products, thereby learning something about the aetiology of these conditions.

The first single gene disorder to be looked at at the molecular level was thalassaemia – severe genetic anaemia. The basic problem is haemoglobin synthesis and difficulty in making beta chains, and the question is what is the matter with the gene which regulates the structure of the beta chains of haemoglobin in these children? Now it is possible to take the genes out from these children, clone and then sequence them. Studying this disease has told us perhaps the whole repertoire of things that can go wrong with genes.

It is now apparent that over 50 different mutations can cause the clinical picture of thalassaemia. Sometimes the genes are missing (deleted) but in the majority of cases there are simple basic changes in the DNA which cause inefficient transcription or translation. For example base changes in the coding regions (exons) may scramble the genetic code and lead to the production of a useless messenger RNA. Similarly, base changes in the critical regions near the junctions between introns and exons may prevent the normal splicing reactions which join the exons together and form the definitive messenger RNA. Other more subtle mutations may involve regulatory regions outside the gene. As other genetic diseases are studied in this way similar lesions are turning up. For example haemophilia is very heterogenous; some cases are due to deletions of the factor VIII gene while others are due to mutations that scramble the genetic code. It is now possible to use this information to develop prenatal diagnosis programmes using fetal DNA obtained by chorionic villus in the first trimester.

Another major success story in this field is the development of methods for finding genes for diseases, the cause of which is completely unknown. This has entailed linkage studies using DNA polymorphisms, i.e. normal variation in the structure of DNA that produces a new site for a cutting enzyme. For example it has been possible to find the gene for Duchenne muscular dystrophy on the X chromasome. Once having found a gene it is possible, from its sequence, to work back to its protein product and hence to find out what is the basis of the disease. In the case of the Duchenne muscular dystrophy it is the defective production of a muscle protein called dystrophin.

In the future it should be possible to use a similar linkage approach to define some of the genes that are involved in the genetic susceptibility to diseases like coronary artery disease and major psychiatric illness. Recent studies on the pathogenesis of cancer have also been facilitated by the molecular approach in that it is now possible to define many cancers in terms of one or more mutations of specific cellular housekeeping genes called oncogenes.

Recombinant DNA technology is also allowing us to manufacture a variety of pharmaceutical products by putting human genes into bacteria and having them express themselves in their new home. Genetically engineered erythropoietin for the treatment of the anaemia of renal disease is a good example; many will follow. Recombinant DNA technology is also allowing us to produce a wide range of diagnostic agents for the rapid identification of bacteria, viruses and parasites. In the long term it should help us develop vaccines for many of these conditions.

Clearly molecular medicine is here to stay and has wide application right across clinical medicine. Indeed clinical genetics can be defined as 'anything interesting', a term first used by Sir Cyril Clarke many years ago and certainly more true than ever today.

Sir David ended with the thought that the most important benefits of all from the biotechnology field in the next 100 years would come from growing better plants.

In reply to questions –

Dr Mott asked him to speculate on the development of new vaccines. Sir David discussed the efforts to develop a vaccine against malaria, various phases have been gone through; first identification of likely antigens which might be protective and then making large quantities by cloning them. This initial approach has not been very successful so far. The next stage may be to find out which part of the antigen is the 'business bit' e.g. small peptides and to use those as immunogens. The yeast cloning of antigens has been very successful against hepatitis. It may go the same way with malaria.

Dr Laszlo asked about the need to regulate research into gene therapy. Sir David said that he had just been chairing a committee at the MRC to get some guidelines for gene therapy in human beings. The committee has said that scientists should not be allowed for the forseeable future to put genes into fertilised human eggs for replacement – genes that would subsequently be expressed in future generations. He mentioned the government's white paper on embryo research and he hoped that the Bill would go through as it stands. He said that society must be able to feel that these matters were being looked at carefully. He did not think that scientists could have total freedom in this field, if they do not act responsibly the public will just come down on them and they will end up with a situation in which they can do nothing.

Dr Payne asked him to look into the future and tell us what the difference in life expectation might be in a few hundred years time. Sir David said that it was likely that the known hazards to life from malignant and degenerative disease would be removed and then the question would be would it ever be possible to prolong the ageing process ? Ageing must be genetic because different species have their own very tight kind of natural age. How this works is fascinating, if we could discover which genes are at work in cell ageing we might be able to modify them. It is conceivable that ultimately we may be able to do this and to live a lot longer.

Heart and Lung Transplantation – Present and Future

Mr J. Wallwork
Papworth Hospital, Cambridge

Mr Wallwork began by emphasising that movement in this subject is so rapid that he could speak only of the situation today, tomorrow it will certainly have changed.

In 1979, when heart transplants started at Papworth there were only 5 centres active in the world, in 1987 there were 100 centres in the USA, probably over 55 centres in Europe. The heart-lung transplant service at Papworth started in 1984, and next year in 1988 it is planned to do 35 heart lung transplants.

The history begins with a Russian, Demikof who did an animal heart-lung transplant in 1946 and it survived two hours. Denton Cooley had a patient last 14 hours, Lillehei in 1969 had a patient with a few days survival, Christian Barnard did a heart transplant in 1971 that lasted 23 days. This was 'it' until the 1980s. About 59 single lung transplants were performed all ending in disaster.

