Virchows Arch [Pathol Anat] (1985) 407:295–307

Virchows Archiv A

Human cardiac transplants
Diagnosis of rejection by endomyocardial biopsy
Causes of death (about 30 autopsies)

G. Chomette[1], M. Auriol[1], A. Delcourt[1], B. Karkouche[1], A. Cabrol[1], and C. Cabrol[2]

[1] Department of Pathology (Direktor: Prof. Dr. G. Chomette)
[2] Department of Cardiovascular Surgery (Direktor: Prof. Dr. C. Cabrol)
of the University of Paris, F-75013 Paris, France

Summary. 1,000 endomyocardial biopsies performed in 110 patients treated by cardiac graft were reviewed. These biopsies permitted early detection of acute rejection after cyclosporin treatment and a good appreciation of its intensity. By this method, almost all rejection episodes were resolved after adequate treatment. Chronic rejection was diagnosed by arteriography used in vivo or in cardiac transplants removed by surgery or necropsy. Rejection provoked an obliterative fibrous endarteritis often complicated by atherosclerosis and its ischaemic consequences.

34 autopsies were performed in patients dead at a variable time after cardiac or cardio-pulmonary transplantation. In early death (14 cases), graft failure and systemic disorders were observed. Acute and chronic rejection was noted less frequently (9 cases). Systemic infections (10 cases) occured either early (post-surgical complications) or late (bacterial, fungal and parasitic lesions). In one case, death was due to a contemporaneous bladder carcinoma.

The complications of cyclosporin treatment are briefly discussed.

Key words: Human cardiac transplant – Endomyocardial biopsy – Pathological study – Histopathology of rejection

Introduction

Pathological study contributes significantly to the better knowledge of the various complications which follow human cardiac transplantation. Following the use of a new immunosuppressive drug, cyclosporin A[1] (1981), the pathology of post-operative endomyocardial biopsies (Billingham 1979; Oyer et al. 1979; Fowles et al. 1981; Billingham and Mason 1982; Gokel

Offprint requests to: G. Chomette Service d'Anatomie pathologique. Hôpital de la Pitié. 83, Boulevard de l'Hôpital, F-75013 Paris, France

1 An antifungic agent (cyclic peptid) isolated from Trichoderma polysporum, with probable specific T cell subset inhibitory properties

et al. 1985; Pomerance and Stovin 1985) has contributed significantly to the early diagnosis of acute rejection episodes. In addition, pathological examination in necropsied patients is necessary to appreciate correctly the local or systemic lesions responsible for death after grafting.

We report here the results of our own pathological experience on cardiac transplantations performed during a 15-year period in a department of cardiovascular surgery (Pr. C. Cabrol). Clinical data have been already published (Cabrol et al. 1983).

Patients and methods

1. Patients

Clinically, the 110 patients of our series received an intense immunodepressive treatment after cardiac graft:

- before 1981, steroids, anti-lymphocyte serum and azathioprine were used simultaneously.
- since 1981, after 2 or 3 days with high doses of steroid, azathioprine and anti-lymphocyte serum, the cyclosporin A was added with an initialdose of 4 to 5 mg/kg progressively increased to obtain 100 to 150 ng/ml in the serum. This concentration was then maintained and simultaneously anti-lymphocyte serum and azathioprine were reduced and steroids were decreased to 3 mg/kg/day. In case of rejection detected by endomyocardial biopsy, massive doses of steroids (17 mg/kg by intraveinous injection) were used, eventually associated with anti-lymphocyte serum in sever rejections.

For this study, we have used various data.

A. *1000 endomyocardial biopsies* were performed. Each patient, since 1981, has had repeated biopsy procedures (1 per week during the first 3 months, 2 per month in the 3 following months and 1 per month later on). In every biopsy procedure, 3 pieces of myocardium were obtained, each of them measuring 0.1 to 0.3 cm in maximum dimension.

B. *2 cardiac grafts* were *surgically removed* for retransplantation after a chronic rejection.

C. *34 autopsies* were performed (from 1969 to 1984) in patients dead after cardiac graft (30 cases) or cardio-pulmonary transplantation (4 cases). The transplantations were performed before 1981 (21 patients) and after that time for 9 patients, who had thus received treatment by cyclosporin A.

2. Methods

The myocardial biopsy tissue was fixed immediately and embedded in paraffin (usual time for fixation and embedding was about 18 h). All biopsies were stained with haematoxylin and eosin. In addition, some of them were stained with Masson's trichrome and methyl-green pyronin. For the evaluation of grades of rejection, without using a true quantitative method, we examined all the pieces of myocardium and gave our results according to the mean number of lymphocytes and their predominant topography (perivascular or interstitial).

Surgical specimens of cardiac grafts and cardiac transplants removed at necropsy were systematically studied by means of blocks taken from ventricular and auricular walls, sutures, valves and the conduction system.

In addition, in cases of chronic rejection, angiographic data were obtained after injection of the coronary arteries with a minium-gelatine mixture (Delarue et al. 1963) followed by radiographic study. Thus, correlations were established between radiological and histological patterns and corroborated, in some cases, by means of cleared blocks.

All necropsies were submitted to a detailed macroscopical and histological analysis (for example, search for lethal factors, associated malignant diseases, toxic effects of the cyclosporin A etc.).

