Specialty Conference

Cardiac Transplantation
Selection, Immunosuppression, and Survival

Discussants
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Cardiac transplantation has evolved from an experiment to an accepted therapy for severe heart failure. Increasing competition for donor organs mandates a greater emphasis on selection and timing for transplantation and paradoxically forces more reliance on aggressive medical therapy for all patients after evaluation. The growth of recipient and donor pools may enhance the opportunity for assessing histocompatibility, for which distinguishing between autoantibodies and human leukocyte antigen-determined reactivity is important, and some general nonresponders may be detected. Therapy with cyclosporine has improved the outcome after transplantation, but further refinement is needed, perhaps with pharmacologic synergy, to minimize nephrotoxicity and maximize specific immunosuppression. Survival is more than 80% at 1 year, after which the incidence of acute rejection and infection declines and accelerated atherosclerosis becomes prominent. Although resuming employment is not always possible, the overall quality of life is excellent after cardiac transplantation.

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LYNNE WARNER STEVENSON, MD*: Cardiac transplantation has slowly evolved from an experiment to an accepted therapy for end-stage heart disease. In 1905 Carrel and Guthrie reported transplanting a heart into the neck of a dog.[1] Mann and associates later showed functioning of a transplanted heart for four days before rejection occurred.[2] The elucidation of the graft rejection response by Lance and Medawar contributed to the design of immunosuppressive therapy[3] and ultimately to successful human renal transplantation.[4] Lower and Shumway pioneered the surgical technique and immunosuppressive regimen[5] that permitted the first human cardiac transplantation to be done in 1966 in Capetown.[6] After the initial enthusiam led to widespread failure of the procedure,[7] Shumway persevered and ultimately proved the clinical value of the technique, which by 1981 was yielding a 63% one-year survival.[8] The introduction of cyclosporine in 1981 has further improved the results of transplantation.[9] After an exhaustive review of the Battelle report,[10] cardiac transplantation has been federally approved as the best therapy for eligible patients.

With the acceptance of cardiac transplantation, the numbers of transplant centers and accepted candidates are increasing the strain on the already limited donor supply.[11] Attention must be directed to the selection for and timing of transplantation. Donor procurement and matching must be increasingly efficient. An increased understanding of tissue antigenicity and improved diagnosis and therapy for immunosuppression will be necessary to maximize graft acceptance and minimize complications.

Selecting and Treating Patients Referred for Transplantation

When heart transplantation was in its experimental stage, recipient selection was not a major problem. For an experiment, patients were not eligible until they were overtly moribund.[12] On the other hand, any potential contraindication could be rigidly applied. For a life-saving procedure, however, that is now considered standard therapy but is limited by scarce resources, selection and timing become critical issues.

Many patients with severe heart disease are not candidates for transplantation. Even among patients passing the initial screening in an outpatient clinic, fewer than half are placed on the waiting list after a full in-hospital evaluation (Table 1).

The first question that arises during the evaluation of a possible candidate for transplantation is whether the heart is sufficiently diseased to warrant replacement. As more than 95% of the patients are referred because of dilated ventricular failure, the medical history of this disease should determine when transplantation is indicated. The original criteria for transplantation included New York Heart Association class IV symptoms. Increasingly more patients are being

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ABBREVIATIONS USED IN TEXT

DTT = dithiothreitol
HLA = human leukocyte antigen
Ig = immunoglobulin

referred earlier in the course of their disease, however. To investigate whether any of these patients should be considered for transplantation, survival was determined retrospectively for a group of 28 patients who, during evaluation at UCLA or the Stanford University Medical Center, were considered to be too well for transplantation. All patients had idiopathic cardiomyopathy and ejection fractions of less than 30%. Only half of the patients survived a year without transplantation, with 82% of the deaths occurring suddenly.[13] A history of ventricular arrhythmias was strongly predictive of subsequent sudden death, whereas a stroke volume of less than 40 ml per beat was predictive of eventual circulatory failure. Neither subsequent antiarrhythmic nor vasodilator therapy correlated with the outcome, but the regimens were designed empirically by the referring physicians and were not standardized by a rigorous demonstration of clinical efficacy. We have found that most patients referred even with severe symptoms of chronic heart failure can achieve a reasonable level of function on therapy tailored specifically to hemodynamic goals,[14] but they also remain at a high risk for sudden death. Thus, we currently consider for transplantation not only patients with severe symptoms of heart failure but also those with limited symptoms who are felt to be at a particularly high risk. The same study also showed that ventricular function improved significantly during follow-up in 20% of patients, all of whom had a symptom duration of seven months or less at the time of presentation. Thus, for patients with a short symptom duration who do not appear to have an unusually high risk, it may be particularly important to defer transplantation.

Once patients have been discerned to have cardiac disease severe enough to warrant transplantation, they must be evaluated for other conditions that would limit the likelihood of a good outcome after the procedure. In general, a patient must not have any noncardiac disease that would itself shorten life expectancy or increase the risk of complications (Table 2). The specific criteria are undergoing perpetual remodeling from those originally prepared for the transplantation experiment.[15] Most limits have been pushed in our own program (Table 3) and in others. The most obvious limit is age, which was originally 40, then was extended to 55. Carrier and co-workers have shown that carefully selected patients older than 50 do well.[16] Such patients, however, who often have many other problems, must be selected with particular care.

TABLE 1.—*Results of Full Evaluation for Cardiac Transplantation, UCLA, 1984-1987*

Patients Evaluated, N=250	*Number*
Accepted	110
Died during evaluation	5
Rejected	90
Physical contraindications	70
Noncompliance	20
Deferred	45
Recent disease onset	15
No prior medical therapy	10
Patient refusal	20

Fixed pulmonary hypertension can lead to fatal right heart overload in a newly transplanted heart but may not be distinguishable from reversible pulmonary hypertension without extensive pharmacologic trials. Renal and hepatic function are also profoundly influenced by the degree of circulatory compromise and may not meet criteria standards until after days of hemodynamic optimizing therapy.