Sir Roy Calne first used cyclosporin A as an immuno-

suppressive agent in 1979 in Cambridge. It was then used in heart transplantation in Stanford with success. In 1981 the first successful heart-lung transplant was done at Stanford and Mr Wallwork 'happened to be there'! In 1984 the first successful case in this country was done at Papworth and then in 1985 they started to take the organs from the donor at a distance which was a very important development.

The advantages of a heart along with the lungs are several, it replaces all the diseased tissue, it is technically simpler and the trachea heals better because it gets its blood supply from the coronary arteries.

Among diseases suitable for heart-lung transplantation are a whole group of congenital heart conditions with pulmonary hypertension, particularly children who have had difficult corrective or semi-corrective procedures in infancy and for whom there is no further possibility of anatomical correction, a few patients with primary pulmonary hypertension, emphysema, interstitial pulmonary disease and the cystic fibrotics who are becoming a very important group.

Selection of cases for this restricted service requires some harsh choices. Nobody over the age of 50 has yet been taken, surgery for the younger age group is increasing with collaboration with Great Ormond Street. Total referrals so far have been 300, many were unsuitable because they were too old or too ill. Emergency transplantation would not be the best use of our scarce resource. The waiting list contains more women than men in contrast to heart transplantation where only one in ten are female. 17 have died waiting. 33 heart-lung transplants have been done with a one year survival of about 78%. All patients were chronically disabled and many about to die from their disease. This is about the same survival rate as from heart transplantation. The waiting time for an appointment is about six months and a further 10 months on average before transplantation, varying from four weeks to two years. Those patients with pulmonary hypertension who are very ill have been given long term self-administered infusions of prostacycline, initially it was hoped it might reverse their pulmonary hypertension, it does not do this but they are dramatically improved and it buys them extra time. It is very expensive and is not used as a primary form of therapy.

The methods of handling donors have been developing at Papworth in quite a unique way and have been adopted by other heart-lung transplant centres. Lungs must be in good condition and able to work right away, unlike transplanted kidneys which can be supported initially by dialysis. Donors over 40 years old are not used. A major cause of recipient death in earlier series has been cytomegalovirus (CMV) infection. So all donors are tested for CMV and CMV positive organs are not put into CMV negative patients. Another important point is to get the size right – it is no good putting large organs into small patients and the size can be gauged from the X-rays and the height and weight of the donor.

Organs at the donor's hospital and the method of preserving them is very important. Organs must be cold and the lungs inflated. Lungs are perfused with a single cold flush. The solution is important, essentially blood from the donor with an extracellular solution of mannitol is used. The patient is given a prostacycline infusion to dilate all the vascular bed and put it in at 4 degrees under gravity. There have been no primary organ failures in 33 transplants. The ischaemic time, from removal to insertion, has been up to four hours. In some centres organs have been transported by aereoplane with complicated apparatus to perfuse and oxygenate them, but this is unneccessary and liable to fail.

An essential in the operative technique is to get the timing right. The operation to remove the recipients heart and lungs is begun at the same time as the operation at the donors hospital to remove the organs. The operation to remove the recipient's organs is the hardest part. The phrenic, the vagus and the recurrent laryngeal nerves must not be damaged. The whole trachea must be saved to preserve the cough reflex. It is easier to avoid damaging these important structures if the heart and the lungs are removed separately and not all together as was done originally. The operation becomes much more difficult if patients have adhesions from previous lung surgery. This can cause much bleeding and may rule them out as transplant recipients. Putting the organs in is much easier and takes only about 35 minutes – first join up the trachea, then the aorta and then the right atrium.

There is nothing special in postoperative management, patients are extubated usually in 48 hours, sometimes in 12 hours. Fluids are restricted to prevent the lungs from getting wet, they have lost their lymphatic connections and so will take a long time to get rid of oedema. The patients are got up as early as possible, and usually 3 or 4 days after surgery they are sitting in a chair exercising and beginning to become mobile.

The routine for prevention of rejection is basically with Cyclosporin A and Immuran. Steroids are given only for rejection episodes. The major problem is how to detect rejection in the lungs. The difficulty is to distinguish rejection from infection. The stethoscope, to detect new wheezes and crackles, simple pulmonary function tests – e.g. the FEV 1, and transbronchial biopsies may give evidence before there are X-ray changes. Rejection episodes generally occur within the first 3 months but these methods have picked up some later episodes. If missed they may go on to obliterative bronchiolitis and long term damage. Various infections may occur and all patients are given septrin when receiving steroids to prevent pneumocystus. They are barrier nursed for 3 days, they go into the general wards for 2 or 3 weeks and then out into the hospital flats for another week before going home.

Results – of the first 31 patients, age 12 to 46 and mostly women, 23 are alive and well. One is back at work at his job in the army, another plays very good squash. Their quality of life is good, this is especially important when the length of life is as yet unknown. Actuarial survival is 78% at one year and 68% at 2 years.

The full cost for the first year is about £15,000 per patient, or one tenth the cost of keeping a patient on prostacycline for a year.

In reply to a comment by Mr Keen, Mr Wallwork said that the surgery is now the straightforward part of the exercise and the organisation has been worked out. The long term results are going to depend on the physicians and the immumologists.