In two patients, presenting with acute and chronic rejection respectively, myocardial biopsy specimens were studied by *electron microscopy* and *histoenzymology* in addition to the routine examination:

– for electron microscopy, small blocks of fresh tissue were immediately fixed in glutaraldehyde, embedded in epon and examined with a Hitachi H 300 electron microscope.
– for histoenzymological investigations, specimens were immersed in liquid nitrogen and sections were obtained using a cryostat. Enzyme activities were tested according to Pearse's methods (Pearse 1972): oxidative enzyme activities (especially succinodehydrogenase); hydrolases activities (acid and alkaline phosphatases, ATPases).

Results

1. Acute rejection

It does not occur in our patients before the 7th day. It reaches a maximum both in frequency and intensity before the sixth months. Since the use of cyclosporin, it has never been observed after this period. It is easily detected by endomyocardial biopsies. According to Billinghan (1979), we have established *four grades of rejection* with increasing intensity:
– in the non significative grade (+ −), rare lymphocytes are seen round vessels or in the interstitium.
– in the mild grade (+), the number of lymphocytes is abnormally high in some vascular lumina or in vascular adventicia (nodular patterns – Fig. 1). These lymphocytes are sometimes seen in small groups in the interstitium. Interstitial oedema is occasionally present.
– the moderate grade (+ +) is characterized by a diffuse interstitial infiltrate (Fig. 2) of lymphocytes (isolated or arranged in small trabeculae) associated with perivascular infiltrates. Except for some artefacts (contraction bands – Fig. 3), few myocytes are shrunken: nuclear alterations; acidophilic changes in the cytoplasm (staining blue after trichrome method). Arteriolar damage is also frequently noted (a lymphocytic intimal infiltrate is sometimes seen involving the media of muscular arteries).
– in the severe grade (+ + +), the myocardium is largely infiltrated by lymphocytes (Fig. 4) and also macrophages, polynuclear leukocytes and fibrin exudates. Myocytes are damaged and become scarce (Fig. 5). They show fragmentation, acidophilic degeneration and breakdown by macrophages. In addition, arterial lesions are obvious (vasculitis is often associated with luminal obstructions by cells and fibrin).

Special techniques used in some cases have permitted other conclusions: most of the lymphocytes seen in these cardiac biopsies have a pyroninophilic cytoplasm and, by electron microscope, show numerous ribosomes, ergastoplasmic cisternae and an indented nucleus (Fig. 6 and 7). Furthermore, in areas where myocytes are injured, the histoenzymological methods demonstrate a reduction or suppression of oxidative metabolic activities (Fig. 8).

After immunosuppressive treatment, this rejection is variably influenced by therapy. In mild grades (+), the histological features become quite normal after less than 8 days. In contrast, moderate rejection (+ +) is slowly regressive (approximatively 15 days). As for severe rejection, it may be also stopped by the treatment, but its prognosis often remains poor. In two of our cases, it was corrected only by retransplantation. In another case, despite a long cyclosporin treatment, this severe rejection persisted

