

## HAS HEART TRANSPLANTATION ANY FUTURE?

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**This is the second Sir Denis Browne Memorial lecture, delivered on the 12th September, 1969, under the auspices of the Malta Section of the International College of Surgeons, at the Medical School of the Royal University of Malta.**

We have come here tonight to commemorate a man who set down so many stepping stones that he could have built a stairway to heaven. I consider it a great honour to have been invited by the Malta Section of the International College of Surgeons to give this lecture and to recall this great man to your mind. I hope that I will be able to do justice to his memory.

On the 3rd December, 1967, a young girl and a mother crossed a street three miles away from one of the major hospitals in Cape Town. They were both hit down by a motor car; the mother was killed instantly, and the girl received irreversible brain damage. She was admitted to hospital within minutes, and after examination by the neurosurgeons and neurologists, they declared that her brain was dead, and there was nothing in the power of medicine that could save her life.

In a room of the hospital, not very far from where the girl lay dead, there was a man suffering from an irreversible heart condition, in the terminal stages of this disease, not responding any more to all the treatment that the medical profession could think of.

After the girl had been declared dead, permission was obtained from her father. He was asked to donate the heart of his daughter to a man that he had never seen and whom he did not know, to a man his daughter would never see. He was asked to donate this heart in an attempt to alleviate the sufferings of this man, and in an attempt to prolong his life. The father

said that if there was nothing more that could be done for his daughter, then he believed that it would have been her wish that her normal heart be removed in an attempt to save this man's life. The operation

A human to human heart transplant was performed that night on this man, and within hours the news crossed all the oceans that surround Cape Town. Overnight the heart transplant became world news. It was received with great enthusiasm in some quarters, while other quarters expressed bitter criticism. And every few months the question was asked: Is there any future for heart transplantation?

Now we must ask ourselves: Why should not there be a future for heart transplantation? Is it perhaps because we are crossing the ethical and moral boundaries of medicine? And perhaps we should deal with this question first to see whether there is any future in human transplantation, because, if we behave unethically and immorally, then there is no future for this operation. I would, therefore, like to examine the three major points of contention. First, is the act itself moral and ethical? Second, does the recipient receive ethical and moral treatment? And lastly, do the donors receive ethical and moral treatment?

Let us deal with the first question. Is the heart transplant, the act itself, ethical? News coverage of transplantation in the popular mass media has been widespread and on the whole enthusiastic, and, unfortunately, too often sensational and misleading. It has been misconceived in certain sections of the public both as a panacea and as an unethical and unjustified form of treatment. We believe that neither of these contentions is accurate. Within our limited experience of immu-

nology and immunological reactions on transplanted organs, we believe that it is not possible to prevent the rejection of a transplanted organ completely. In other words, we do not believe that a heart transplant is a curative procedure. We do not believe that the heart disease from which the patient suffered will be cured. But we do believe that we are able to palliate; to alleviate his symptoms and possibly to prolong his life. This is not unheard of in medicine. Palliative procedures are performed every day. Most of the operations on cancer of major organs, such as removal of the lung for bronchial carcinoma, the removal of the oesophagus for oesophageal carcinoma, and even the removal of the stomach for gastric carcinoma, are not curative procedures. We cannot tell the patient that by removing his cancer we will cure him. But we can tell him that with this operation we can alleviate his suffering and may even be able to prolong his life. So palliative procedures are certainly not unheard of in medicine.

It has often been said that the money that is spent on this operation and the number of persons involved are unjustified by the limited scope of heart transplantation. It has been said that we spend so much money and use so many people and yet can only treat a few patients in one year. This same criticism was levelled at open heart surgery using the heart-lung machinery when this new type of operation first began to be performed. It was said that the operation was too big, that it was too expensive and too many people were employed. But gradually we solved these problems and we simplified the procedures and today open heart surgery, using the heart-lung machine, saves hundreds of thousands of lives.

