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Editorial correspondence should be addressed to Felix T. Rapaport, M.D., Department of Surgery, Health Sciences Center, State University of New York at Stony Brook, Stony Brook, N.Y. 11794.

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VOL. XV, NO. 4

SUPPLEMENTS 1 AND 2 DECEMBER 1983

CONTENTS

Foreword *F. G. Moody* 2207

PREFACE

Cosmas and Damian Revisited *B. D. Kahan* 2211

MECHANISMS OF ACTION

Cyclosporine: Historical Perspectives *J. F. Borel* 2219

Synthesis of Cyclosporine and Analogues: Structure, Activity, Relationships of New
Cyclosporine Derivatives *R. Wenger* 2230

Cyclosporine-A (CsA): Models for the Mechanism of Action *K. J. Lafferty,*
J. F. Borel, and P. Hodgkin 2242

Effect of Cyclosporine on the Induction of Cytotoxic T Lymphocytes: Role of
Interleukin-1 and Interleukin-2 *A. D. Hess, P. J. Tutschka, and G. W. Santos* 2248

Lack of Evidence for a Cyclosporine Receptor on Human Lymphocyte Membranes
S. J. LeGrue, A. W. Friedman, and B. D. Kahan 2259

Cyclosporine Binding Component in BW5147 Lymphoblasts and Normal Lymphoid
Tissue *M. Merker, J. Rice, B. Schweitzer, and R. E. Handschumacher* 2265

Effects of Cyclosporine on Experimental Infections *G. A. Cole, S. P. Nickell,*
F. Mokhtarian, and L. W. Scheibel 2271

Potential for Tolerance Induction With Cyclosporine ... *D. J. G. White, H. ff. S. Davies,*
N. Kamada, and T. Nagao 2278

(Continued)

CONTENTS

(continued)

IMMUNOSUPPRESSIVE PROPERTIES CELL-MEDIATED IMMUNITY

- The Effect of Cyclosporine A on Lymphocytes in Animal Models of Tissue Transplantation *P. J. Morris, D. W. Mason, and I. V. Hutchinson* 2287
- X Cyclosporine Effects on Immunoregulatory Cells in Man *C. T. Van Buren, R. Kerman, S. Flechner, and B. D. Kahan* 2293
- Analysis of Lymphocytes Concerned in Spontaneous Blastogenesis During Acute Rejection..... *T. Oka, N. Yoshimura, Y. Ohmori, I. Aikawa, T. Matsumura, T. Usui, K. Arakawa, and I. Hashimoto* 2298
- Immunologic Monitoring of Renal Allograft Recipients Treated with Cyclosporine
R. H. Kerman, S. M. Flechner, C. T. Van Buren, W. Payne, and B. D. Kahan 2302
- Cyclosporine Effects on Mitogen-Induced T- and B-Cell Proliferation
H. G. A. Bower and D. J. Hinrichs 2306
- Cyclosporine Selectively Inhibits Certain Mitotic Responses to Thymocytes
I. Gery, W. R. Benjamin, S. Jones, and R. B. Nussenblatt 2311
- Cyclosporine Modulates the Human In Vitro T-Dependent Antigen-Induced Synthesis of Specific Antibody *J. B. Harley and A. S. Fauci* 2315
- X Dissociation of T Helper-Cell Function and Helper-Cell Priming by Cyclosporine
G. G. B. Klaus and A. Kunkl 2321
- Differential Effect of Cyclosporine on the Generation of Allogeneic Versus Syngeneic Cytotoxic T Lymphocytes *Z. K. Ballas and W. E. Schulte* 2323
- Differential In Vitro Action of Cyclosporine on Non-T-Cell and T-Cell Responses to Non-HLA Alloantigens: Significance for MHC-Independent Graft-Versus-Host Disease..... *L. Delmonte* 2328
- Induction of Suppressor T Lymphocytes in Mice Treated with Cyclosporine
N. Yoshimura, T. Oka, Y. Ohmori, I. Aikawa, M. Fukuda, Y. Kondoh, and I. Hashimoto 2334
- Suppressor Cells in Cyclosporine-Induced Long-Term Graft Acceptance in the Rat
K. Sakamoto, T. Ochiai, N. Shinohara, T. Asano, and H. Sato 2340
- Suppressor-Cell Amplification Circuitry in Cyclosporine-Treated MLR Cultures
A. D. Hess, A. D. Donnenberg, P. Engel, P. J. Tutschka, and G. W. Santos 2343
- X The Immunosuppressive Action of Cyclosporine in Man..... *R. M. Ferguson and R. Fidelus-Gort* 2350
- Population of Cyclophosphamide-Sensitive T Suppressor Cells Maintain Cyclosporine-Induced Allograft Survival *J. W. Kupiec-Weglinski, P. A. Lear, T. B. Strom, and N. L. Tilney* 2357
- Effects of Cyclosporine on the Efferent Limb of the Immune Response
M. Mochizuki, R. B. Nussenblatt, T. Kuwabara, and I. Gery 2364

(Continued)

CONTENTS

(continued)

- Pulmonary Macrophage and Polymorphonuclear Leukocyte Function in Response to Immunosuppressive Therapy *D. B. Drath and B. D. Kahan* 2367
- Effect of Cyclosporine Alone or Combined with Prednisolone or Azathioprine on Macrophage Phagocytosis *A. Rios, L. H. Toledo-Pereyra, and S. Buscetta* 2373
- Inhibitory Effect of Cyclosporine on Adherent Cells in Oxidation-Induced Lymphocyte Proliferation *K. Uyemura, J. F. P. Dixon, and J. W. Parker* 2376

HUMORAL MEDIATORS

- Effect of Cyclosporine on Human Leukocyte Interferon Production: Selective Inhibition of IFN-Gamma Synthesis *J. Abb and H. Abb* 2380
- Effects of Cyclosporine on the Production of Various Interferons *V. K. Kalman and G. R. Klimpel* 2383
- Cyclosporine Inhibits Interleukin-2 and Interferon Gamma Synthesis by Human Thymocytes *G. H. Reem, L. A. Cook, and M. A. Palladino* 2387
- Cyclosporine and Lymphokines Affecting Macrophage Behavior *A. W. Thomson, D. K. Moon, C. L. Geczy, and D. S. Nelson* 2390
- Relationship Between IL-2 Receptors and Cyclosporine-Induced Suppression of T Leukemia and T Helper Cells *C. C.-Y. Shih, R. L. Truitt, P. Abramoff, and M. M. Bortin* 2394
- Effect of Cyclosporine on Prostacyclin Synthesis by Vascular Tissue in Rabbits *G. H. Neild, G. Rocchi, L. Imberti, F. Fumagalli, Z. Brown, G. Remuzzi, and D. G. Williams* 2398

PHARMACOKINETICS

- x Methods to Measure Cyclosporine Levels—High Pressure Liquid Chromatography, Radioimmunoassay, and Correlation *W. T. Robinson, H. F. Schran, and E. P. Barry* 2403
- Cyclosporine: Pharmacokinetics, Metabolism, and Drug Interactions *A. J. Wood, G. Maurer, W. Niederberger, and T. Beveridge* 2409
- Cyclosporine Pharmacokinetics in Man *J. Newburger and B. D. Kahan* 2413
- Pharmacokinetics and Toxicity of Cyclosporine in Marrow Transplant Patients *M. S. Kennedy, G. C. Yee, H. J. Deeg, R. Storb, and E. D. Thomas* 2416
- Distribution and Binding of Cyclosporine in Blood and Tissues *W. Niederberger, M. Lemaire, G. Maurer, K. Nussbaumer, and O. Wagner* 2419
- In Vitro Stability and Storage of Cyclosporine in Human Serum and Plasma *J. Smith, J. Hows, and E. C. Gordon-Smith* 2422
- Distribution and Transfer of Cyclosporine Among the Various Human Lipoprotein Classes *W. Mraz, R. A. Zink, A. Graf, D. Preis, W. D. Illner, W. Land, W. Siebert, and H. Zöttlein* 2426

(Continued)

CONTENTS

(continued)

Blood and Tissue Distribution of Cyclosporine in Humans and Mice	<i>K. Atkinson, J. Boland, K. Britton, and J. Biggs</i>	2430
Cyclosporine Levels in Human Tissues of Patients Treated for One Week to One Year <i>M. Ried, S. Gibbons, D. Kwok, C. T. Van Buren, S. Flechner, and B. D. Kahan</i>		2434
The Clinical Relevance of Cyclosporine Blood Levels As Measured by Radioimmunoassay	<i>P. A. Keown, C. R. Stiller, N. R. Sinclair, G. Carruthers, W. Howson, M. Stawewski, J. McMichael, J. Koegler, N. McKenzie, and W. Wall</i>	2438
Pharmacologic Monitoring in the Clinical Use of Cyclosporine <i>F. Lokiec, A. Devergie, O. Poirier, and E. Gluckman</i>		2442
Detrimental Effect of Intestinal Disease on Absorption of Orally Administered Cyclosporine	<i>K. Atkinson, K. Britton, P. Paull, C. Farrell, A. Concannon, A. Dodds, and J. Biggs</i>	2446
Variable Tempo of Cyclosporine Peaks and Troughs in a Lung Transplant Recipient: Importance of Frequent Monitoring	<i>S. L. Nehlsen-Cannarella, F. J. Veith, S. L. Kamholz, C. M. Montefusco, F. P. Mollenkopf, J. Goldsmith, and R. Kaleya</i>	2450

