NORMAN BROWSE: SPARE-PART SURGERY

FIG. 1

FIG. 2

FIG. 4

FIG. 3

FIG. 1.—An artificial hip joint (Ring prosthesis) inserted by a member of the Orthopaedic Department of St. Thomas's Hospital. The patient was an elderly woman with disabling arthritis of the right hip. Hip movements and mobility a year later are excellent.

FIG. 2.—A Dacron bifurcation aortic graft used after resection of an aneurysm or to bypass atherosclerotic blocks.

FIG. 3.—An aortogram of a bifurcation graft, similar to that shown in Fig. 2, five years after its insertion. Note the progression of the disease in the host aorta, the occlusion of the left limb, and the aneurysm at the end of the right limb.

FIG. 4.—A Starr-Edwards artificial heart valve. The anchoring stitches are placed through the soft cushion at the base.

FIG. 5.—Chest x-ray film following a triple-valve replacement (aortic, mitral, and tricuspid) performed by Mr. M. V. Braimbridge, of St. Thomas's Hospital, in June 1966. The patient is alive and well.

FIG. 8.—An intravenous pyelogram of a transplanted kidney, inserted by Professor R. Y. Calne, of Cambridge. Note the healthy calices indistinguishable from those of a normal kidney. (Reprinted by kind permission of Edward Arnold Ltd. from *Renal Transplantation*, second edition.)

Middle Articles

GROWING POINTS

Spare-part Surgery

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[WITH SPECIAL PLATE ON FACING PAGE]

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Spare-part surgery began when the first prehistoric man to survive a traumatic amputation of a limb attached a piece of wood to the remaining stump to help himself to walk or grasp. It remained in this phase, with a few exceptions, until the present century, when the combined advances of many different aspects of medicine made possible the insertion of artificial materials and living tissues *into* rather than *on to* the body.

A notable exception to this recent development is the ancient use of skin grafts. It is often quoted that as long ago as the sixth century B.C. Indian surgeons were moving pedicles of skin from the forehead to the nose to repair severe nasal defects (usually a result of the punishment of "cutting off the nose"). The Italian, Tagliacozzi, gives a description of rhinoplasty using pedicle grafts from the arm in a work published in 1597, and the *Madras Gazette* of 1792 describes in detail the rotation of a forehead flap to the nose. The old maxim "there is nothing new in medicine" comes to mind yet again.

Spare-part surgery can be divided into three sections. Firstly, the attachment of devices to the outside of the body to replace missing parts (*external spare parts*); secondly, the insertion of parts made of foreign dead material into the body; and, thirdly, the insertion of foreign, living, functioning tissue into the body (*internal spare parts*). Each present their own problems, the last being by far the most complex.

External Spare Parts

This aspect of spare-part surgery is well known and it is not intended to discuss the tremendous advances that have been made in this field. Artificial limbs are being improved continually. For example, it is possible to make a power-driven upper limb that can be controlled by the patient from the electrical potentials developed in the muscles of the stump. Although such complex prostheses are seldom required by adults, they may be valuable to children, and the cripples of the thalidomide disaster have been a great stimulus and challenge to the limb-makers. One must not forget that spectacles, hearing aids, false teeth, and even wigs can be defined as external spare-parts. The benefit to mankind of this type of spare-part medicine is incalculable.

For the future this branch of spare-part medicine holds promise of the development of other artificial sense organs. Many years hence we may see an artificial eye relaying its message to the brain, for preliminary experiments have already been performed with this object in mind. Such progress will

be especially important in the replacement and bypassing of organs incapable of repair, such as the optic and auditory nerves.

Internal Spare Parts

Dead and Inert Foreign Materials

Artificial spare parts of metal, plastic, or dead tissues have been of most value in the replacement of those parts of the body that have a simple, relatively inert, mechanical function, such as arteries and joints. Three problems face the surgeon. The first is to insert the prosthesis without infection, for infection around a foreign body almost always results in its extrusion from the host. Secondly, the material inserted must be acceptable to the tissues. The chemical and the physical properties of a prosthesis are important. Vitallium and stainless steel evoke little tissue reaction, and most of the newer plastic materials based on nylon, Terylene, or polyethylene none at all. Nevertheless, even an inert material if it is porous will evoke a foreign-body reaction in response to the changes of tissue and surface tension in and around the pores, and any constituent that is at all water-soluble may cause a chemical inflammatory response. Thirdly, but by no means least, the material must be strong enough to withstand the enormous stresses of daily life. The strains placed on an artificial hip joint by a few years' weight-bearing are far in excess of the stresses and strains that we expect our motor-car engines to withstand. Fortunately the newer metals and plastics are both inert and strong; indeed, much of this field of spare-part surgery could not have developed without the brilliant discoveries of the chemical and other industries.

