Papers and Originals

Heart Transplantation in Man—Necropsy Findings

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[WITH SPECIAL PLATE BETWEEN PAGES 514 AND 515]

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The first cardiac transplantation in man, in Cape Town, South Africa, was followed by the death of the patient, a white man aged 54, 18 days later. The aim of this communication is to give a full report of the findings at necropsy and to stress the difficulties in their evaluation.

Angiographic studies had shown before transplantation ample grounds for the patient's severe cardiac failure (Schrire and Beck, 1967). The circumflex branch of the left coronary artery did not fill, and the anterior branch showed multiple areas of narrowing. The right coronary artery was severely narrowed 2 cm. from its origin and had a thread-like lumen thereafter. These findings were confirmed when the excised heart was received as a surgical specimen. Without the major portions of both atria it weighed 470 g. The circumflex branch of the left coronary artery was completely occluded by an old organized thrombus, and the anterior branch was almost completely occluded by atheromatous and fibrous plaques showing extensive calcification. The severe narrowing of the right coronary artery was mainly due to fibrous intimal plaques, and there was little atheroma. More than half of the myocardium of the left ventricular wall was replaced by fibrous tissue; at the apex no myocardium survived, and the thin fibrous tissue replacing it was covered by recent thrombus.

Summary of Clinical Course

The following summary of his clinical course was provided by Dr. W. Beck, of the Cardiac Clinic of Groote Schuur Hospital, Cape Town.

Heart transplantation was performed on 3 December 1967, and the immediate postoperative course was entirely satisfactory, with all bodily functions showing steady improvement.

On the fifth postoperative day the electrocardiographic voltage was slightly reduced. This was interpreted as a possible sign of rejection, and the steroid dosage was increased from 60 to 200 mg. daily and then gradually reduced to its previous level. Steady improvement continued until 15 December, when the chest radiograph showed a small area of consolidation at the right base. On 16 December a temperature of 98.6° F. (37° C.) was noted, the patient complained of right-sided pleuritic pain, and a friction rub was noted on clinical examination. The chest x-ray film showed an extension of the original shadow in the right base and the appearance of several more areas of pneumonic consolidation. Sputum examination showed Gram-positive cocci, and on culture *Diplococcus pneumoniae* was isolated. A diagnosis of pneumococcal pneumonia was made and therapy with large doses of penicillin (20 million units intravenously) and with gentamicin was begun. Thereafter his condition steadily deteriorated, with the appearance of further pneumonic areas throughout both lungs. Pneumococci were

absent from the sputum on the following day and a rejection pneumonitis was suspected. Steroid therapy was therefore again increased to 200 mg. and later to 400 mg. daily. However, the patient continued to deteriorate steadily and on 17 December *Pseudomonas* was isolated from his sputum.

On 18 December he was put on to a respirator as his PO_2 was down to 51 mm. Hg. Deterioration continued, and even while he was being ventilated on 100% oxygen his PO_2 could not be raised much above 30 mm. Hg. Cardiac function was good throughout and only terminally did the E.C.G. show occasional premature systoles.

Death was due to unrelieved anoxia, and occurred at 7 a.m. on 21 December.

Necropsy Report

Necropsy was performed by me one and a half hours after death. No subcutaneous oedema was noted. The surgical incisions in chest and in the right inguinal region appeared to be healed. The peritoneal cavity contained about 200 ml. of clear yellow fluid. Pleural sacs were dry, and the lungs were covered by a thin layer of fibrinous exudate changing to yellow and purulent over the base of the left lobe. The pericardial sac was large in relation to the heart, contained about 50 ml. of slightly blood-stained fluid, and both layers were covered by a thin fibrinous exudate, adherent and organizing in places, and not suggesting an infective origin.

Lungs

The left lung weighed 1,432 g. The entire lower lobe was the seat of lobar pneumonia in the stage of grey hepatization. In the upper lobe were extensive patches of a similar pneumonia affecting roughly one-quarter of its substance, and posteriorly there was pulmonary oedema.

The right lung weighed 943 g. Approximately one-quarter of all three lobes was occupied by areas of pneumonia of lobar type with a bluish-green colour. Between these areas were some reddish foci of pneumonia and considerable pulmonary oedema.

Both major pulmonary arteries were slightly dilated and showed moderately severe atheroma.

Heart

With major portions of four atria, the donor's and the recipient's, and an 8-cm. length of aorta and pulmonary artery, the heart weighed 350 g. The two sutured right atria measured vertically 8 cm. from tricuspid valve to the opening of the superior vena cava (Special Plate, Fig. 1). The maximum transverse diameter was 5 cm. No thrombi were present. The donor's atrial wall was significantly thinner than that of the hypertrophied recipient's. There were a few subendocardial haemorrhages in relation to the line of suture, affecting roughly three-quarters of its length and extending further on to recipient's than on to donor's atrium. The blood in these foci appeared red and recent, and similar haemorrhages

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were present under the pericardium. The suture lines appeared otherwise healthy and were free from thrombi.

Pulmonary and tricuspid valves appeared healthy. The right ventricle was not hypertrophied or dilated and its wall was normal in appearance and consistency. The donor's pulmonary artery was sutured to the recipient's 2.5 cm. from the free margin of the pulmonary valves. The suture lines appeared healthy and free from haemorrhages or thrombi. The donor's pulmonary artery was smooth, virtually free from atheroma, and much thinner than that of the recipient's, which showed extensive small plaques of atheroma.

