Some histological features of canine cardiac transplants

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The cellular reaction in cardiac homografts was observed mainly in the perivascular areas and in the subepicardial and subendocardial layers. All the valvular structures were involved by the cellular infiltration, but the aortic and pulmonary cusp changes were less severe. Although the vascular changes seemed to be severe, yet, for unknown reasons, some vascular segments and consequently some myocardial areas were spared. The intermittent immunosuppressive therapy (azathioprine) seemed to have influenced the pathological changes; it did not completely prevent the rejection process, suggesting that better control of the host-versus-graft reaction could be obtained by continuous immunosuppression.

The histological features of cardiac transplants have been extensively studied in heterotopic grafts, either on the neck (Chiba et al., 1962; Reemtsma, 1964) or in the abdominal position (Abbott, DeWitt, and Creech, 1965), but few detailed studies concerning orthotropic cardiac transplants have been reported (Blumenstock, 1966; Kondo, Grädel, and Kantrowitz, 1965a and b; Lower and Shumway, 1960; Shumway and Lower, 1964). This paper deals with some pathological changes in relation to the rejection process, and is based upon examination of canine specimens taken from survivors (some of them long-term) belonging to two experimental series previously reported (Cacheria, Lacombe, Bui-Mong-Hung, Leandri, Laurent, and Dubost, 1966): (i) 10 survivors out of 31 dogs, either adult or young, submitted to autotransplantation (2 days to 7 months); and (ii) 7 survivors out of 31 puppies submitted to isotopic homotransplantation (30 hours to 119 days) after three to five hours of heart storage in hypothermic and hyperbaric conditions, according to Lyons, Dietzman, and Lillehei's (1966) technique. The present comparative study may throw some light on some particular aspects of the graft-versus-host reaction on which other workers have not already commented.

THE CELLULAR REACTION

The essential features of the cellular reaction observed in our homografts were of a specific type described as 'graft-versus-host' changes. The polymorphonuclear cells, lymphocytes, monocytes, and pyroninophilic plasma cells were preferentially spread over the perivascular spaces (Fig. 1), particularly in the subepicardial and subendocardial layers. A dense cellular invasion was observed continuously along the entire pericardial and endocardial surfaces. Within the myocardium different characteristics were noted, namely vessel-centred nodules and scattered infiltrates. These infiltrates broke up the bundles of myocardial fibres, especially in the subepicardial and subendocardial layers, and invaded the epicardial fat, where they appeared diffuse and surrounded nerve fibres and vessels. This cellular infiltration was already present in the earlier specimens (8 and 9 days) (Fig. 2): at that time, similar inflammatory changes were also detected in the vicinity of the suture lines. It is noticeable that in the specimens taken from longer-term survivors (after 20 days) no infiltration was present near the sutures, although inflammatory infiltrates were still conspicuous in the other elective sites.

Unfortunately, in the present series, between the first and the eighth day after transplantation, no specimen was available, and consequently no precise account of the actual onset of the early cellular tissue reaction can be given.¹

¹Nevertheless, in a subsequent experimental series, 3- to 7-day survivals were obtained in four instances: typical cells were observed in only the 6-day specimen; but the cellular reaction could hardly be discerned in the other cases, being masked by the immediate non-specific inflammatory infiltrates. The earliest phenomenon seemed to be a swelling of the vascular endothelia; the intimal layer consisted of strikingly altered cells with a bulky nucleus and dense cytoplasm. This change was visible all over the valvular leaftet surfaces.
The striking cellular reaction visible in the canine cardiac transplants was of the same intensity on both ventricles, in contrast with the right ventricular predominance encountered in a parallel series of heterotopic cardiac transplants in rats, already mentioned by Abbott et al. (1965); in the latter experimental series the working right ventricle was grossly infiltrated by the cells, the left ventricle undergoing rapid necrotic changes.

The intensity of the cellular reaction seemed to be influenced by the immunosuppressive therapy: on the twentieth day an untreated graft exhibited a more severe and diffuse cellular infiltration than did transplants from treated dogs on the 76th and 119th days. In these two specimens the rejection process seemed to have proceeded by successive steps influenced by the intermittent immunosuppressive drug, azathioprine: the occurrence of fibrous scars was in favour of such a hypothesis.

**VALVULAR CHANGES**

Valvular changes were constantly observed in specimens taken from dogs that survived more
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than 20 days. The cellular infiltration of the inner line (Fig. 3) and of the valvular tissue itself (Fig. 4) was mixed with an active fibroblastic reaction. Mitral and tricuspid valves, including the chordae tendineae, were particularly involved; by contrast the aortic and pulmonary cusps exhibited less marked changes. The slight subintimal infiltration of the cusps diminished along the vascular wall and disappeared near the suture lines: this striking contrast could be related to a tolerance of the host towards a poorly vascularized grafted tissue. It has been shown that human aortic cusps are vascularized only in pathological conditions or in the first and last decades of life (Dow and Harper, 1932; Gross, 1937), since mitral and tricuspid leaflets are often vascularized even if no pathological changes are present.

