

HANDBUCH DER ALLGEMEINEN PATHOLOGIE

SECHSTER BAND / ACHTER TEIL

TRANSPLANTATION



**SPRINGER-VERLAG
BERLIN · HEIDELBERG · NEW YORK**

22-12
22-1
6.1.1)

Handbuch der allgemeinen Pathologie

Herausgegeben von

H.-W. Altmann · F. Büchner · H. Cottier · E. Grundmann
G. Holle · E. Letterer · W. Masshoff · H. Meessen
F. Roulet · G. Seifert · G. Siebert

Sechster Band, Achter Teil



Springer-Verlag Berlin Heidelberg New York 1977

ISBN 3-540-07751-0 Springer-Verlag Berlin · Heidelberg · New York
ISBN 0-387-07751-0 Springer-Verlag New York · Heidelberg · Berlin

Library of Congress Catalog Card Number 56-2297

The use of general descriptive names, trade names, trade marks, etc. in this publication, even if the former are not especially identified, is not to be taken as a sign that such names, as understood by the Trade Marks and Merchandise Marks Act, may accordingly be used freely by anyone. This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically those of translation, reprinting, re-use of illustrations, broadcasting, reproduction by photocopying machine or similar means, and storage in data banks. Under § 54 of the German Copyright Law where copies are made for other than private use, a fee is payable to the publisher, the amount of the fee to be determined by agreement with the publisher.

© by Springer-Verlag, Berlin · Heidelberg 1977.

Printed in Germany.

Typesetting, printing and binding: Universitätsdruckerei H. Stürtz AG, Würzburg
2122/3120-543210

Transplantation

By

K.T. Brunner · C.E. Calkins · J.-C. Cerottini · C.C. Congdon · E.L. Cooper
H. Cottier · D.A.L. Davies · F. Eitel · J. Hagmann · E.S. Henderson
M. Hess · M.W. Hess · E.N. Hinzpeter · H.P. Hobik · T. Hraba · M. Jäger
P.H.K. Jap · M. Jeannet · C.R. Jerusalem · G.R.F. Krueger · H.U. Keller
Z.J. Lucas · G.O.H. Naumann · R. Pichlmayr · L. Schweiberer
M. Segall · R. Storb · O. Stutman · C.J. Wirth · K. Wonigeit

Edited by

Johann Wilhelm Masshoff

With 233 Figures



Springer-Verlag Berlin Heidelberg New York 1977

Preface

Organ transplantation has almost disappeared from headlines in the daily press, possibly because it failed to fulfill exaggerated expectations. Transplantation pathology has become more and more important, not only with relation to therapeutic transplantations but even more in its fundamental theories. There is some analogy here to the development in space science where spectacular achievements were followed by sobering frustrations and where, for the time being, the effect on technology is more fruitful than the outcome of the original far-reaching projects. That transplant rejection was defined, in most of its stages, as an immunologic process, has given many new impulses to immunology in general. Transplantation assays have become a pet experiment in immunobiology and an abundant source of general information and knowledge.

The implications of such a development could not be predicted when the present volume was outlined and planned. In accordance with the concept of WILLI MASSHOFF, general transplantation pathology was given a central position as a fundamental science, while the chapters on the transplantation of various tissues are of a more paradigmatic character. It was MASSHOFF who invited competent authors and who managed to balance their articles, despite some overlapping, so as to draw a comprehensive picture of contemporary transplantation pathology. WILLI MASSHOFF died while he was editing the first manuscripts. As co-editors we have undertaken to complete the publication that we began together.

Some delays were unavoidable. The progress of evolution, especially in immunology, is so rapid that some of the articles written nearly 2 years ago no longer correspond to the present status of knowledge. Our readers will notice this by comparing the dates of bibliographic references. The decision of the authors who approved of publication in spite of the delay is very much appreciated because a new editing and updating of these chapters would in turn have outdated the more recent ones. The chapter on "Cell Systems Participating in Graft Rejections" by HAGMANN was added to update the volume in this important aspect of cellular immunology.