The left atrium measured vertically 8.5 cm., and transversely the maximum diameter was 6 cm. (Special Plate, Fig. 2). At the suture lines were fewer haemorrhages than in the right atrium, but again they appeared red and recent. The recipient's atrial wall was thicker than that of the donor's. The mitral valve admitted two fingers and showed no abnormalities. The left ventricle was not dilated or hypertrophied and its texture was normal. The aortic cusps appeared healthy. The donor's aorta was joined to the recipient's 3 cm. from the free margin of the cusps and the suture lines appeared healthy, and no haemorrhages or thrombi were present. Both coronary arteries were free from atheroma.

Other Organs

Aorta.—In the ascending thoracic aorta atheroma was of moderate intensity. The descending thoracic aorta was similar, but in the abdominal aorta below the renal arteries the atheroma was severe and was associated with extensive ulceration and a little adherent thrombus and some calcification.

The **kidneys** together weighed 476 g. Both showed a slightly increased consistency with some congestion and a few yellow streaks of uric acid infarction in the medullae. Signs of infection were not present.

The **stomach** showed an excess of mucus, and the entire gastric wall was congested and oedematous. Four small haemorrhages were present near the pylorus; the largest was 1 by 0.6 cm. None showed altered blood, and they were regarded as of traumatic origin from the passage of a tube into the stomach.

The **duodenum** showed an excess of mucus. No bile was evident in its contents and none could be expressed from the gall bladder. The common bile duct was of normal diameter and free from bile staining. The gall bladder contained a solid pasty mass of bile 1 cm. broad and up to 0.8 cm. thick extending from fundus to neck. The mucosa showed no abnormalities.

The **liver** weighed 1,728 g. and was not enlarged. The lobules could be identified and seemed smaller than usual, but the appearances of chronic passive congestion were absent. Its consistency was increased.

Intestine.—The proximal jejunum was congested, thick-walled, and oedematous, with a considerable excess of mucus. The large intestine was oedematous, especially in the submucosa, from the caecum to the sigmoid colon.

Pancreas.—In the fat on the surface of the body and tail were a few small areas of fat necrosis. These were absent from the pancreas itself, which here showed no abnormalities. The head of the pancreas was swollen and showed on section areas of fat necrosis up to 0.3 cm. in diameter in the interior. Some of these had a bluish green instead of the ordinary opaque yellow colour, and three, 0.5 to 1 cm. in diameter, appeared to be abscesses and contained greenish semi-solid pus-like material.

The **brain** weighed 1,246 g. No external abnormalities were present. It was sectioned after fixation and no lesions were demonstrated.

The **spleen** weighed 203 g. and showed the appearances of chronic passive congestion. Its consistency was increased and signs of reaction were absent.

Adrenals.—The left adrenal was a large, thick structure. Most of its bulk was formed by the cortex, in which lipoid survived only in small patches. The right adrenal showed in its centre a diffuse thickening to 1.2 cm. mainly from medullary hyperplasia.

Bone Marrow.—Bone marrow in lumbar and thoracic vertebral bodies and in ribs consisted of a clear, red, watery fluid suggesting myeloid depression. In the right femur a few areas of watery red marrow were present in head and neck, together amounting to not more than the equivalent of a 2-cm. length of shaft.

Paratracheal and bifurcation lymph nodes were enlarged to an average diameter of 2 cm., with soft and congested reactive peripheries contrasting with the anthracotic centres.

At the site of the *thymus* only adipose tissue was evident.

Microscopical Examination

Histological examination confirms most of these anatomical findings and adds a few more. In the anterior pituitary is a small recent infarct about two low-power fields in size under the capsule. No vascular lesions are evident.

Brain

Pieces of brain for histological examination were taken from cerebral cortex, basal ganglia, and pons. The only abnormality found is a single subcortical focus of cerebral softening the size of a low-power field consisting of massed compound granular corpuscles. Polymorphs, lymphocytes, or plasma cells are here absent and there is no gliosis. No vascular lesions are seen. In the right adrenal are two small foci of cortical infarction, each about two high-power fields in size. They are very recent and some of the dead cells still show pyknotic nuclei. Most of the capillaries in this area contain blood, no polymorphs are recognizable, and vascular lesions are not seen. In the absence of vascular lesions one can only speculate regarding the mechanisms of these infarcts. The minute focus of cerebral softening is clearly older, but the infarcts in the pituitary and adrenal are very recent and are presumably the result of the terminal anoxia.

Lungs

The lobar pneumonia is confirmed. In sections from the right lung the abundant fibrin and polymorphs appear fresher and more recent than in sections from the left, and the fibrinous exudate on the pleura is thinner. Elsewhere in the lungs is considerable oedema, and throughout in the alveoli are numerous histiocytes laden with haemosiderin from the previous heart failure. In the pneumonic areas the capillaries in air vesicles are largely bloodless; in the sections from non-pneumonic areas they contain blood, but the appearances of chronic passive congestion are not present. Some of the pulmonary arteries show an acute arteritis, with oedematous fluid, lymphocytes, and histiocytes lying between the endothelial lining and the internal elastic lamina. No fibrinoid necrosis and no thrombi are evident in these vessels. Identical lesions to these have been noted in other cases of lobar pneumonia, including one dated 1945 which had not received antibiotics or steroids. These arteritic lesions are not seen in the non-pneumonic areas of the lung, and one has no doubt that they are related to the pneumonia and should not be interpreted as rejection phenomena.

It may well be that the pneumonia was due to *Pseudomonas* from the beginning and the initial culture of pneumococci from the sputum was misleading. The pneumonia started with a pleurisy just like ordinary pneumococcal lobar pneumonia, but its distribution as evaluated radiologically was patchy without complete involvement of any one of the affected lobes, at least initially. The process was very extensive at necropsy but segmental areas were still readily identified. We have seen other cases where a *Pseudomonas pneumonia* presented the same features of lobar type but with a segmental arrangement of the lesions.