I believe that to curb heart transplantation at this stage will be very short-sighted. I believe that organ transplantation is the surgery of the future and the treatment of many diseases for which we can do nothing today. Therefore, I believe that there is nothing new in the act of transplantation; it is a palliative procedure, and as such we can accept it in medicine.

The next question to consider is whether the recipient receives ethical treatment. As has been pointed out, heart transplantation is not a curative but a palliative procedure, and patients should only be submitted for heart transplantation when other forms of surgical treatment have failed. In other words, we must select the patients on three criteria. The first criterion is that operation is indicated only on patients with incurable heart conditions; secondly, we must only operate on them when all other forms of treatment have failed; and thirdly, we must only operate when the disease has reached the terminal stages. If we accept and apply these three criteria, then I believe that the doctor performs his duty by doing a heart transplant. It is only right to give the patient all the treatment that is available and, if a particular centre is equipped and can do a heart transplant, then the doctors will not be doing their duty unless they give the patient this chance to save or, at least, to prolong his life.

The last question is whether the acquisition of donor organs is ethically acceptable. It is interesting to note that when we first started heart transplantation, the world doubted the ability of the doctor to diagnose the moment of death. The world said that the doctor does not really know when a patient is dead. But we know from experience that in any major hospital, especially during the night, when a nurse doing her rounds comes upon a patient whom she thinks is dead, she will call a doctor; this is usually the houseman, the most junior doctor in the hospital. He will come and determine that the patient is dead using three criteria: there is brain death because there are no reflexes, there is no spontaneous respiration and there is no cardiac activity. On these three criteria brain death, no spontaneous respiration and no cardiac activity, the doctor will certify the patient dead, and no one will doubt his ability to do so. Once the patient has been certified dead and permission for a post-mortem is obtained, then there is nothing to stop the pathologist from doing a post-mortem immediately, and, if he

feels that the heart is an interesting specimen, he will remove that heart and put it in a bottle to demonstrate its pathology to the students later on. But when a highly qualified team of doctors, using all the means not to make a mistake, having determined death using the same criteria, remove that heart, but instead of putting it in a bottle, they put it into a patient in an attempt to save his life, is the world right in questioning the ability of these doctors to diagnose the moment of death? That this is an unethical and immoral method? To me the question is not whether it is unethical or immoral to transplant a heart in an attempt to alleviate suffering; to me the question is whether it is moral and ethical to bury that heart so that it can be devoured by worms.

Ladies and gentlemen, I therefore feel that we cannot stop this operation because it is immoral or unethical.

We must ask ourselves further. Why did the heart transplant cause such a tremendous uproar? Could it have been due to the fact that for countless ages the peoples of the world of all races and religions have regarded the heart as the seat of affections and passions, for man as well as beast, and, in the case of man, even as the seat of the soul itself? This age-old mystique enveloping the heart has persisted down to this very day in all classes of society — a mystique enshrined for all nations of the world in their every day thoughts, their sayings, their rituals and their observances. Man in the course of evolution, resulting from his struggle for existence, came to regard the heart as the source of his being and handed down this belief as a social-cultural heritage.

From time immemorial the heart was regarded as the most vital part of the body and the seat or abode of a number of qualities, many of them even of a conflicting nature, such as courage and cowardice, love and hate, generosity and meanness, kindness and cruelty, sincerity and falsehood, and so on. Since the beat of the heart is regarded as a sign of life and its cessation as a mark of death, it is

therefore not surprising that the heart in the course of time came to be regarded by all races as the most important organ of the body and the seat of emotional life in all living beings; of love and hate, courage and timidity, hope and despair, lust and desire, joy and grief, and, in the case of men, of belief and disbelief.

The most important influence in the formation of this social-cultural matrix sustaining the mystique of the heart in western civilisation is undoubtedly the Bible. There are numerous references both in the old and in the new testament to the heart and the rôle that it is supposed to play in human thoughts and actions. In fact, of all the internal organs of the body the heart is mentioned 826 times in the bible, whereas the kidneys are mentioned 27 times, the liver 14 times, the secretions of the gall bladder 10 times, the stomach once only and the lungs not at all. It is therefore not surprising that even the physicians of antiquity believed like Hippocrates that the heart could not be touched for "as soon as the heart is touched immediate death will result".