Artificial Joints

Since 1938, when Smith-Petersen found Vitallium to be a suitable metal for inserting into the body, many types of hip prosthesis have been made. Metal cups have been inserted between the joint surfaces; the head of the femur has been replaced; and in recent years complete joints, acetabulum, and head of the femur have been inserted. Fig. 1 (Special Plate) is a radiograph of a Ring prosthesis, which consists of a cup screwed into the acetabulum and an artificial head of femur. The problem of wear due to friction, not so serious in the older operations where one surface was living and capable of self repair, has not been completely solved and at the moment these prostheses are being inserted only in elderly patients. Time will tell how successful such operations can be. The production of a "frictionless" joint is now being pursued by many workers,

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and the complete replacement of the hip joint will probably soon be a common routine procedure.

Apart from the problem of wear at the joint surfaces the orthopaedic surgeon has also to solve the problem of making a permanent joint between the prosthesis and the bone. Occasionally the metal wears right through the bone or, more often, just becomes loose. Much work will have to be done before we have a prosthesis that the skeleton will accept without complaint. Probably this aim will not be achieved until the growth and turnover of the host bone around the prosthesis can be controlled, and the stresses can be transmitted from the prosthesis to the host in a more physiological manner.

Many other joints have been replaced, the finger joints in patients with severe rheumatoid arthritis, the elbow, and the knee. The problems are similar but greater than those of hip prostheses; fixing metal to bone becomes more difficult as the bones get smaller and the mechanics of the joint more complex.

Artificial Arteries

The replacement of arteries with artificial tubes has developed over the last 15 years. The techniques of vascular anastomosis have been understood since the beginning of the century, but suitable materials with which to make artificial arteries have become available only recently. Fifteen years ago the enterprising surgeon simply sewed together two strips of man-made fibre cut almost literally from his shirt-tails, but now we have a vast array of vascular prostheses. Fig. 2 (Special Plate) shows an aortic bifurcation prosthesis made of Dacron (Terylene). One difficulty with these tubes is that they kink when bent, and we still hope to develop a more flexible elastic graft. With such prostheses one can replace a segment of vessel knowing that the holes in it will be effectively stopped by blood clot; that a firm fibrous reaction will develop at the suture line to bind it to the host vessel; and that, provided there is enough blood flowing through, it will not become occluded with thrombus.

These grafts are not perfect. Fig. 3 (Special Plate) is an aortogram of a Dacron aortic bifurcation graft that was inserted five years ago. The left side has become occluded, but the right is patent and looks the same as the day it was inserted. Thus, though the material is strong enough to withstand the arterial blood pressure for many years, it does not conduct blood as well as a normal vessel and thrombosis is a hazard. Two other points must be noted: the disease in the host aorta is still present and slowly advancing towards complete aortic occlusion; and the right femoral artery has been destroyed by the combined effect of the underlying disease and turbulent flow at the anastomosis, so that it has become aneurysmal. Thus partial replacement of an organ may fail because of the progression of the primary disease. As total replacement of the vascular tree is impossible, we will continue to have late failures until we can also cure or arrest the underlying disease. It follows, therefore, that the aim of spare-part surgery should be the complete removal and total replacement of a diseased organ or system.

Artificial Heart Valves

The aortic valve is often so extensively destroyed by disease that repair is impossible. In such circumstances the damaged valve must be replaced with an artificial one or one from another person. The valve most commonly used is the Starr valve (Fig. 4, Special Plate), made entirely of metal and plastic, but freeze-dried aortic valve homografts, taken at necropsy soon after death, are also used. Both may be considered as inert foreign material, for the cells of the freeze-dried valve are dead and disorganized and do not cause an immune response.