Bifurcation and Paratracheal Lymph Nodes

These show marked signs of reaction with abundant histiocytes and plasma cells but relatively few polymorphs.

Spleen

Malpighian bodies are still recognizable but are relatively small and germinal centres are absent. The pulp contains much blood, but one cannot recognize sinusoids as easily as one can in a typical chronic passive congestion spleen. There is here a marked excess of cells, mainly plasma cells and histiocytes. Polymorphs, fresh or degenerated, are strikingly absent for a case of lobar pneumonia.

Bone Marrow

Approximately one-third is adipose tissue and rather more than one-third is occupied by widely dilated sinusoids filled with red blood cells. Of the nucleated cells present, large histiocytes with abundant cytoplasm are common, some containing haemosiderin; plasma cells are abundant. Blood-forming marrow is relatively scanty and most of it appears to be of the erythroblastic series. Myeloid cells are much reduced and maturing myeloid cells are little in evidence. Megakaryocytes are present in normal proportions.

Liver

The liver has the appearances of an early cardiac cirrhosis with some linking up of portal tracts, which show some bile-duct proliferation and contain an increase in cells, mainly lymphocytes but with a few plasma cells. The sinusoids are wider in places but the appearances of chronic passive congestion are not present. Glycogen is scanty inside the liver cells, but in areas some of their nuclei are distended by glycogen.

Kidneys

The glomeruli do not show the prominent dilated capillaries of a chronic passive congestion, nor are the intertubular capillaries dilated. There is some patchy thickening of the basement membranes of the glomeruli with focal increases in cellularity at these points and obliteration of the lumina of the capillaries. No embolic lesions are recognizable and there is no necrotizing arteritis. Some tubular dilatation is present.

Pancreas

The areas of fat necrosis are mainly in adipose tissue infiltrating the pancreas, and all appear to be of similar age. They are surrounded by a layer of fibroblasts which are infiltrating and replacing fibrin at the edges. The pancreas generally shows in the interstitial tissue numerous lymphocytes and histiocytes with some plasma cells. Some of the smaller arteries and arterioles show marked hyaline change of diabetic type, sometimes containing small rounded calcified bodies. No necrotizing arteritis is present. One solitary nucleus showing cytomegalic inclusion is seen, but no others are found after prolonged search, and no cytomegalic inclusions are seen in sections of the submaxillary glands or of the other organs. A striking and unexplained hyperplasia of islet tissue is present in some areas, in which an occasional mitotic figure is seen.

Heart and Great Vessels

Multiple blocks were taken from all the suture lines—aortae, pulmonary arteries, and both atria; from the aortic, mitral, tricuspid, and pulmonary cusps; from both coronary arteries; and from both ventricles and the four atria.

Junctions of Aortae and Pulmonary Arteries

The donor's aorta, thinner than that of the recipient, has a slight excess of mucopolysaccharide as the only abnormality. The thicker recipient's aorta shows a superficial fibrous plaque. At the line of suture the donor's aorta shows complete necrosis of the outer half for 4 mm. There is no cellular response to this in the media but there is some fibrin and granulation tissue on the serosa. The recipient's aorta shows rather more similar necrosis in the outermost half of the media. It extends to the edge of the section and the exact length of this necrotic strip was not defined, but is more than 1 cm. in length. Cellular response occurs in the adventitia as in the recipient's aorta but not in the media itself. Presumably the survival of the innermost half of the media of both aortae after section of vasa vasorum was determined by plasma coming direct from the lumen.

The donor's pulmonary artery is thinner than that of the recipient and has a much more open texture with abundant mucopolysaccharides. It is free from necrosis right up to the line of junction except for circular areas round the actual sutures. Cellular

response here is absent. The recipient's pulmonary artery is appreciably thicker and again necrosis is confined to the site of the sutures. Outside both pulmonary arteries is a granulation tissue response with abundant fibroblasts and histiocytes. There are little differences between the two in this area, and lymphocytes and plasma cells are scanty in both. The much better survival of the pulmonary arteries compared with the aortae suggests that most of their nourishment came from the lumen of the vessel and less from the vasa vasorum.

Right Atria

On the pericardium over both is a little fibrinous exudate which is being organized. The recipient's atrium is much thicker than that of the donor and very little of it here survives, nuclear staining being absent except for a few myocardial fibres next to the pericardium and under the endocardium. The bulk of the recipient's atrial wall where it is sutured to the donor's has the appearances of infarction with necrosis of all tissue, blood vessels, and connective tissue as well as muscle, and contains small collections of yellow bilirubin. The donor's right atrium largely survives. There is a small area of necrosis one low-power field in size of infarct-like type near to the suture line and there are a few central areas of recent collapse fibrosis with replacement of muscle fibres with stroma and histiocytes containing lipofuscin. Cellular infiltration is not here a feature (Special Plate, Fig. 3).

These sections, however, give an erroneous idea of the extent of survival of the recipient's right atrium. Three sections taken from the recipient's right atrium away from the suture lines show varying amounts of necrosis, but none as large as in the portions next to the suture lines. A section from the crista galli has a maximum thickness of 0.6 cm. Preservation of the myocardium here is very good apart from a few small foci of collapse fibrosis, but infarct-like lesions are not seen and no vascular changes are evident. Cellular infiltration is slight and virtually confined to the collapsed areas. While many of the surviving muscle fibres are thin and atrophic, the extent of survival is unexpected if the atrium has lost most of its arterial blood supply.

