter criticism. This has undermined public confidence in the medical profession and seriously impeded progress in an important endeavour aimed at reducing human suffering. This unfortunate situation has arisen from widespread ignorance amongst the public and the medical profession of the background, present achievements, and future potential of organ grafting. Short statements by experts, frequently misquoted or cut short by television interviewers, and misinformed derogatory pronouncements by prejudiced medically qualified men, with no knowledge of the field, have produced a sorry state of confusion. It is the purpose of this book to attempt to clarify organ transplantation. The principles of organ transplantation are common to all organs but I will confine most of the discussion to transplantation of four vital organs, namely the kidney, liver, heart, and lung.

ROY CALNE

Cambridge
January 1970

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CHAPTER ONE

THE IDEA

The treatment of many progressive life-threatening diseases is surgical removal of the affected organ. An infected and inflamed appendix is removed, so is a cancerous stomach. The body can function normally without the appendix; removal of the stomach, however, can impair digestion, but this may not be a serious disability. Diseases of organs essential to life such as both kidneys, both lungs, the heart, or the liver, cannot be treated in this way since although the damaged organs can be removed, death will result unless the function is replaced. To cure disease by restoring the function of a diseased organ by a biological graft is an ancient concept. Fig. 1 (frontispiece) is a reproduction of a painting of the legend of SS. Cosmas and Damian. The saints removed the cancerous leg from a sleeping man and replaced it with a healthy leg removed from a man who had recently died. According to the legend the transplant was a complete success. There was no outcry against the saints for unethical conduct, in fact their achievement has been praised by succeeding generations and depicted in numerous medieval paintings throughout Europe. The idea of cadaveric organ transplantation is therefore well established. If the organs of a dead person can save the life and prevent suffering of another human being, this is surely a good thing. The objective of therapeutic clinical organ transplantation is to restore the function of a diseased vital organ and so return to a useful and happy life a man, woman, or child who would otherwise die. There are difficulties in the fulfilment of this gift of life. The surgery must be accurate and swift, the natural tendency of the body to reject the graft must be overcome and the community must be aware of the potential benefits that organ transplantation has to offer; for at present the only suitable donors of organ grafts are human beings. The relief of human suffering by organ transplantation depends on the generosity and charity of mankind.

The idea of organ transplantation remained a miraculous legend until the middle of the present century when Dr. Joseph Murray and his colleagues in Boston successfully transplanted a kidney from a healthy individual to his identical twin, who was dying from incurable kidney disease. Identical twins arise from the same egg cell, they are biologically the same person and are therefore unable to reject each others grafts. Successful surgery cures the sick twin, provided his kidney disease does not recur in the graft. The twin grafts confirmed predictions from animal experiments, that modern vascular surgery could achieve the transfer of a living organ from one man to another so that it would function normally and restore a dying man to health. I will be chiefly concerned in this book with living, functioning grafts of which a kidney transplant is an example. There are, however, other methods of providing the body with a function that it lacks.

MECHANICAL ORGAN SUBSTITUTES

The idea of manufacturing an artificial organ goes back to the legend of Daedalus and Icarus in Greek mythology (Fig. 2). They constructed prosthetic wings to escape imprisonment on an island. According to the tale, the prosthesis of Icarus came adrift at its junction with the body because the adhesive, beeswax, melted in the sun. One of the most well-known and useful prostheses is the artificial leg which, in its modern form, is functionally far superior to a leg graft, because of the poor nerve regeneration in a living