CLINICAL TRANSPLANTATION

KIDNEY TRANSPLANTATION

The Colorado-Pittsburgh Cadaveric Renal Transplantation Study with Cyclosporine <i>T. E. Starzl, T. R. Hakala, J. T. Rosenthal, S. Iwatsuki, and B. W. Shaw, Jr.</i>		2459
Comparison of Cyclosporine Versus Azathioprine-Antilymphocyte Globulin in Renal Transplantation	<i>J. S. Najarian, M. Strand, D. S. Fryd, R. M. Ferguson, R. L. Simmons, N. L. Ascher, and D. E. R. Sutherland</i>	2463
Cyclosporine Immunosuppression Mitigates Immunologic Risk Factors in Renal Allotransplantation	<i>B. D. Kahan, C. T. Van Buren, S. M. Flechner, W. D. Payne, M. Boileau, and R. H. Kerman</i>	2469
The Canadian Trial of Cyclosporine: Cyclosporine Therapy Compared to Standard Immunosuppression in Renal Transplants: An Exploration of Nephrotoxicity <i>C. Stiller, London, Canada, for The Canadian Transplant Study Group</i>		2479
Australian Trial of Cyclosporine (Csa) in Cadaveric Donor Renal Transplantation <i>A. G. R. Sheil, B. M. Hall, D. J. Tiller, M. S. Stephen, J. P. Harris, G. G. Duggin, J. S. Horvath, J. R. Johnson, J. R. Rogers, and J. Boulas</i>		2485
The Requirements for Maintenance Steroids in Cyclosporine-Treated Renal Transplant Recipients	<i>C. Stiller, London, Canada, for The Canadian Transplant Study Group</i>	2490
A Prospective Randomized Substitutive Trial of Cyclosporine as a Prophylactic Agent in Human Renal Transplant Rejection	<i>R. A. Sells</i>	2495

(Continued)

CONTENTS

(continued)

- Living Related Kidney Transplants Treated with Cyclosporine..... *T. Oka, Y. Ohmori, I. Aikawa, J. Ioka, Y. Kadotani, H. Nomura, S. Suzuki, and I. Hashimoto* 2501
- Improved Outcome in Renal Transplant Recipients Above 55 Years of Age Treated with Cyclosporine and Low Doses of Steroids*O. Ringdén, L. Öst, G. Klintmalm, A. Tillegård, I. Fehrman, H. Wilczek, and C. G. Groth* 2507
- Randomized Comparison Between Cyclosporine and Conventional Therapy Plus Minnesota Antilymphocyte Globulin in Cadaveric Renal Transplantation
P. Halloran, D. Ludwin, M. Aprile, J. Lien, N. White, and the Canadian Transplant Study Group 2513
- Cadaveric Renal Transplantation with Cyclosporine: Experiences in 148 Patients at a Single Institution..... *W. Land, L. A. Castro, K. Günther, C. Hammer, C. Hillebrand, W. -D. Illner, N. Schmeller, B. Schneider, W. Siebert, R. A. Zink, and H. Zöttlein* 2517
- Cyclosporine in Cadaveric Renal Transplantation: A Prospective Randomized Trial
P. McMaster, I. G. Haynes, J. Michael, D. Adu, T. Vlassis, S. Roger, J. Turney, S. Stock, J. Buckels, P. Mackintosh, and M. Ezzibdeh 2523
- Renal Transplantation Using Cyclosporine in Pediatric Patients 3 to 17 Years Old
S. B. Conley, E. D. Brewer, S. M. Flechner, C. T. Van Buren, and B. D. Kahan 2528
- Cyclosporine and Steroids: Effects on the Clinical Course After Renal Allotransplantation*H. Bunzendahl, K. Wonigeit, J. Klemptner, C. Brölsch, and R. Pichlmayr* 2531
- Cyclosporine for Steroid-Resistant Rejection in Azathioprine-Treated Renal Graft Recipients *A. S. MacDonald, P. Belitsky, A. Cohen, J. Crocker, R. Gupta, S. G. Lannon, and J. White* 2535
- A Critical Look at Renal Allografts That Failed in Patients Receiving Cyclosporine
T. Kovithavongs, W. H. Lakey, R. Boake, K. B. Bettcher, P. McCormick, and J. B. Dossetor 2538

HEART AND LUNG TRANSPLANTATION

- Cyclosporine in Cardiac Transplantation: A 2½ Year Follow-Up.....*P. E. Oyer, E. B. Stinson, S. W. Jamieson, S. A. Hunt, M. Perloth, M. Billingham, and N. E. Shumway* 2546
- Experience with Cyclosporine in Cardiac Transplantation..... *R. L. Hardesty, B. P. Griffith, R. F. Debski, and H. T. Bahnson* 2553
- Cyclosporine for Cardiac Transplantation: U. K. Trial*J. Wallwork, R. Cory-Pearce, and T. A. H. English* 2559
- Cardiac and Cardiopulmonary Transplantation Using Cyclosporine For Immunosuppression: Recent Texas Heart Institute Experience
D. A. Cooley, O. H. Frazier, G. A. Painvin, L. Boldt, and B. D. Kahan 2567

(Continued)

CONTENTS

(continued)

- New Onset of Hypertension Following Cardiac Transplantation: A Preliminary Report and Analysis *M. E. Thompson, A. P. Shapiro, A. M. Johnsen, R. Reeves, J. Itzkoff, E. Ginchereau, R. L. Hardesty, B. L. Griffith, H. T. Bahnson, and R. McDonald, Jr.* 2573
- Single Lung Transplantation with Cyclosporine Immunosuppression
S. L. Kamholz, F. J. Veith, C. M. Montefusco, K. L. Pinsker, F. P. Mollenkopf, R. Kaleya, J. Goldsmith, A. J. Norin, E. E. Emeson, S. N. Cannarella, and M. L. Gliedman 2578

LIVER AND PANCREAS TRANSPLANTATION

- Report of Colorado-Pittsburgh Liver Transplantation Studies *T. E. Starzl, S. Iwatsuki, D. H. Van Thiel, J. C. Gartner, B. J. Zitelli, J. J. Malatack, R. R. Schade, B. W. Shaw, Jr., T. R. Hakala, and J. T. Rosenthal* 2582
- Special Aspects of Immunosuppression with Cyclosporine in Liver Transplantation
K. Wonigeit, C. Brölsch, P. Neuhaus, M. Burdelski, E. Schmidt, W. Lang, and R. Pichlmayr 2586
- Hepatic Homograft Survival in Pediatric Orthotopic Liver Transplantation with Cyclosporine and Steroids *B. J. Zitelli, J. C. Gartner, Jr., J. J. Malatack, B. W. Shaw, Jr., S. Iwatsuki, and T. E. Starzl* 2592
- Pancreas Transplantation: Overview and Current Status of Cases Reported to the Registry Through 1982 *D. E. R. Sutherland* 2597
- Cyclosporine in Clinical Pancreatic Transplantation *J. Traeger, J. M. Dubernard, E. Bosi, A. Gelet, S. El Yafi, A. Secchi, G. Pozza, and J. L. Touraine* 2602
- Experience with Cyclosporine Versus Azathioprine for Pancreas Transplantation
D. E. R. Sutherland, P. L. Chinn, F. C. Goetz, B. A. Elick, and J. S. Najarian 2606

BONE MARROW TRANSPLANTATION

- Cyclosporine in Clinical Marrow Transplantation: The Baltimore Experience
P. J. Tutschka, A. D. Hess, W. E. Beschorner, E. R. Farmer, R. Saral, R. Brookmeyer, and G. W. Santos 2613
- Allogeneic Bone Marrow Transplantation: The Basel Trial with Cyclosporine
B. Speck, A. Gratwohl, B. Osterwalder, E. Signer, C. Nissen, M. Corneo, and M. Jeannet 2617
- Preliminary Results of Prospective Randomized Trials Comparing Methotrexate and Cyclosporine for Prophylaxis of Graft-vs.-Host-Disease After HLA-Identical Marrow Transplantations *R. Storb, H. J. Deeg, E. D. Thomas, C. D. Buckner, R. A. Clift, N. Flournoy, M. S. Kennedy, K. Doney, F. R. Appelbaum, J. E. Sanders, P. Stewart, H. Shulman, K. M. Sullivan, and R. P. Witherspoon* 2620

(Continued)

CONTENTS

(continued)

- Cyclosporine for the Prevention of Graft-vs.-Host Disease in 72 Patients with Acute Myeloblastic Leukemia in First Remission Receiving Matched Sibling Bone Marrow Transplants
R. L. Powles, B. Evans, C. Poole, A. Pedrazzini, M. Crofts, C. Pollard, and G. Hughes 2624
- Use of Cyclosporine as Prophylaxis of Graft-vs.-Host Disease After Human Allogeneic Bone Marrow Transplantation: Report of 38 Patients
E. Gluckman, A. Devergie, O. Poirier, and F. Lokiec 2628
- Postgraft Immunosuppression with Cyclosporine in Allogeneic Bone Marrow Transplantation for Severe Aplastic Anemia
J. M. Hows, J. L. Yin, P. M. Chipping, S. M. Fairhead, S. Palmer, and E. C. Gordon-Smith 2634

CLINICAL CASE PRESENTATIONS

- The Management of Kidney Transplant Recipients Treated With Cyclosporine
B. D. Kahan 2641
- The Management of Heart Transplant Recipients Treated With Cyclosporine
B. D. Kahan 2649

WORKSHOPS ON PATIENT MANAGEMENT

- Practical Aspects on Renal Transplant Management.....*B. D. Kahan* 2665
- Pancreas Transplantation*J. M. Dubernard and E. Bosi* 2676
- Practical Aspects of Cardiac Transplant Patient Management *C. T. Van Buren* 2678

CYCLOSPORINE TOXICITY

- The Nephrotoxicity of Cyclosporine in Renal Transplant Recipients
S. M. Flechner, C. Van Buren, R. H. Korman, and B. D. Kahan 2689
- Renal Effects of Cyclosporine: Clinical and Experimental Observations
R. Devineni, N. McKenzie, J. Duplan, P. Keown, C. Stiller, and A. C. Wallace 2695
- Cyclosporine in Patients With Oligoanuria After Cadaveric Kidney Transplantation
L. A. Castro, G. Hillebrand, W. Land, B. Schneider, K. Günther, and H. J. Gurland 2699
- Nephrotoxicity of Cyclosporine in Combination With Aminoglycoside and Cephalosporin Antibiotics.....*P. H. Whiting, J. G. Simpson, and A. W. Thomson* 2702
- Renal Failure in Heart Transplant Patients Receiving Cyclosporine
J. Egel, A. Greenberg, M. E. Thompson, R. L. Hardesty, B. P. Griffith, H. T. Bahnson, R. L. Bernstein, and J. B. Puschett 2706

(Continued)

CONTENTS

(continued)