Donor's Right Atrium

Survival of the muscle away from the suture lines is good, though small central foci of recent collapse fibrosis are present. There is no subendocardial cellular infiltration and only a few lymphocytes are noted, mainly in relation to the small foci of collapse fibrosis.

Left Atria

Sections through the lines of suture show a similar difference in thickness, the recipient's being appreciably thicker than the donor's (Special Plate, Fig. 4). In both, necrosis next to the lines of suture is less evident than in the right atria, and in most of the foci the dead cells have disappeared and are replaced by a collapse fibrosis with histiocytes containing lipofuscin. No infarct-like areas of necrosis are present. The main difference between the two is the striking and significant cellular infiltration in the donor's left atrium consisting of lymphocytes, histiocytes, fibroblasts, and plasma cells (Special Plate, Figs. 5 and 6). These are mainly perivascular, and under the pericardium a similar cellular infiltration is mixed with abundant fibroblasts. The same fibroblastic response is present under the pericardium of the recipient, and is presumably a response to trauma and the organization of the fibrinous pericardial exudate, but plasma cells and lymphocytes are here absent. In both atria what blood vessels are present appear normal.

Right Ventricle

On the surface of the pericardium is a thin layer of organizing fibrinous exudate. Beneath it, apart from fibroblasts and histiocytes, are occasional groups of lymphocytes and plasma cells. The myocardium shows a pronounced oedematous separation of fibres and groups of fibres, and round the blood vessels a similar oedema is noted. The muscle fibres immediately under the pericardium show

an excess of glycogen, and many of the fibres elsewhere show varying degrees of granularity and loss of transverse striation. It is clear that a number of myocardial nuclei no longer stain and some stain imperfectly. Other blocks from the right ventricle show these features to a much less marked degree, but in all of them isolated foci of collapse fibrosis similar to those in the atria readily can be found. The cellular proliferation shows a similar wide variation in intensity, but in none of the sections are these cells absent (Special Plate, Fig. 7). The subendocardial cellular infiltration consists of fibroblasts, histiocytes, and lymphocytes with a few plasma cells, but is slight and patchy. In the myocardium the cells are most frequently perivascular, and Anitschkow's myocytes and histiocytes are the commonest, followed by fibroblasts, lymphocytes, and plasma cells. The vascular changes are identical with those in the left ventricle and are described with them.

Left Ventricle

The changes here are similar but the subendocardial cellular infiltration and proliferation is more significant and less patchy (Special Plate, Fig. 8). The oedema is more marked round blood vessels (Special Plate, Fig. 9) and less evident between muscle fibres. Perivascular Anitschkow's myocytes are more numerous (Special Plate, Fig. 10). Lymphocytes and plasma cells are no more frequent than in the right ventricle, but rather more lie between muscle fibres and fewer are perivascular. Signs of recent myocardial degeneration are as frequent as in the right ventricle.

Vascular Changes

In both ventricles, but not in the atria, small arteries showing patches of recent fibrinoid necrosis are easily seen (Special Plate, Fig. 11). Only small segments of the vessels are affected, and usually the outermost portion only (Special Plate, Fig. 12). Exceptionally, the whole thickness of the wall is involved. They appear to be very recent, as occasionally red blood cells can be seen inside the fibrinoid patch (Special Plate, Fig. 13), and some muscle fibres still retain their nuclear staining, though nuclear fragments are more frequent. Reactive changes to these mainly take the form of proliferation of the lining endothelial cells. There is no eosinophilic infiltration. Some vessels show fibroblastic proliferation in the adventitia, but this is rare. No narrowing of the vessels and no thrombi are present. Some small arteries show both endothelial and adventitial proliferation though no necrosis is present. All the vessels showing these lesions are small arteries with well-developed muscular media, and the arterioles are not affected. No abnormalities are seen in the veins and venules. The capillaries are in places prominent and dilated.

Valves

Sections from all four valves fail to show any abnormalities. There is no significant oedema, cellular infiltration, or cellular proliferation.

Coronary Arteries

These show an occasional fibrous intimal thickening without significant luminal narrowing. In the anterior descending branch of the left, near its commencement, some lipoid-laden histiocytes are also present.

Further Studies

Tissue mast cells in sections stained with toluidine blue are readily demonstrated in all four atria and both ventricles. They are most frequent in the recipient's left atrium, and here some suggest exhaustion of granules from their pale staining. Comparison with other hearts leads to the conclusion that the number of mast cells in human hearts is very variable. The original heart of the second heart transplant in Cape Town shows about four times as many tissue mast cells as did the present patient's original heart, and about twice as many as the heart transplanted to him.

Other Organs.—Histological examination of stomach, small gut, colon, gall bladder, and thyroid shows no significant abnormalities and in particular vascular lesions are absent.

Nerves.—A careful study was made in the two dozen or so sections from the donor heart, recipient's atria, and both pulmonary arteries and aortae. The greatest collection of nerves is seen under the sutured pulmonary arteries, and both donor's and recipient's can be identified from their relationship to the two portions of sutured pulmonary artery. In only one, the donor's, are some myelinated fibres evident, and all the others are non-myelinated, the bulk being of donor origin. In both donor's and recipient's are mitotic figures readily identified in these nerve bundles. In the sections from the heart chambers nerve fibres are seen mainly under the pericardium and are occasionally associated with well-preserved ganglion cells. In a few, myelinated fibres free from signs of degeneration are recognized, especially in the left atria. Intramural nerve fibres are exceptional in both ventricles and appear normal in sections stained with haematoxylin and eosin.

The general impression is that in both donor's heart and recipient's atria no significant changes are present in the peripheral nerves. Mitotic activity is noted only in the nerve bundles under the pulmonary artery, and presumably originated in the cells that accompany non-myelinated fibres. The good preservation of the ganglion cells in the donor heart is noteworthy (Special Plate, Fig. 14).