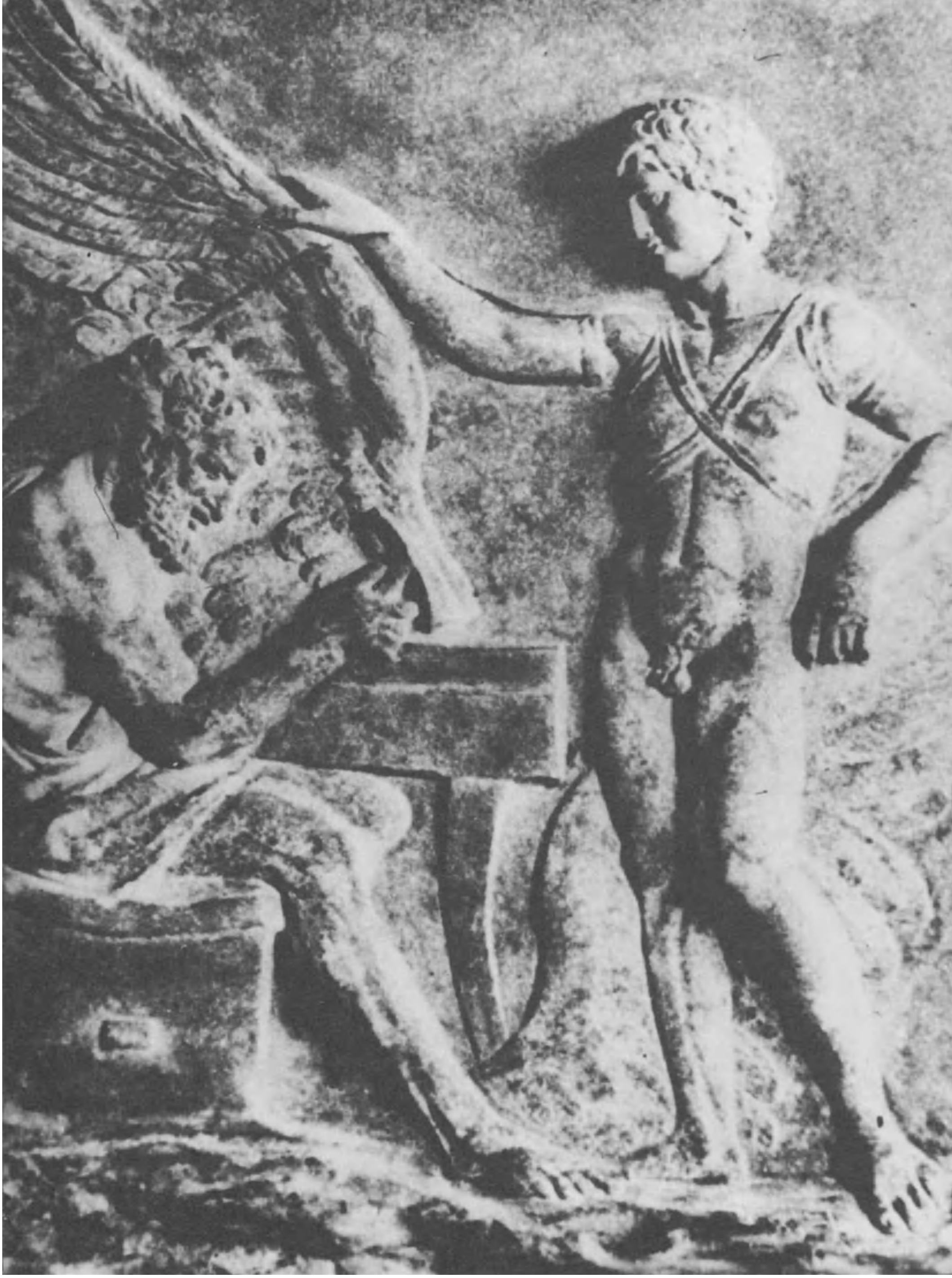

FIG. 2. Daedalus (*left*) being helped by his son Icarus in the construction of prosthetic wings. From a Roman frieze at the Villa Albani, Rome.

transplant.[1] Bone grafts provide a structural scaffold and are probably best considered as mechanical prostheses.

The cornea has rather simple functions, to protect the eye and transmit light. Corneal grafts usually fulfil these requirements, and certain inert synthetic materials may prove to be equally effective and preferable in unusual cases where grafts have failed. Countless eyes have been saved by corneal grafts, which have no blood supply and are therefore seldom rejected.