The first chapters deal with the genetic background of transplant reactions, their clinical significance, and the mixed leucocyte culture test (MLC). In its phylogenetic and ontogenetic aspects, transplant theory adheres to the field

of general biology; the discussion of humoral and cell-mediated mechanisms and of tolerance phenomena relates it to general immunology. Subsequent chapters report on the transplantation of cells—mostly from bone marrow—and of skin, connective tissue, cornea and bone. An overview is given in the central comprehensive chapter by CH.R. JERUSALEM and P.H.K. JAP. Therapeutic possibilities and their implications for general pathology are discussed in chapters on radiation-induced tolerance, and the application of antisera and various medications. The volume ends with a presentation of the graft-versus-host reaction as an inverted transplant rejection.

The editors have often questioned the utility of this kind of review volume in a large handbook. The rapid progress of science will outstrip, as a rule, their work in editing and preparing contributions. Whoever wants to keep abreast of recent developments will find the latest publications in scientific periodicals. The fundamental facts of contemporary knowledge, however, can only be gathered from comprehensive presentations where the widespread results are collected, compared and evaluated. Here we see the role of our volume and the reason for its publication.

WILLI MASSHOFF began his editing under these aspects, and we have endeavoured to complete his work. Having been in close contact with him over many years we felt sufficiently informed about his plans, and we hoped to fulfill them to the best of our ability. WILLI MASSHOFF had to die without having seen the final shape of this volume which we dedicate to his memory as a token of friendship and reverence.

HANS COTTIER
EKKEHARD GRUNDMANN

Vorwort

Die Organtransplantation ist aus den Überschriften der Tagespresse verschwunden. Mag sein, daß sie manche übersteigerte Erwartung nicht erfüllt hat. Die Transplantations-Pathologie ist um so wichtiger geworden. Das gilt sowohl für die Transplantation als klinische Therapie als auch in noch stärkerem Maße für ihre theoretischen Grundlagen. Eine gängige Parallele bietet sich an: Die Weltraumforschung brachte neben spektakulären Höhepunkten auch Ernüchterung; der Gewinn an Technologie ist vorerst größer als der der primär projektierten Ziele. Die Erkenntnis, daß die Abstoßung eines Transplantates in nahezu allen Phasen ein immunologischer Vorgang ist, brachte der Immunologie eine Fülle von Impulsen. Die Transplantation wurde ein bevorzugtes Experiment der Immunbiologie, und viel allgemeingültiges Wissen wurde so gewonnen.

Als der jetzt vorliegende Band geplant wurde, war diese Entwicklung noch nicht in dieser Konsequenz vorauszusehen. Es ist das Verdienst von WILLI MASSHOFF, den Band schließlich so gegliedert zu haben, daß die allgemeine Transplantations-Pathologie als Grundlagenwissenschaft in den Mittelpunkt kam, während die speziellen Gewebskapitel mehr paradigmatische Stellung erhielten. MASSHOFF gelang es, kompetente Autoren zu gewinnen und die Beiträge im Ansatz so aufeinander abzustimmen, daß sie trotz mancher Überschneidungen ein geschlossenes Bild der Transplantations-Pathologie liefern. Während der Bearbeitung der eingehenden Manuskripte verstarb WILLI MASSHOFF. Die unterzeichnenden Mitherausgeber haben es übernommen, gemeinsam das begonnene Werk zu Ende zu führen.

Dabei waren Verzögerungen nicht zu vermeiden. Die Erkenntnisse gerade in der Immunologie schritten in raschem Tempo weiter, und es ist mancher Beitrag — vor fast zwei Jahren abgeschlossen — schon nicht mehr auf dem aktuellen Stand. Der Leser kann das leicht an den Jahreszahlen der Literaturzitate erkennen. Wir sind den Autoren dieser Beiträge besonders dankbar, daß sie trotzdem ihre Zustimmung zur Veröffentlichung gegeben haben: eine nochmalige Überarbeitung dieser Artikel hätte wiederum die anderen veralten lassen. Durch Einfügung des Beitrages von HAGMANN et al. über „Cell Systems Participating in Graft Rejection“ wurde wenigstens dieser für die zelluläre Immunologie wichtige Aspekt aktualisiert.

