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First Year of Cardiac Transplantation

In the past year man has transplanted the human heart and orbited the moon. The public imagination was fired no less by the surgical than by the lunar feat. While kidney grafting and the first liver transplant passed almost without comment, transfer of the human heart was accompanied by embarrassing publicity. The alacrity with which Professor C. Barnard's lead was taken up by surgical teams all over the world was remarkable. Now a year and nearly a hundred human cardiac transplants later it is time to take stock. How many of the patients have not only survived but benefited ? Does cardiac transplantation offer predictable short-term palliation ? In other words, is it yet at all comparable with renal transplantation ?

Years of experimental work by N. E. Shumway[1] and by W. R. Webb[2] and their colleagues, including long-term survival experiments on dogs,[3 4] led up to the first human cardiac transplant, which was carried out by J. D. Hardy in Jackson, Mississippi, in January 1964.[5] This operation was unsuccessful and was attended by little publicity. A chimpanzee's heart was used because the potential donor did not die before the recipient reached the point of death. Nearly four years elapsed before Barnard performed the second operation, in Cape Town in December 1967.[6]

The functional capacity of the transplanted and denervated heart has now been thoroughly studied.[7 8] It has been well established that, though experimental denervation alters the manner of the cardiac response to exercise, the heart's efficiency is hardly impaired provided circulating adrenal-medullary catecholamines remain available. In the absence of endogenous noradrenaline, which is normally released in the myocardium by the cardiac nerves, the heart can increase its output only through the Frank–Starling mechanism, whereby an increase in length of myocardial fibre generates an increased stroke output. A normal heart, but not a damaged one, can increase its stroke volume two or three times by this means alone. The denervated heart, however, is unduly sensitive to medullary catecholamines, which, released on exercise, are the means whereby an increase in rate and a further increase in force of contraction can still be achieved.[9 10]

The single real obstacle to preventing the earlier application to man of cardiac transplantation was immunological, and there has still been no new discovery, no breakthrough, only slow but steady progress towards understanding the complex physiology of rejection.[11] The rejection process is mediated by lymphocytes[12] which invade the foreign tissue. Oedema, intravascular thrombosis, and perivascular fibrosis obliterate small vessels. Necrosis and fibrosis progressively destroy the graft. The process may be held up in two ways. One is by minimizing the antigenic stimulus by accurate matching of donor with host; the other is by suppressing the host's tissue reaction, if possible, selectively. Neither

approach is yet very successful, and usually both have been employed together by the use of Starzl's regimen for renal transplants.[13] Despite Van Rood's progress with leucocyte typing[14-16] and the development of an antilymphocytic globulin[17] the main reliance continues to be on non-specific immunosuppression with azothiaprine and steroids. Indeed, success depends on a high tolerance of steroids, immunological good fortune, and the avoidance of infection.

Leucocyte grouping cannot yet be carried out completely, and its relevance to the antigenic identification of tissues has not yet been proved. Though rejection seems to be initiated through the lymphocyte, specific antisera to prevent it have not yet proved effectual in man. Moreover, the crude preparations available at present cause local pain and general reactions, and attempts at purification have resulted in loss of activity. Moreover, the patient's reactions to antilymphocytic sera can obscure symptoms showing whether a rejection process has started or whether an infection has begun. Immunosuppression delays healing of wounds and invites colonization by antibiotic-resistant fungi and viruses of normally low pathogenicity. Waiting for overt signs of rejection[18] almost certainly allows the development of irreversible necrosis in the graft besides predisposing to venous thromboembolism, which has been responsible for several of the deaths.[19 20]

Many ethical, philosophical, and legal problems on the selection of recipients and acquisition of donors have been discussed.[11 21 22] It has been agreed that suitable patients should have advanced, disabling, and otherwise irremediable progressive heart disease, but no serious disorder in other systems. The patients selected should have a prognosis that is not only hopeless but limited to a few weeks, because the life of the successful transplant at present is usually short. In heart disease prognosis is notoriously uncertain, and this is particularly true of patients with coronary artery disease, who are the obvious candidates for this operation. Not until the life of the grafted heart is much more certain can younger patients with congenital defects or cardiomyopathies be helped. Simple logistics also have to be faced. Whereas a kidney graft for everyone in need is a practical proposition, there will never be enough human hearts to go round. Even if heterografts from animals were ever utilized, and if double the present number of cardiac surgical teams did nothing else, the demand would not be met. The B.M.A.'s Planning Unit discusses some of these questions in its report this week at p. 106.

Until the rejection problem has been more successfully overcome it would seem correct for cardiac transplantation to be restricted largely to the experimental animal, while immunological studies are concentrated on the grafted kidney. The kidney has an enormous and unlocalized functional reserve, so there exists an ideal situation in which no crisis follows failure of the transplant and effective treatment by intermittent dialysis is readily available. The improvement in the immediate survival rate from cardiac transplantation has nevertheless been exciting, with two survivors out of the first 20 patients and 30 out of the next 46 patients. D. A. Cooley and his team, who have the largest single experience, report 7 out of 12 survivors and a maximum survival so far of 4½ months.[23] Dr. Philip Blaiberg is still alive a year after receiving his new heart, and his operation is an undoubted success. Professor Barnard and his associates earned and have received the world's acclaim for their technical brilliance and close-knit team work. Both the surgeon and his patient deserve our esteem for their courage and resolution.