Fig. 5 (Special Plate) is a chest x-ray film of a patient with three artificial valves—aortic, mitral, and tricuspid. This is as near as we can go at present towards giving a patient an

artificial heart, but it is unlikely to be long before an artificial pump will be inserted as a long-term replacement for the myocardium.

The heart valve presents another complication of spare-part surgery. The materials of which it is made are inert when placed in soft tissues, but not when placed in a continuous stream of blood. Whereas the normal valve falls back away from the mainstream of blood ejected from the ventricle during systole, the ball of the Starr valve lies right in the middle of the stream. Turbulent flow around the valve may cause sufficient haemolysis to produce anaemia, and if the thrombus around the valve becomes infected a condition identical to sub-acute bacterial endocarditis will develop, which may be fatal.

It is in many ways surprising that either artificial or freeze-dried valves function so well; some Starr valves have been in position for as long as five years and the one-year success rate for these operations is now well above 70%.

Artificial Hearts

The "heart-lung" machine is both an artificial heart and an artificial lung, and is used extensively during cardiac surgery. It is only recently that very small pumps have been devised that can be left connected to the conscious patient to replace or aid the myocardium for long periods.

Fig. 6 shows the principle of these devices. When perfected they will be used when the myocardium is so weak that it is

FIG. 6.—Diagrammatic illustration of an artificial left ventricle used to take the strain off a failing heart in the early postoperative period. Blood is taken from the left atrium and pumped directly into the aorta.

unable to function properly following the repair or replacement of chronically diseased valves, or after myocardial infarction. Thus this device is not an artificial heart, just a temporary artificial left ventricle—though it represents the beginning of another new field of spare-part surgery.

Artificial Nerves

For the Heart.—The commonest conducting system to be replaced with an artificial device is the conducting system of the heart. Failure of ventricular contraction due to a permanent or transient heart block results in hypotension and collapse. Conversely, an excessively fast ventricular rate, as occurs in ventricular tachycardia or auricular flutter, will also cause hypotension and collapse. In either case, whatever the cause, it is necessary to control the heart rate to maintain life. The cardiac pacemaker takes over the role of the sino-auricular node and conducting system. The battery and timing device replace the natural pacemaker (sino-auricular node) and the wires the conducting bundles, the ends of the wires being placed on that portion of the heart that one wishes to control—usually the ventricle.

The problems of implanting wires and fixing them to the heart are no different from those already discussed, but a new

problem arises—the source of power. Early models had the wires coming to an external electrical source, and temporary pacing is still done in this way. This is unsuitable as a permanent method, as the site at which the wires come through the skin is extremely susceptible to infection. Permanent pacing is therefore achieved with either long-life implanted batteries (needing regular renewal) or by induction. In the latter system the wires from the heart are brought to a coil beneath the skin and current is induced therein from an overlying primary circuit (Fig. 7). The source of power is then external, removable, and without any direct connexions with the internal secondary circuit. This overcomes the problems of sepsis, breakage of wires, and renewal of power supply. Recently attempts have been made to harness electric current produced within the body as a source of power.

FIG. 7.—Diagram of the electrical circuit of an inductive cardiac pacemaker.

Perhaps we are not far from the day when a patient may have three artificial heart valves and an artificial left ventricle paced by a pacemaker, which is in turn fired from the electrical activity of right ventricular systole. This, I suspect, is as near as we will get to a truly artificial heart, at least for the next 50 years.

Other Sites.—The development of the cardiac pacemaker is far ahead of all other artificial nerve implants. Electrodes have been implanted on the bladder to stimulate micturition in paraplegics, and attempts have been made to control the sphincter of the bladder to prevent incontinence of urine. Anal incontinence has also been studied, and the most promising approach is the stimulation of the sphincter from the outside with a dumbbell-shaped electrode fitted into the anal canal. These efforts will no doubt lead to the development of permanently implanted electrodes with external inductive power circuits to maintain sphincter competence but which allow it to relax on demand.

A final example of the way in which man is attempting to take over the nervous control of the body is the study of methods of pacing the nerve to the carotid sinus. In the previous examples the battery and wire has replaced an efferent motor nerve. Stimulation of the carotid sinus nerve, on the other hand, is an attempt to mimic the afferent impulses coming from the baroreceptor endings. This aims to effect some degree of regulation of the blood pressure.