Post-mortem Bacteriology Results.—From the right bronchus there was a heavy growth of *Pseudomonas aeruginosa*. The same organism was grown from the right lower lobe of the lung and from the left lower lobe. In both these situations another strain of *P. aeruginosa* with slightly different sensitivities to antibiotics was also obtained. From the softened areas of fat necrosis in the head of the pancreas only *Streptococcus faecalis* was cultured (Dr. W. du T. Naudé).

Discussion

It is clear from the terminal stages of the patient's clinical history and from the necropsy findings that the cause of death was bilateral pneumonia. It the absence of the heart transplantation one would have expected to find at the necropsy marked signs of congestive cardiac failure, including the changes of chronic passive congestion in the internal organs. How far did the transplant reduce these anticipated features? The patient's subcutaneous oedema before the transplant was so marked that Southey's tubes were used as a last resort, after the failure of the usual therapy. At necropsy no oedema of subcutaneous tissues was found. Massive effusions would have been expected in the serous sacs, and none was found in the pleural sacs and only a slight excess in the peritoneal cavity. There was also a slight excess in the pericardial sac, but the fluid here was slightly blood-stained and was presumably related to the necrosis and subpericardial haemorrhages round the suture lines in the atria where the walls were necrotic. Much of the lung was occupied by lobar pneumonia, but the appearances of chronic passive congestion were not present in the non-pneumonic areas. Throughout the lungs indications of the previous chronic passive congestion were evident in large numbers of heart failure cells full of haemosiderin.

In the liver the appearances of chronic passive congestion were absent, but there was an early cardiac cirrhosis, and this usually with liver nodular regeneration largely obscures the nutmeg appearances of chronic passive congestion. In the kidney and spleen signs of chronic passive congestion were virtually absent. The usual morbid anatomical indication of chronic passive congestion in stomach and intestines is an excess of mucus, and this was found in these organs at necropsy. It would be fair to conclude that the substitution of an efficient heart for the original one had resulted in the virtual disappearance of the anticipated morbid anatomical indications of congestive cardiac failure.

It is clear from the maintenance of cardiac function that he did not die from rejection of the transplanted heart, and the main matter at issue is whether rejection signs are present

J. G. THOMSON: HEART TRANSPLANTATION IN MAN—NECROPSY FINDINGS

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1.—Anterior aspect of the transplanted heart. The right atrium shown is that of the recipient and the bulk of the donor's right atrium is not visible. There are small haemorrhages round suture lines joining the two atria. There is no dilatation of the ventricles.

FIG. 2.—Posterior view of the transplanted heart. The haemorrhages in relation to the suture lines joining the two atria are evident.

FIG. 3.—Donor's right atrium showing a small central area of recent collapse fibrosis. Some of the muscle fibres above this have lost their nuclear staining. (H. and E. $\times 125$.)

FIG. 4.—Junction of the two left atria. The recipient's left atrium, including the endocardium at top, is three times thicker than that of donor's. The pale zones at the line of junction are foci of collapse fibrosis where dead muscle has been removed. (H. and E. $\times 3.5$.)

J. G. THOMSON: HEART TRANSPLANTATION IN MAN—NECROPSY FINDINGS

FIG. 5

FIG. 6

FIG. 5.—Recipient's left atrium. The endocardium on top is thickened and the myocardium is hypertrophied, but cellular infiltration is absent. (H. and E. $\times 120$.)

FIG. 6.—Donor's left atrium. A portion of the endocardium is seen at top left. The pericardium is at the bottom. Note the intense cellular infiltration. (H. and E. $\times 120$.)

FIG. 7.—Right ventricle. Oedema and diffuse cellular infiltration are marked but endocardium at top shows oedema only. (H. and E. $\times 105$.)

FIG. 8.—Left ventricle. There is a marked sub-endocardial cellular infiltration of lymphocytes and plasma cells. (H. and E. $\times 210$.)

J. G. THOMSON: HEART TRANSPLANTATION IN MAN—NECROPSY FINDINGS

FIG. 9.—Left ventricle. The oedema is here mainly perivascular and there is a concentric arrangement of fibroblasts round the artery. (H. and E. $\times 125$.)

FIG. 10.—Left ventricle showing a collection of Anitschkow's myocytes with typical date-stone nuclei. (H. and E. $\times 255$.)

FIG. 11.—Right ventricle showing a focus of recent necrotizing arteritis with disappearance of nuclei. There is a marked perivascular oedema, but there is no cellular response round the necrotic area. (H. and E. $\times 125$.)

J. G. THOMSON: HEART TRANSPLANTATION IN MAN—NECROPSY FINDINGS

FIG. 12.—Left ventricle. A small artery showing recent necrotizing arteritis in which a few pyknotic nuclei remain. The perivascular cellular infiltration is not confined to this focus. The oedema affects mainly the surrounding myocardium. (H. and E. $\times 255$.)

FIG. 13.—Left ventricle. High-power view of an area of recent necrotizing arteritis on left. Some nuclear staining persists and red blood cells are present in the necrotic portion of the vessel wall. (H. and E. $\times 255$.)

FIG. 14.—Left ventricle. A subpericardial peripheral nerve showing well-preserved ganglion cells. (H. and E. $\times 125$.)

or not. It would seem wise at this stage to accept two assumptions: that some degree of rejection is probable, and that the patient's immunosuppressive therapy had some effect in modifying its intensity and possibly its type. We would not therefore expect to see the full-blown picture of rejection of transplanted hearts as in dogs, and failure to see this does not indicate that rejection phenomena are absent.