After transplantation, patients need to take 12 to 25 doses of medicine daily and submit to 15 to 25 biopsies in the first year. A history of medical compliance and emotional stability are crucial for a good long-term outcome. Even patients without a history of noncompliance or depression may respond to fluctuating steroid dosages and repeated complications by stopping immunosuppressive therapy in a passive suicide attempt. Of four deaths from acute rejection, three were caused by noncompliance. Most patients showing noncompliance were previously predicted to be at some risk. Two patients, however, were accepted into our program after being refused elsewhere on psychosocial criteria and are currently alive after 18 months, although some of the anticipated problems have arisen.[15] The existence of strong family support is important for compliance and outcome but in most programs is no longer essential for acceptance. The active

TABLE 2.—*UCLA Standard Criteria for Heart Transplantation*

Indications
- Severe heart disease despite adequate medical therapy
  - Unacceptable quality of life because of disabling symptoms of congestive heart failure
    or
  - Unacceptable risk of cardiac death within the next year, despite limited symptoms of congestive heart failure
- No other reasonable surgical option

General Eligibility
- The patient must not have any noncardiac condition that would in itself shorten life expectancy or increase the risk of death from rejection or from complications of immunosuppression, particularly infection

Specific Contraindications
- Age older than 65; age older than 55 is a relative contraindication
- Active infection
- Active ulcer disease
- Severe diabetes mellitus
- Severe peripheral vascular disease
- Limited pulmonary function* or history of chronic bronchitis
  - Forced expiratory volume in 1 s, forced vital capacity, or single breath diffusion capacity for carbon monoxide less than 60% predicted is absolute contraindication; less impairment is relative contraindication
- Creatinine > 2 mg/dl; creatinine clearance < 50 ml/min*
- Bilirubin > 2.5 mg/dl, serum aspartate aminotransferase > double normal, prothrombin time > 14 s off warfarin sodium therapy*
- Pulmonary artery systolic pressure > 60 mm of mercury*
- Mean transpulmonary gradient > 15 mm of mercury*
- High risk of life-threatening noncompliance
  - Inability to make strong consistent commitment to transplantation program
  - Cognitive impairment severe enough to limit comprehension of medical regimen
  - Psychiatric instability severe enough to jeopardize incentive for adhering to long-term medical regimen
  - History of alcohol or drug abuse
  - Failure to establish stable address or telephone number
  - Previous demonstration of repeated noncompliance with medication or follow-up

*May need to provide optimal hemodynamics by administering sodium nitroprusside, dobutamine hydrochloride, or both for 72 hours to determine reversibility of organ dysfunction caused by heart failure.

participation of a psychiatrist and a social worker with the transplant team is essential for the thorough evaluation of these patients and for continued psychosocial risk assessment and modification after transplantation.

Although the general criteria for evaluating candidates are relatively uniform, there are currently no guidelines as to the urgency with which transplantation should proceed once a patient has been accepted. In our program, 15% of patients have died waiting for a transplant, which is comparable with that of other large programs.[17] Most of these deaths have occurred suddenly in patients at home awaiting transplantation. With the current donor shortage, waiting periods will increase and the issue of assigning priority status will become more important.[11] The priority status should be adjusted according to the degree of outpatient jeopardy,[17] but the current priority scale has only one outpatient grade.

Priority is frequently given to patients considered so refractory to medical therapy that they cannot be discharged from hospital on oral therapy. A patient should not, however, be deemed refractory on the basis of oral therapy adjusted empirically by a clinical evaluation. Of 40 patients transferred to UCLA from other hospitals where they were considered to have refractory heart failure amenable only to urgent transplantation, 32 (80%) could be discharged home on oral therapy.[18] Despite the apparent failure of previous vasodilator therapy, such patients benefited from titration with the intravenous administration of sodium nitroprusside and diuretics tailored to achieve specific goals that could subsequently be met with high doses of oral vasodilators and diuretics. For severe dilated ventricular failure, the goals are a pulmonary wedge pressure of 15 mm of mercury or less and a systemic vascular resistance of 1,200 dynes $\cdot$ s $\cdot$ cm^{-5} or less,[14] during which the cardiac output is frequently maximal due to the concomitant reduction in regurgitant flow through the secondarily incompetent mitral valve.[19] Maintaining a low filling pressure also decreases the venous congestion that limits these patients and contributes to an increased risk of perioperative complications.

There is a small subset of patients for whom cardiac transplantation must be done urgently, if it is to be done at all. Frequently, truly urgent candidates are those who have acute massive infarction or who cannot be weaned from cardiopulmonary bypass. Urgent priority candidates cannot always be screened as thoroughly as elective candidates and may also be at a higher risk of subsequent complications due to prolonged circulatory compromise. Survival after urgent priority transplantation in 1985 to 1986 for patients of western regional centers was 88% at one month and 80% overall.[18] These results are outstanding for such a sick population but represent an early mortality twice as high as that in the regular priority patients. With the competition for donor organs, an increasing proportion may be diverted to urgent transplantation, with potential compromise of the continued success of cardiac transplantation.

There are currently more than 80 hospitals doing cardiac transplantation in the United States (Figure 1). The evaluation and treatment of patients referred with severe heart failure constitute major responsibilities for any institution committed to cardiac transplantation. Selection and the timing of transplantation should be designed to maximize the years of life gained for each heart transplanted. In addition, the success of transplantation has created a donor shortage that paradoxically forces a greater reliance on medical therapy to allow patients to live comfortably at home until appropriate donors become available.

Histocompatibility Considerations in Heart Transplantation

Human Leukocyte Antigen Matching

PAUL TERASAKI, PHD*: At individual centers, there are only a limited few prospective heart transplant patients. When these few patients are grouped into those with different ABO blood types and different physical sizes, generally little can be done to provide human leukocyte antigen (HLA)-matched donor organs. It is difficult to increase the waiting pool by pooling patients in extended geographic regions because the methods for preserving hearts do not permit long-term storage. Thus, because of the small pool of waiting recipients available for any given donor and the respective storage time, it is practically impossible to do heart transplantation with good HLA matches.

