INTRODUCTION
Cardiac transplantation has become firmly established as a treatment for terminal cardiac failure. The early experimental work in animals\(^1\)\(^-\)\(^7\) that preceded the first human-to-human cardiac transplant in 1967 is now mainly of historical interest. Thomson\(^8\) documented the pathological findings in the donor heart of Louis Washansky, who was the recipient in this first historic operation. Shortly thereafter Lower et al.\(^9\) reported their experience with human cardiac transplantation.

Despite advances in patient selection, donor heart procurement and preservation, and immunosuppressive therapy, acute rejection remains an important cause of graft loss and recipient mortality.

MACROSCOPIC APPEARANCE OF ACUTE REJECTION
Mild or moderate acute rejection usually fails to produce detectable naked-eye changes in the donor heart apart from an increased organ mass (Figure 1)\(^10\)\(^-\)\(^11\). Cyclosporine-induced systemic hypertension may also contribute to the cardiac hypertrophy. Such hearts are seldom examined pathologically unless the recipient has died of other causes.

Severe acute rejection may produce a swollen, mottled myocardium with scanty subendocardial hemorrhages. A heterotopic transplant which has undergone irreversible, severe rejection may not lead to the death of the recipient if the latter’s own heart has enough residual function to support the circulation.

Figure 1  Transverse slices of recipient heart (left) and donor heart (right) 21 days after heterotopic transplantation. The severely rejected donor myocardium presents a pseudohypertrophied appearance. (Reproduced with permission from ref. 10)
Explanted heterotopic grafts usually show very severe acute rejection since immunosuppression is often reduced in the period between cessation of graft function and surgical excision of the graft. Such hearts (Figure 2) have a severely hemorrhagic, mottled appearance. Geographic zones of pale-colored, focal infarction stand out against the plum-colored, hemorrhagic, but still viable myocardium. Stasis thrombi may be present within the cardiac chambers. Orthotopic transplants that have failed primarily due to acute rejection usually show less obvious naked-eye alterations despite the presence of severe acute rejection histologically.

Figure 2 Close-up view of donor heart left ventricular outflow tract. Severe acute rejection has produced diffuse intramyocardial hemorrhage and the myocardial cut surface shows pale areas of necrosis which contrast with the hemorrhagic background.

ROLE OF ENDOMYOCARDIAL BIOPSY IN THE DIAGNOSIS OF ACUTE REJECTION

Endomyocardial biopsy histology with grading of the severity of rejection continues to be the so-called gold standard for the diagnosis of acute rejection. Usually biopsies are performed weekly during the first 6 weeks post-transplantation and then fortnightly for the next few months. Gradually thereafter the intervals between the biopsies are increased until a stage is reached at which the biopsies are done approximately every 3 months.

Non-invasive methods for diagnosing acute rejection, such as magnetic resonance imaging, assessment of peripheral blood lymphocytic activation and soluble interleukin-2 receptor levels, have failed to live up to expectations and have not superseded graft histology. It remains to be seen whether other non-histologic modalities, e.g. radioimmunoassay assessment of vascular adhesion molecules in endomyocardial biopsies, may play a role in the routine management of cardiac transplant patients. The latter invasive procedure is still dependent on the taking of endomyocardial biopsies.

Earlier criticism of endomyocardial biopsy has focused primarily on the possibility of sampling error and the subtlety of the histologic changes in diagnosing rejection. One study attempted to validate the technique by examining biopsy samples taken with a biopomc from formalin-fixed explanted human donor hearts, and comparing these in a blind fashion with standard histologic sections taken from the same hearts. Agreement of results between the biopsy samples and the routine sections was found in 86% of cases. False-negative results were less than 1%. Acute rejection involved both ventricles equally.

Due to the rigidity of the biopomc catheter, endomyocardial biopsy usually only samples the septal wall of the right ventricle towards the apex. Four or five tissue samples are regarded as adequate. In practice most pathologists usually receive three or four endomyocardial samples per biopsy procedure. In the study referred to earlier, it was found that even as few as two endomyocardial samples revealed the presence of acute rejection. If fewer samples are received this should be noted in the pathologic report, since it holds the implication that significant rejection may be missed (false-negative biopsy). In the light of other clinical and laboratory parameters, the cardiac surgeon has to decide whether an immediate or earlier than usual repeat biopsy is indicated. The size of the biopsy specimen varies according to the biopomc used. If the biopsy specimens are small, then a suboptimal number of samples has more severe implications than would be the case if the samples were large.

At some centers the endomyocardial biopsies are submitted to the laboratory in 5% buffered glutaraldehyde to facilitate subsequent ultrastructural examination of one of the fragments, if this is deemed necessary. Selected fragments for light microscopic assessment of rejection are transferred into 5% buffered formaldehyde and processed in a hypercenter tissue processor for expedited handling.

Paraffin-embedded sections are stained by the hematoxylin–eosin, Masson’s trichrome, elastic van Gieson, and Unna–Pappenheim methods. One or two biopsies may also be submitted unfixed for immediate frozen section. This gives immediate information regarding the presence of rejection, and additional sections may be cut for the determination of lymphocyte subsets. The latter is performed more for research purposes than for influencing management of the patient. Electron microscopy and immunofluorescence microscopy play only a small role in the routine diagnosis of acute rejection.

HISTOPATHOLOGY OF ACUTE REJECTION

One of the earliest changes observed in acute rejection is the development of interstitial edema (Figure 3), which is most prominent perivascularly and less evident in the endocardium, which has a denser connective tissue component. The edema is probably a result of microvascular damage. Interstitial edema is less severe in patients receiving cyclosporin compared to the earlier, steroid-based immunosuppression. The vascular endothelium is that portion of the graft which first encounters the host lymphocytes which are attracted into the graft, since these cells reach the graft via the bloodstream.

In the early stages of acute rejection the small blood vessels within the graft contain increased numbers of mononuclear cells (Figure 4), which may also be seen to be passing through the vessels’ walls into the surrounding myocardium. The early