For maintenance of the circulation during and after complicated surgical procedures on the heart, the success of mechanical substitutes has been proved. Provided the mechanical heart does not have to function more than a few hours, before the patient's heart takes over, the results are excellent. The mechanical heart has pumping chambers, valves, and a supply of energy. Unfortunately no method has yet been devised of imitating the inbuilt rhythmic energy supply that is the cardinal property of normal heart muscle. Mechanical hearts are therefore cumbersome and this is the main limitation of their use as heart substitutes. Heart transplants, however, function exceedingly well provided rejection does not supervene and at present they are the only possible long-term heart substitute.

Substitutes of the lung have much in common with the heart. For short-term oxygenation of the blood, mechanical devices are excellent, but the machinery involved cannot be carried around by a patient.

Substitution of the kidney function is an interesting subject since both biological and mechanical replacements can be effective for prolonged periods. If two solutions are separated by a cellophane membrane the dissolved substances pass back and forth across the membrane until their concentrations are the same on each side. This process is called dialysis; the patient's blood containing waste products is on one side of the dialysing membrane and dialysing

1. See p. 11

fluid containing normal body salts is on the other. The membrane stops blood cells and protein from leaving the blood stream, but allows waste products to escape (Fig. 31). Regularly repeated haemodialysis will keep a patient in reasonable health. The disadvantages are that for fourteen hours two or three times a week the patient must be attached by his blood stream to a large, complicated, and potentially dangerous machine (Fig. 33). Moreover the points of attachment to an artery and vein of the patient have limited live sand when all have been used up dialysis is impossible. A kidney transplant is therefore preferable.

Many of the functions of the liver are unknown and since most of the vital synthetic processes of the liver that have been determined cannot be artificially reproduced, it is hardly surprising that the liver cannot be replaced by a mechanical device. For the liver, biological replacement is the only possibility.

From this brief summary of the present position of some organ substitutes, it appears that there is a continuous spectrum extending from an obvious choice of grafting for the liver, since there is no alternative, to a preference for prostheses for limbs. With other organs, replacement by either grafts or mechanical devices can be satisfactory depending on the circumstances. It is also possible to provide new parts for organs. Heart valves removed *post mortem* and manufactured valves can be grafted and will restore bedridden patients to a normal existence. Other dead grafts such as preserved arteries and bones or synthetic cloth arterial substitutes, act as functioning mechanical scaffolds into which living tissue grows. This results in their incorporation into the body as valuable prostheses.

For advances to occur in organ substitution certain difficulties must be overcome in both the mechanical and biological fields. The chief problem with mechanical organ substitution is the same as that experienced by the ill-fated Icarus, namely the junction of the prosthesis with the body. This is particularly pertinent where blood flow is required through the appliance, since blood is a complicated living tissue with a very special relationship to the physical and chemical structure of the blood vessel walls. Any roughness or changes in the electrical potential can set in motion a chain of events that result in the laying down of blood clot deposits. These may build up on the wall of the vessel and eventually occlude it or break off and block smaller vessels in the circuit. Drugs that inhibit clotting can prevent these changes but they remove the patient's defences against haemorrhage and render him vulnerable to severe bleeding from minor trauma. Also the bulk of equipment required to drive and monitor certain artificial organs is a serious impediment to the ideal solution of an implantable prosthesis. To substitute kidney function, apparatus is required that would fill the average-sized bedroom, yet a human kidney will fit into a man's hand. On the credit side, artificial organs are not attacked immunologically and this is the main, though not the only complication of biological organ grafts.