In a retrospective study, Yacoub and colleagues reported that there was a higher survival rate when one HLA-DR antigen was mismatched than when two HLA-DR antigens were mismatched.[21] If these differences can be confirmed, it still may be possible to select donors and recipients on the basis of DR antigen matching. The polymorphism in the DR locus is less than in the HLA-A and -B loci, making it easier

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TABLE 3.—*Transplantation Beyond Standard Criteria*

Contraindications	*Patients, Number*	*Outcome*
Age > 60 yr	10	Postoperative death, 2: death at 4 mo from infection, 1; normal course, 7
Creatinine > 3.0 mg/dl	5	Postoperative death, 2; ongoing hemodialysis, 1; cyclosporine nephrotoxicity, 2
Acute hepatic failure	3	Normal hepatic function, 3
Chronic hepatic failure	1	Chronic hepatic failure, 1
Glucose intolerance	7	Insulin-requiring diabetes, 6*
Heavy smoking history	12	Recurrent bronchitis, 7
Pulmonary asbestosis	1	Recurrent pneumonia contributing to death, 1
Thrombocytopenia	2	Postoperative pericardial tamponade, 1
Marfan's syndrome	1	Aortic dissection at 2 mo; alive and well at 8 mo
Recklinghausen's neurofibromatosis	1	Normal course
Jehovah's Witness	1	Normal course, without transfusion
Noncompliance history	5	Recurrent severe rejection with death at 20 and 23 mo, 2; persistent noncompliance, 3

*One patient died of mucormycosis and lymphoma.

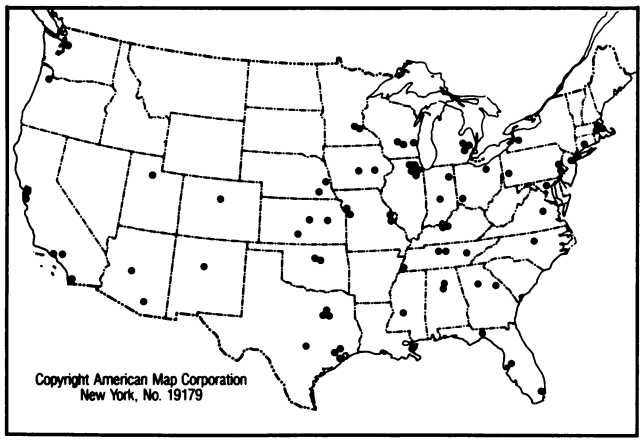

Figure 1.—The map shows the major cardiac transplantation programs in the United States (from Stevenson and Perloff[20]).

to match for the DR locus. Thus, though complete matching may not be possible, matching for certain HLA antigens may become practicable.

Presensitization Screening

All waiting patients should be tested for preformed cytotoxic antibodies to HLA against a test panel of cells from at least 50 randomly selected persons. The standard microlymphocytotoxicity test should be used, preferably with T cells as targets. As a reference, testing against B lymphocytes can also be done. It is important to test patients with dithiothreitol (DTT)-treated serum to establish that the reactions obtained are produced by immunoglobulin (Ig) G antibodies.

In the standard microlymphocytotoxicity test, target lymphocytes can be killed by non-HLA antibodies. Such antibodies are usually autoantibodies that are IgM in nature and react more strongly at 5°C than at 37°C. They occur in various disease states.[22] They even occur in pregnant women and in a small fraction of healthy people.[23] Their exact role is not known, although it has been postulated that they could act as immunoregulatory antibodies.[24] These autoantibodies do not seem to influence the long-term outcome of the transplant or to produce hyperacute rejection.[25]

The specific crossmatching test results available just before transplantation can be confirmed by referring to the previous panel screening test results. A negative crossmatch test in a patient who did not have antibodies to the panel can be readily accepted. A positive crossmatch test in a person shown to be negative on the panel is likely to be a false-positive crossmatch and should be reexamined. It is also helpful to know in advance what frequency of positive crossmatches one would expect for each patient.

Specific Crossmatch Test

Although there have been some reports of successful heart transplants across a positive crossmatching test,[26] it seems that transplants cannot be regularly done across a positive test. We are aware of one definite hyperacute graft failure occurring elsewhere as a consequence of a positive crossmatch. Some of the reported positive crossmatches that have succeeded may have been across a positive auto-T-cell crossmatch test. At UCLA, one patient with a positive crossmatch test had autoantibodies. Once the autoantibodies were inactivated by DTT, the crossmatch reactions were negative. A subsequent heart transplantation in this patient resulted in a successful graft in which there has been no rejection for the first 12 months. It is thus important to establish that the antibody reaction is not a reaction against autoantigens, as described above for the screening test, but is actually against HLA-A and -B loci antigens. The simplest method has been, again, the use of DTT to treat serum. This does not completely guarantee that the antibody is not against HLA, as it principally distinguishes between IgM and IgG antibodies. The HLA antibodies tend to be IgM antibodies. We have thus recommended that crossmatching be done with DTT if a patient's serum has previously been shown to contain IgM antibodies.

In the case of kidney transplants, we have seen some kidney transplants that never recovered function, despite a negative crossmatch between donor and recipient. This phenomenon occurs more often in sensitized patients and patients who have been regrafted than in nonsensitized patients or those with their first transplant. To detect low levels of sensitization, Garovoy and colleagues and others have been studying the use of flow cytometry as a means of doing a more sensitive crossmatching test.[27]

In our experience of 231 renal transplants tested, if the flow-cytometry crossmatch test was negative, the one-month nonfunction rate was 8% compared with 33% if the flow-cytometry crossmatch was positive. This means that among patients who have standard negative crossmatching tests, a positive flow-cytometry crossmatch is predictive of nonfunction for a month in 33% of the transplants, whereas this phenomenon normally occurs in 8% of those judged to have a negative flow-cytometry crossmatch.

Even with a positive flow-cytometry crossmatching test, 67% of the kidneys function within the first month. Thus, there is no absolute contraindication for transplantation by flow cytometry. The rate of nonfunctioning kidneys, however, is much higher in patients with a positive flow-cytometry crossmatch than with a negative flow-cytometry crossmatch. With heart transplantation, when it is critical to have an organ function immediately, it may be more important to use flow cytometry as a crossmatching method.

From the kidney transplant experience, the flow-cytometry crossmatching test should be used in patients who have cytotoxic antibodies or who have had cytotoxic antibodies against a panel of cells. It is less useful in patients who have never had preformed antibodies. Flow cytometry is most valuable in patients who are being regrafted. Fortunately, in heart transplantation the regraft rate is low. As more transplants are done, a greater need for second transplants will arise and the flow-cytometry crossmatch may be more commonly used.

In Vitro Responsiveness Concept

We have been working on the concept that about half of the transplant patients are nonresponsive and can be transplanted with organs from essentially any HLA-incompatible donor. The other half are responders and should receive hearts from donors who have antigens against which the recipient is specifically nonresponsive. Preformed cytotoxic antibodies serve to warn us of specificities against which the recipient will respond. In vitro tests are being developed to predict which specificities would be acceptable and which would not be by any recipients. With these tests, knowledge of antigenicity and responsiveness may be applied to improve the acceptance of a transplanted heart.