What could be the future behaviour of such valvular changes? They could favour the development of thrombosis and/or bacterial endocarditis, and they could undergo a fibrous process which could hinder the valvular function. The fibrotic changes observed by Hudson (1966) in aortic homografts in man may correspond to such a process, originating from an anterior cellular infiltration.

VASCULAR CHANGES

The vascular inflammatory changes, slight in the recently transplanted hearts (before 20 days), became marked on specimens taken from long-term survivors: the coronary trunks were especially involved, arteries more severely than veins, but the capillary network seemed to be intact. Nevertheless these vascular changes, patchy in type, did not involve the whole myocardial vasculature. The panvascularitis included medial and subintimal infiltration with a cellular reaction; it led to narrowing of the lumina of vessels, was a source of thrombosis (Figs 1 and 5), and damaged some of the myocardium. Similar vascular changes were seen in renal homotransplants in dogs, but they spread along the whole vascular system and they appeared earlier, as pointed out by Porter (1964, 1965), Porter, Owen, Mowbray, Thomson, Kenyon, and Peart (1963), and Dormont, Crosnier, De

FIG. 3. Dog 3207, 76 days’ survival. Tricuspid leaflet. The cellular reaction induces thickening of the subendocardial layers along the edges of the valve and the neighbouring chordae tendineae. This infiltration continues on the endocardial layer of the right ventricle (below). The infiltration is less marked on the inner part of the leaflet. H. and E. ×50.
Montera, and Hamburger (1965); the findings on the 18th day in kidney grafts were similar to the vascular changes of our myocardial transplant after 118 days. Cutaneous homografts exhibited the same vascular changes as the kidney transplants (Medawar, 1944). In the present study no fibrinoid necrosis was observed. Focal haemorrhages were seen only once—in an untreated puppy, who survived 19 days.

**OCCURRENCE OF NECROSES**

Necrotic areas have been described in cardiac homotransplants by numerous authors (Blumenstock, 1966; Shumway and Lower, 1964): according to their studies necroses were present from three to 21 days after grafting.

Large necroses were commonly observed in autotransplanted hearts: necrotic areas could be secondarily calcified and even ossified. These lesions were undoubtedly due to electrical burning (defibrillation). Macroscopically, they were identical in shape in the autotransplants and in the homografts, linear strips corresponding to the application of the electrodes (Fig. 6). It seemed difficult *a priori* to distinguish such burns from the necrotic foci which follow the rejection pro-

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**FIG. 4.** Dog 3286, 119 days' survival. Mitral valve. Microscopical view of the aortic leaflet. The inner portion of the valvular tissue is the site of cellular infiltration. The subintimal layers are also involved. H. and E. ×45.
FIG. 5. Dog 3207, 76 days' survival. Coronary artery and vein. Endovascularitis and intraluminal thrombosis in both vessels; a slight perivascular fibrosis mixed with the cellular reactions is observed. H. and E. x60.

FIG. 6. Dog 3400, 8 days' survival. Macroscopical view of the right ventricle and its cavity. The necrotic striae due to electrical burning are seen not only on the endocardial surface but also along the septal wall and in the papillary muscle. These bands of necrotic tissue follow the outlines of the converter electrodes.
cess. Both lesions were either subepicardial or deep, even involving the chordae tendineae, the papillary muscles, and occasionally the interventricular septum. The early burns were sharply limited and the localized surrounding cellular reaction was rapidly fibroblastic in type. By contrast, the delayed necroses were poorly limited and spread over the whole myocardium: different aspects were observed according to the time elapsed, and sometimes fibrous scars persisted. Various types of necroses, either remote or recent, were observed: pure loss of striation, vacuolization, necrosis with cytoplasmic homogenization, and, at the worst, cytoplasmic lysis allowing a persistence of sarcolemmic outline (Fig. 7).

**FIBROTIC CHANGES**

Some fibrotic areas, predominantly in either the subendocardial or subepicardial layers and in the perivascular spaces, were seen in the survivors who lived longer. These fibrotic changes may represent sequelae of the previous rejection process, lessened by immunosuppressive drugs.

Nevertheless, it is possible to imagine that the delayed myocardial necroses, observed at different stages in the same specimens, could undergo fibrotic scarring changes. These fibrotic changes, as mentioned above, could also affect the valvular tissue.

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