Human Heart Transplantation

SIR,—From what I can deduce from a study of canine heart allotransplants and the human heart allotransplant described by J. G. Thomson (1 June, p. 511), vascular lesions similar to those in allotransplanted kidneys¹ seem to form the basis of rejection. Thomson has rightly stressed the microscopist's difficulty in assessing rejection. For many years I have pointed out the value of autotransplantation and the nonspecificity of the allotransplant reaction in relation to type of cell and damage which ensues, and particularly in relation to the significance of early anuria² in allotransplanted kidneys. The pre-existing lesion—particularly pyelonephritis and the artifact—has also been my favourite theme. While one has to take all this into account one can arrive by formal experimentation at a general description of rejection in allotransplanted organs, but modifications reflecting the unique conditions of any given organ at any given age require to be made. A general description of rejection requires data from disciplines other than microscopy—physiology, biochemistry, and enzymology, etc.

Acute rejection of the cardiac allotransplant manifests itself as a cellular invasion of and damage to the vessels at all levels, and foci of muscle necrosis develop in those areas where capillary damage has been severe. Widespread oedema is the outcome. The valves show a varying degree of cell invasion at the fixed margin where capillaries are usually clearly seen. The endocardium and subendocardium are oedematous and infiltrated by cells. The integrity of the endocardium in places will be broken and mural thrombi may develop. Only in a very severe acute rejection will this process be responsible for cardiac arrest in the immunosuppressed human, but the price of controlling it may be pulmonary infection.

The lesion of chronic rejection will involve the coronary system at all levels and at varying intensities and rates. The early lesion will show widespread oedema of the vessel wall and the early stages of the obliterative lesion found in human allotransplanted kidneys which involves fibrinoid necrosis. As Thomson points out, there is no evidence that cobalt x-irradiation is responsible for this lesion,³ and indeed kidney transplanters are quite happy with even larger doses.⁴ Cell invasion of the interstitium will be minimal in many areas. Foci of chronic residual oedema will eventually lead to fibrosis,⁴ and areas of damaged myocardium will become calcified. Perhaps giant cells resembling Aschoff bodies will be found in areas involving muscle necrosis⁵ in those cases which have suffered acute rejection, had it reversed, but later die. These lesions will progress for a time with little signs of cardiac insufficiency. The natural history of this involvement of the coronary system will surely follow the usual unpredictable course of coronary disease and not necessarily one of gradual decline of cardiac efficiency—as your recent leader (11 May, p. 315) suggests. The good collateral circulation and the ability to hypertrophy well after focal damage sets the cardiac transplant apart in this respect from the renal transplant.

I have argued the principle of clinical heart transplantation since 1961.⁶ One of the many reasons why I hesitate to argue

the case for immediate clinical application is because the relation between the acute rejection process and cardiac arrest is still, surprisingly, ill-understood, and until it is clarified some patients with cardiac transplants will suffer unnecessarily.—“Even the bravest heart will swell in the moment of farewell.”

From my data on several canine allotransplants it seems that the microscopic changes *per se* are not always sufficient explanation of sudden arrest of function, and one has

FIG. 1.—An arteriogram of a heart about one hour after transplantation to the carotid jugular circulation.

FIG. 2.—An arteriogram of the same heart some days later when the E.C.G. voltage was markedly reduced and the P wave had disappeared. Cardiac arrest occurred shortly after this arteriogram was performed. There is some filling of the left ventricle. Intense spasm of the coronary vessels is obvious.

been forced to assess rejection with other techniques. A decrease of QRS voltage and arrhythmias are usually premonitory signs of cardiac rejection,⁷ but the natural history is not always so clear-cut and cardiac arrest can occur within hours of recording only the disappearance of the P wave. Extravascular pressure is one important factor in determining coronary flow along with the action of the heart's contraction, which normally tends to impede its own circulation. The perfusion pressure of the oedematous orthotopic cardiac allotransplant will also tend to fall and enhance the trend to myocardial ischaemia.

But another factor has to be considered. A vasomotor vascular shut down was described by me⁸ in the late stage of rejecting kidney allotransplants, and this phenomenon has only recently been confirmed.⁹ It has been my experience that severe coronary spasm occurs at a relatively late stage in the natural history of the canine cardiac allotransplant, and I think that this determines the onset of cardiac arrest (Figs. 1 and 2). The coronary spasm is not explicable on the microscopic state of the vessels.

Even with 24-hour E.C.G. monitoring it would be extremely difficult to control acute coronary spasm in very acute human rejection processes mounted within the first week. Since a pyrexial toxic syndrome¹⁰ appears not to occur in dogs rejecting cardiac transplants, any fever which develops at a time when the QRS voltage falls should be interpreted as a complication (probably pulmonary) rather than as a direct sign of rejection. One has to consider the possible consequences of a mild left ventricular failure and a mild pulmonary oedema in a patient on mounting doses of immuno-suppressive drugs.

It appears that we have come full circle back to coronary artery disease and its prevention and management. There will be those who will advocate that it is wiser to spend available funds on research into the causes of coronary vascular disease, especially when a fair proportion of cases have a generalized vascular disease. Clinical empiricism in heart transplantation may force us to take a new look at the coronary system and the way in which immunological damage can be suppressed by steroids in those cases which can utilize them efficiently. The efficient utilization of steroids in general medicine shows an individual and species variation. And this factor seems to me more important than tissue matching.—I am, etc.,

W. J. DEMPSTER.

Royal Postgraduate
Medical School,
London W.12.

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