Nephrotoxicity in Marrow Graft Recipients Treated With Cyclosporine <i>J. M. Hows, J. M. Smith, A. Baughan, and E. C. Gordon-Smith</i>	2708
Increasing the Hepatic Metabolism of Cyclosporine Abolishes Nephrotoxicity <i>C. Cunningham, P. H. Whiting, M. D. Burke, D. N. Wheatley, and J. G. Simpson</i>	2712
Demonstration of Cyclosporine in Renal Transplants by Fine Needle Aspiration Biopsy <i>E. von Willebrand and P. Häyry</i>	2716
Cyclosporine, the Renin-Angiotensin-Aldosterone System, and Renal Adverse Reactions <i>H. Siegl, B. Ryffel, R. Petric, P. Shoemaker, A. Muller, P. Donatsch, and M. Mihatsch</i>	2719
Cyclosporine-Associated Hyperkalemia <i>R. J. Foley, C. T. Van Buren, R. Hamner, and E. J. Weinmann</i>	2726
Cyclosporine and Sodium and Potassium Excretion in the Rat <i>A. S. Tonnesen, R. W. Hamner, and E. J. Weinmann</i>	2730
Nephrotoxicity of Cyclosporine-An Animal Model: Study of the Nephrotoxic Effect of Cyclosporine on Overall Renal and Tubular Function in Conscious Rats <i>H. Dieperink, H. Starklint, and P. P. Leysac</i>	2736
Rat Composite Tissue Allograft Recipients Demonstrate a Dose-Related Increase in Renal Toxicity With Therapeutic Doses of Cyclosporine <i>C. W. Hewitt, K. S. Black, L. A. Fraser, E. B. Howard, A. Ingerman, B. Philosophe, B. M. Achauer, D. C. Martin, and D. W. Furnas</i>	2742
Complications of Cyclosporine Therapy-A Comparison to Azathioprine <i>A. Laupacis, London, Canada, for the Canadian Transplant Study Group</i>	2748
Cyclosporine and Liver Function in Renal Allograft Recipients <i>R. S. C. Rodger, J. H. Turney, I. Haines, J. Michael, D. Adu, and P. McMaster</i>	2754
Cholestasis in Heart Transplant Recipients Treated With Cyclosporine <i>R. R. Schade, A. Guglielmi, D. H. Van Thiel, M. E. Thompson, V. Warty, B. Griffith, A. Sanghvi, H. Bahnson, and R. Hardesty</i>	2757
Cyclosporine-Associated Hepatotoxicity After Allogeneic Marrow Transplantation in Man: Differentiation From Other Causes of Posttransplant Liver Disease <i>K. Atkinson, J. Biggs, A. Dodds, and A. Concannon</i>	2761
Infections in Kidney, Heart, and Liver Transplant Recipients on Cyclosporine <i>M. Ho, C. P. Wajszczuk, A. Hardy, J. S. Dummer, T. E. Starzl, T. R. Hakala, and H. T. Bahnson</i>	2768
Infection in Renal Transplant Recipients on Cyclosporine: Pneumocystis Pneumonia <i>A. M. Hardy, C. P. Wajszczuk, T. R. Hakala, J. T. Rosenthal, T. E. Starzl, and M. Ho</i>	2773
Cellular Immune Response and Cytomegalovirus Infection in Renal Transplant Recipients Receiving Cyclosporine <i>C. R. Rinaldo, Jr., W. H. Hamoudi, R. L. DeBiasio, B. Rabin, T. R. Hakala, and M. Liebert</i>	2775

(Continued)

CONTENTS

(continued)

- Infections in Patients on Cyclosporine and Prednisone Following Cardiac Transplantation *J. S. Dummer, H. T. Bahnson, B. P. Griffith, R. L. Hardesty, M. E. Thompson, and M. Ho* 2779
- Glomerular Thrombi and Infarction in Rabbits with Serum Sickness Following Cyclosporine Therapy *G. H. Neild, K. Ivory, and D. G. Williams* 2782
- Occurrence of Hemolytic Uremic Syndrome Under Cyclosporine Treatment: Accident or Possible Side Effect Mediated by a Lack of Prostacyclin-Stimulating Plasma Factor?
C. Leithner, H. Sinzinger, E. Pohanka, M. Schwarz, G. Kretschmer, and G. Syr  2787
- Lymphomas Complicating Organ Transplantation *I. Penn* 2790
- Immunoglobulin Abnormalities and Infectious Lymphoproliferative Syndrome (ILPS) in Cyclosporine-Treated Transplant Patients
J. L. Touraine, S. El Yafi, E. Bosi, C. Chapuis-Cellier, J. Ritter, N. Blanc, J. M. Dubernard, C. Pouteil-Noble, M. Chevalier, R. Creyssel, and J. Traeger 2798
- Histiocytic Lymphoma in Renal Transplant Patients Receiving Cyclosporine
J. T. Rosenthal, S. Iwatsuki, T. E. Starzl, R. J. Taylor, and T. R. Hakala 2805
- Malignant Lymphoma in Nontransplanted Cynomolgus Monkeys Receiving Cyclosporine
N. L. Garnett, H. R. Taylor, G. J. Hoffman, R. L. Heberling, R. F. Ambinder, A. C. Huber, and B. A. Valentine 2808

PROBLEMS IN DIFFERENTIAL DIAGNOSIS—TOXICITY VERSUS ALLOGRAFT REJECTION

- Clinical and Laboratory Signs in Nephrotoxicity and Rejection in Cyclosporine-Treated Renal Allograft Recipients
G. Klintmalm, O. Ringd n, and C. G. Groth 2815
- Morphological Findings in Kidney Transplants After Treatment with Cyclosporine
M. J. Mihatsch, G. Thiel, H. P. Spichtin, M. Oberholzer, F. P. Brunner, F. Harder, V. Olivieri, R. Bremer, B. Ryffel, E. St cklin, J. Torhorst, F. Gudat, H. U. Zollinger, and R. Loertscher 2821
- Morphology of Cyclosporine Nephrotoxicity and of Acute Rejection in Cyclosporine-Prednisone-Immunosuppressed Renal Allograft Recipients
R. K. Sibley, R. M. Ferguson, D. E. R. Sutherland, R. L. Simmons, and J. S. Najarian 2836
- Effects of Cyclosporine on Human Renal Allograft Rejection: An Ad Interim Report
P. H yry, J. Ahonen, E. von Willebrand, B. Eklund, K. H ckerstedt, K. Salmela, E. Pettersson, A. Kauste, E. Taskinen, M. Lalla, H. Sarelin, B. Kuhlback, M. K ari inen, R. Paldanius, E. Lampainen, K. Huttunen, M. Viranta, T. V nttinen, J. Forstr m, V. A. Myllyniemi, L. Tarssanen, U. M. Henttula, A. Helanter , A. Relander, H. Borgm stars, A. Linkola, E. Leijala, P. Kunelius, A. Vartia, M. Eloranta, S. Pajunen, and H. Granlund 2842

(Continued)

CONTENTS

(continued)

- Tubular Changes in Renal Transplant Recipients on Cyclosporine*S. Thiru, E. R. Maher, D. V. Hamilton, D. B. Evans, and R. Y. Calne* 2846
- Pathology in Renal Transplant Patients Treated with Cyclosporine
A. Farnsworth, B. M. Hall, P. Kirwan, G. A. Bishop, G. C. Duggin, B. Goodman, J. Horvath, J. Johnson, A. Ng, A. G. R. Sheil, and D. J. Tiller 2852

CYCLOSPORINE CONVERSION AND USE AS ADJUNCTIVE THERAPY

- Conversion Rejection Consequences by Changing the Immunosuppressive Therapy
From Cyclosporine to Azathioprine After Kidney Transplantation
W. Land, L. A. Castro, G. Hillebrand, K. Günther, and J. M. Gokel 2857
- The Consequences of Conversion From Cyclosporine to Azathioprine and Prednisolone
in Renal Allograft Recipients*R. F. M. Wood, J. F. Thompson, N. H. Allen, A. Ting, and P. J. Morris* 2862
- The Effect of Conversion From Cyclosporine to Azathioprine Immunosuppression for
Intractable Nephrotoxicity*S. M. Flechner, C. T. Van Buren, R. Kerman, and B. D. Kahan* 2869
- Cyclosporine Nephrotoxicity in Renal Allograft Recipients: Conversion to
Azathioprine to Improve Renal Function*D. M. Canafax, D. E. R. Sutherland, N. L. Ascher, R. L. Simmons, and J. S. Najarian* 2874
- Conversion Problem—Azathioprine to Cyclosporine.....*K. Rolles, R. Merion, and R. Y. Calne* 2878
- Total Lymphoid Irradiation and Cyclosporine.....*D. E. R. Sutherland, R. M. Ferguson, M. I. Aeder, W. I. Lewis, F. R. Bentley, N. L. Ascher, R. L. Simmons, and J. S. Najarian* 2881
- Use of Cyclosporine and Monoclonal Antibodies in Clinical Renal Transplantation
N. L. Tilney, R. L. Kirkman, J. L. Araujo, C. B. Carpenter, E. L. Milford, E. L. Reinherz, S. F. Schlossman, and T. B. Strom 2889

EFFECTS IN AUTOIMMUNITY, VIRAL AND FUNGAL INFECTIONS

- Effect of Cyclosporine on Antigen Presentation: Relationship to Lupus
M. Fischbach and N. Talal 2899
- Response of Murine Autoimmune Disease to Cyclosporine and Thiols
M. G. Jones, G. Harris, and G. Cowing 2904
- The Effect of Cyclosporine on Lymphocyte Subsets in Experimental Allergic
Encephalomyelitis: Functional Loss of Disease-Suppressing Cells In Vivo
L. M. Fredane, G. A. Hashim, and R. E. McCabe 2909

(Continued)

CONTENTS

(continued)

Cyclosporine Therapy in the Treatment of Uveitis	<i>R. B. Nussenblatt, A. G. Palestine, C. C. Chan, W. C. Leake, A. H. Rook, I. Scher, and I. Gery</i>	2914
The Effects of Cyclosporine on Viruses	<i>X. E. Gui, R. W. Atchison, and M. Ho</i>	2917
In Vitro Effects of Cyclosporine on Lymphocyte Responses to Cytomegalovirus	<i>P. J. Converse, A. D. Hess, P. J. Tutschka, and G. W. Santos</i>	2923
In Vitro and In Vivo Antifungal Activity of Cyclosporine.....	<i>M. S. Osato, T. J. Roussel, K. R. Wilhelmus, and D. B. Jones</i>	2927