Evaluation of Rejection Changes

In assessing changes in a transplanted heart it is all too easy, as in animal experiments, to regard any pathological change in the transplanted heart as being the result of rejection, if infection is excluded. This would seem reasonable in the case of any healthy animal receiving a young healthy heart, but there is implicit in this a belief that the heart is not altered between removal from the donor and the recommencement of circulation at the end of transplantation, when there is presumably a period of anoxia of varying duration and intensity. It also ignores direct traumatic damage to the heart during operative manipulations. Areas of myocardial necrosis followed by calcification have been described in the transplanted hearts of dogs and regarded as the result of rejection (Lower *et al.*, 1965; Kondo *et al.*, 1965). But necrotic lesions followed by calcification are also described in the hearts of dogs subjected to liver transplantation (Moore *et al.*, 1960). The authors found that these cardiac lesions can be produced in dogs by long difficult operations, particularly those producing hypotension and requiring blood transfusion or by haemorrhagic shock.

It is one thing to transplant hearts in experimental animals, where both donors and recipients are mainly young and presumably healthy. It is quite another to transplant a heart into an aged dying man, who at the time of transplantation had of necessity changes, structural and functional, in organs other than the heart, ranging from diabetes to the effects of chronic passive congestion of internal organs, to mention only those known to be present before the operation.

A major point in the evaluation of rejection changes is that the myocardium has a very limited range of reactive response, and that some of these are common to quite different disease processes. The myocardium has no complexity of structure like that of the kidney or liver. A further point is the difference in the regenerative capacity between kidney and liver on the one hand and the myocardium on the other. In the kidney the cells most sensitive to anoxia, the lining cells of the convoluted tubules, can die in varying amounts in the interval between removal and re-establishment of the circulation of the grafted organ, but regeneration of this is easy, rapid, and complete. Liver cells similarly have a high capacity for regeneration, but no regeneration of myocardial fibres occurs in man, and any myocardial cells dying under these conditions will constitute a permanent loss. The differences between human and animal transplants are, however, not all one-sided. The rest, the relative immobility, and the nursing care which follow heart transplantation in man cannot be achieved in experimental animals, and the strain on the new heart is presumably greater in them. After all, a racehorse with a broken leg is usually shot; a human being with a similar injury is not. It may well be that the bad results and high frequency of rejection phenomena in dogs may be in part due to the operation of these factors, apart from the fact that there is no matching of leucocyte antigens. At all events one should not anticipate in man a similar frequency or intensity of such changes.

The findings in the heart at necropsy could, theoretically at least, have resulted from the operation of any or all of the following five factors: (1) changes present in the donor's heart during life; (2) damage, ischaemic and traumatic, to the donor's heart before the circulation was re-established in the body of

the recipient; (3) changes directly related to the infective condition in the lungs and indirectly from the resultant severe anoxia; (4) changes due to the intensive immunosuppressive therapy—Imuran (azathioprine), actinomycin C, high doses of steroids, and the cobalt bomb radiation; and (5) changes indicative of graft rejection, modified by the immunosuppressive therapy.

Pathological Findings

The pathological findings in the heart can be listed as follows: (1) organizing fibrinous pericarditis with underlying cellular infiltration and proliferation; (2) some loss of nuclear staining and striations of myocardial fibres in both ventricles; (3) small foci of collapse fibrosis in atria and both ventricles following recent removal of dead myocardial fibres; (4) infarct-like necrosis in all four atria, particularly the recipient's; (5) oedema, especially in both ventricles, and an infiltration of lymphocytes, plasma cells, and Anitschkow's myocytes in donor's left atrium and both ventricles and a limited sub-endocardial cellular infiltration in both ventricles; and (6) foci of necrotizing arteritis in both ventricles.

The changes in other organs which may or may not be related to rejection phenomena are the fat necrosis in and around the pancreas, and the presence of plasma cells in bone marrow, spleen, thoracic lymph nodes, pancreas, and portal tracts of liver, the last two being associated with numerous lymphocytes.

To take these seriatim:

(1) *Organizing Fibrinous Pericarditis with Underlying Cellular Infiltration and Proliferation.*—The fibrinous pericarditis appears to be the result of trauma and of prolonged exposure of the sensitive serous sac to the air, and neither infection nor rejection is necessary to explain its presence. It is identical to what one has repeatedly seen in the pericardium after open heart operations of comparable duration.

(2) *Loss of Myocardial Nuclei and Transverse Striations.*—This is not more pronounced than is commonly seen in people dying with anoxia from congestive cardiac failure, and presumably has a similar explanation.

(3) *Small Foci of Collapse Fibrosis Following Recent Focal Death of Myocardial Fibres.*—These lesions are obviously much older than any others in this list, but could very well date from the time of the operation. They are microscopic, one low-power field or less in size, and it is suggested that their origin was anoxia or trauma which occurred between the removal of the heart from the donor and re-establishment of the circulation in the body of the recipient. The transplanted heart of the patient was without perfusion for intermittent periods totalling 25 minutes. Speculation about the precise mechanism seems relatively unimportant, as they constitute an insignificant proportion of the myocardium and are too old to be interpreted as indicating rejection.

Some information on this matter was obtained from the second human heart transplant in Cape Town. A small portion of the left atrium was removed as soon as the heart was taken from the donor's body. This was compared with another portion from the same atrium taken just before the donor's and recipient's atria were sutured. The first portion showed no abnormalities, but the second showed close-set pericardial serosal cells obviously swollen and which possibly have proliferated, and occasional muscle fibres both under the endocardium and under pericardium were swollen, eosinophilic, and with pyknotic nuclei, some with a perinuclear halo of oedema. These contrasted with the bulk of the myocardium, which appeared normal. Even though the donor's heart was perfused as soon as possible there was a period when no circulation was present.