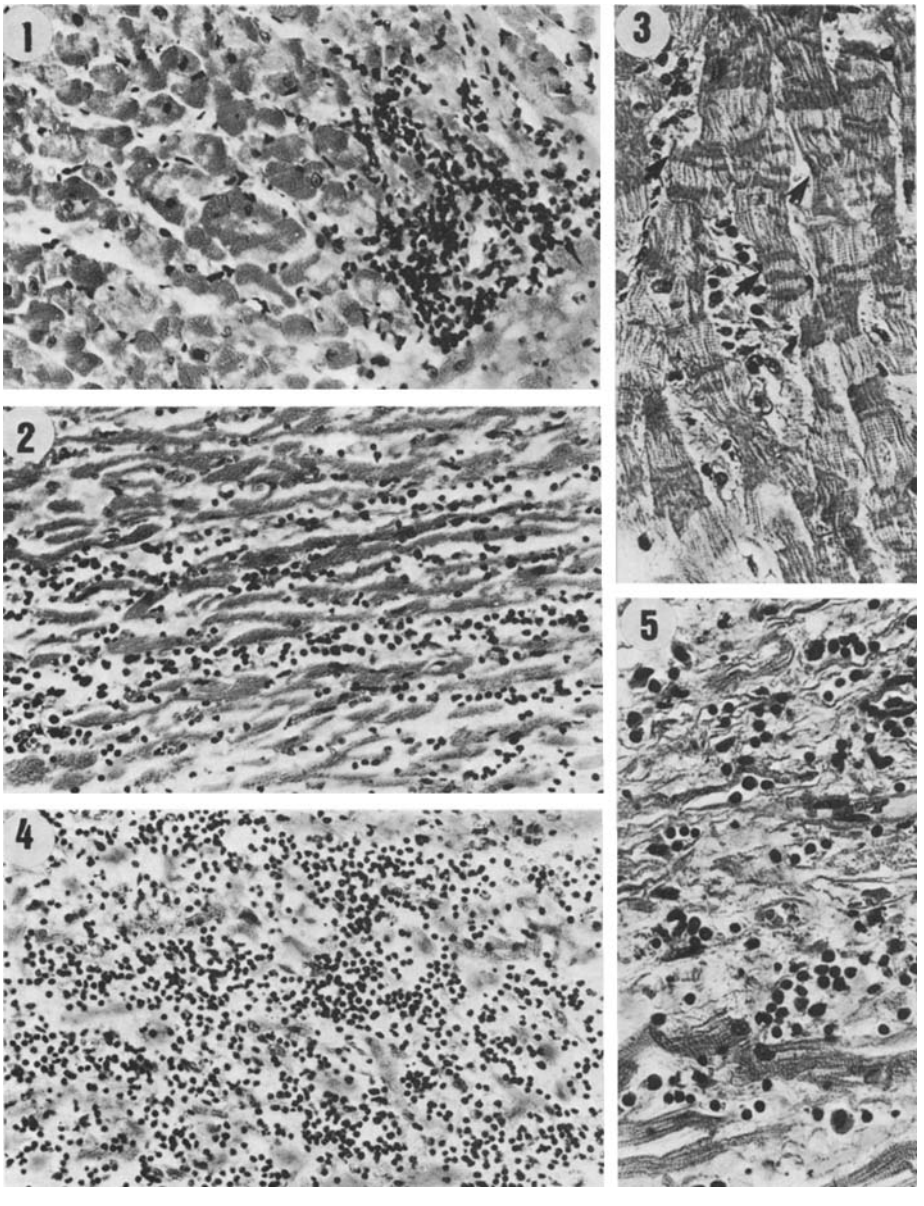


Fig. 1. Man 35 years old. Alive. Biopsy 25 days after transplantation. Myocardium. Acute rejection (+). Nodular perivascular lymphocytic infiltrate. Haematoxylin-eosin × 220

Fig. 2. Man 28 years old. Alive. Biopsy 10 weeks after transplantation. Myocardium. Acute rejection (+ +). Interstitial infiltration of lymphocytes. (Slow resolution after treatment 14 weeks after graft). Haematoxylin-eosin × 220

Fig. 3. Man 25 years old. Biopsy at 4 months (death at 5 months – case 7) Myocardium. Acute rejection (+ +). Interstitial lymphocytes Contraction bands in myocytes (➡). Haematoxylin-eosin × 380

Fig. 4. Man 39 years old dead at 6 months (case 30). At necropsy, acute rejection (+ + +) in myocardium. Massive lymphocytic infiltration with destruction of myocytes. Haematoxylin-eosin × 220

Fig. 5. Man 39 years old. Death at 6 months (case 30). At necropsy, acute rejection (+ + +) in myocardium. Partial or total destruction of myocytes. Haematoxylin-eosin × 380