Immunosuppression With Cyclosporine

BARRY D. KAHAN, MD, PhD*: Clinical immunosuppressive therapy for cardiac transplantation has improved substantially since the introduction of cyclosporine, a fungal cyclic endecapeptide of novel chemical structure.[28] The previously used immunosuppressive combination of azathioprine, a competitive inhibitor of nucleic acid biosynthesis, and corticosteroids such as prednisone, although manipulated with exquisite attention to detail, had been limited by a narrow therapeutic index. The use of azathioprine and corticosteroids causes a severe depression of the proliferation of nonspecific host immune elements, namely polymorphonuclear leukocytes and monocytes or macrophages, leading to infection with various pathogens, including not only those normally controlled by T cells—viruses, fungi, and protozoa—but also those subject to nonspecific resistance and humoral antibody B-cell-producing bacteria. As a result of the low therapeutic index of the azathioprine-prednisone combination, rejection prophylaxis was rarely achieved and high-dose steroid therapy or antilymphocyte serum, or both, were frequently required for additional immunosuppression. Antilymphocyte serum treatment resulted in further depressing T-cell elements with a frequent occurrence of cytomegalovirus infection and a further reduction in the number of circulating granulocytes.

The initial use of cyclosporine for heart transplantation in the United States at Stanford[29] in 1981 was followed the next year at the Texas Heart Institute (Houston)[30] and at the University of Pittsburgh.[31] From the initial experience, it became apparent that the use of cyclosporine in conjunction with the immunosuppressive regimen previously used resulted in a high risk of lymphomas; many patients had a much more benign, rejection-free posttransplant course than was ever observed using previous immunosuppressive regimens; cyclosporine therapy masks early clinical signs of allograft rejection—namely, fever, atrial arrhythmia, and congestive heart failure—increasing the dependence on the endomyocardial biopsy; and the overall result of transplantation using cyclosporine was improved one-year patient survival by 25%, from 50% to at least 75%. Because of the improved efficacy of cyclosporine therapy, cardiac transplantation was readily extended to patients beyond 50 years of age.[32] The safe dose, however, is limited by side effects of which the most dominant is nephrotoxicity. At present the optimal cyclosporine regimen is unclear; the time of initiation, the dosage of drug, and the use of combination therapy with the other immunosuppressive agents to optimize the prophylaxis of allograft rejection continue to be under intensive investigation.

Mechanism of Action

Cyclosporine inhibits various immune responses based on a cell-mediated host resistance, including allograft rejection, contact sensitivity, adjuvant-induced arthritis, and graft-versus-host disease.[28] The drug acts selectively and reversibly on T lymphocytes, tending to spare other cellular elements. It does not inhibit T-cell-deficient nude mice from responding to lipopolysaccharide by T-cell-independent, B-cell antibody production. Cyclosporine has minimal effects on polymorphonuclear leukocytes, macrophages or monocytes, or natural killer cells.[33] Cyclosporine does not delete T-cell precursors but rather inhibits the capacity of lymphocytes, both primed and particularly unprimed cells, to produce lymphokines.[34]

Lymphokines, which serve as growth factors, recruit and activate cellular elements that amplify the immune response. The effect of cyclosporine in inhibiting lymphokine production affects several subpopulations of T cells including T-helper, T-cytotoxic, and T-delayed hypersensitivity cells. Because there is neither a protein store nor constitutive synthesis of lymphokines, their production is exquisitely sensitive to inhibitors. Separate sets of cyclosporine-sensitive T-helper cells may produce interleukin-2, which stimulates the proliferation and differentiation of cytotoxic and helper T cells and interferon-γ, which stimulates macrophages to produce interleukin-1. The second signal accompanies the first signal antigen to stimulate T-helper cell activation[35] on the one hand and B-cell growth factor, on the other hand, which promotes the proliferation of B cells in the T-cell-dependent responses.

The mechanism by which cyclosporine affects lymphocytes is unclear. Although cyclosporine may alter plasma membrane transduction of the activation signal,[36] it seems more likely that after passive entry into the cell by partitioning into the lipid bilayer, cyclosporine inhibits key enzymes in the activation cascades by competitively binding to hydrophobic sites. One site is the calcium-binding protein, calmodulin, which participates in ligand-induced redistribution of specific receptors to produce capping and ligand-cytoskeletal interactions associated with the initiation of lymphocyte activation via microfilaments, microtubules, coated vesicles, and intermediate filaments.[37] A second site is diacylglycerol, which is normally almost absent from membrane but is transiently produced in response to extracellular signals. A third site is protein kinase C, a Ca^{2+}- and phospholipid-dependent enzyme that phosphorylates seryl and threonyl but not tyrosyl residues of many endogenous proteins.[38] Finally, cyclosporine may affect the pathway of inositol phospholipids to effect arachidonic acid metabolism.

There are several alternative hypotheses to the one that postulates cyclosporine binding to hydrophobic domains of cytoplasm critical for activating the lymphocyte response. The inhibition of the cytoplasmic release of selective lymphokine gene depressor substances, or the masking of regulatory genes determining lymphokine expression at the nuclear level, represent two additional mechanisms by which cyclosporine selectively inhibits lymphokine depression. These mechanisms prevent the generation of lymphokine messenger RNA (mRNA), the step in the activation cascade that has been clearly documented to be inhibited by cyclosporine therapy. Although one cannot exclude a direct cyclosporine effect on the processing or transition of mRNA, it seems unlikely that the drug affects pretransitional protein modification or secretion or leads to a rapid destruction of secreted lymphokines. Because the exact site of cyclosporine action is unknown, one cannot presently define the cyclosporine tissue binding site that mediates the inhibition of lymphokine generation.

Clinical Results of Cyclosporine Transplantation

The use of cyclosporine has clearly had an effect on kidney and liver transplantation. It has not only improved the survival of these allografts but also streamlined the process, extending transplantations to high-risk recipients, such as

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elderly patients. Furthermore, the use of cyclosporine has mitigated the need for pretransplant immune conditioning with blood transfusion[39] and probably lessened the impact of HLA tissue typing. These favorable clinical data result from a high immunosuppressive therapeutic index; neither the incidence of infection[40] nor that of malignant lesions is increased with cyclosporine compared with previous regimens in Penn's worldwide registry[41] or in Sheil's Australian experience.[42] For heart transplantation, the overall duration and thereby cost of the initial admission after the surgical procedure were reduced from $91,000 to $52,000 for patients on a combined regimen of cyclosporine and prednisone. Nephrotoxic side effects limit the safe drug dose, however.