(4) *Infarct-like Necroses in All Four Atria, Particularly the Recipient's.*—It is surprising that the great bulk of the

recipient's atria survived when their usual coronary circulation no longer existed. Presumably they have some blood supply from arteries other than the coronary, as nourishment through the endocardium would seem unlikely, at least in the left atrium with its thick endocardial lining. All four atria were trimmed before suturing, and the necroses in the vicinity of the suture lines are to be expected. The recent haemorrhages evident to the naked eye under the endocardium and pericardium are confined to living tissue at its junctions with the infarcted areas.

(5) *Oedema and Cellular Infiltration in Myocardium.*—The cellular infiltration and proliferation are unimpressive when compared with transplanted dogs' hearts, but are difficult or impossible to explain without evoking rejection as their basis. It is significant that the cellular infiltration of lymphocytes and plasma cells was present to a considerable degree in the donor's left atrium and not in the recipient's left atrium. The subendocardial cellular infiltration is of the type described in dogs' hearts showing graft rejection but is limited in amount and has a very limited distribution. In the sections studied the bulk of the endocardium does not show this change. Another difference from animal experiments is the absence of changes in the four heart valves, cellular infiltration and cellular proliferation being uniformly absent. The absence of polymorphonuclear leucocytes could be ascribed to the profound myeloid depression determined by the immunosuppressive therapy, but there were plenty of polymorphs in the pneumonic lungs, and extension of the pneumonia was evident radiologically three days before the patient died. Polymorphs were also found in the bifurcation lymph nodes, and all one can conclude is that if the signs of rejection developed at any time up to the fifteenth day the polymorphonuclear leucocyte was not involved in this process. It might have appeared in the subsequent three days had it not been for the myeloid depression. Other differences from the transplanted dog hearts showing graft rejection are the marked proliferation of Anitschkow's myocytes, and the failure to demonstrate an increase in tissue mast cells. The fact that these changes do not compare in intensity or extent with those seen in dog transplanted hearts does not diminish their assessment as indicating rejection.

(6) *Foci of Necrotizing Arteritis in Both Ventricles.*—These appear to be terminal lesions for the reasons already given, but present the greatest difficulty in evaluation. Arterial changes in transplanted dog hearts are described rather vaguely, but in those hearts with fully developed rejection features with massive cellular infiltration, including polymorphs, haemorrhages, etc., it is not surprising that some arteritis is present. In the patient's heart, however, we have a dissociation between very slight cellular infiltration and a necrotizing arteritis. Vascular lesions of this type have not been seen in the earlier stages of rejection of dogs' hearts personally studied. The lesions presumably developed in the last two days of the patient's life when he was receiving 100% oxygen but still remained in a state of severe anoxia.

In an endeavour to get controls of cases with comparable anoxia due to lung inadequacy, the hearts from 10 cases of respiratory distress syndrome were studied. These had all been on oxygen for a variable number of days, and all had terminally an anoxic state. Only one showed, particularly in the right ventricle, a considerable perivascular oedema and a notable excess of cells round the blood vessels, histiocytes, fibroblast-like cells, some Anitschkow's myocytes with scanty lymphocytes, and a very few plasma cells, but no vascular lesions were present in this or any of the others.

Conclusions

The natural tendency for those familiar with the vascular lesions in transplanted kidneys would be to regard necrotizing arteritis as indicating rejection. Those familiar with dog trans-

planted hearts might well ascribe it to other causes. It may be significant that in the donor's left atrium, where the cellular infiltration is maximal, there is no necrotizing arteritis, and the Scottish verdict of "not proven" would seem at this stage the most reasonable one. More evidence from other cases is desirable.

We do not think that the occurrence of plasma cells in large numbers in thoracic lymph nodes, spleen, bone marrow, pancreas, and portal tracts of liver has anything to do with graft rejection. A similar distribution of plasma cells of comparable intensity can readily be seen in other cases of pneumonia. It is, however, of interest that the intensive immunosuppressive therapy apparently did not inhibit the formation of plasma cells, and presumably the production of antibodies to the pulmonary infection.

No obvious explanation for the fat necrosis in and around the pancreas is evident. The greenish colour and softened nature of some suggest that they may have been infected by pseudomonas, but no positive culture was obtained. They appear to be of about a week's duration and are delimited by a zone of fibrin outside which is considerable fibroblastic proliferation. The surrounding infiltration of lymphocytes and plasma cells is not interpreted as supporting the view that they were basically of bacterial origin; the infection was more probably a secondary one.

Of the changes in the heart one can only try to put them into the five categories previously given. One can say virtually nothing about lesions present in the donor's heart during life. A portion of the donor's pulmonary artery did show an excess of cells in the intima with some lymphocytes and plasma cells, but this was related to an early atheromatous plaque histologically, and has been observed in other pulmonary arteries. The other tissues available from the necropsy on the donor show no evidence of vascular lesions of any kind. It is clear from the data given earlier that some damage can be done on a traumatic or ischaemic basis to the donor's heart before the circulation is re-established in the body of the recipient, but this is minor. It is also evident that the atria, particularly those of the recipient, suffer ischaemic damage. It is most unlikely, however, that this will be of functional significance in view of the low pressures in these chambers. It may well be that the replacement of these dead areas by scar tissue and its cicatricial contraction might be beneficial in the end by reducing the size of the over-large sutured donor's and recipient's atria. The subpericardial haemorrhages in the dead recipient's atria resulted in the pericardial fluid being blood-stained, and this might well be misinterpreted as indicating rejection, leakage from suture lines, or a severe infection. No evidence was obtained that the extensive bilateral pneumonia with associated toxæmia led to significant changes in the myocardium.