1 Shumway, N. E., Angell, W. W., and Wuerflein, R. D., *Transplantation*, 1967, **5** (Suppl.), 900.
2 Webb, W. R., Howard, H. S., and Neely, W. A., *J. thorac. Surg.*, 1959, **37**, 361.
3 Lower, R. R., Dong, E., Jr., and Shumway, N. E., *Surgery*, 1965, **58**, 110.
4 Kondo, Y., Grädel, F., and Kantrowitz, A., *Circulation*, 1965, **31** (*Suppl.* No. 1), 181.
5 Hardy, J. D., *et al.*, *J. Amer. med. Ass.*, 1964, **188**, 1132.
6 Barnard, C. N., *S. Afr. med. J.*, 1967, **41**, 1271.
7 Cooper, T., Willman, V. L., Jellinek, M., and Hanlon, C. R., *Science*, 1962, **138**, 40.
8 Donald, D. E., and Shepherd, J. T., *Amer. J. Physiol.*, 1963, **205**, 393.
9 Daggett, W. M., Willman, V. L., Cooper, T., and Hanlon, C. R., *Circulation*, 1967, **35** (Suppl. 1), 96.
10 Donald, D. E., *Circulation*, 1968, **38**, 225.
11 Dempster, W. J., Melrose, D. G., and Bentall, H. H., *Brit. med. J.*, 1968, **1**, 177.
12 DeBono, A. H. B., and Warren, B. A., *Biorheology*, 1968, **5**, 91.
13 Starzl, T. E., *et al.*, *Transplantation*, 1967, **5**, Suppl. 1100.
14 Van Rood, J. J., *et al.*, in *Histocompatibility Testing*, edited by H. Balner, F. J. Cleton, and J. G. Eernisse, Series *Haematologica*, 1965, **11**, p. 37. Copenhagen.
15 Van Rood, J. J., Van Leeuwen, A., and Bruning, J. W., *J. clin. Path.*, 1967, **20**, Suppl. 504.
16 Van Rood, J. J., Van Leeuwen, A., Bruning, J. W., and Porter, K. A., *Abstracts of the 1st International Congress of the Transplantation Society*, Paris, 1967, p. 162.
17 James, K., *Clin. exp. Immunol.*, 1967, **2**, 615.
18 Barnard, C. N., *Amer. J. Cardiol.*, 1968, **22**, 811.
19 Ross, D., *Amer. J. Cardiol.*, 1968, **22**, 838.
20 Haller, J. D., and Cerruti, M. M., *Amer. J. Cardiol.*, 1968, **22**, 840.
21 *Brit. med. J.*, 1967, **4**, 757.
22 *Brit. med. J.*, 1968, **2**, 315
23 Cooley, D. A., Hallman, G. L., Bloodwell, R. D., Nora, J. J., and Leachman, R. D., *Amer. J. Cardiol.*, 1968, **22**, 804.

Hospital Disaster

From time to time the annals of our mental hospitals are darkened by accounts of frightful fires to which an extra dimension of horror is added because, as often as not, the victims are as helpless in body as they are in mind. The latest of these disasters, probably the worst since that at Colney Hatch (Friern Barnet Hospital) in 1903, occurred at Shelton Hospital, Shrewsbury, where, on the night of 25–26 February 1968, 24 female patients died. A committee of inquiry into the circumstances leading to the fire has now reported its findings.[1]

The evidence received showed that the hospital, built in the mid-nineteenth century, was structurally sound and "in some respects safer than many much more modern buildings so far as fire was concerned." The central heating was modern, as was the electrical system. There was a sufficient number of hydrants in the hospital grounds and a full provision of hose reels. The fire-fighting equipment appeared to be in first-class condition. The fire-alarm system was a conventional "break-glass" one, well maintained and adequate within its limits. Telephones, both G.P.O. and internal, that could also be used to raise the alarm existed "almost in profusion, but quite a high level of proficiency was required in using the various media if confusion and delay were to be avoided." It seems clear therefore that all the paraphernalia of fire-fighting and alarm-raising were present and in good order.

In contrast the report finds that what faults there were, and these grievous ones, were human. It is all too easy in an inquiry of this sort to set out to find a culprit and emerge with a scapegoat. This the committee with scrupulous fairness does not do. The night nurse in sole charge of the ward to which the fire was confined comes in for criticism for her

[1] Report of a Committee of Inquiry into the circumstances leading to a fire at Shelton Hospital on the night of 25 to 26 February 1968, and to the deaths of 24 patients. Submitted to the Rt. Hon. Kenneth Robinson, M.P., Minister of Health, Alexander Fleming House, Elephant and Castle, London S.E.1. 1968.