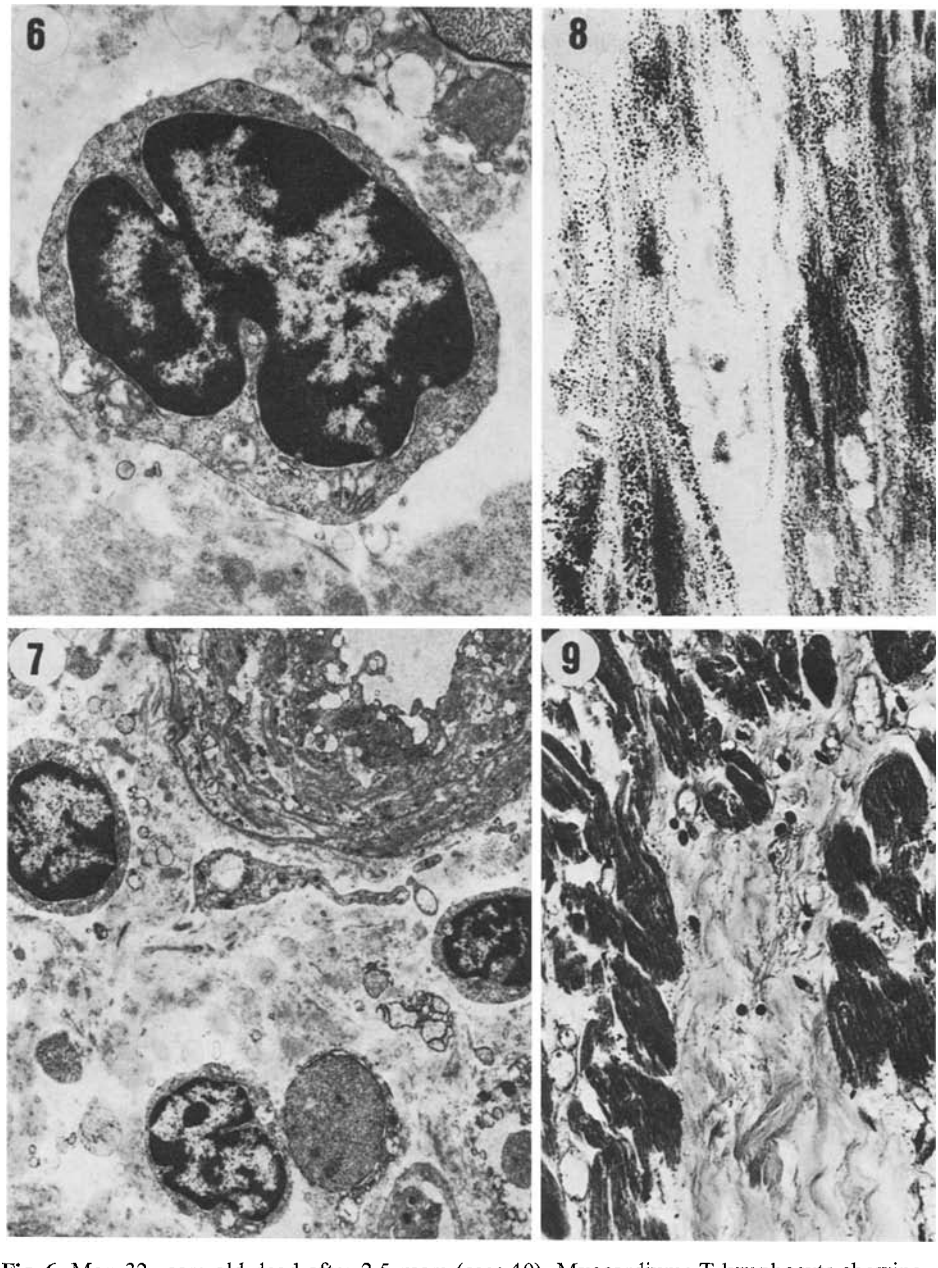


Fig. 6. Man 32 years old dead after 2,5 years (case 10). Myocardium: T-lymphocyte showing indented large nucleus. Electron microscopy $\times 10{,}000$

Fig. 7. Case 10. Myocardium. T-lymphocytes round a vessel. Electron microscopy $\times 3{,}500$

Fig. 8. Case 10. Myocardium. Irregular activity of Succinodehydrogenase in altered myocytes. Histoenzymology $\times 360$

Fig. 9. Woman 32 years old. Biopsy 2 weeks after treatment for rejection (+ +). Myocardium: small fibrous scar of acute rejection containing some small lymphocytes. Haematoxylin-eosin $\times 380$

during 6 months postoperatively and finally caused death. When healed, the acute rejection may disappear without sequelae. More often, it is followed by some fibrous scars containing non pyroninophilic lymphocytes and haemosiderin pigment (Fig. 9).

2. Chronic rejection

Rarely, it occurs as early as the 6th month and may thus be mixed with episodes of acute rejection. Its maximum of frequency is noted after the first year. In our cases only coronary arteriography, performed in vivo or in cardiac grafts obtained after transplantation and necropsy were able to detect this kind of rejection. Such a method demonstrates slots, moniliform narrowings and zones of non opacification of some arteries on the main coronary vessels and on their proximal collateral branches entering into the myocardium (Fig. 10).

In its earlier episodes, chronic rejection may have "inflammatory" features: numerous lymphocytes penetrate the intima and sometimes the media of arteries (Fig. 11). As a rule, however, it consists of an obliterative fibrous endarteritis (Fig. 12) often infiltrated by atheromatous lipid deposits (Fig. 13). The media, not so intensively injured, may be disrupted by fibrous areas and its internal elastic lamina is often fragmented. By electron microscopy, few lymphocytes are sometimes seen against the intima of arteries (Fig. 14); a great number of myocytes migrate from media to intima and are surrounded by numerous collagenous fibers; an abundant sub-endothelial production of basal membrane-like material is also seen (Fig. 15). In case of atheromatous deposits, these myointimal cells are filled with lipid droplets (Fig. 16).

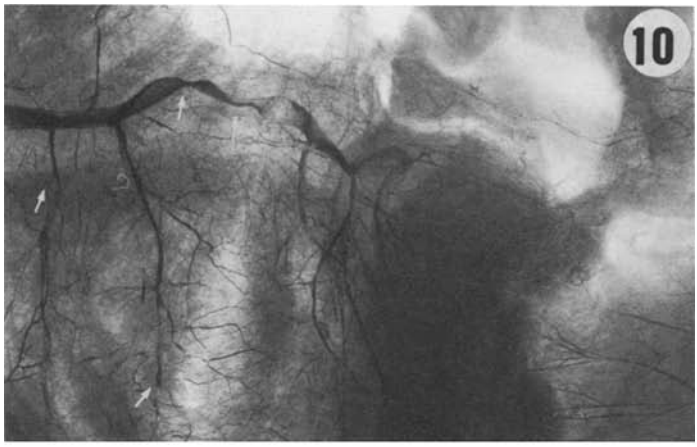
The consequences of chronic rejection may be severe; there may be luminal thrombosis followed by ischaemic cardiopathy and congestive heart failure. In other cases, ischaemic areas only discovered by the post-mortem study had not provoked any functional complication in vivo.

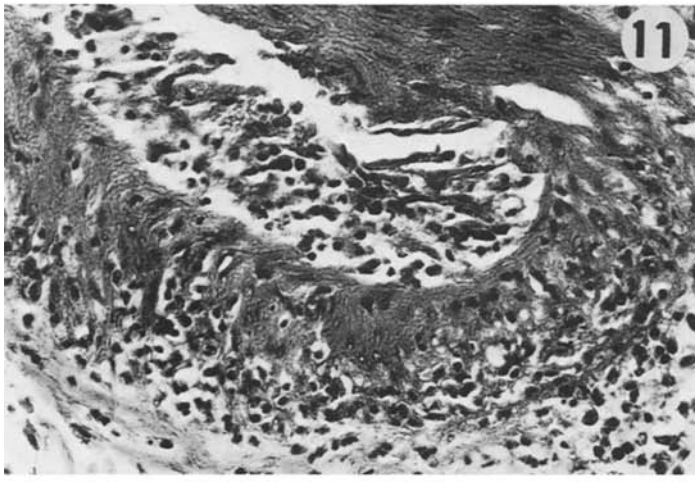
3. Causes of death

In our series (34 necropsied patients), the indication for cardiac grafting were cardiomyopathies (25 cases), ischaemic heart diseases (5 cases) and congenital cardiopathies (tricuspid atresia-1 case-). Indications for cardiopulmonary transplantation were cardiopathies with chronic pulmonary hypertension (primary pulmonary hypertension – 2 cases; secondary pulmonary hypertension consecutive to a mitral or aortic cardiopathy – 2 cases). The age of patients varied from 19 to 66 years. The survival rate was a few hours to 9 years.