EXPERIMENTAL TRANSPLANTATION

KIDNEY

Combination Immunotherapy With Low-Dose Cyclosporine and Azathioprine in Splenectomized Canine Recipients of Renal Allografts.....	<i>M. I. Aeder, D. E. R. Sutherland, W. I. Lewis, and J. S. Najarian</i>	2933
Cyclosporine Enhances an Effect of Donor-Specific Blood Transfusion in Canine Renal Transplantation	<i>T. Ochiai, M. Gunji, M. Nagata, T. Suzuki, K. Enomoto, T. Asano, N. Yamada, H. Sato, and M. Ohtsuka</i>	2939
Immunosuppression of Renal Allograft Rejection by Perioperative Administration of the Combination of Histocompatibility Antigen in the Form of 3M KCl Extract or Blood Transfusion and Cyclosporine	<i>T. Yasumura and B. D. Kahan</i>	2942
Reversal of Kidney and Prevention of Pancreas Transplant Rejection With Cyclosporine in Beagles.....	<i>G. K. Kyriakides, L. Olson, C. Flaa, and J. Miller</i>	2950
Inhibition of Chronic Kidney Allograft Rejection by Cyclosporine	<i>R. L. Marquet, W. Weimar, E. Heineman, and J. Jeekel</i>	2953

HEART AND LUNG

Orthotopic Cardiac Transplantation in the Cyclosporine-Treated Neonate	<i>L. Bailey, Z. Li, F. Lacour-Gayet, P. Perier, D. Killeen, J. Perry, C. Schmidt, H. Roost, and W. Jolley</i>	2956
Benefit From Circadian Timing of Cyclosporine Revealed by Delay of Rejection of Murine Heart Allograft	<i>M. Cavallini, G. Magnus, F. Halberg, L. Tao, M. Y. Field, R. Sibley, J. S. Najarian, and D. E. R. Sutherland</i>	2960
Synergistic Effect of a Nucleotide-Free Diet and Cyclosporine on Allograft Survival	<i>C. T. Van Buren, A. Kulkarni, and F. Rudolph</i>	2967
Prolonged Heart Allograft Survival in Cyclosporine-Treated Presensitized Rats	<i>J. A. Schulak, J. Shelby, E. Wakely, and R. J. Corry</i>	2969
Effect of Cyclosporine on Lymphocyte Migration in Rat Cardiac Transplantation	<i>N. Kuromoto, C. Iga, R. Fawwaz, R. Nowygrod, K. Reemtsma, and M. A. Hardy</i>	2973

(Continued)

CONTENTS

(continued)

- Studies With T Cells From Long-Term Surviving Canine Lung Allograft Recipients:
Reduced Lymphocyte-Mediated Cytotoxicity But Not Reduced Mixed
Lymphocyte Reactivity *A. J. Norin, E. E. Emeson, K. L. Pinsker,
S. L. Kamholz, and F. J. Veith* 2979

LIVER, PANCREAS, INTESTINE

- Histologic Evidence of Modification of Liver Allograft Rejection in Inbred Miniature
Swine by Cyclosporine *M. W. Flye* 2983
- Induction of Liver Graft Tolerance in a Primarily Nontolerant Rat Strain
Combination With Temporary Treatment of Cyclosporine
R. Engemann, K. Ulrichs, A. Thiede, W. Müller-Ruchholtz, and H. Hamelmann 2986
- The Effect of Cyclosporine Alone and in Combination With Steroids on Experimental
Segmental Pancreatic Allografts in the Baboon
*D. F. Du Toit, J. J. Heydenrych, G. Louw, T. Zuurmond, L. Laker, D. Els,
and S. Woolfe-Coote* 2992
- Segmental Pancreatic Allotransplantation With High-Dose Cyclosporine and
Low-Dose Prednisone
H. W. Sollinger, D. Kamps, K. Cook, T. Warner, N. R. Glass, and F. O. Belzer 2997
- Pancreas and Kidney Allograft Rejection Responds Differently to Cyclosporine
Immunosuppression
J. Klemptner, E. Wagner, B. Steiniger, K. Wonigeit, and R. Pichlmayr 3001
- Effect of Cyclosporine on Allotransplanted Pancreatic Islets in
DLA-MLC-Compatible Dogs *M. D. Williams, R. Walshaw,
R. W. Bull, W. D. Schall, G. A. Padgett, V. V. Gossain, and R. F. Nachreiner* 3004
- The Effect of Cyclosporine on Simultaneous Skin and Pancreatic Islet Allografts in the
Rabbit *W. B. Jolley, K. Knierim, J. Ham, and J. K. Longerbeam* 3011
- Pharmacokinetics of Cyclosporine in a Canine Intestinal Transplantation Model
*Z. Cohen, S. R. Nordgren, R. D. Mackenzie, A. G. Lossing, C. R. Stiller,
and B. Langer* 3013
- Successful Small Bowel Allografts in Piglets Using Cyclosporine
*C. Ricour, Y. Revillon, F. Arnaud-Battandier, D. Ghnassia, P. Weyne,
A. Lauffenburger, J. Jos, J. L. Fontaine, P. Gallix, and M. Vaiman* 3019
- Prevention of Graft-Versus-Host Reaction Following Small Bowel Transplantation by
Temporary Cyclosporine Treatment
*E. Deltz, K. Ulrichs, R. Engemann, T. Schack, B. Friedrichs,
W. Müller-Ruchholtz, H. K. Müller-Hermelink, and A. Thiede* 3027
- Uptake of ¹⁴C-Glucose by the Transplanted Small Intestine
*S. Nordgren, Z. Cohen, R. Mackenzie, D. Finkelstein, G. R. Greenberg,
and B. Langer* 3032

(Continued)

CONTENTS

(continued)

BONE MARROW

- Studies on the Immunobiology of Syngeneic and Autologous Graft-Versus-Host Disease in Cyclosporine-Treated Rats.. *A. Glazier, P. J. Tutschka, and E. Farmer* 3035
- Suppressor and Cytotoxic Cells in DLA Nonidentical Canine Radiation Chimeras Given Cyclosporine and Methotrexate as Prophylaxis for Graft-Versus-Host Disease.....*H. J. Deeg, R. F. Raff, E. Severns, F. R. Appelbaum, E. D. Thomas, and R. Storb* 3042
- The Effect of Cyclosporine on Host-Versus-Graft Disease in Canine Bone Marrow Transplantation *A. M. Miller, E. P. Walma, W. Klapwijk, and D. W. Van Bekkum* 3046

EFFECTS ON WOUND HEALING, COMPOSITE GRAFTS, SKIN, CORNEA, AND VEIN ALLOGRAFTS

- Effects of Cyclosporine on the Healing of Vascularized and Nonvascularized Bone Allografts in Rodents *P. F. Halloran, M. Bushuk, and J. A. Stewart* 3053
- Modification of Experimental Limb Allograft Rejection With Cyclosporine and Prednisone: A Preliminary Report.... *B. H. J. Press, R. K. Sibley, and A. R. Shons* 3057
- Cyclosporine and Long-Term Survival of Composite Tissue Allografts (Limb Transplants) in Rats (With Historical Notes on the Role of Plastic Surgeons in Allotransplantation) *D. W. Furnas, K. S. Black, C. W. Hewitt, L. A. Fraser, and B. M. Achauer* 3063
- Diagnosis of Rejection and Functional Analysis of Composite Tissue (CT) and Skin Allografts Prolonged with Cyclosporine
K. S. Black, C. W. Hewitt, E. B. Howard, L. A. Fraser, B. J. Mah, J. C. Koumas, and B. M. Achauer 3069
- Cyclosporine Prolongs Skin Allografts in a Rat Burn Model
B. M. Achauer, C. W. Hewitt, K. S. Black, B. Philosophe, R. L. Linfesty, and D. W. Furnas 3073
- Concomitant Transfusion and Cyclosporine-Induced Enhancement of Rabbit Skin Allografts: Histocompatibility Requirements
G. J. A. Clunie, L. J. Dumble, H. P. King, L. G. Bowes, P. Masendycz, and A. Mirisklavos 3077
- Cyclosporine and Experimental Corneal Transplantation
T. J. Roussel, M. S. Osato, and K. R. Wilhelmus 3081
- Improved Survival of Venous Allografts in Dogs Following Graft Pretreatment With Cyclosporine
K. O. Bandlien, L. H. Toledo-Pereyra, M. I. Barnhart, S. P. Choudbury, A. Diaz-Velez, G. H. MacKenzie, and J. A. Cortez 3084

(Continued)

CONTENTS

(continued)

- Effect of Cyclosporine on Wound Healing *J. Ahonen, A. Nemlander,
K. Wiktorowicz, E. von Willebrand, R. Hekali, M. Lalla, and P. Häyry* 3092

SUMMATION

- Basic Science Summation *J. F. Borel and K. J. Lafferty* 3097
Clinical Aspects of Cyclosporine Therapy: A Summation *T. E. Starzl* 3103

SUPPLEMENT 2

CYCLOSPORINE: NURSING AND PARAPROFESSIONAL ASPECTS

- Administration of Cyclosporine *B. Ota* 3111
Clinical Results of the Use of Cyclosporine in Renal Transplantation *L. Schoenberg* 3124
Clinical Results in Orthotopic Liver Transplantation With Cyclosporine and Steroids
S. Maletic-Staschak 3130
Clinical Results: Cardiac Transplantation *P. Gamberg* 3135
Use of Cyclosporine in Bone Marrow Transplant Patients—A Nursing Perspective
R. Ford 3142
Side Effects of Cyclosporine in 100 Renal Allograft Recipients.. *B. Ota and M. Bradley* 3150
The Nephrotoxicity of Cyclosporine: A Nursing Perspective *J. E. Kobrenski* 3157
Infectious Complications and Lymphomas in Cyclosporine Patients
B. Dhein, L. Bartell, and R. M. Ferguson 3162
Pharmacokinetic Monitoring of Cyclosporine *C. A. Wideman* 3168
Long-Term Follow-Up of 100 Cyclosporine-Treated Renal Allograft Recipients
D. L. Golden 3176

**SPECIAL EDITORIAL
ANNOUNCEMENT**

Cadaveric Renal Transplantation with Cyclosporine: Experiences in 148 Patients at a Single Institution

W. Land, L. A. Castro, K. Günther, C. Hammer, C. Hillebrand, W.-D. Illner, N. Schmeller, B. Schneider, W. Siebert, R. A. Zink, and H. Zöttlein

SINCE NOVEMBER 1980, 195 renal transplantations have been performed at our center using cyclosporine as a new immunosuppressive agent. Twenty-five patients were treated with cyclosporine as the sole immunosuppressive agent in the European Multicentre Trial.¹ Outside a control study, cyclosporine, in combination with small doses of methylprednisolone, was used in 157 cadaveric renal transplantations as well as in 5 living related donor transplantations. Cyclosporine, in combination with steroids, was used in 8 combined renal and pancreatic transplantations. This article reports our experiences with 148 cadaveric renal transplantations performed by March 1983, using cyclosporine in combination with steroids as basic immunosuppressive therapy.