Living Autogenous Tissue

In many instances we have within ourselves the tissues required to fashion a spare part. Pedicles of skin can be fashioned into new noses, the ileum can be made into a bladder, the colon can become an oesophagus.

The use of autogenous tissues depends to a large extent on the ingenuity and technical skill of the surgeon. Provided the blood supply of the part remains intact or is re-established, the tissue will live, and often shows a remarkable degree of adaptation to its new function.

Living Foreign Tissue

The problems of placing living foreign tissue into the body are those outlined for inert materials, with the addition of

several greater ones, all yet to be fully resolved. Thus, firstly, one must obtain suitable material. Secondly, the latter must be kept alive during transit from donor to host. Thirdly, it must be kept alive within the host. These problems are best discussed in the context of renal transplantation.

Source of Materials

Organs for transplantation must be living and healthy. The obvious source is another living person, as tests of function can be performed preoperatively and the organ removed at leisure and at a time most suited to the well-being of the donor, recipient, and surgeon. Is it morally and ethically right to ask or expect a healthy subject to donate a kidney? This problem does not arise with other organs such as the liver, heart, or lungs, for the living have none to spare; but, as it is well known that man can live a normal life with one kidney, relatives are often eager to volunteer as donors. Donation is not, however, free from risk. Nephrectomy has its hazards, such as haemorrhage, in addition to those associated with all operations, such as pneumonia and pulmonary embolism. After the donor has survived the operation there is still the possibility of an accident or disease process affecting the function of the remaining kidney. Against these problems must be set the undoubted fact that transplants from live, related donors do better than those from dead, unrelated donors. The problem is one for the individual surgeon concerned. Cadaveric donation has its problems. The best source is the recently dead young person, but there are legal problems concerning the rights of the relatives. Most relatives agree to the removal of a kidney, but it is an essential precaution when the donor is a patient dying in the hospital that the surgeon has nothing to do with the donor's care, lest he should be accused of hastening death in order to obtain the kidney.

Preservation of Organs

Whatever organ is used, and whatever its source, it inevitably undergoes a period of ischaemia between removal and insertion. The effects of this ischaemia are minimized by keeping it as short as possible and by keeping the organ cool. A cold kidney (4° C.) can survive six hours or more of total ischaemia and function. A warm kidney is severely damaged after 30 minutes, but may still recover after one and a half hours of ischaemia.

Any organ must of course be removed in aseptic conditions, and if the donor is alive this is done as an elective procedure in an operating-theatre adjoining that in which the recipient is being prepared. The kidney is then carried from one room to the next, and the ischaemia time is that which is needed to make two vascular anastomoses (10–20 minutes). With cadaveric donors the preparation of the recipient takes longer, as it is begun as an emergency after the donor has died. The kidney is therefore washed through with cold heparinized saline solution and kept in ice until the recipient is ready.

In ideal conditions a transplanted kidney will produce urine as soon as the clamps are removed from the blood vessels. There may follow a diuretic or anuric phase, depending upon the degree of tubular necrosis.

The problems of short-term preservation of the liver, lung, and heart have not yet been solved. To do this the organs will probably have to be artificially perfused with oxygenated blood. In the future one hopes to see banks of viable organs ready for insertion, but the problems of long-term preservation are enormous.

Preparation of the Recipient

Surgeons like to operate on a fit patient, for an ill one is more susceptible to all the common postoperative com-

plications. Patients in renal or hepatic failure are not usually subjected to operation, but in transplantation these are the very subjects with whom the surgeon has to deal. The immediate success of renal transplantation is entirely dependent upon the efficiency of preoperative dialysis. Careful use of the artificial kidney gives a fit patient who can withstand surgery and the postoperative medication with cytotoxic drugs. Without preparation with chronic dialysis the mortality rate is high.

There is no machine to replace the hepatic function, and hence liver transplantation is performed on sick patients. Passing the patient's blood through a pig or human cadaveric liver has not been outstandingly successful in the treatment of hepatic coma. Once an artificial liver is available to prepare the patient liver transplantation will become a practical proposition.