Lethal factors were variable according to the survival time after operation. They could be divided into five groups:

1. *11 patients* ($^1/_3$ of cases) were dead soon after the graft (Table 1). Rarely (3 cases), graft failures were observed (myocardial failure). Usually, systemic disorders were discovered: pulmonary embolism and thromboem-





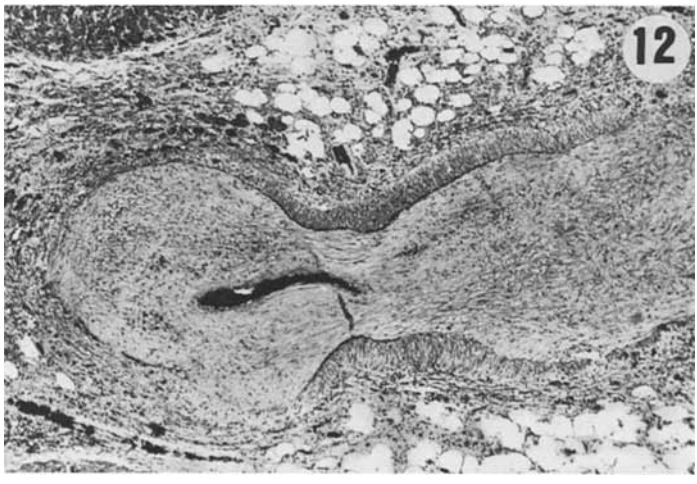


Fig. 10. Man 39 years old, dead at 6 months (case 30). Chronic rejection. Coronarography (minium-gelatin solution). Right coronary artery with moniliform stenosis (→) of its muscular branches

Fig. 11. Man 39 years old, dead at 6 months (case 9). Chronic rejection. "Inflammatory" arteritis: lymphocytes penetrating media and adventicia of a coronary artery. Haematoxylin-eosin × 380

Fig. 12. Man 39 years old dead at 6 months (case 30). Chronic rejection. Obliterating fibrous endarteritis. Haematoxylin-eosin × 110