In a Bradshaw lecture in 1919, Sir Charles Ballance gave a number of delightful references to injuries to the heart mentioned in the classics. He pointed out that many physicians, such as Galen, had made examinations of gladiators and pointed out that when a wound was inflicted to the heart immediate death resulted. In fact, they even pointed out that if the left ventricle was injured, then death was more rapid. But certain people doubted this, amongst them pathologists like Hollerius, Turbi and others, and showed that at post-mortem they found evidence of wounds of the heart in gladiators who had had a history of a chest injury, and they showed that these gladiators had not died from the wounds of the heart. So after 18 centuries people started to doubt the thoughts of Hippocrates that injuries to the heart were always fatal, and they started to investigate this hypothesis in the laboratory, and we have people, such as Becker, Klebs, Cohnheim and Rosenbach, who in the laboratory showed that the heart could be approach-

ed surgically, that wounds could be inflicted to the heart and that these animals will survive. But in spite of the success obtained in laboratory animals, Billoth, himself not a very timid surgeon, wrote in 1875: "Paracentesis of the pericardium is an operation which in my opinion approaches very closely to that kind of intervention which some surgeons would term a prostitution of the surgical art and others madness". And in 1885 he wrote: "Let no man who hopes to retain the respect of his medical brethren dare to operate on the human heart". In 1896 Paget stated: "Surgery of the heart has probably reached the limit set by nature to all surgery. No new methods and no new discovery can overcome the natural difficulties that attend a wound of the heart". And one year later these predictions, a surgeon by the name of Rehn sutured the beating human heart and the patient recovered.

I think we will all agree that it is not easy to rid ourselves of this so to speak ingrained habit of thought and think rationally of the heart as only a muscular pump, responding now vigorously, now more gently to the needs and demands of the body as life's situations change or fluctuate from time to time, or even from moment to moment. And why should we rid ourselves of these ingrained habits of speech and thought, provided we do not allow them to inhibit our scientific thinking on matters clothed through the ages in garbs of emotional and poetic figures of speech? In spirit we live by utterances only, and myth and legend and symbolism is what we thrive on. For although our little life, in the immortal words of Shakespeare, "is rounded with a sleep", we remain "such stuff as dreams are made of". Let the spirit on the heart of the bible, literature, myth, legend and every-day speech, therefore, remain, so to speak, untouched by the surgeon's knife, but let not our scientific thinking be clouded by these thoughts. And let us, therefore, not condemn the future of heart transplantation as a result of this.

We have asked ourselves if there is a future in heart transplants. We have

seen that there are no ethical or moral reasons why the operation should not be performed. When can we say that a procedure has a future? I think that a surgical procedure has a future when we can answer two questions. First when we can say that there is a need for this procedure, and second, when we can say that we can perform this procedure; we are technically able to do this operation and we are capable of looking after the post-operative complications of this operation.

Let us now see if there is any need for heart transplantation. In the last 25 years the world has witnessed a tremendous improvement and increase in the ability of physicians to treat heart disease. They are today able to treat most of the congenital deformities that children are born with; they are able to correct the ravages of rheumatic fever; put in new valves, open up narrow valves; they are now able to correct lesions of the pericardium, and able to operate round the heart correcting a patent ductus arteriosus and coarctation of the aorta. But in spite of all these advances, little progress has been made in the treatment of diseases affecting the heart muscle, and apart from revascularisation operations and the excision of small aneurisms, we are unable to treat the patient once there is failure of the pump. This has become the greatest challenge in the treatment of heart disease, because diseases affecting the heart muscle, failure of the pump, is today the most common cause from heart disease. In the United States alone it is estimated that half a million people die every year of one of the conditions affecting the heart muscle; and in the whole world millions of people must die every year from these affections.