Surgical Techniques

The anastomosis of the vessels of the graft to those of the host is a fairly simple procedure requiring the basic skills of vascular surgery. A kidney is placed in the iliac fossa and its vessels anastomosed to the internal or common iliac vessels. The ureter is either joined to the bladder or to the host ureter. Fig. 8 (Special Plate) shows an intravenous pyelogram of a kidney transplanted to the right iliac fossa; it is indistinguishable from that of a pyelogram of a normal kidney in the loin.

The transplantation of other organs, such as the liver or the lungs, is more difficult, as there are more (usually smaller) vessels to anastomose.

The development of the techniques of transplantation have depended upon work in animals. Many thousands of canine renal, liver, heart, and lung transplants have been performed and techniques perfected, so that the practical problems of inserting the graft into the recipient are now the least of the transplanters' worries.

Prevention of Rejection

Once inside the recipient, perfused with recipient blood, the transplanted organ is subjected to the major hazard of this whole problem—namely, that of host rejection.

From a very early stage in interuterine growth special cells develop, particularly in the thymus, which are capable of recognizing any protein which is foreign to the body. They then migrate to populate the reticuloendothelial system. These "self-recognizing" cells can initiate a series of responses by which any "non-self" material is destroyed. This, in very simple terms, is the basis of immunity. Any cell capable of initiating an immune response is called an immunologically competent cell.

Foreign tissue is destroyed either by antibody production or a local cellular reaction. It is thought that the local cellular response is the most important line of defence. Circulating antigens are released by implanted tissues, but in small amounts, so that there are probably only low levels of circulating antibody.

If one accepts this mechanism of graft rejection then a number of methods of preventing this response become apparent; they are shown diagrammatically in Fig. 9. Only two are of practical value today.

Make the Graft Non-antigenic.—Homozygous twins have an identical genetic make-up. Tissue grafted from one to the other is totally accepted. The results of kidney transplants between identical twins are excellent, some functioning 6–8 years after transplantation. Such good results justify the use of a living donor, but regrettably few patients with renal failure have an identical twin.

Attempts are being focused on ways of typing the tissues of both the donor and recipient to get the best degree of immunological compatibility. These studies are in their infancy and involve many sophisticated techniques.

Recipient and donor should have the same blood group. Leucocytes can also be "typed" in the same way as red cells, but this is a much more difficult procedure.

FIG. 9.—The ways of overcoming the immune response.

A host-versus-graft reaction can be detected before transplantation by injecting the recipient's lymphocytes into the skin of the donor and observing the local reaction. This test can be used only with living donors.

The presence or absence of histocompatibility antigens can also be detected by studying the effect of known specific antigens against donor and recipient lymphocytes. The preliminary results of these attempts at tissue typing are encouraging and suggest that they will have an important role in determining the success or failure of a transplant. If tissue typing is to be used with cadaveric donors the donor will have to be studied before death, so that the methods used will have to become rapid and simple.

Any attempt to destroy the antigenicity of the graft before transplantation always causes death of the transplant.

Prevent the Host Recognizing "Non-self" Material.—Once a foreign tissue is in the body and fully vascularized there is only one way to stop the host recognizing and starting an immune reaction against it—to destroy those cells involved in the recognition process. This is known as immunosuppression. The small lymphocytes are the target cells and there are three possible methods of attack.

Irradiation.—Total body irradiation was the first method to be tried, but was given up when it was found that the dose required to achieve effective immunosuppression invariably killed the host. Local irradiation of the graft is used occasionally to help suppress a severe rejection phase.

Cytotoxic Drugs.—Many drugs have been studied, but by far the most successful is azathioprine (Imuran). Imuran will destroy all types of white cell, and complete depression of marrow and lymph node activity can occur if the dose is not carefully controlled. Cortisone has an inhibitory effect on the reticuloendothelial system and is used in combination with azathioprine. The other cytotoxic drug in common use is actinomycin C.

The present-day successes of renal transplantation are due either to chance histocompatibility or the control of rejection by azathioprine and cortisone, but better substances are needed.

Antilymphocyte Serum.—The wholesale destruction of bone marrow and lymphoid tissue is a blunderbuss approach. Antilymphocyte serum can specifically destroy those cells believed to be responsible for graft rejection. It is made by injecting human white cells into the horse and then preparing the antiserum in just the same way that the antisera against many bacteria are made. Preparations can now be made of pure antilymphocyte globulin. As white cells from many different subjects have to be pooled to get enough for an adequate antigenic stimulus, the antiserum is species—but not individual—specific.