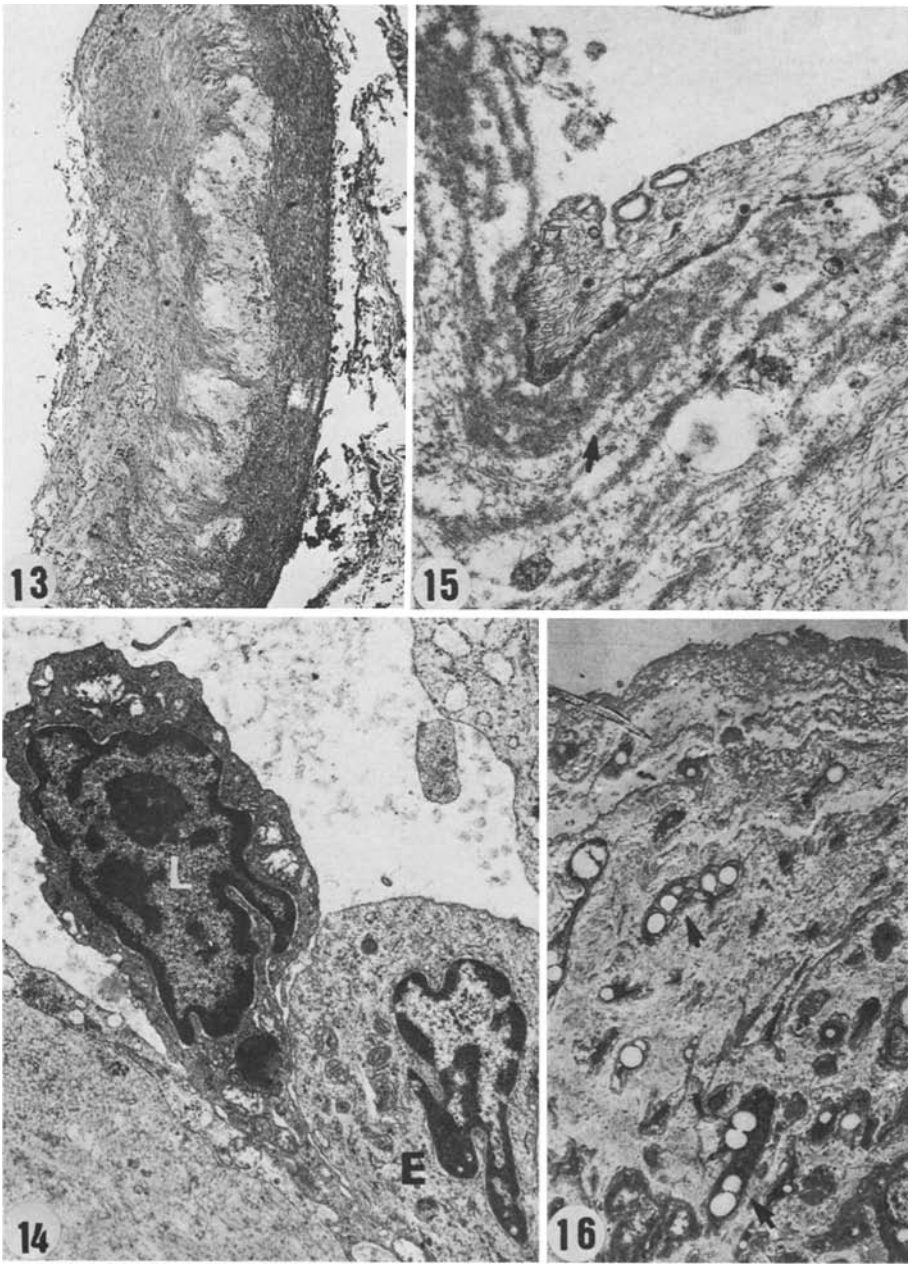


Fig. 13. Man 45 years old dead at 9 years (case 13) (cardiac graft had been taken from a 18 years-old man victim of an accident). Chronic rejection. Atheromatous lesions in chronic coronary arteritis. Haematoxylin-eosin $\times 120$

Fig. 14. Case 10 (survival of 2,5 years). Chronic rejection. T-lymphocytes (L) against an intimal cell (E) of a coronary artery. Electron microscopy $\times 6{,}500$

Fig. 15. Case 10. Chronic rejection. Coronary artery. Replication of subendothelial basement membran (→). Electron microscopy $\times 2{,}000$

Fig. 16. Case 23. Coronary artery. Chronic rejection with atheromatous complication. Medial and myointimal myocytes filled with lipidic droplets (→). Electron microscopy $\times 1{,}000$

Table 1. 30 autopsies of patients treated by cardiac graft

N°	Sex	Age	Preop. diagnosis	Cyclo-sporin	Acute rejection	Time of survival	Cause of death
1	m	66	CMP	–	–	56 h	Pulmonary embolism
2	m	34	CMP	–	–	10 h	Graft failure
3	m	51	IC	–	–	4 days	Haemorrhagic syndrome
4	m	45	CMP	–	–	9 h	Graft failure
5	f	32	CMP	–	+ +	8 days	Acute rejection
6	m	47	CMP	–	+ +	54 days	Acute rejection
7	m	25	CMP	–	+ +	5 months	Acute rejection
8	m	45	CMP	–	–	8 days	Acute endocarditis
9	m	39	CMP	–	+ +	6 months	Acute rejection
10	m	32	CMP	–	–	2.1/2 y.	Chronic rejection
11	m	35	CMP	–	–	2 days	Pulmonary embolism
12	m	57	IC	–	+	1 month	Thromboembolic disease
13	m	43	CMP	–	–	8 days	Suppurative mediastinitis
14	m	49	IC	–	–	2 months	Aspergillosis
15	m	61	IC	–	–	8 days	Bronchopneumonia
16	m	39	IC	–	–	11 days	Bacterial septicemia
17	m	19	CMP	–	+	18 months	Chronic rejection
18	m	36	CMP	–	+ +	3 months	Acute rejection
19	m	36	CMP	–	–	14 months	Nocardiosis
20	m	32	CMP	–	+ +	2 months	Acute rejection
21	m	31	CMP	–	+	34 days	Aspergillosis
22	f	52	CMP	+	–	13 days	Acute pancreatitis
23	m	45	CMP	+	–	9 years	Vesical carcinoma
24	m	34	CMP	+	–	1 day	Graft failure
25	m	32	CMP	+	–	1 month	Bacterial septicemia
26	m	30	CMP	+	+ –	18 days	Bronchopneumonia
27	m	50	CMP	+	+	10 days	Thromboembolic disease
28	m	36	CC	+	–	6 days	Pulmonary embolism
29	m	40	CMP	+	–	8 days	Haemorrhagic syndrome
30	m	39	CMP	+	+ + +	6 months	Acute rejection

Abbreviations. m = male; f = female; cyclosporine + = treatment by cyclosporine; cyclosporine – = treatment by other immunosuppresseurs; CMP = cardiomyopathy; IC = ischemic cardiopathy; CC = congenital cardiopathy

bolic disease (5 cases) with cerebral embolic or haemorrhagic accidents; haemorrhagic syndrome with diffuse intravascular coagulation (2 cases); ischaemic acute pancreatitis (1 case). Most of these accidents were noted in case of late transplantations in patients with severe cardiac failure.

2. *Acute and chronic rejection* are a little less frequent than the preceding group (7 acute rejections; 2 chronic rejections) (Table 1). Nevertheless the number of lethal acute rejections is only one half of all the rejections demonstrated by necropsy (16 cases). Since the institution of cyclosporin treatment in our necropsy material, only one acute rejection was found as lethal factor.

3. *Systemic infections* represent the 3rd cause of lethality (9 cases) (Table 1). Some of them, occuring early during the 1st month are post surgical complications such as mediastinitis (1 case), endocarditis (1 case), pneumopathy (2 cases). The others, later observed (from the 1st to the 6th month)

Table 2. Autopsies of 4 patients treated by cardio-pulmonary graft

N°	Sex	Age	Preop. diagnosis	Cyclo-sporine	Acute rejection	Time of survival	Cause of death
1	m	50	2ary PAHT	+	+	3 months	Pulmonary infection
2	m	23	1ary PAHT	+	–	13 days	Pulmonary infection
3	f	23	1ary PAHT	+	–	3 weeks	Pulmonary candidosis
4	m	19	2ary PAHT	+	–	23 days	Pulmonary infection

Abbreviations: m = male; f = female; PAHT = pulmonary arterial hypertension cyclosporine + = treatment by cyclosporine

are bacterial, parasitic or fungal lesions (2 bacterial septicemia; 1 case of Nocardiosis; 2 cases of Aspergillosis).