As I have just said, the heart is a pump and these diseases affect the pump. How can we then correct them? The only way that we can correct them is to replace the pump, either by means of a mechanical device or by means of a heart transplant, the heart either being taken from a human donor or from an animal donor. With our present knowledge of artificial hearts, it is not yet possible to

use a mechanical heart to replace heart function completely for any length of time. Therefore, in searching for a solution to this immense problem of disease of the heart muscle, it became obvious that, if we wanted to treat our patients today, the only way that it could be done was by a heart transplant. We also realised, as we will see later, that due to our imperfect knowledge of the immunological reactions to a foreign transplanted organ, it would not be possible to use a xenograft, and therefore an animal donor could not be used, and as such we had to use a human donor.

Let us now see the type of patient that may benefit by the operation. The first indication for heart transplantation in our cases has been mainly ischaemic heart disease. We have so far done 5 heart transplants and two of them were done for ischaemic heart disease; one was done for cardiac myopathy and two transplants were done for rheumatic heart disease. Let us analyse these cases more closely and see whether they really needed this operation.

A study of the haemodynamic findings of the first patient six months before transplant shows that there is an elevation in the right heart pressure because both the right atrial and right ventricular pressure are elevated, indicating that there is failure of the right side of the heart. There was also a marked elevation in the pressures on the left side of the heart, indicating that the left side is also failing, the left atrial pressure being 35mm. of mercury, the enddiastolic pressure in the left ventricle being 25-30mm. of mercury. The cardiac index was remarkably reduced to 2.43 litres per minute per meter square, indicating that here we have a patient with total heart failure. And when his heart is examined, it will be seen that the mass of the left ventricular muscle has been destroyed by ischaemic heart disease; instead of the beautiful red muscle which can contract and expel the contents of the left ventricular chamber, the left muscle is now completely replaced by white fibrous tissue due to the ischaemic death of this muscle. The question that

we must ask ourselves is whether we are going to allow this patient to die, or to offer him the hope of further life by means of a heart transplant.

The haemodynamic findings in the second patient also show right heart failure, severe left heart failure and low cardiac output. And when his heart is examined, the left ventricular chamber will be seen grossly dilated as a result of the damage of ischaemic heart disease; the heart muscle is replaced by fibrous tissue. This man was in the terminal stages of heart disease; he was receiving 600mg. Lasex daily; he was short of breath by day and by night, and he had had a pulmonary embolus which nearly killed him about a week before the operation. There is also a localised aneurysm of the left ventricle. And we should ask ourselves: Do we believe that this patient can benefit by a heart transplant?

The third case was a patient suffering from cardiac myopathy. He had been ill for many, many months and had actually had an operation because it was thought that he was suffering from mitral valve disease. His general condition gradually deteriorated and he failed to respond to further medical treatment. Again, one will find total heart failure, both on the right side as well as on the left and a low cardiac index. The patient attempted to commit suicide one day before the transplant, because he thought that life was not worth living any more. If you look at his heart you will see that the left ventricular wall is grossly thickened by this unknown disease; it cannot contract any more and it cannot therefore act as a pump.

The next case was a patient who suffered from aortic valve disease as a result of rheumatic fever. Because of a haemodynamic defect, the aortic valve was replaced, but despite the correction of the valvular lesion, the patient's condition continued to deteriorate and eventually he was in the terminal stages of heart failure. On re-examination, it was found that there was no further defect of the valve, but there was total failure because the heart muscle had been destroyed by

the rheumatic fever. There was severe right heart failure showing a right atrial pressure of 21mm. of mercury, a left atrial pressure of 28mm., an endiastolic pressure of 20-12mm. of mercury, with a cardiac index of 1.2 litres per minute per meter square. The heart after removal showed extensive damage of the muscle both as the result of the rheumatic fever and the long-standing left heart failure.