Der Band beginnt mit Artikeln über die genetischen Grundlagen der Trans-

plantatreaktion, deren klinische Bedeutung und die Testmöglichkeiten mit der mixed leukocyte culture (MLC). Die phylogenetischen und ontogenetischen Aspekte stellen die Transplantatlehre in den Bereich der Allgemeinen Biologie; die Erörterungen der humoralen und zellvermittelten Mechanismen sowie der Toleranzphänomene geben allgemein-immunologische Beziehungen. Es folgen Abhandlungen über die Transplantation von Zellen – im wesentlichen des Knochenmarkes, der Haut, des Bindegewebes, der Cornea, des Knochens; als zentraler Beitrag bringt der Artikel von CH.R. JERUSALEM und P.H.K. JAP das Résumé der vorangegangenen Beispiele. Den therapeutischen Möglichkeiten und ihren Folgen für die Allgemeine Pathologie widmen sich die Artikel über die strahlen-induzierte Toleranz, die Anwendung von Antiseren und von verschiedenen Medikationen. Eine Darstellung der Graft-versus-Host-Reaktion als einer umgekehrten Transplantat-Abstoßung schließt diesen Band.

Die Herausgeber haben oft über den Sinn solcher zusammenfassenden Handbuchbände diskutiert. Das wissenschaftliche Erkenntnistempo überholt in der Regel die redaktionelle Bearbeitung. Wer das Allerneueste wissen will, findet es in den wissenschaftlichen Zeitschriften. Die Grundlage des heutigen Wissensstandes kann er aber nur aus zusammenfassenden Darstellungen erfahren, die das weit verbreitete Wissensgut sammeln, ordnen und werten. Hier liegt nach unserer Ansicht die Daseinsberechtigung auch dieses Bandes.

Unter dieser Vorstellung hatte WILLI MASSHOFF die Redaktion übernommen. Wir, die Unterzeichnenden, haben versucht, seine Arbeit abzuschließen. Wir standen über viele Jahre in engem Kontakt mit ihm, glauben, seine Pläne zu kennen, und hoffen, sie wenigstens nach unserem Vermögen verwirklicht zu haben. Es ist WILLI MASSHOFF nicht vergönnt gewesen, den fertigen Band vor sich zu haben. Wir widmen ihn in Freundschaft und Verehrung seinem Gedächtnis.