Several alternative regimens have been recommended to achieve optimal immunosuppression with minimal toxicity. A single-drug regimen using cyclosporine only, beginning at 25 mg per kg body weight per day, was recommended for renal transplant recipients by Calne and associates[43] because of the high frequency of neoplasms occurring with their previous regimen of the same dose of cyclosporine combined with the usual doses of cyclophosphamide and prednisone. This concern was reinforced by a high incidence of lymphomas when cyclosporine was merely substituted for azathioprine in the Stanford protocol of rabbit antilymphocyte serum and steroids. Because most kidney recipients in the US experience rejection episodes on monodrug therapy, it is almost certainly insufficient for rejection prophylaxis in cardiac transplantation, unless there are substantial refinements to individualize the cyclosporine regimen.

The most widely used double-drug regimen involves cyclosporine and prednisone. For our cyclosporine regimen we use a continuous infusion of 2.5 mg per kg per day to achieve steady-state serum concentrations of 150 ng per ml, as measured by the radioimmunoassay technique, for the first three posttransplant days before oral therapy.[44] For renal transplant recipients the regimen begins at a dose of 14 mg per kg per day, thereafter tapering to 10 mg per kg per day at two weeks and 7 mg per kg per day at two months, guided to keep the serum trough levels at 100 to 250 ng per ml. The steroid regimen begins at 120 mg given orally daily, tapering to 30 mg at day 6 and 20 mg by day 60. In cardiac transplantation, the regimen is modified, using higher cyclosporine doses to maintain serum trough values at 200 to 400 ng per ml. The steroid regimen also begins at 120 mg orally daily but does not reach 20 mg a day until eight months posttransplant. Our one-year patient survival on this regimen was 74% with unrestricted cardiac transplantation of 132 recipients between 6 months and 62 years of age, regardless of transfusion status and without splenectomy. The immunosuppressive therapeutic window was inferior to that noted in renal transplantation; 81% of heart recipients experienced infectious episodes, of which 60% were fatal, and 75% of patients experienced rejection episodes. On an average, patients experienced 1.9 rejection episodes, receiving at least one and generally two courses of high-dose steroids. Steroid-resistant rejections, which occurred in about 40% of our heart recipients, required the intravenous administration of equine antilymphocyte serum or murine OKT3 monoclonal antibody.

A double-drug regimen alternative to cyclosporine and prednisone uses cyclosporine and azathioprine. Yacoub and associates reported 81% one-year and 77% two-year patient survival rates in 188 heart recipients.[21] Because corticosteroid use was restricted to antirejection therapy, the overall morbidity seemed to be reduced.

The early use of cyclosporine-prednisolone immunosuppression at the Stanford University Medical Center led to a high incidence of nephrotoxicity and the need for long-term dialysis therapy in several otherwise successful transplant recipients.[45] This adverse outcome probably resulted from the initial use of high and prolonged cyclosporine doses.[46] To reduce the cyclosporine dose, the Stanford group now uses triple-drug therapy with cyclosporine (8 mg per kg per day), azathioprine (2 to 3 mg per kg per day), and prednisone, a regimen that has reduced the incidence of renal dysfunction and afforded 75% one-year cardiac graft survival. Because of the increased risk of nephrotoxicity in renal allografts during the immediate posttransplant phase, Simmons and co-workers recommended the use of antilymphocyte serum for an initial five- to ten-day postoperative period to spare the newly engrafted kidney from injury.[47] When this approach of an initial four days of antilymphocyte serum-azathioprine-prednisone therapy without cyclosporine was used to avoid early postoperative renal dysfunction after cardiac transplantation, Schüler and colleagues reported decreased patient survival.[48] These workers now advocate beginning cyclosporine therapy at 24 hours rather than 96 hours posttransplant. A quadruple-drug regimen has recently been introduced to intensify the immunosuppression and reduce the incidence of allograft rejection episodes. Cyclosporine in moderate (6 to 8 mg per kg per day) doses is combined with azathioprine (2 to 3 mg per kg per day), usual doses of prednisone, and a five- to ten-day course of antilymphocyte serum.

There are several criticisms of complex immunosuppressive cocktails used in triple- and quadruple-drug regimens. First, there are few well-controlled animal or human data suggesting that the other agents afford additional, let alone synergistic, immunosuppression with cyclosporine. Second, there is no evidence that the immunosuppressive combinations reduce cyclosporine-induced toxicity. The overall rates of graft function and patient survival found at most centers seem similar independent of the drug regimen. Randomized, controlled, prospective trials of cyclosporine-azathioprine-prednisone immunosuppression versus cyclosporine and prednisone failed to document a benefit on renal graft survival for the combined regimen,[49] which may actually increase morbidity and mortality.[50] The benefits of combined regimens for cardiac transplants should be assessed with placebo-controlled, double-blind trials.

Pharmacologic Combination Regimens to Potentiate the Cyclosporine Effect

Various pharmacologic combinations have been advocated to augment the immunosuppressive action or reduce the renal injury of cyclosporine. Because calcium ion is critical to early lymphocyte activation events and because cyclosporine itself has no effect on calcium permeation,[33] calcium channel inhibitors might potentiate cyclosporine immunosuppression. In normal lymphocytes, McMillen and associates found verapamil to potentiate cyclosporine action.[51] Verapamil inhibited the capacity of phorbol myristate acetate to override cyclosporine inhibition of protein kinase C, presumably by interfering with the interaction with adenosine triphosphate. Similarly, Holman and co-workers found amiloride to potentiate the cyclosporine effect,[52] presumably

by blocking adenosine triphosphate availability to protein kinase C.[53] Because the phorbol myristate acetate cannot totally override cyclosporine inhibition, they concluded that cyclosporine probably also inhibits events distal to protein kinase C. The further development of therapeutic agents selectively inhibiting cytoplasmic activation events should yield drugs displaying pharmacologic synergism with cyclosporine.