The last patient was a coloured woman who suffered from mitral incompetence. Her mitral valve was replaced using a pig's xenograft, but despite the haemodynamic correction of the valve lesion, she continued to remain in severe heart failure. Her condition deteriorated and for six months before surgery her cardiac index was diminished to 1.2 litres per minute per meter square.

These are the patients who we believe can benefit by heart transplantation, and therefore, I think that the answer to our first question "Is there a future for this procedure because there is a need for it?" must be in the affirmative, because I do not think that any body can tell me what else we could have done for the patients that I have just described. Thus there is a definite need for replacement of the pump.

I have already dealt with the donors, but I would like to add that a patient can only be used as a heart donor because death is not instantaneous. If the circulation of a patient should stop at this minute, then the brain will die within 3-5 minutes, the liver will probably die or have irreparable damage within  $\frac{1}{2}$ -1 hour, the kidneys will probably be damaged so that they will not function adequately within 2-3 hours. The heart will tolerate anoxia extremely well and could probably be transplanted  $2\frac{1}{2}$ -3 hours after the circulation has stopped. It is interesting to note that the nails and hair will only die six days later. It is for this reason that we can use a human donor that has been certified dead. We can actually wait until the heart stops beating and there is a possibility that this heart will start functioning adequately after it is transplanted.

I have said that we consider a patient is dead using three criteria. However, you

will agree that a patient is really dead when his brain is dead, and if his doctors can prove brain death without a shadow of a doubt, then there is no reason why the heart cannot be removed for transplantation while it is still beating. Let me explain this further, because this is some thing that has not been properly understood both by doctors and by the lay public. If I could have a human being that has just been hanged where there is brain death due to the hanging, I could re-start his heart immediately, or, if his heart is still beating, I could continue that heart beat by ventilating artificially for this patient, and I could probably keep that heart beating for a week by means of artificial ventilation. But you will all agree with me that the person cannot return to life because his brain has been killed by the hanging. Therefore, why should one wait until the heart stops beating? There is no sense in this reasoning because there is no further hope of life for the patient. There is no reason why a beating heart cannot be removed, especially when one remembers that once brain death has been declared, responsibility does not lie towards the donor any more. We have a responsibility then towards the recipient and one must do everything in one's power to give that patient the best chance of survival, and if his best chance of survival is by removing a beating heart, then this can be done.

Once a donor has been given to the transplant team, then the patient and donor are prepared, and they are moved into adjoining operating rooms. I have mentioned that the heart will only die gradually and that it will probably take between 2-3 hours before it is really dead. We would like to prevent this gradual death, and we would like to prevent as much as possible the damage of ischaemia to that heart, and therefore we take certain precautions, such as either to cool the heart down to diminish its metabolic demands, or to perfuse the heart with oxygenated blood, or to cool it down and perfuse it with oxygenated blood. We prefer to protect the heart from ischaemic death, after the donor has been declared

dead, by perfusing it with oxygenated blood and by cooling it down. And this is done as follows: The donor and patient are moved into adjoining operating rooms; both the donor and the patient's chests are opened by a median sternotomy which runs down the middle of the chest and the sternum is cut in half. As soon as the donor's heart is exposed, it is connected to a heart-lung machine to supply it with oxygenated blood. This is done very simply by cannulating the right atrium for venous drainage, passing the blood through the heart-lung machine and pumping it back into the arterial system by means of a catheter inserted into the ascending aorta. If other organs, such as the liver and kidneys, are also being used for transplantation, then total body perfusion is continued, but if only the heart is going to be used, then a clamp is applied to the ascending aorta distal to the arterial catheter; the flow is reduced to about 400mm. per minute and only the heart is perfused. Once the heart has been perfused for 20 minutes and cooled down to about 20°C, perfusion is stopped and the heart is excised as follows: The superior vena cava is ligated and divided distal to the ligature; the aorta is divided more or less where the ascending aorta joins the arch; the right and left pulmonary arteries are divided, as well as the four pulmonary veins. Care is taken not to damage the pace-maker or sinoauricular node that lies in the area of the superior vena cava, and therefore we do not cut where the superior vena cava enters the right atrium. The heart is then completely removed, and we are left with an empty pericardial sac, the stump of the aorta, the openings of the pulmonary arteries and veins and the inferior vena cava. The heart is transported to the operating theatre of the patient. At this stage it has already been determined that the donor's heart is normal, and the patient is connected to the patient's heart-lung machine by joining the catheter that has been left in the ascending aorta to the arterial line of the heart-lung machine of the patient and applying a clamp distal to the entrance of this catheter. Because the aortic valve is competent and the