It is impossible at this stage to recognize or evaluate possible myocardial damage from the intensive immunosuppressive therapy. It could, for example, be suggested that the cobalt bomb radiation was responsible for the necrotizing arteritis, but we have no acceptable evidence for this, unless we postulate that the transplanted heart was abnormally sensitive to radiation. It is felt that to discuss this now is not a profitable procedure.

One would like to try to assess the factors responsible for the mildness of the rejection signs compared with those usually found in dog heart transplants, but there are too many variables present. We cannot presume that the intensive immunosuppressive therapy was the more important, as species difference in rejection response are unknown for the human transplanted heart and comparisons with the kidney may not be valid; nor can we evaluate the effect of the good leucocyte antigen matching. The probability is that all these factors were operative to varying degrees, but individual assessment is merely a guessing matter at the moment.

As regards changes which could lead to irreversible lowering of cardiac function, the arteritis might prove in the long run the most significant if it progressed. There is no evidence in the affected vessels of obstructive phenomena at the time of the patient's death and no effects on the myocardium were noted. It would seem reasonable to infer that if this necrotizing arteritis was a manifestation of graft rejection it would probably have progressed, as the patient had almost maximal treatment with the immunosuppressive drugs and procedures available today. But we cannot be certain at this stage that the arteritis was the result of rejection. It may be significant that the second heart transplant patient in Cape Town was alive and improving 126 days after transplantation at the time of writing, having had similar treatment throughout, apart from intensified precautions against infection. It would seem reasonable to presume that whatever rejection phenomena he may have developed during this period, an arteritis of the type and extent seen in the first human transplant has not so far developed.

Summary

Necropsy on the first heart transplantation in man confirmed that death was due to extensive bilateral pneumonia and not to rejection of the heart. Signs of rejection, however, were demonstrated histologically, but were of a low order compared with those seen in the transplanted dog heart. How far the mildness of the rejection signs is to be ascribed to species differences, immunosuppressive drugs and procedures, postoperative rest, and nursing and medical care, or to the good matching of leucocyte antigens cannot at the moment be assessed.

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Long-Term Hazards of Thorotrast

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For some 20 years after its introduction into clinical practice in 1928 a colloidal suspension of 232-thorium dioxide (Thorotrast) was extensively used as a radiographic contrast medium either to outline body cavities such as the renal pelvis or the cerebral ventricles or for the visualization of blood vessels. For all practical purposes thorium, once injected, is retained indefinitely by the body either locally at the site of injection, or, when given into the blood stream, mainly in reticuloendothelial cells in the liver, spleen, bone marrow, and lymph nodes. The effects of this retention are complex, and both chemical and radiation damage have to be considered, the former producing a slowly progressive tissue fibrosis, while the latter is reflected in an increased mortality from certain tumours. In considering the tumour hazard after the intra-arterial injection of Thorotrast account must be taken of the biological effects which may derive not only from 232-thorium deposited in soft tissues but also from its daughters, some of which become deposited in the organic and mineral components of bone and one of which, thoron, is excreted through the lungs. The late effects of increased body burdens of thorium include the development of tumours of the liver and spleen, leukaemia, aplastic anaemia, thrombocytopenia, and possibly carcinoma of the bronchus (da Silva Horta *et al.*, 1965).

Material and Methods

A search of departmental records allowed identification of patients receiving Thorotrast in the course of investigation in the Department of Surgical Neurology, Edinburgh.¹ All

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¹ Initial extraction of relevant case records was carried out by the late Mr. P. B. Ascroft as part of a preliminary study of the present series (Ascroft and Maccabe, 1962).

records relating to the years 1926 to 1955 inclusive were examined and yielded a total of 168 patients who had received Thorotrast either by intra-arterial injection (141 patients) or by direct injection into the cerebral ventricles or subarachnoid space (27 patients). Subsequent experience of these patients has been ascertained by follow-up inquiries directed towards tracing and establishing the current status of each individual. Wherever possible, surviving patients have been seen or, failing this, questionnaires have been sent to their medical practitioners. For patients found to be dead copies of death certificates have been obtained and case records relating to any deaths in hospital have been examined.

Results of Intra-arterial Injection of Thorotrast

Nine of the 141 patients in this group came from abroad for treatment and one further patient has since emigrated. These 10 patients have been excluded and are noted as such in Table I. All the remaining 131 patients were traced and their status was determined on 1 January 1966 or later. Twenty-two patients died within one year of Thorotrast administration as a direct result of the disease bringing them

TABLE I.—Distribution of 141 Patients Receiving Thorotrast Intra-arterially by Year of Injection, Age at Injection, and Volume Injected

Year of Injection	No. of Patients		Age at Injection (Years)	No. of Patients		Thorotrast Injected (ml.)	No. of Patients	
	Study Group	Excluded*		Study Group	Excluded*		Study Group	Excluded*
1930-4	6	1	0-4	1	—	0-9	—	—
1935-9	20	13	5-14	7	2	10-19	35	16
1940-4	52	7	15-24	25	3	20-29	33	6
1945-9	30	11	25-34	27	10	30-39	20	5
1950-4	—	—	35-44	28	8	40-49	8	3
1955-9	1	—	45-54	16	8	50-59	4	—
			55-64	5	1	60-69	1	—
						70-79	1	—
						80-89	8	2
						N.K.		
Total	109	32	Total	109	32	Total	109	32

* 10 patients with permanent foreign residence (current status unknown) and 22 patients who died within one year after Thorotrast administration.