Another drug possibly synergistic with cyclosporine is the dopamine antagonist, bromocriptine, which blocks pituitary prolactin release. Russell and colleagues suggest that the mechanism of cyclosporine is to inhibit the binding of prolactin to the outer surface of lymphocytes.[54] On antigenic stimulation of normal, untreated lymphocytes, surface prolactin is believed to amplify the immune response of the same and surrounding cells by inducing ornithine decarboxylase, the initial enzyme in the polyamine cascade preceding DNA synthesis.[55] Bromocriptine potentiated the immunosuppressive effect of subtherapeutic amounts of cyclosporine in animal models of graft-versus-host reaction in vivo[56] and S-antigen-induced posterior uveitis in female rats.[57]

Just as pharmacologic agents may potentiate the therapeutic action, so may they mitigate cyclosporine-induced nephrotoxic effects, provided that these actions occur by distinct mechanisms. A major component of renal impairment is reduced blood flow[58] due to a glomerular afferent arteriolar vasoconstriction. After a bolus of cyclosporine was administered to rats, Murray and associates[59] and Moss and co-workers[60] noted a sympathomimetic vasoconstriction, which was ameliorated by renal denervation or by administering dibenzylene or prazosin hydrochloride. Ryffel and colleagues found that ergoloid mesylates (dihydroergotoxine mesylate), a vasodilator with dopaminergic effects that causes central and peripheral α-adrenoreceptor blockade, ameliorated cyclosporine toxicity in spontaneously hypertensive rats.[61] A clinical trial in autoimmune diseases of the eye by Nussenblatt and associates, who administered a daily dosage of 3 mg of cyclosporine,[62] did not confirm the benefit observed with 6 to 8 mg by Benatzen and co-workers.[63] Vincent and colleagues claim that ergoloid benefits renal allograft hemodynamics,[64] but a double-blind, placebo-controlled study by the Canadian Multicenter Group of ergoloid mesylates added to cyclosporine from the time of renal transplantation has not yet shown a clear benefit.

Because cyclosporine-treated renal transplant recipients studied by Bantle and associates displayed a suppressed rather than stimulated renin-angiotensin system,[65] the only other likely mechanism of renal vasoconstriction is an imbalance of eicosanoid products, which regulate cortical blood flow and glomerular function. Cyclosporine might reduce production of the renal cortical vasodilator, prostacyclin, relative to the vasoconstrictor prostanoid, thromboxane. Indomethacin or meclofenamate inhibition of prostaglandin E_2 synthesis is known to increase nephrotoxicity. Although Brown and Neild found that cyclosporine inhibits prostacyclin synthesis by cultured human endothelial cells,[66] other investigators have not found this inhibition at the glomerular level[67,68] or on rat renal cortical slices.[69] Paller and Murray showed cyclosporine administration to increase rat urinary prostacyclin excretion, suggesting an elevated degree of intrarenal synthesis.[70] Adu and co-workers, however, found that prostaglandin excretion decreased in renal allograft patients who received cyclosporine.[71] Previous studies by Makowka and colleagues were inconclusive because the administered prostaglandins also decreased the cyclosporine internal absorption and increased hepatic blood flow, promoting drug metabolism.[72]

Kawaguchi and associates showed that cyclosporine increased thromboxane A_2 urinary degradation products in rats bearing heterotopic cardiac allografts,[73] findings confirmed by Perico and co-workers.[74] Perico and co-workers also found that a thromboxane A_2 synthetase inhibitor (U-63557) improves but does not normalize renal blood flow. By administering 5-eicosapentaenoic acid as a codfish oil dietary supplement, Elzinga and colleagues deviated prostanoid metabolism to the generation of thromboxanes lacking vasoconstrictor properties, thereby mitigating nephrotoxicity in rats.[75] Foegh and associates prolonged allograft survival with the thromboxane synthetase inhibitor, OKY1581, or an active thromboxane receptor antagonist alone without cyclosporine.[76] Because increased thromboxane synthesis represents a common effector phase of rejection injury,[77] renal ischemia,[78] cyclosporine nephrotoxicity, and various renal diseases,[79] the exact mechanism of the observed prolongation is unclear. Concomitant pharmacologic therapy that alters cortical prostanoids seems to be a promising new approach. Because calcium may mediate the toxic effects of renal injury by influxing into anoxic arterial walls, mediating the vasoconstrictor effects of angiotensin II and promoting the generation of cytotoxic superoxides, calcium antagonists have been used to mitigate the adverse effect of cyclosporine on a freshly harvested, vulnerable kidney allograft. Iaina and co-workers reported that using verapamil reduced the severity of renal insufficiency and histologic damage caused by combined cyclosporine use and ischemia.[80] Administering the calcium antagonist diltiazem to cyclosporine-treated recipients immediately before transplantation and for two days afterwards reduced the incidence of delayed grafted function.[81] In addition, one-third lower doses of cyclosporine were needed because diltiazem interacts with cytochrome P-450,[82] interfering with cyclosporine metabolism. Further investigation of pharmacologic agents to improve the therapeutic index of cyclosporine will doubtless prove preferable to empiric trials of combinations of known immunosuppressive agents. Such studies must assess the effects of these regimens on both the immunosuppressive and the nephrotoxic potency of cyclosporine to assure that a reduction in toxicity is not accompanied by a reduction in therapeutic activity.

Clinical Cardiac Transplantation

HILLEL LAKS, MD,* and DAVIS C. DRINKWATER, MD†: The growth of cardiac transplantation is currently limited by the supply of donor hearts, which is adequate for less than 10% of the estimated 15,000 people a year who could benefit from the procedure.[11] The recent National Organ Transplantation Act has increased support of the regional organ procurement agencies and established a national registry to match donors and recipients,[83] but the imbalance will continue to worsen as the number of cardiac transplantation programs increases.