catheter supply has a high pressure in that section of the aorta, it will perfuse the coronaries. I would like you to notice that the whole heart is removed for transplantation: the whole of the right atrium, the whole of the left atrium, both ventricles, the pulmonary artery and its bifurcation and a good length of aorta.

The patient is connected to the heart-lung machine by draining the venous blood through two vena cava catheters and returning the arterialised blood from the oxygenator through a catheter placed either in the ascending aorta or in the femoral artery. During this operation, while the heart is removed and the new heart transplanted, the heart-lung machine will supply oxygenated blood to the body and keep it alive.

Once the patient's heart has been excluded from the circulation with a heart-lung machine, it is also removed by applying a clamp to the ascending aorta, proximal to the catheter, then dividing the aorta, close to the coronary ostia, dividing the pulmonary artery on the pulmonary valves and then detaching the ventricles from the atria. What remains in the patient, therefore, using this technique, are the two venae cavae catheters in the right atrium draining the venous blood and the arterial catheter in the aorta supplying oxygenated blood. A section of the right atrium and intra-atrial septum is left behind, as well as a section of the left atrium; the aorta and a pulmonary artery with the two branches are also left behind. The new heart is now connected to the remnants that have been left. But before this can be done, the new heart has to be prepared for transplantation by dissecting between the aorta and pulmonary artery so that there will be more mobility of these two vessels. The bridge which forms the bifurcation of the pulmonary artery is also excised. This bifurcation is used because as a rule the patient has big, dilated pulmonary arteries while the donor has a smaller normal pulmonary artery; therefore, there is a disparity in size which makes it difficult to anastomose. If the bifurcation is used, there is a bigger opening and the disparity will be less. In



In addition the atria have also to be prepared for transplantation for connection to the remnants that have been left behind in the patient. The back wall of the atrium is opened and the holes thus made are connected to the remnants that have been left behind. To ensure that there will be sinus rhythm, care is taken not to injure the area where the superior vena cava enters the right atrium. The back wall of the left atrium is opened by excising that piece of muscle between the entrance of the four pulmonary veins. We now have a hole in the back of the right atrium, a hole in the back of the left atrium, the aorta and the pulmonary arteries, which must be anastomosed. I would like you to note that great care has been taken not to injure the sino-auricular node, and by cutting into the intra-atrial septum, the atrio-ventricular node will not be injured. With this technique, therefore, one can be certain that the transplanted heart will start in sinus rhythm without any conduction defect and no heart block. It is not difficult to anastomose the opening in the back wall of the left atrium to the left atrium by using the left wall and the intra-atrial septum and anastomosing the opening in the back wall of the right atrium using the remnant of the right atrium and again the intra-atrial septum. The pulmonary arteries and the aorta are also anastomosed.

During this whole procedure the donor heart is supplied through the catheter in the ascending aorta with oxygenated blood so that there will be no further ischaemic damage, and the patient's body is likewise oxygenated through the catheter in the ascending aorta.

The operation is now complete.

It can now be seen that the systemic venous blood will return into a small section of the patient's original atrium, then flow through the anastomotic opening into the donor's right atrium and then into the right ventricle. The same applies for the pulmonary venous blood.

At this stage the clamps are removed from the aorta, the heart is rewarmed and it is usual for it to start in spontaneous sinus rhythm, if it has been well protect-

ed. If it does not, it can be defibrillated by an electric shock.