CHAPTER TWO

THE SURGERY

Every organ in the body receives its nourishment from its arterial blood supply and discharges its waste products in its venous drainage. This allows the cells of the organ to live and function. The liver has an additional blood supply which comes from the stomach and intestines, called the portal vein. The blood in this vein contains absorbed food products, minerals, and vitamins which the liver processes according to the body's needs. If the blood circulation through an organ ceases, the cells rapidly die and eventually decompose and putrify. The speed at which this occurs is governed by the temperature of the organ. Cooling slows the process. Blood circulation stops throughout the body at death, in fact cessation of circulation is the most certain criterion of death. The circulation ceases in an organ taken from a living individual as soon as the blood vessels are clamped. It follows that for a transplant to be successful, the operation must be performed quickly, whilst the cells are still capable of recovering and if the organ is cooled during the grafting operation there will be more time available in which to perform safe and accurate surgery. A minute piece of living tissue or a thin graft of skin only a few cells thick can acquire sufficient nourishment to stay alive if they are implanted into the body or laid on a surface of living cells (Fig. 3). After a few days new blood vessels grow into the graft and its early precarious existence becomes firmly established. Grafts of whole organs, however, will not survive unless their main blood vessels are immediately joined to blood

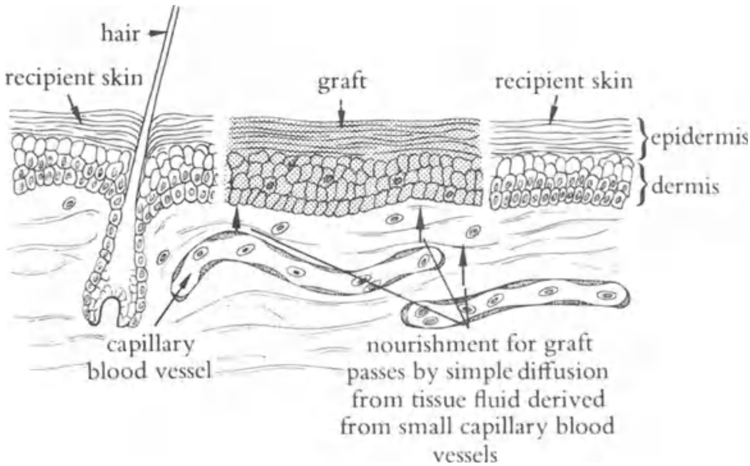

FIG. 3. Free graft of skin. Initially, it has no blood supply and gains nourishment from fluid between the cells of the recipient in the bed of the graft.

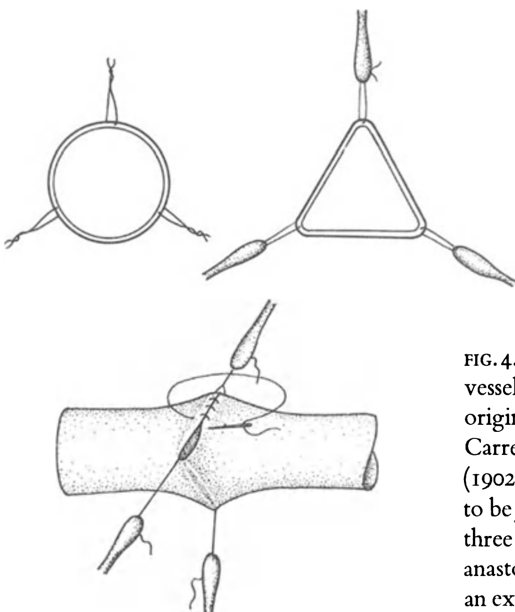

FIG. 4. Anastomosis of blood vessels: illustration taken from original description by Alexis Carrel, published in *J. Med. Lyon* (1902). The mouths of the vessels to be joined were triangulated by three stay stitches and then the anastomosis was performed with an extremely fine needle and thread, as used by the lace-makers of Valenciennes.

vessels of the recipient. Such a junction is called an anastomosis. The fate of organ grafts could not be studied until the turn of the century when Alexis Carrel described a reliable, simple method of joining blood vessels using sutures (Fig. 4). Carrel performed many of the pioneering studies on kidney transplantation in animals. He showed that kidneys transplanted by vascular anastomosis would function satisfactorily provided the time the organ was without a blood supply—the ischaemia time—was not too long. If the kidney was transplanted from its normal position to another site in the same animal (autograft) it would function indefinitely and alone support life after removal of the opposite kidney. Kidneys transplanted from one animal to another of the same species (allografts or homografts) functioned for a few days and were then rejected.