Criteria for acceptable donor hearts vary somewhat according to the priority status of recipients but are relatively

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standard (Table 4). The use of echocardiography to evaluate regional and global ventricular function may permit the use of some hearts that would otherwise have been rejected because of a history of chest trauma.[84]

More than half of the potential donor hearts are unacceptable due to apparent ventricular dysfunction.[85] In otherwise eligible donors, underlying cardiac disease is rare and the dysfunction seems to result from the acute systemic effects of central nervous system injury. Limitations of fluid volume and a reliance on inotropic support are necessary to maximize possible recovery after a cerebral injury but, unfortunately, may further compromise donor organs after brain death has occurred. A better understanding of the cardiac effects of head injury, such as reported in baboons, may permit improved cardiac preservation within a donor.[86] Most hearts are currently procured at a site distant from the recipient hospital. The currently accepted maximal ischemic time after the donor heart is removed is four hours. The duration of ischemia seems to correlate negatively with long-term survival.[85]

After the operation, many patients need low-dose catecholamine infusions to maintain their heart rate. The initial rhythm of the donor heart is frequently junctional or low atrial, with the gradual appearance of coordinated P waves. Pacing support is occasionally needed on a temporary basis, and on one occasion a permanent pacemaker was implanted in a patient who did not recover recognizable sinus node activity until six months postoperatively. Early postoperative electrocardiographic abnormalities are common, most likely reflecting acute denervation, but are rarely of clinical significance.[87]

Most patients are extubated within 24 hours and ambulatory at 48 hours. The postoperative course generally reflects the perioperative one. During the pretransplant period, most patients in our program are carefully maintained at a minimal fluid balance to minimize extravascular pulmonary, abdominal, and peripheral fluid. Of our 80 patients, major perioperative infection has developed in only 6. Mediastinitis has been a problem in some series but has thus far occurred only once in our population. The average postoperative hospital stay for our patients is 16 days during the entire program and has been 9 days for the last 20 adult patients. The 30-day survival is 96%.[9]

For a diagnosis of rejection, we depend on endomyocardial biopsy, using criteria modified from Billingham.[88] The increase in endocardial fibrosis and the number of previous biopsy sites causes progressive difficulty in acquiring adequate specimens. We are relying increasingly on computer-assisted measurement of two-dimensional echocardiograms, from which we have found an increase in the end-systolic volume or a decrease in the ejection fraction from individual patients' baselines to identify more than 75% of episodes of histologically documented moderate rejection.[89] Although some previous studies have reported that rejection affects diastolic more than systolic function,[90] we have found such echocardiographic measurements of relaxation less reliable than a serial quantification of systolic function. Rejection has been shown to decrease the ejection fraction also in serial radionuclide studies.[91] One of the advantages of doing routine systolic measurements is that patients are occasionally identified who have equivocal or normal biopsy results but nonetheless have depressed systolic function that improves after therapy for rejection. Immunologic monitoring for circulating activated lymphocytes has been a helpful adjunct to the monitoring of rejection in some centers.[92] Preliminary data suggest that antimyosin antibodies may be able to directly identify and quantitate cases of rejection noninvasively.[93]

TABLE 4.—*Standard Donor Criteria for Cardiac Transplants*

Documented brain death in the absence of conditions of hypothermia or drug overdose
Age younger than 35 for men, 45 for women*
No evidence of chest trauma
No history of cardiac disease, significant hypertension, or sustained cardiac arrest
Inotropic requirement < 10 μg/kg/min with central venous pressure 5 to 10 cm H_2O
No evidence of malignancy or infection
Low risk for acquired immunodeficiency syndrome and, whenever obtainable, a negative screen for associated viruses
Appropriate informed consent from family members
ABO compatibility
Comparable body size, within 20% height and weight, particularly when donor smaller than recipient
Anticipated ischemic time < 4 h*

*These criteria are no longer absolute, particularly when transplantation is urgent.

Among our first 80 patients, there have been 110 episodes of rejection, with 10 patients being rejection-free. The expected average incidence is one episode per patient in the first three months and one episode in the following nine months. Programs in isolated areas of relatively homogenous ethnic populations may have a lower incidence of rejection due to better tissue compatibility. In our population, 106/110 episodes were treated successfully, which reflects the benefit of early diagnosis before significant injury and hemodynamic compromise. Of seven patients in whom cardiogenic shock developed due to rejection, three were successfully treated, the case of one having been previously reported.[94] Four of the patients admitted to recently discontinuing their immunosuppressive therapy. In patients receiving cyclosporine, rejection of this severity and rejection occurring after the first year are generally due to noncompliance.

The expected major infection rate is 1.5 episodes per patient for the first year, with a declining frequency thereafter. Superficial infections with *Candida* and herpesviruses are common but respond well to oral therapy. We have emphasized meticulous preoperative care and a minimal use of immunosuppressive drugs and have had only 33 significant infections, 80% of which have been successfully treated.

More than 85% of our long-term survivors are New York Heart Association class I. Transplanted hearts are able to respond adequately to circulatory demands despite the absence of direct autonomic innervation. The basal heart rate is usually 90 to 105 beats per minute because of the lack of vagal tone. Cardiac output increases immediately on initiating exercise because of the increased venous return.[95] The heart rate and the contractile state do not peak until at least five minutes, however, when circulating catecholamines have increased. The maximal oxygen consumption is lower than age- and size-predicted values and, in fact, is similar to that of patients with chronic heart failure who can be maintained on a stable afterload-reducing regimen.[96] Many cardiac transplant patients nonetheless engage regularly in demanding activities such as skiing, scuba diving, and even in one case the Boston marathon (a patient from the Harefield program, England).

Our one-year actuarial survival is 85%, with a two-year survival of 82%, which compares favorably with the overall survival in the International Heart Transplant Registry for patients treated with cyclosporine.[9] The main causes of death are infection and rejection. The general decrease in the severity of these during the first 90 days on cyclosporine therapy is the main reason for the overall increase in one-year survival from the 66% rate previously reported for patients on a regimen of azathioprine and prednisone.[9]

Relatively less progress has been made toward reducing the incidence of complications after the first year. Acute rejection is not a major cause of late mortality, except in cases of noncompliance, as discussed. The major problem remains accelerated graft atherosclerosis, as shown nine months after transplanting a 33-year-old donor heart into a 39-year-old man with idiopathic cardiomyopathy (Figure 2). Although a previous history of atherosclerosis and abnormal blood lipid values seems to increase the risk,[97] the major factor may be the nature of immunologic injury to endothelial surfaces. There is currently no evidence that the risk can be modified, but at UCLA patients are maintained on a regimen of aspirin, dipyridamole (Persantine), and a low-lipid diet, supplemented with low doses of lovastatin (mevinolin) in some cases, while hypertension and glucose intolerance, resulting in part from immunosuppressive medication, are aggressively treated.

Because of the diffuse distribution of atherosclerosis, its occurrence may be underestimated from coronary arteriograms but is currently estimated to be significant in 30% of patients after three years.[95] Thallium exercise studies may be of some help in screening patients with graft atherosclerosis, in whom angina does not occur. Although doing coronary artery bypass grafting is not appropriate due to poor distal vessels, angioplasty can occasionally be done to relieve ischemia when a specific focal lesion is present.[98] The rapidly progressive nature of atherosclerosis in patients afflicted frequently leads to sudden death or in some cases retransplantation.