When the heart is in place, it will be seen to lie in a fairly large pericardial sac, because the latter has been dilated as the result of the disease.

I would like to point out that the cardiac output of the donor heart before it was removed was 6.9 litres per minute, while the patient's cardiac output was 2.5 litres per minute. After transplantation, the donor heart had a cardiac output of 6.0 litres per minute, nearly the same as before transplantation, indicating that immediately after transplantation, the heart can supply an adequate output. With this technique it is also possible to have the patient in sinus rhythm. This is important because one of the signs of rejection is a change in the electrocardiogram, such as arrhythmias and heart block, and with this technique one can be certain that these changes are not due to the surgery.

It can therefore be seen that technically this operation is possible, and in the transplant experience of the world, one will find very few technical failures. But this is not all that is necessary to make a transplant successful because, as I have pointed out, the body has the ability to detect this foreign organ that has been transplanted. The body has the ability to distinguish between self and non-self, and as soon as it recognises that the transplanted organ is foreign to it, it will set up immunological reactions against it. Substances liberated by the transplanted organ, the antigens, will be detected by the immunologically competent cells, which will change and produce antibodies which will circulate back to the transplanted organ and destroy it.

However we have the ability to suppress the central mechanism that reacts to the antigen by slowing down the amount of antibodies that are liberated to destroy the transplanted organ. Unfortunately this is not specific for the transplanted organ; it suppresses the whole body's ability to react to foreign substances. Therefore it will also suppress the body's ability to react to infection. Thus in deciding on the immuno-suppres-



sive drugs that are to be used, and on the dosage, one is in great difficulty, because enough has to be given to prevent rejection while at the same time the dose must not be such as to increase the liability to infection. And this is the problem that we have today, to use enough of the immunosuppressive agents to prevent rejection but still allow the body its ability to react to infection. We therefore aim at keeping the drugs at a low level, and it is only when rejection become clinically evident that we increase the dosage to slow down the rejection process.

Our problem has been how to detect rejection in the transplanted heart. I think that rejection can be compared to an infection, and we can diagnose rejection using the same groups of symptoms that appear in infection or inflammation. As in inflammation one will thus find systemic changes, such as a rise in temperature, increase in pulse rate, anorexia, malaise and occasionally mental changes. Likewise, as in inflammation, in rejection one will find local changes, an enlargement of the transplanted organ, deterioration in function and, if the rejection is well advanced, one may find evidence of parenchymal destruction, and lastly, one finds other changes which may not really be part of the rejection episode but are associated with it. So other immunological changes may be present.

Let us now see how all these factors have helped us to diagnose rejection in the transplanted heart:

**Systemic changes:** In one case there was an episode of rejection about 20 days after surgery. There was a rise in temperature, a rise in pulse rate and a rise in respiratory rate. The dose of the immunosuppressive drugs was increased and this was soon accompanied by a drop in temperature, pulse rate and respiratory rate. The sedimentation rate was also raised showing systemic activity as rejection occurs, but when the latter was treated, there was a drop in the sedimentation rate.

So systemic changes can be looked for and these can help us to diagnose the onset of rejection. These changes will

serve as a warning to step up the immunosuppressive drugs in order to slow down the rejection episode again.

**Local changes:** These consist in enlargement of the heart during the rejection episode. This enlargement is not so much due to a swelling of the heart muscle, but mainly to a dilatation of the heart during rejection. It can be detected by the onset of a gallop-rhythm and a functional mitral systolic murmur. There is also a pericardial reaction, during rejection and a part of the enlargement is due to a pericardial effusion.

One would expect that when the heart muscle is damaged due to rejection there will be liberation of enzymes which could help in the diagnosis of rejection. Unfortunately this has not proved to be of much value because we have not been able to find evidence of a rise in the enzyme levels during an episode of rejection. This is difficult to explain, but we believe that enzyme changes occur late in rejection. If rejection is diagnosed and treated early, then enzyme changes do not occur. However, it is interesting to note that one gets a certain rise in the enzyme level after the rejection has been reversed, and this is probably due to the increase in the immunosuppressive drugs which cause a certain amount of liver damage.