4. *A malignant tumour* was the cause of death in one case. The 45-year-old patient presented a highly evolutive and metastasizing vesical carcinoma. In spite of surgical treatment, he died of this cancer 9 years after the cardiac transplantation (Table 1).

5. As to the 4 patients treated by means of a cardio-pulmonary graft, they all died a few days to 3 months after the operation. In all cases, the cause of death was bronchopulmonary infection (3 bacterial infections, 1 fungic infection – candidosis –) (Table 2).

4. Complications due to cyclosporin

In our series, we have observed 3 types of complications:

– *myocardial fibrosis*, interstitial sclerosis surrounding each myocardial fiber individually was noted in 5 of our endomyocardial biopsies and in one of our necropsies.

– a *tubulointerstitial nephropathy* with acute renal insufficiency was observed in one patient who died 6 months after the graft from acute rejection episodes non regulated by the treatment. Lesions affected only the distal convoluted tubules which showed partial cellular necrosis.

– *gingival hypertrophy* was frequently noted (10 of the patients alive). Clinically, it is often enormous. By histological examination of gingival biopsies, we were able to demonstrate a true gingivitis with confluent infiltrates of mononuclear cells (lymphocytes and plasmocytes) without any change in the pattern of collagen fibers.

Discussion

As is the case with all allografts (Chomette et al. 1969a; Chomette et al. 1969b), cardiac transplants are exposed to acute rejection episodes which may compromise their functions. The acute rejection process remains a complex problem. It is mainly dependant on transplantation immunity, which consists in an intravascular and interstitial proliferation of T lympho-

cytes (Billingham et al. 1977). These cells are activated as demonstrated by their pyroninophilic cytoplasm and their ribosomes and ergastoplasmic cisternae in electron microscopy and then attack endothelial cells and cardiomyocytes either by direct action or after the intervention of macrophages. Later, humoral immunity participates in the rejection process, as demonstrated by a positive immunofluorescence for IgG and C3 in myocytes and around blood vessels (Bieber et al. 1970; Fowles et al. 1981).

Acute rejection is less frequent and more easily resolved following the use of the cyclosporin which has greatly improved prognosis in cardiac transplantations (70% one-year survival rate and 40% five-year survival rate – Uys and Rose 1984; 124 patients still alive up to four years after operation – Pomerance and Stovin 1985). Its detection is only possible by means of repeated endomyocardial biopsies during the first six months after operation. It occurs later in human transplants (7th day) than in experimental grafts (2d to 5th day) (Kosek et al. 1968; Billingham et al. 1973). From the autopsies of patients dead shortly after grafting, it is apparently located in particular zones of the transplant such as sutures (Ellis et al. 1971) and the conduction system (Bieber et al. 1970). Simultaneously, it occurs in the myocardium (myocardium of the right ventricle, site of biopsies). It rarely injures endocardium, valves and pericardium. Nowadays, for the best management of cardiac allograft recipients by immunosuppressive treatment, the exact grade of intensity of this rejection must be evaluated by means of Billingham's histological criteria (1979). Thus, almost all episodes of mild or moderate acute rejection can be resolved. They are sometimes followed by small scars (Billingham 1979). On the other hand, the prognosis for severe grade rejection remains somewhat poor.

Chronic rejection rarely occurs before the 6th month. Generally, its maximum frequency is noted after the first year (Uys and Rose 1984). Detected by means of in vivo or post-mortem arteriography, it consists of a true stenosing endarteritis frequently complicated by atherosclerosis and contemporary ischaemic cardiopathy. It seems to be explained by the same mechanisms as those proposed by Porter (1974) and Callard et al. 1975 for renal grafts. Thus, it results from an injury to the arterial wall (especially the intima) followed by an abundant subendothelial production of basal membrane-like material. Then, parietal myointimal cells undergo mobilization towards the intima. The aetiology of that initial injury is not clear. The preponderant initial event is the migration of lymphocytes into the wall of vessels. Later, the most important process is certainly the aggregation of platelets and fibrin on endothelial cells.

In our series of 34 necropsied patients, as in other similar studies, apart from general accidents and episodes of rejection not resolved by treatment, one can note various "specific" viral, fungal, parasitic infections due to immunosuppression (Remington et al. 1972; 3 of our cases). However, the frequency of these complications is decreasing since the use of the cyclosporin and their prognosis is better. As demonstrated by several statistical reports, cardiac transplantation provides an increased risk of de novo malignancy (Krikorian et al. 1978; Pomerance and Stovin 1985). Cutaneous carci-

nomas, especially Kaposi's sarcomas and malignant lymphomas, are among the most frequently mentioned tumours. Other areas can also be affected (Lanza et al. 1983; Penn 1977) such as the mammary gland, the lungs and the urinary bladder (one case in our series).