MATERIALS AND METHODS

Patient Population

This study includes 140 consecutive transplants of cadaveric renal allografts performed between March 1982 and March 1983 on recipients aged 9–61 years. No patients were excluded from cyclosporine treatment, neither patients with known liver disease nor patients with primarily nonfunctioning kidneys without immediate diuresis. Of the 140 patients, 115 got a primary renal allograft and 25 received a secondary or tertiary allograft. All recipients had received at least 3 random type-specific blood transfusions prior to transplant. Eight patients (aged 25–49 years) suffering from Type I diabetes mellitus and end-stage renal disease received combined renal and pancreatic allografts.

Immunosuppressive Protocol

Basic immunosuppression. Cyclosporine was administered intravenously before the operation and on day 1 postoperatively in a dose of 4 mg/kg of body weight and continued by oral administration in a dose of 15 mg/kg for 1 month after transplantation, when it was decreased by 2 mg/kg monthly to a maintenance level of 6–7 mg/kg. Methylprednisolone was begun at 8 mg daily immediately after the operation and maintained at that level.

Antirejection treatments. Antirejection treatment consisted of 3 i.v. bolus injections of 500 mg methylprednisolone during the first rejection episode. The second and third rejection episodes were treated by administration of ALG/ATG over a period of 7 days, in combination with methylprednisolone in a dose of 125 mg i.v. daily until reversal.

"Triple" immunosuppressive therapy. In recipients of a secondary or tertiary renal allograft and in patients with preformed antibodies higher than 50%, cyclosporine, azathioprine, and methylprednisolone were administered during the first week posttransplant as follows: cyclosporine was given as described above; azathioprine in a dose of 2 mg/kg initially, then decreased to 1 mg/kg; methylprednisolone (i.v.) in a dose of 500 mg daily, tapering to 30 mg daily.

From the second week after transplantation, the original basic immunosuppressive treatment was continued. Antirejection treatment was applied as described above.

Combined Renal and Pancreatic Transplantation

Pancreas transplantation was performed using the technique of segmental pancreatic allografting by occluding the duct system with Ethibloc. Postoperative management consisted of cyclosporine administration in combination with steroids; in addition, administration of heparine, antibiotics, and Somatostatine.

Incidence of Infections Under Cyclosporine Therapy

The incidence of infections described in this report concerns only the manifestation of severe infections requiring hospitalization of the transplant patient. In addition to careful clinical assessment and appropriate

From the Transplantation Center, Klinikum Grosshadern (Departments of Surgery, Internal Medicine I and Urology), University of Munich, Munich, Germany.

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Reprint requests should be addressed to Prof. Dr. W. Land, Dept. of Surgery, Klinikum Grosshadern, Marchioninstr. 15, D-8000 München 70, Germany.

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microbiologic tests for evidence of infectious diseases, detailed laboratory investigations were carried out whenever an overt virus disease was suspected.

Fine-Needle Aspiration Cytology

The methodology used has been described elsewhere.² In brief, fine-needle aspiration has to be done under sterile conditions by placing a spinal needle into the cortex of the graft. The aspirated material was dispersed into a centrifuge vial by means of 5 ml RPMI medium held in the suction syringe.

The mouse monoclonal antibodies used were directed against pan-T lymphocytes (OKT3), helper-inducer T lymphocytes (OKT4), and cytotoxic/suppressor T lymphocytes (OKT8).

RESULTS

Cadaveric Renal Transplantation

The overall graft survival rate (graft survival probability as calculated by the Cutler-Ederer test) after primary cadaveric renal transplantations in 115 consecutively treated patients under cyclosporine-methylprednisolone therapy is depicted in Fig. 1; the result in the historical control group (steroids + azathioprine; $N = 150$) is shown for comparison. At 1 year, the graft survival probability is 70% in the cyclosporine group compared to 50% in the control group. The difference of 20% is statistically significant. The overall graft survival rate after secondary or tertiary cadaveric renal transplantation in 25 patients under cyclosporine-methylprednisolone therapy is depicted in Fig. 2. The 1-year graft survival probability of 70% is identical to that obtained in the primary renal allograft group, although during the first 6 months after transplantation there was a slightly higher incidence of graft losses. Of these 25 patients, 18 were treated during the first week following transplantation by using the "triple" immunosuppressive protocol (see below).

Of the original 115 patients treated with cyclosporine after primary renal transplantation, 111 are currently alive. Of the 4 patients who died, 2 did so with functioning grafts, 1 from spontaneous intracerebral hemorrhage at 1 month and the other from acute cardiac failure at 6 months. One patient with a primary nonfunctioning kidney (ATN) died

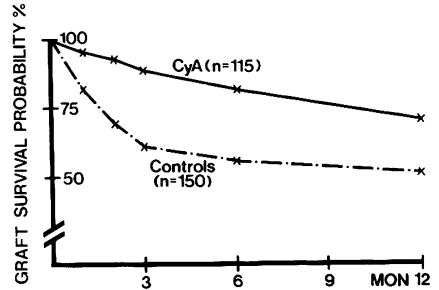


Fig. 1. Graft survival rates in primary renal transplantation, comparing cyclosporine-methylprednisolone treatment (CsA) vs. historical controls (azathioprine-steroids treatment).

from acute cardiac failure at 1 week, another patient from sepsis at 6 months. There was an immunologic cause of graft loss only in 14 patients, and a nonimmunologic cause of graft loss in 3. All the original 25 patients treated with cyclosporine after retransplantation are alive. There was an immunologic cause of graft loss in 6 patients and a nonimmunologic cause of graft loss in 1.

"Triple" Immunosuppression in Immunologically High-Risk Patients

As described in Materials and Methods, 26 immunologically high-risk patients (18 retransplantations and 8 recipients with preformed antibodies $> 50\%$) were treated with cyclosporine, azathioprine, and steroids during the first week after transplantation. The result of this pilot study is depicted in Fig. 3. We observed a 1-year graft survival probability of 70%. Remarkably, all irreversible graft rejections occurred during the first 3 months after transplantation. In none of these 26 patients treated initially with the "triple" immunosuppressive regimen has either severe infection or malignancy been seen so far.

Combined Renal and Segmental Pancreatic Transplantation

The results obtained with this kind of surgical treatment in Type I diabetics with end-stage renal disease are listed in Table 1. Although our experience with cyclosporine therapy in combined renal and pancreatic transplantation is limited to 8 cases, the

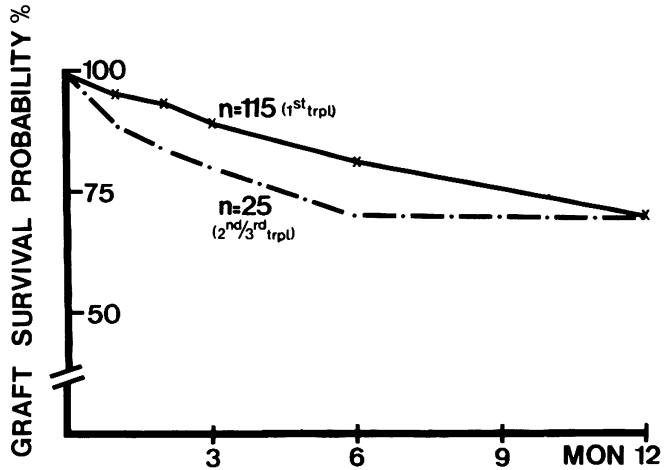


Fig. 2. Graft survival rates in primary renal transplantation (N = 115) compared to retransplantation (N = 25).

results obtained with this new immunosuppressive agent are encouraging and promising.

Incidence of Infectious Diseases Under Cyclosporine Treatment

The incidence of clinically manifested severe infections that required hospitalization is listed in Table 2. Of the original 140 patients treated with cyclosporine after cadaveric renal transplantation, only 13 (9%) were hospitalized with a bacterial infection (1 death due to sepsis), 9 (6%) with a viral infection, and 2 (1.3%) with a fungal infection.

Immunologic Monitoring: Fine-Needle Aspiration Cytology

Due to the difficulty in detecting acute rejections in patients treated with cyclosporine,

recourse was made to fine-needle aspiration cytology. The method allows not only estimation of onset, severity, and course of rejection but also measurement of the impact of treatment and differentiation between cyclosporine side effects, acute tubular necrosis, and acute cellular rejection. Differentiation of the inflammatory cell populations by monoclonal antibodies has proved that with increasing severity of rejection, high numbers of lymphocytes of the cytotoxic/suppressor cell compartment invade the graft. Helper cells therefore decrease relatively in terms of percent (Fig. 4).

This observation of a high influx of cytotoxic cells into the graft during rejection was not changed after introduction of cyclosporine as the immunosuppressant. Despite its powerful effect on graft rejection, no change in lymphocyte numbers in the peripheral blood could be seen. During rejection under cyclo-

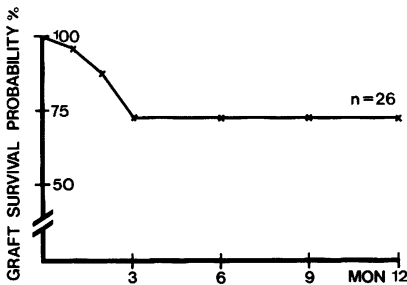


Fig. 3. Graft survival rate in immunologically high-risk patients treated with cyclosporine, azathioprine, and methylprednisolone during the first week following transplantation.

Table 1. Results of Combined Pancreatic and Renal Transplantation in 8 Patients Treated with Cyclosporine and Steroids*

Patients alive	7
Function of both grafts	5†
Function of the renal graft (2 years)	1
Rejection of both grafts (1 month)	1
Death (acute liver failure)	1

*At the Transplantation Center, Munich, 1979-1983; N = 12/11.

†2 years, 1 year, 5 months, 4 months, and 3 months, respectively.