**Functional changes:** One would imagine that if the heart is invaded by cells and oedema occurs, functional changes will manifest themselves. This can be detected at the bedside by the onset of right heart failure, a rise in venous pressure, enlargement of the liver, dilatation of the heart as shown by a gallop rhythm and the onset of a systolic murmur. But in most cases the earliest indication of a disturbance in the heart function is a change in the electrocardiogram. Changes, such as arrhythmias and conduction disturbances, may be present, but the most important is a drop in the voltage of the electrocardiogram. When the rejection is treated, the voltage returns. In fact, we believe that this is the earliest and most important sign of rejection and we will treat a patient for rejection if there is

only a drop in voltage of the electrocardiogram.

We have investigated other immunological changes, such as the development of heterophile antibodies, of cytotoxic antibodies and so on, but we have not found these changes of any value in the early diagnosis of rejection.

To sum up, we have been able to detect rejection of the transplanted heart early by observing the voltage of the electrocardiogram, and then usually the rejection can be reversed by increasing the immuno-suppressive drugs.

Despite our ability to diagnose rejection and despite our ability to reverse a clinically evident rejection episode, rejection, as I stated in the beginning, takes place all the time and the heart will eventually be killed by these episodes. When the heart of Dr. Blaiberg was removed at postmortem, we found very little evidence of rejection in the mitral valve; the heart muscle also looked fairly normal and there was little change in the coelium of the atrium. But the transplanted aorta, which was normal during the transplant, showed extensive atherosclerotic changes and it must be remembered that the patient's original disease was atherosclerosis. The coronaries were also thickened from the deposition of cholesterol and the vessels extremely narrowed. This is due to a combination of the rejection damage and the deposition of cholesterol. In other words, rejection after 19 months had caused so much vascular damage that the patient again developed ischaemic heart disease, that the heart muscle was again destroyed by the original process that had caused the illness in his first heart.

I have shown that there is an indication for heart transplantation. I have shown that we have the ability to diagnose rejection and to reverse it. But I have also shown that at the end the transplanted heart will be destroyed. But in series of slides I can show you a patient 12 days after surgery, a man who was dying from heart disease, was short of breath by day and night and could not eat because his liver was so congested. And then you can see him normal, without any symptoms of

heart disease only 12 days after the heart had been transplanted.

Another shows a man who 18 days after transplantation was able to shave himself again when for 6 months before surgery he could not do so because he had been so ill. Our slide shows him celebrating the New Year, when I am quite certain that without the transplant he would have been dead or at the most bedridden. Another shows him able to enjoy a sport that he had loved all his life — fishing. And another one shows him celebrating with another transplant patient the first anniversary of his own transplant.

Yet another slide shows a patient who was dying from heart disease, who attempted to commit suicide one day before the transplant, now able to play tennis again.

I think, ladies and gentlemen, it would be better if I were to ask you whether there is a future in heart transplantation. Or perhaps it would be better if we ask these patients if there is a future in heart transplantation? I agree that we have a number of difficulties and we are far from solving the many problems. But is transplantation worthwhile? Is there a future to it? Are we able to solve the problems that lie ahead?

We have so far done 5 heart transplantations. One patient lived for 18 days, one for 593 days, one is alive and well 365 days after transplant, one died 64 days after transplant and one is alive and well 143 days after transplant. The average life expectancy of these patients if a transplant had not been done would have been 30 days. So do you think there is a future in heart transplantation? Do you think that we are going to solve the problems that lie ahead? I think that it is all in the state of the mind:

If you think you are beaten, you are,  
 If you think you dare not, you don't  
 If you think you'd like to win but can't,  
 Its almost a cinch you won't.  
 If you think you'll lose, you've lost,  
 For out in the world you'll find  
 Success begins with a fellow's will;  
 It's all in the state of the mind.