Several complications seem to be directly provoked by the cyclosporin. Among them is myocardial fibrosis (Billingham 1981; Gokel et al. 1985; Cohen et al. 1984). Though differing from the more compact ischaemic scars of chronic rejection and from sequelae of acute rejection, its histological interpretation is somewhat difficult. Tubulointerstitial nephropathy (Calne et al. 1980) may provoke temporary renal insufficiency or exceptionally fatal renal failure (1 case – Pomerance and Stovin – 1985). This change is well demonstrated by electron microscope showing lesions in the distal convoluted tubules associated with early regenerative changes. Gingival hypertrophy is frequently observed in our series. Its inflammatory substratum differs from that of other congenital or iatrogenic hypertrophies. Its pathogenesis remains unclear. Two mechanisms may play a role in its causation: a toxic one and another, truly infectious in nature and probably dependant on the immunosuppressive state.

References

Bieber CP, Stinson EB, Payne R, Shumway NE, Kosek JC (1970) Cardiac transplantation in man VII Cardiac allograft pathology. Circulation 41:753–772

Billingham ME, Caves PK, Shumway NE (1973) Diagnosis of canine orthotopic cardiac allograft-rejection by transvenous endomyocardial biopsy. Transplant Proc 5:741–744

Billingham ME, Warnke R, Weissmann I (1977) The cellular infiltrate in cardiac allograft-rejection in mice. Transplantation 23:171–176

Billingham ME (1979) Some recent advances in cardiac pathology. Human Pathol 10:367–387

Billingham ME (1981) Diagnosis of cardiac rejection by endomyocardial biopsy. Heart Transpl 1:25–30

Billingham ME, Mason JW (1982) The role of endomyocardial biopsy in the management of acute rejection in cardiac allograft recipients. In: Endomyocardial biopsy; techniques and applications. Fenoglio JJ CRC Press, Bocaraton Floride USA

Cabrol C, Gandjbakhch I, Pavie A, Cabrol A, Mattei MF, Lienhart A, Gluckmann JC, Rottembourg J (1983) Transplantation cardiaque. Etat actuel à l' Hôpital de la Pitié. La Presse méd., 12:2521–2526

Callard P, Bedrossian J, Idatte JM, Belair MF, Grossetete J, Mandet Ch, Bariety J (1975) Les lésions artérielles au cours des phénomènes de rejet des allogreffes rénales. Actualités néphrologiques de l'Hôpital Necker Flammarion (ed) Paris, pp 165–185

Calne RY, Rolles K, White DJG, Thiru S, Evans DB, Mc Master P, Dunn DC, Craddock GN, Henderson RG, Aziz S, Lewis P (1980) Actualités néphrologiques de l' Hôpital Necker Flammarion (ed) Paris, pp 316–327

Chomette G, Auriol M, Brocheriou C (1969a) Réaction du greffon contre l' hôte et réaction de rejet. Etude morphologique. Pathol Eur 4:387–408

Chomette G, Garnier H, Clot JP, Pinaudeau Y, Auriol M, Brocheriou C (1969b) Etude microscopique de transplantations hépatiques allogèniques chez le porc. Virchows Arch [Pathol Anat] 347:176–184

Cohen RG, Hoyt EG, Billingham ME, Bieber CP, Jamieson SW, Shumway NE (1984) Myocardial fibrosis due to cyclosporine in rat heterotopic heart transplantation. Heart Transpl 3:355–358

Delarue J, Chomette G, Auriol M (1963) Les cancers secondaires du foie. Anatomie pathologique et contribution à l'étude de leur vascularisation. Arch Mal App Dig Nutr 52:1296–1307

Ellis B, Madge G, Kolhatkar M, Still W (1971) Clinical and pathological findings in human cardiac rejection. Arch Pathol 92:58–65
Fowles RE, Shroeder JS, Stinson EB (1981) Transplantation and the heart. In: Immunology of cardiovascular disease. Lessof MH (ed) M Dekker, Basel, pp 339–360
Gokel JM, Reichart B, Struck E (1985) Human cardiac transplantation. Pathol Res Practeriol 178:354–364
Kosek JG, Hurley EJ, Lower RR (1968) Histopathology of orthotopic canine cardiac homografts. Lab Invest 19:97–112
Kosek JC, Bieber C, Lower RR (1971) Heart graft arteriosclerosis. Transplant Proc 3:512–514
Krikorian JG, Anderson JL, Bieber CP, Penn I, Stinson E (1978) Malignant neoplasms following cardiac transplantation. JAMA 240:639–642
Lanza PP, Cooper DKC, Cassidy MJD (1983) Malignancy following cardiac transplantation. JAMA 249:1746–1748
Oyer PE, Stinson EB, Bieber CP, Reitz BA, Raney AA, Baumgartner WA, Shumway NE (1979) Diagnosis and treatment of acute cardiac allograft rejection. Transpl Proc XI:296–303
Penn I (1977) Development of cancer as a complication of clinical transplantation. Transpl Proc IX:1121–1127
Pearse AGE (1972) Histochemistry theoretical and applied. 3rd ed. Churchill Livingstone, London
Pomerance A, Stovin PGI (1985) Heart transplantation pathology. A British experience. J Clin Pathol 38:146–159
Porter KA (1974) Renal transplantation. In: Heptinstall RH (ed) Pathology of the kidney. 2d ed. T.II. MB Strauss, LG Welt Little, Brown and Company Boston, p 1007
Remingtion JS, Gaines DJ, Griepp RB, Shumway NE (1972) Further experience with infection after cardiac transplantation. Transpl Proc 4:699–705
Uys CJ, Rose AG (1984) Pathologic findings in long-term cardiac transplants. Arch Pathol Lab Med 108:112–116

Accepted May 7, 1985