Table 2. Incidence of Infectious Diseases in 140 Cyclosporine-Methylprednisolone-Treated Patients

No. of Patients (N = 13/140)	Bacterial Infections			Outcome
	Manifestation	Associated with ART*		
9	UTI, prostatitis, pyelonephritis	No		Recovery
1	Graft infection at biopsy	Yes		Transplantectomy
1	Otitis media	No		Recovery
1	Endocarditis	No		Recovery
1	Pneumonia, sepsis	No		Death

No. of Patients (N = 9/140)	Viral Infections			Outcome
	Manifestation	Pathogen	ART	
5	Interstitial pneumonia: cerebral signs, general symptoms	CMV	Yes (3) No (2)	Recovery
2	Herpes genitalis, Herpes simplex (generalized)	Herpes virus	Yes (1) No (1)	Recovery
2	Fever, pneumonia	Unknown	No	Recovery

No. of Patients (N = 2/140)	Fungal Infections			Outcome
	Manifestation	Pathogen	ART	
1	Tracheitis	<i>Candida albicans</i>	No	Recovery
1	Sepsis, UTI	<i>Candida albicans</i>	Yes	Recovery with graft loss

*ART: Antirejection therapy.

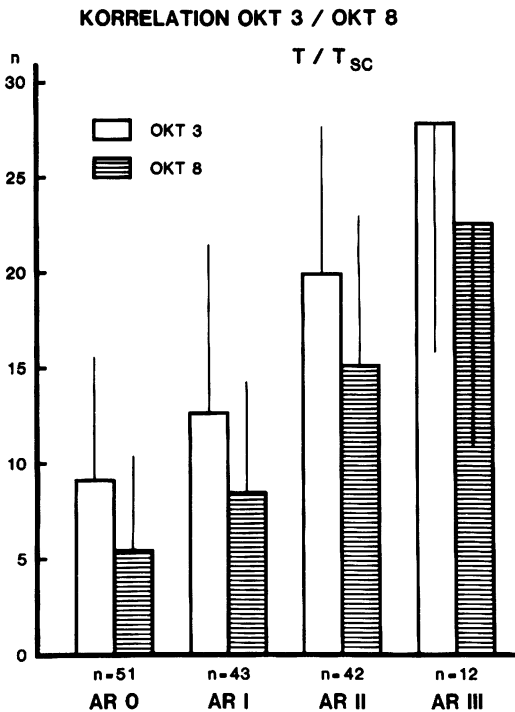


Fig. 4. OKT8⁺ cells increase in the graft with increasing severity of the rejection reaction.

sporine therapy, lymphocyte numbers increased in the graft, but less than with conventional therapy. Surprisingly enough, no impact on helper cells was seen under cyclosporine therapy. A new aspect was analyzed (Table 3) when conversion of numbers of helper and cytotoxic suppressor cells was measured in the peripheral blood and in the graft. High numbers of lymphocytes in the periphery and the graft, preferably belonging to the

Table 3. Behavior of Peripheral Granular Lymphocytes and T4/T8⁺ Cells in Rejection Episodes vs. Viral Infections

	Rejection Episode 0	Rejection Episode 2	Virus Infection
Lymphocytes in fine-needle biopsy	8.5	23.9	31.7
Lymphocytes in peripheral blood	7.7	6.3	18.3
OKT3	9.8	18.3	29.2
OKT4	4.8	8.2	4.5
OKT8	4.9	13.3	25.6
OKT4/OKT8 ratio	1.2	0.7	0.2
In peripheral blood	2.6	2.4	0.45

T8 compartment, heralded in virus infection. The ratio of T4 to T8⁺ cells was below 0.5 in aspirate and peripheral blood.

A further sign distinguishing virus infection from acute rejection seems to be the number of large granular lymphocytes—supposedly responsible for the natural killer activity. During acute rejection, peripheral blood lacks large granular lymphocytes. In the graft, large granular lymphocytes reach up to 12% of the inflammatory cell compartment. During virus infection, however, large granular lymphocytes increase in the peripheral blood and the graft to values up to 25%, with the mean of 14, i.e., 10%.

DISCUSSION

The results reported confirm the potential usefulness of cyclosporine in combination with low doses of steroids to improve the graft survival in cadaveric renal transplantation with an extremely low incidence of morbidity and mortality. Compared with the historical controls treated with conventional therapy at our center, a 20% difference in the results obtained with the use of cyclosporine was observed. Interestingly enough, the 70% 1-year graft survival probability under cyclosporine-methylprednisolone therapy was observed in primary renal transplantation as well as in retransplantation. By using a short-term "triple" immunosuppressive regimen (cyclosporine, azathioprine, methylprednisolone) immediately after surgery, a 70% 1-year graft survival rate of cadaveric renal allografts could also be achieved in immunologically high-risk patients. Although these results are similar to those reported by others,³⁻⁶ one has to be careful in interpreting the current improved graft survival rates as definite long-term results. Thus, within 1/2 year the 6-month graft survival rate of 90% came down to the 12-month graft survival rate of 70% at our own institution. Nevertheless, when evaluating the results at our institution, one has to take into account that no exclusion criteria for the use of cyclosporine were applied, as had been done in the European Multicentre Trial.

This circumstance represents one of several difficulties in comparing the efficacy of the combined cyclosporine treatment with that of cyclosporine monotherapy.

As far as the results in immunologically high-risk patients are concerned, a valid conclusion cannot be drawn from the data obtained at the present time. Nevertheless, two aspects seem worthwhile to discuss: (1) Our first clinical impression of a strong immunosuppressive potency of the "triple" regimen used is confirmed by experimental studies showing a synergistic immunosuppressive effect of cyclosporine and azathioprine in three different animal allograft models.⁷ (2) According to our observations (no incidence of severe infection or malignancy), such a combined immunosuppressive therapy seems to be safe for the patient, provided all three drugs are administered only for a short period of time.

Apart from the improved results in graft survival rates, the decreased morbidity, particularly in terms of decreased infectious diseases, is one of the remarkable advantages of cyclosporine treatment. Infections remain an important and typical complication of renal transplantation, which often has led to graft loss or patient death. Therefore, the decreased incidence of severe infectious diseases (of bacterial, viral, or fungal origin) as observed by us and others^{3,8} is tremendously encouraging. In this context, it remains to be studied in the future why particularly the incidence of viral infections is lower than expected in light of the mode of action of cyclosporine. Despite all the advantages, there is, however, one serious disadvantage in the use of cyclosporine: It makes the early detection of rejection episodes a difficult procedure, especially in patients with primarily nonfunctioning kidneys. A lot of "classical" rejection symptoms have completely (or partially) disappeared and are no longer seen by clinicians. This obvious difficulty with cyclosporine use has given rise to a search for new and better methods for immunologic monitoring. One of us (C. H.) tried to use P. Häyry's fine-needle aspiration cytology

as a method helpful for the accurate detection of rejection episodes. Although this method is not fully convincing from the practical point of view at the present time, some conclusions can be drawn: Fine-needle biopsy, in combination with highly specific monoclonal antibodies, provides some important new information about the background of high-lymphocytic inflammation. Clinical statements like onset, severity, and progress of an acute rejection given by the aspiration cytology can be confirmed and precised with this method in certain circumstances. A possible new prominent example is to differentiate between acute rejection and virus infection with the help of monoclonal antibodies and by differentiating large granular lymphocytes from other cell populations. With this information, unneces-

sary and dangerous immunosuppressive therapy in cases of nondiagnosed viral infections might be avoided.

Parallel to the improvement of the results in cadaveric renal transplantation under cyclosporine therapy, the results of combined renal and pancreatic transplantation have improved, although the number of patients treated with this surgical method at our institution is too small to draw any valid conclusion. Nevertheless, in view of the current uncertain state of the art relating to the technique of pancreatic grafting, the introduction of cyclosporine in the clinical pancreatic allografting program seems to improve the results in this field of organ transplantation slightly but steadily.