Studies with this substance in man are just beginning ; those experiments that have been performed show great promise. Antilymphocyte serum is the only specific immunosuppressive agent yet developed and those patients who have received it both preoperatively and postoperatively have shown a worthwhile improvement in their tolerance to the grafted kidney.

Current Practice following Renal Transplantation

The usual practice following a kidney transplant is to start the patient on azathioprine and corticosteroids immediately. Renal function is watched carefully. A reduction of renal function indicates the development of the rejection process within the kidney. The earliest change is a reduction of renal plasma flow. The doses of azathioprine and corticosteroids are immediately raised and actinomycin C is added. The signs of rejection usually subside within a few days, and drug doses are then reduced. Episodes of rejection get less frequent and less severe as the months pass, but the patient must be very closely observed for six months, and then seen frequently for the next 12 months. If immunosuppression fails the kidney gets bigger, function fails, the small intrarenal vessels thrombose, and the kidney dies.

In addition to all these problems the surgeon has to manage a patient with a low leucocyte count, who is taking corticosteroids, and who has a wound, drains, and a urethral catheter. The chance of infection is high. These patients are usually barrier-nursed in special units until all the impedimenta of the postoperative period have been discarded.

The one-year survival rate of the graft in good centres is continually improving. Figures of 80 and 90% have been claimed, while the overall world figure for living related donors is about 70%—for unrelated cadaveric donors the figure is about 50%.

Liver Transplantation

A few livers have been transplanted between humans and many have been exchanged between dogs. The latter work has shown the procedure to be technically possible and that the problems of rejection can be met in the same way as kidney transplants. Many animals have survived six months, some as long as a year and a half, but there are no long-term survivors in man.

The functions of the liver are more complex than that of the kidney and certainly less well understood. Thus, though the blood of a man in hepatic coma can be passed through another human or pig liver to lower the concentration of bilirubin and ammonia, there is often no change in the level of coma. A fully functioning transplanted liver would presumably restore a patient in liver failure to normal, but this has rarely been achieved for even a short term with extracorporeal liver perfusion techniques.

At present anyone attempting liver transplantation for hepatic failure must work with a very ill recipient, and the chances of success are slight. With the kidney this problem was overcome by the development of the artificial kidney ; little progress can be expected with liver transplantation until we have an effective artificial liver. It would help in the making of such a machine if we understood the biochemistry of hepatic coma.

Liver transplantation may be valuable to some patients not in liver failure. For example, the patient with an extensive, locally infiltrating, primary carcinoma of the bile duct could be cured if the surgeon could remove the porta hepatis and the liver *en masse*. Liver transplantation may make this possible. The patient, though jaundiced, would not be in hepatic failure and the chances of success would seem to be moderately good.

Liver transplantation will become a practicable procedure when the problems of temporary support for the patient in liver failure and the rapid collection and perfusion of the cadaveric donor liver have been solved.

Other Organs

The transplantation of the heart, lung, pancreas, gut, and endocrine glands are all technically feasible procedures. An ape heart has been inserted into a man, though its function quickly failed. One patient has had a successful pancreas transplant, which is reported to be functioning four months after operation. So continued progress is being made. Any organ that can withstand ischaemia for 30 minutes may be transplanted, and as our knowledge of the immune reactions increases so these transplants can be kept alive for longer periods.

Other Tissues

Perhaps the most important body tissue to be transplanted, and certainly the one that has made all the recent developments of transplantation possible, is blood. Blood transfusion is a form of tissue transplantation, the value of which is inestimable. A major part of modern surgery could not be done without it. The transfer of blood-cell-producing tissues, the bone marrow, has not been so easy. It is beset with all the problems of organ transplantation. Experiments have shown that antilymphocyte serum will improve the results of bone-marrow exchange. If a diseased haemopoietic system could be completely destroyed and replaced with a healthy one a great number of diseases such as aplastic anaemia and leukaemia might become curable.

The future of transplantation is bright. Solving the problems of immunity will solve many of the fundamental problems of cellular biology. Transplanting organs successfully will give life to many. All this will repay the singlemindedness and courage of the few who have pressed on in this field during the last 20 years in the face of failures, discouragement, and seemingly insurmountable barriers.