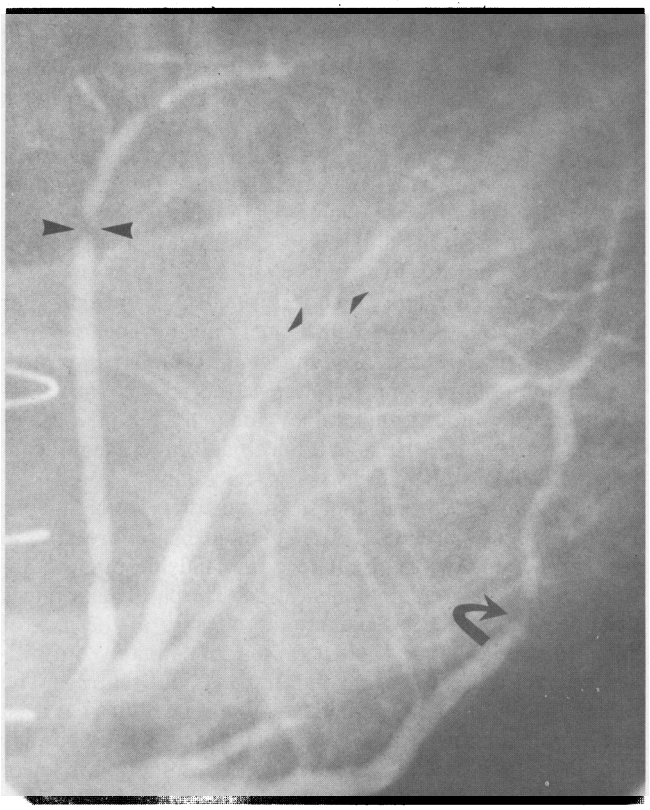

Figure 2.—A left coronary angiogram is shown in the left lateral projection of a 33-year-old donor heart transplanted 10 months previously into a 39-year-old man with idiopathic cardiomyopathy. A 90% stenosis is seen in the left anterior descending artery (curved arrow) with sequential 90% stenosis in the circumflex artery (large arrows) and two adjacent 90% stenoses in the obtuse marginal branch (small arrows).

Other late complications include malignancy, the prevalence of which is increased in all populations on immunosuppressive therapy. The reported incidence of malignancy in cardiac transplant recipients is 10%, of which skin cancer is the most common and lymphomas the second.[41] Most of the lymphomas are non-Hodgkin's lymphomas of B-cell origin, with extranodal sites, particularly brain and gastrointestinal tract, more common than in nontransplant patients with lymphoma. Lymphomas and Kaposi's sarcoma occurring in transplant patients may respond dramatically to a reduction of immunosuppression and are otherwise treated with standard chemotherapeutic regimens.

The overall five-year survival with cyclosporine therapy is currently 77%.[9] Evans and co-workers have estimated that the cost to Medicare per year of life gained from cardiac transplantation is $23,478, compared with $25,000 per year for renal dialysis and $110,000 per year for total parenteral nutrition.[11] Physical and psychologic function are eventually good for most patients, although the initial recovery from long periods of inactivity and dependency, which preceded the transplant, often stresses families. Although some patients return to work, many who are physically eligible do not obtain appropriate employment because of a financial dependency on the disability status and employers' concern about liability.[10] As the efficiency of cardiac transplantation becomes more widely appreciated by employers and their insurers, most transplant recipients should be able to enjoy professional as well as physical rehabilitation.

The major current limitation to cardiac transplantation is the scarcity of hearts, approximately one of which is available for every ten potential recipients.[11] With an increasing number of patients being referred for transplantation, it is vital that candidate selection and priority status be determined uniformly at all institutions.[18] Concern for the equitable distribution of limited donor hearts to those patients with the greatest expected benefit should eclipse institutional and regional affiliations. In addition, all transplant programs should be committed to design and maintain the optimal medical regimen for every patient referred to transplantation in order to minimize the number of urgent transplants and to maximize the status both of the patients awaiting transplant and of the greater number of patients who cannot receive them.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Geriatric Ambulatory and Institutional Care

James D. Lomax, MD, Director, Department of Family Practice, Long Island College Hospital, Brooklyn, New York. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Ct, Maryland Heights, MO 63043, 1987. 209 pages, $27.50 (paperback).

This multiauthored paperback is intended to supplement traditional textbooks of geriatric medicine and gerontology. It is clearly not intended to be comprehensive or encyclopedic but rather, to cover ten topics that the authors thought were absent or inadequately covered in more traditionally formatted texts. As is common in multiauthored books, the utility of each chapter varies with the depth of coverage and quality of the writing. Most chapters have references; some are as recent as 1985.

After an introductory chapter on the demographics of aging, a chapter on health resources discusses Medicare, nursing homes, home care, hospices, day hospitals, and life care communities. These topics are briefly touched upon in a depth suitable for only the briefest of survey courses in gerontology.

The chapter on rehabilitation provides a good introduction to some elements of physical medicine, including the rudiments of prescribing assistive devices such as canes and wheelchairs. The advice shows common sense, and the illustrations in this chapter are useful. The chapter on geriatric dentistry gives an excellent introduction to a topic often stinted in medical education. A useful feature of this chapter is a section on medical-dental interactions, including aspects of dental care for patients on anticoagulant medication, with pacemakers, or undergoing radiation therapy and chemotherapy.

The chapter on urinary incontinence is brief but covers many important aspects of this major problem. The book includes an excellent and comprehensive chapter on sex and aging. The chapter on ostomy therapy is useful, covering material often lacking in standard geriatrics texts. The application of a problem-oriented systematic approach to the nursing care of elderly patients is also addressed in sufficient detail. A lengthy chapter on prescribing a physical activity program for older persons is comprehensive and may serve as a useful reference. One chapter stresses aspects of health care education pertinent to the elderly, and a brief chapter on death and dying offers some helpful advice concerning care of the terminally ill.

Overall, this book might serve as a useful adjunct to more comprehensive texts in an elementary course on geriatric medicine. The material is not covered in sufficient depth to satisfy the needs of geriatric fellows or other advanced students of this field. As the content of programs on geriatric medicine becomes better defined, the need for such a supplementary collection of topics will diminish as pertinent areas are added to more traditionally formatted textbooks.

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