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AUTHOR INDEX

- Abb, H., 2380
 Abb, J., 2380
 Abramoff, P., 2394
 Achauer, B. M., 2742, 3063, 3069, 3073
 Adu, D., 2523, 2754
 Aeder, M. I., 2881, 2933
 Ahonen, J., 2842, 3092
 Aikawa, I., 2298, 2334, 2501
 Allen, N. H., 2862
 Ambinder, R. F., 2808
 Appelbaum, F. R., 2620, 3042
 Aprile, M., 2513
 Arakawa, K., 2298
 Araujo, J. L., 2889
 Arnaud-Battandier, F., 3019
 Asano, T., 2340, 2939
 Ascher, N. L., 2463, 2874, 2881
 Atchison, R. W., 2917
 Atkinson, K., 2430, 2446, 2761
- Bahnson, H. T., 2553, 2573, 2706, 2757, 2768, 2779
 Bailey, L., 2956
 Ballas, Z. K., 2323
 Bandlien, K. O., 3084
 Barnhart, M. I., 3084
 Barry, E. P., 2403
 Bartell, L., 3162
 Baughan, A., 2708
 Belitsky, P., 2535
 Belzer, F. O., 2997
 Benjamin, W. R., 2311
 Bentley, F. R., 2881
 Bernstein, R. L., 2706
 Beschorner, W. E., 2613
 Bettcher, K. B., 2538
 Beveridge, T., 2409
 Biggs, J., 2430, 2446, 2761
 Billingham, M., 2546
 Bishop, G. A., 2852
 Black, K. S., 2742, 3063, 3069, 3073
 Blanc, N., 2798
 Boake, R., 2538
 Boileau, M., 2469
 Boland, J., 2430
 Boldt, L., 2567
 Borel, J. F., 2219, 2242, 3097
 Borgmästars, H., 2842
 Bortin, M. M., 2394
 Bosi, E., 2602, 2676, 2798
 Boulas, J., 2485
 Bouwer, H. G. A., 2306
 Bowes, L. G., 3077
 Bradley, M., 3150
- Bremer, R., 2821
 Brewer, E. D., 2528
 Britton, K., 2430, 2446
 Brölsch, C., 2531, 2586
 Brookmeyer, R., 2563
 Brown, Z., 2398
 Brunner, F. P., 2821
 Buckels, J., 2523
 Buckner, C. D., 2620
 Bull, R. W., 3004
 Bunzendahl, H., 2531
 Burdelski, M., 2586
 Burke, M. D., 2712
 Buscetta, S., 2373
 Bushuk, M., 3053
- Calne, R. Y., 2846, 2878
 Canadian Transplant Study Group, 2479, 2490, 2513, 2748
 Canafax, D. M., 2874
 Cannarella, S. N., 2578
 Carpenter, C. B., 2889
 Carruthers, G., 2438
 Castro, L. A., 2517, 2699, 2857
 Cavallini, M., 2960
 Chan, C. C., 2914
 Chapuis-Cellier, C., 2798
 Chevalier, M., 2798
 Chinn, P. L., 2606
 Chipping, P. M., 2634
 Choudbury, S. P., 3084
 Clift, R. A., 2620
 Clunie, G. J. A., 3077
 Cohen, A., 2535
 Cohen, Z., 3013, 3032
 Cole, G. A., 2271
 Concannon, A., 2446, 2761
 Conley, S. B., 2528
 Converse, P. J., 2923
 Cook, K., 2997
 Cook, L. A., 2387
 Cooley, D. A., 2567
 Corneo, M., 2617
 Cortez, J. A., 3084
 Corry, R. J., 2969
 Cory-Pearce, R., 2559
 Cowing, G., 2904
 Creyssel, R., 2798
 Crocker, J., 2535
 Crofts, M., 2624
 Cunningham, C., 2712
- Davies, H. ff. S., 2278
 DeBiasio, R. L., 2775
 Debski, R. F., 2553
 Deeg, H. J., 2416, 2620, 3042
- Delmonte, L., 2328
 Deltz, E., 3027
 Dereg, H. J., 3042
 Devergie, A., 2442, 2628
 Devineni, R., 2695
 Dhein, B., 3162
 Diaz-Velez, A., 3084
 Dieperink, H., 2736
 Dixon, J. F. P., 2376
 Dodds, A., 2446, 2761
 Donatsch, P., 2719
 Doney, K., 2620
 Donnenberg, A. D., 2343
 Dossetor, J. B., 2538
 Drath, D. B., 2367
 Du Toit, D. F., 2992
 Dubernard, J. M., 2602, 2676, 2798
 Duggin, G. G., 2485, 2852
 Dumble, L. J., 3077
 Dummer, J. S., 2768, 2779
 Duplan, J., 2695
- Egel, J., 2706
 Eklund, B., 2842
 El Yafi, S., 2602, 2798
 Elick, B. A., 2606
 Eloranta, M., 2842
 Els, D., 2992
 Emeson, E. E., 2578, 2979
 Engel, P., 2343
 Engemann, R., 2986, 3027
 English, T. A. H., 2559
 Enomoto, K., 2939
 Evans, B., 2624
 Evans, D. B., 2846
 Ezzibdeh, M., 2523
- Fairhead, S. M., 2634
 Farmer, E. R., 2613, 3035
 Farnsworth, A., 2852
 Farrell, C., 2446
 Fauci, A. S., 2315
 Fawwaz, R., 2973
 Fehrman, I., 2507
 Ferguson, R. M., 2350, 2463, 2836, 2881, 3162
 Fidelus-Gort, R., 2350
 Field, M. Y., 2960
 Finkelstein, D., 3032
 Fischbach, M., 2899
 Flaa, C., 2950
 Flechner, S. M., 2293, 2302, 2434, 2469, 2528, 2689, 2869
 Flournoy, N., 2620

- Flye, M. W., 2983
 Foley, R. J., 2726
 Fontaine, J. L., 3019
 Ford, R., 3142
 Forström, J., 2842, 3063, 3069
 Fraser, L. A., 2742, 3063, 3069
 Frazier, O. H., 2567
 Fredane, L. M., 2909
 Friedman, A. W., 2259
 Friedrichs, B., 3027
 Fryd, D. S., 2463
 Fukuda, M., 2334
 Fumagalli, F., 2398
 Furnas, D. W., 2742, 3063, 3069, 3073

 Gallix, P., 3019
 Gamberg, P., 3135
 Garnett, N. L., 2808
 Gartner, J. C., Jr., 2582, 2592
 Geczy, C. L., 2390
 Gelet, A., 2602
 Gery, I., 2311, 2364, 2914
 Ghnassia, D., 3019
 Gibbons, S., 2434
 Ginchereau, E., 2573
 Glass, N. R., 2997
 Glazier, A., 3035
 Gliedman, M. L., 2578
 Gluckman, E., 2442, 2628
 Goetz, F. C., 2606
 Gokel, J. M., 2857
 Golden, D. L., 3176
 Goldsmith, J., 2450, 2578
 Goodman, B., 2852
 Gordon-Smith, E. C., 2422, 2634, 2708
 Gossain, V. V., 3004
 Graf, A., 2426
 Granlund, H., 2842
 Gratwohl, A., 2617
 Greenberg, A., 2706
 Greenberg, G. R., 3032
 Griffith, B. P., 2553, 2573, 2706, 2757, 2779
 Groth, C. G., 2507, 2815
 Gudat, F., 2821
 Guglielmi, A., 2757
 Gui, X. E., 2917
 Gunji, M., 2939
 Günther, K., 2517, 2699, 2857
 Gupta, R., 2535
 Gurland, H. J., 2699

 Haines, I., 2754
 Hakala, T. R., 2459, 2582, 2768, 2773, 2775, 2805
 Hall, B. M., 2485, 2852
 Hallberg, F., 2960
 Halloran, P. F., 2513, 3053
 Ham, J., 3011
 Hamelmann, H., 2986
 Hamilton, D. V., 2846
 Hammer, C., 2517
 Hamner, R. W., 2726, 2730
 Hamoudi, W. H., 2775
 Handschumacher, R. E., 2265
 Harder, F., 2821
 Hardesty, R. L., 2553, 2573, 2706, 2757, 2779
 Hardy, A. M., 2768, 2773
 Hardy, M. A., 2973
 Harley, J. B., 2315
 Harris, G., 2904
 Harris, J. P., 2485
 Hashim, G. A., 2909
 Hashimoto, I., 2298, 2334, 2501
 Haynes, I. G., 2523
 Häyry, P., 2716, 2842, 3092
 Heberling, R. L., 2808
 Heineman, E., 2953
 Hekali, R., 3092
 Helanterä, A., 2842
 Henttula, U. M., 2842
 Hess, A. D., 2248, 2343, 2613, 2923
 Hewitt, C. W., 2742, 3063, 3069, 3073
 Heydenrych, J. J., 2992
 Hillebrand, C., 2517
 Hillebrand, G., 2699, 2857
 Hinrichs, D. J., 2306
 Ho, M., 2768, 2773, 2779, 2917
 Höckerstedt, K., 2842
 Hodgkin, P., 2242
 Hoffman, G. J., 2808
 Horvath, J. S., 2485, 2852
 Howard, E. B., 2742, 3069
 Hows, J. M., 2422, 2634, 2708
 Howson, W., 2438
 Huber, A. C., 2808
 Hughes, G., 2624
 Hunt, S. A., 2546
 Hutchinson, I. V., 2287
 Huttunen, K., 2842

 Iga, C., 2973
 Illner, W. D., 2426, 2517
 Imberti, L., 2398
 Ingerman, A., 2742
 Ioka, J., 2501
 Itzkoff, J., 2573
 Ivory, K., 2782
 Iwatsuki, S., 2459, 2582, 2592, 2805
 Jamieson, S. W., 2546
 Jeannet, M., 2617
 Jeekel, J., 2953
 Johnsen, A. M., 2573
 Johnson, J. R., 2485, 2852
 Jolley, W. B., 2956, 3011
 Jones, D. B., 2927
 Jones, M. G., 2904
 Jones, S., 2311
 Jos, J., 3019

 Kääriäinen, M., 2842
 Kadotani, Y., 2501
 Kahan, B. D., 2211, 2259, 2293, 2302, 2367, 2413, 2434, 2469, 2528, 2567, 2641, 2649, 2665, 2689, 2869, 2942
 Kaleya, R., 2450, 2578
 Kalman, V. K., 2383
 Kamada, N., 2278
 Kamholz, S. L., 2450, 2578, 2979
 Kamps, D., 2997
 Kauste, A., 2842
 Kennedy, M. S., 2416, 2620
 Keown, P. A., 2438, 2695
 Kerman, R. H., 2293, 2302, 2469, 2689, 2869
 Killeen, D., 2956
 King, H. P., 3077
 Kirkman, R. L., 2889
 Kirwan, P., 2852
 Klapwijk, W., 3046
 Klaus, G. B. B., 2321
 Klempnauer, J., 2531, 3001
 Klimpel, G. R., 2383
 Klintmalm, G., 2507, 2815
 Knierim, K., 3011
 Kobrenski, J. E., 3157
 Koegler, J., 2438
 Kondoh, Y., 2334
 Koumas, J. C., 3069
 Kovithavongs, T., 2538
 Kretschmer, G., 2787
 Kuhlback, B., 2842
 Kulkarni, A., 2967
 Kunelius, P., 2842
 Kunkl, A., 2321
 Kupiec-Weglinski, J. W., 2357
 Kuromoto, N., 2973
 Kuwabara, T., 2364
 Kwok, D., 2434
 Kyriakides, G. K., 2950

 Lacour-Gayet, F., 2956
 Lafferty, K. J., 2242, 3097
 Laker, L., 2992
 Lakey, W. H., 2538
 Lalla, M., 2842, 3092