A kidney can withstand one hour at body temperature without a blood supply before permanent damage occurs. This is sufficient time in which to perform the surgery when the operation has been planned and the kidney is taken from a live donor. With human kidney transplantation from a dead donor more time is required and it is necessary to cool the organ to prevent irreversible damage (Fig. 5).

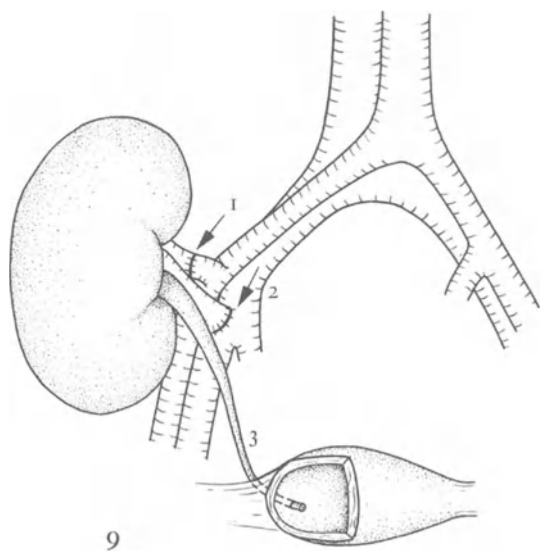

FIG. 5. Diagram of a kidney transplant. The junction of the renal artery (1) and vein (2) are shown by arrows. The ureter draining urine is implanted in the bladder (3).

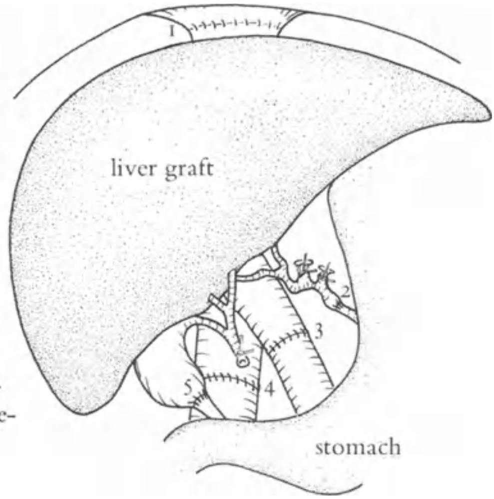

FIG. 6. Diagram of a liver transplant. The liver is placed in the correct position: orthotopic.

Anastomoses: (1) inferior vena cava above the liver, (2) hepatic artery, (3) portal vein, (4) inferior vena cava below the liver, (5) gall bladder of donor to bile duct of recipient.

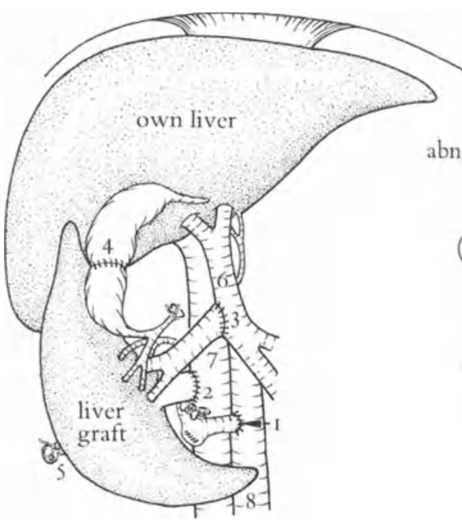

FIG. 7. Diagram of accessory liver transplant. The extra liver is in an abnormal (or heterotopic) position.

Anastomoses: (1) arterial, (2) vena cava below the liver, (3) portal vein, (4) gallbladder to gall bladder, (5) the vena cava above the liver has been tied, (6) recipient portal vein, (7) recipient inferior vena cava, (8) recipient aorta.