- Lampainen, E., 2842
 Länd, W., 2426, 2517, 2699, 2857
 Lang, W., 2586
 Langer, B., 3013, 3032
 Lannon, S. G., 2535
 Lauffenburger, A., 3019
 Laupacis, A., 2748
 LeGrue, S. J., 2259
 Leake, W. C., 2914
 Lear, P. A., 2357
 Leijala, E., 2842
 Leithner, C., 2787
 Lemaire, M., 2419
 Lewis, W. I., 2881, 2933
 Leyssac, P. P., 2736
 Li, Z., 2956
 Liebert, M., 2775
 Lien, J., 2513
 Linfesty, R. L., 3073
 Linkola, A., 2842
 Loertscher, R., 2821
 Lokiec, F., 2442, 2628
 Longerbeam, J. K., 3011
 Lossing, A. G., 3013
 Louw, G., 2992
 Ludwin, D., 2513
- MacDonald, A. S., 2535
 MacKenzie, G. H., 3084
 Mackenzie, R. D., 3013, 3032
 Mackintosh, P., 2523
 Magnus, G., 2960
 Mah, B. J., 3069
 Maher, E. R., 2846
 Malatack, J. J., 2582, 2592
 Maletic-Staschak, S., 3130
 Marquet, R. L., 2953
 Martin, D. C., 2742
 Masendycz, P., 3077
 Mason, D. W., 2287
 Matsumura, T., 2298
 Maurer, G., 2409, 2419
 McCabe, R. E., 2909
 McCormick, P., 2538
 McDonald, R., Jr., 2573
 McKenzie, N., 2438, 2695
 McMaster, P., 2523, 2754
 McMichael, J., 2438
 Merion, R., 2878
 Merker, M., 2265
 Michael, J., 2523, 2754
 Mihatsch, M. J., 2719, 2821
 Milford, E. L., 2889
 Miller, A. M., 3046
 Miller, J., 2950
 Mirisklavos, A., 3077
 Mochizuki, M., 2364
 Mokhtarian, F., 2271
- Mollenkopf, F. P., 2450, 2578
 Montefusco, C. M., 2450, 2578
 Moody, F. G., 2207
 Moon, D. K., 2390
 Morris, P. J., 2287, 2862
 Mraz, W., 2426
 Muller, A., 2719
 Müller-Hermelink, H. K., 3027
 Müller-Ruchholtz, W., 2986, 3027
 Myllyniemi, V. A., 2842
- Nachreiner, R. F., 3004
 Nagao, T., 2278
 Nagata, M., 2939
 Najarian, J. S., 2463, 2606, 2836,
 2874, 2881, 2933, 2960
 Nehlsen-Cannarella, S. L., 2450
 Neild, G. H., 2398, 2782
 Nelson, D. S., 2390
 Nemlander, A., 3092
 Neuhaus, P., 2586
 Newburger, J., 2413
 Ng, A., 2852
 Nickell, S. P., 2271
 Niederberger, W., 2409, 2419
 Nissen, C., 2617
 Nomura, H., 2501
 Nordgren, S. R., 3013, 3032
 Norin, A. J., 2578, 2979
 Nowygrod, R., 2973
 Nussbaumer, K., 2419
 Nussenblatt, R. B., 2311, 2364,
 2914
- Oberholzer, M., 2821
 Ochiai, T., 2340, 2939
 Ohmori, Y., 2298, 2334, 2501
 Ohtsuka, M., 2939
 Oka, T., 2298, 2334, 2501
 Olivieri, V., 2821
 Olson, L., 2950
 Osato, M. S., 2927, 3081
 Öst, L., 2507
 Osterwalder, B., 2617
 Ota, B., 3111, 3150
 Oyer, P. E., 2546
- Padgett, G. A., 3004
 Painvin, G. A., 2567
 Pajunen, S., 2842
 Paldanius, R., 2842
 Palestine, A. G., 2914
 Palladino, M. A., 2387
 Palmer, S., 2634
 Parker, J. W., 2376
 Paull, P., 2446
 Payne, W. D., 2302, 2469
 Pedrazzini, A., 2624
- Penn, I., 2790
 Perier, P., 2956
 Perlroth, M., 2546
 Perry, J., 2956
 Petric, R., 2719
 Pettersson, E., 2842
 Philosophe, B., 2742, 3073
 Pichlmayr, R., 2531, 2586, 3001
 Pinsker, K. L., 2578, 2979
 Pohanka, E., 2787
 Poirier, O., 2442, 2628
 Pollard, C., 2624
 Poole, C., 2624
 Pouteil-Noble, C., 2798
 Powles, R. L., 2624
 Pozza, G., 2602
 Preis, D., 2426
 Press, B. H. J., 3057
 Puschett, J. B., 2706
- Rabin, B., 2775
 Raff, R. F., 3042
 Reem, G. H., 2387
 Reemtsma, K., 2973
 Reeves, R., 2573
 Reinherz, E. L., 2889
 Relander, A., 2842
 Remuzzi, G., 2398
 Revillon, Y., 3019
 Rice, J., 2265
 Ricour, C., 3019
 Ried, M., 2434
 Rinaldo, C. R., Jr., 2775
 Ringdén O., 2507, 2815
 Rios, A., 2373
 Ritter, J., 2798
 Robinson, W. T., 2403
 Rocchi, G., 2398
 Rodger, R. S. C., 2754
 Roger, S., 2523
 Rogers, J. R., 2485
 Rolles, K., 2878
 Rook, A. H., 2914
 Roost, H., 2956
 Rosenthal, J. T., 2459, 2582, 2773,
 2805, 3081
 Roussel, T. J., 2927, 3081
 Rudolph, F., 2967
 Ryffel, B., 2719, 2821
- Sakamoto, K., 2340
 Salmela, K., 2842
 Sanders, J. E., 2620
 Sanghvi, A., 2757
 Santos, G. W., 2248, 2343, 2613,
 2923
 Saral, R., 2613
 Sarelin, H., 2842

- Sato, H., 2340, 2939
 Schack, T., 3027
 Schade, R. R., 2582, 2757
 Schall, W. D., 3004
 Scheibel, L. W., 2271
 Scher, I., 2914
 Schlossman, S. F., 2889
 Schmeller, N., 2517
 Schmidt, C., 2956
 Schmidt, E., 2586
 Schneider, B., 2517, 2699
 Schoenberg, L., 3124
 Schran, H. F., 2403
 Schulak, J. A., 2969
 Schulte, W. E., 2323
 Schwarz, M., 2787
 Schweitzer, B., 2265
 Secchi, A., 2602
 Sells, R. A., 2495
 Severns, E., 3042
 Shapiro, A. P., 2573
 Shaw, B. W., Jr., 2459, 2582, 2592
 Sheil, A. G. R., 2485, 2852
 Shelby, J., 2969
 Shih, C. C. -Y., 2394
 Shinohara, N., 2340
 Shoemaker, P., 2719
 Shons, A. R., 3057
 Shulman, H., 2620
 Shumway, N. E., 2546
 Sibley, R. K., 2836, 2960, 3057
 Siebert, W., 2426, 2517
 Siegl, H., 2719
 Signer, E., 2617
 Simmons, R. L., 2463, 2836, 2874, 2881
 Simpson, J. G., 2702, 2712
 Sinclair, N. R., 2438
 Sinzinger, H., 2787
 Smith, J. M., 2422, 2708
 Sollinger, H. W., 2997
 Speck, B., 2617
 Spichtin, H. P., 2821
 Starklint, H., 2736
 Starzl, T. E., 2459, 2582, 2592, 2768, 2773, 2805, 3103
 Stawecki, M., 2438
 Steiniger, B., 3001
 Stephen, M. S., 2485
 Stewart, J. A., 3053
 Stewart, P., 2620
 Stiller, C. R., 2438, 2479, 2490, 2695, 3013
 Stinson, E. B., 2546
 Stock, S., 2523
 Stöcklin, E., 2821
 Storb, R., 2416, 2620, 3042
 Strand, M., 2463
 Strom, T. B., 2357, 2889
 Sullivan, K. M., 2620
 Sutherland, D. E. R., 2463, 2597, 2606, 2836, 2874, 2881, 2933, 2960
 Suzuki, S., 2501
 Suzuki, T., 2939
 Syré, G., 2787
 Talal, N., 2899
 Tao, L., 2960
 Tarssanen, L., 2842
 Taskinen, E., 2842
 Taylor, H. R., 2808
 Taylor, R. J., 2805
 Thiede, A., 2986, 3027
 Thiel, G., 2821
 Thiru, S., 2846
 Thomas, E. D., 2416, 2620, 3042
 Thompson, J. F., 2862
 Thompson, M. E., 2573, 2706, 2757, 2779
 Thomson, A. W., 2390, 2702
 Tillegård, A., 2507
 Tiller, D. J., 2485, 2852
 Tilney, N. L., 2357, 2889
 Ting, A., 2862
 Toledo-Pereyra, L. H., 2373, 3084
 Tonnesen, A. S., 2730
 Torhorst, J., 2821
 Touraine, J. L., 2602, 2798
 Traeger, J., 2602, 2798
 Truitt, R. L., 2394
 Turney, J. H., 2523, 2754
 Tutschka, P. J., 2248, 2343, 2613, 2923, 3035
 Ulrichs, K., 2986, 3027
 Usui, T., 2298
 Uyemura, K., 2376
 Vaiman, M., 3019
 Valentine, B. A., 2808
 Van Bekkum, D. W., 3046
 Van Buren, C. T., 2293, 2302, 2434, 2469, 2528, 2678, 2689, 2726, 2869, 2967
 Van Thiel, D. H., 2582, 2757
 Vanttinen, T., 2842
 Vartia, A., 2842
 Veith, F. J., 2450, 2578, 2979
 Viranta, M., 2842
 Vlassis, T., 2523
 von Willebrand, E., 2716, 2842, 3092
 Wagner, E., 3001
 Wagner, O., 2419
 Wajszczuk, C. P., 2768, 2773
 Wakely, E., 2969
 Wall, W., 2438
 Wallace, A. C., 2695
 Wallwork, J., 2559
 Walma, E. P., 3046
 Walshaw, R., 3004
 Warner, T., 2997
 Warty, V., 2757
 Weimar, W., 2953
 Weinmann, E. J., 2726, 2730
 Wenger, R., 2230
 Weyne, P., 3019
 Wheatley, D. N., 2712
 White, D. J. G., 2278
 White, J., 2535
 White, N., 2513
 Whiting, P. H., 2702, 2712
 Wideman, C. A., 3168
 Wiktorowicz, K., 3092
 Wilczek, H., 2507
 Wilhelmus, K. R., 2927, 3081
 Williams, D. G., 2398, 2782
 Williams, M. D., 3004
 Witherspoon, R. P., 2620
 Wonigeit, K., 2531, 2586, 3001
 Wood, A. J., 2409
 Wood, R. F. M., 2862
 Woolfe-Coote, S., 2992
 Yamada, N., 2939
 Yasumura, T., 2942
 Yee, G. C., 2416
 Yin, J. L., 2634
 Yoshimura, N., 2298, 2334
 Zink, R. A., 2426, 2517
 Zitelli, B. J., 2582, 2592
 Zollinger, H. U., 2821
 Zöttlein, H., 2426, 2517
 Zuurmond, T., 2992