HANS COTTIER
EKKEHARD GRUNDMANN

List of Contributors

- BRUNNER, K.T., Dr., Schweizerisches Institut für Experimentelle Krebsforschung, Ch. des Boveresses, CH-1066 Épalinges s/Lausanne (Switzerland)
- CALKINS, C.E., Dr., Memorial Sloan-Kettering Cancer Center, Cellular Immunbiology Section, 1275 York Avenue, New York, N.Y. 10021 (USA)
- CEROTTINI, J.-C., Dr., Ludwig Institute for Cancer Research, Ch. des Boveresses, CH-1066 Épalinges s/Lausanne (Switzerland)
- CONGDON, C.C., Dr., The University of Tennessee, Memorial Research Center, 1924 Alcoa Highway, Knoxville, Tenn. 37920 (USA)
- COOPER, E.L., Prof. Dr., University of California, Department of Anatomy, School of Medicine, The Center for the Health Sciences, Los Angeles, Calif. 90024 (USA)
- COTTIER, H., Prof. Dr., Pathologisches Institut der Universität, Freiburgstraße 30, CH-3010 Bern (Switzerland)
- DAVIES, D.A.L., Prof. Dr., G.D. Searle & Co. Ltd., Research Division, P.O. Box 53, Lane End Road, High Wycombe, Bucks. HP12 4HL (England)
- EITEL, F., Dr., Chirurgische Universitätsklinik, Abt. Unfallchirurgie, 6650 Homburg/Saar (Fed. Rep. of Germany)
- HAGMANN, J., Dr., Pathologisches Institut der Universität, Freiburgstraße 30, CH-3010 Bern (Switzerland)
- HENDERSON, E.S., Dr., Chief of Medicine A, Roswell Park Memorial Institute, Department of Health, State of New York, 666 Elm Street, Buffalo, N.Y. 14263 (USA)
- HESS, M., Dr., G.D. Searle & Co. Ltd., Research Division, P.O. Box 53, Lane End Road, High Wycombe, Bucks. HP12 4HL (England)
- HESS, M.W., Prof. Dr., Pathologisches Institut der Universität, Freiburgstraße 30, CH-3010 Bern (Switzerland)
- HINZPETER, E.N., Dr., Allgemeines Krankenhaus Heidelberg, Augen-Abteilung, Tangsteder Landstr. 400, 2000 Hamburg 62 (Fed. Rep. of Germany)
- HOBIK, H.P., PD Dr., Pathologisches Institut der Universität, Westring 17, 4400 Münster/Westf. (Fed. Rep. of Germany)
- HRABA, T., Dr., Institute of Experimental Biology and Genetics, Czechoslovak Academy of Sciences, Budějovická 1083, 14220 Prague 4 (ČSSR)
- JÄGER, M., Prof. Dr., Orthopädische Klinik, Harlachinger Straße 51, 8000 München 90 (Fed. Rep. of Germany)
- JAP, P.H.K., Dr., Katholieke Universiteit, Faculteit der Geneeskunde, Laboratorium voor Cytologie en Histologie, Geert Grooteplein Noord 21, Nijmegen (Holland)
- JEANNET, M., Dr., Hôpital Cantonal, Unité d'Immunologie de Transplantation, 64, av. de la Roseraie, CH-1211 Genève 4 (Switzerland)
- JERUSALEM, C.R., Prof. Dr., Katholieke Universiteit, Faculteit der Geneeskunde, Laboratorium voor Cytologie en Histologie, Geert Grooteplein Noord 21, Nijmegen (Holland)
- KRUEGER, G.R.F., Prof. Dr., Pathologisches Institut der Universität, Immunpathologische Laboratorien, Joseph-Stelzmann-Str. 9, 5000 Köln 41 (Fed. Rep. of Germany)

- Keller, H.U., PD Dr., Pathologisches Institut der Universität, Freiburgstraße 30, CH-3010 Bern (Switzerland)
- LUCAS, Z.J., Prof. Dr., Stanford University Medical Center, Department of Surgery, Stanford, Calif. 94305 (USA)
- NAUMANN, G.O.H., Prof. Dr., Universitäts-Augenklinik, Abteilung und Lehrstuhl II, Schleichstraße 12, 7400 Tübingen (Fed. Rep. of Germany)
- PICHLMAYR, R., Prof. Dr., Medizinische Hochschule, Klinik für Abdominal- und Transplantationschirurgie, Department Chirurgie, Karl-Wiechert-Allee 9, 3000 Hannover-Kleefeld (Fed. Rep. of Germany)
- SCHWEIBERER, L., Prof. Dr., Chirurgische Universitätsklinik, Abteilung für Unfallchirurgie, 6650 Homburg/Saar (Fed. Rep. of Germany)
- SEGALL, M., Dr., Institut für Genetik der Universität, Weyertal 121, 5000 Köln 41 (West-Germany)
- STORB, R., Prof. Dr., University of Washington, Department of Medicine, Division of Oncology, Seattle, Washington 98122 (USA)
- STUTMAN, O., Dr., Memorial Sloan-Kettering Cancer Center, Cellular Immunobiology Section, 1275 York Avenue, New York, N.Y. 10021 (USA)
- WIRTH, C.J., Dr., Orthopädische Klinik, Harlachinger Straße 51, 8000 München 90 (Fed. Rep. of Germany)
- WONIGEIT, K., Dr., Medizinische Hochschule, Klinik für Abdominal- und Transplantationschirurgie, Department Chirurgie, Karl-Wiechert-Allee 9, 3000 Hannover-Kleefeld (Fed. Rep. of Germany)

Contents

The Main Histocompatibility System in Man. M. JEANNET. With 2 Tables	1
A. Introduction	1
B. Historical Background	1
C. Methodology and Serological Considerations	3
I. Leukoagglutination	3
II. Lymphocyte Cytotoxicity	4
III. Platelet Complement Fixation	4
IV. Serum Sources	4
1. Polytransfused Patients	5
2. Pregnancy	5
3. Immunization of Human Volunteers	5
4. After Organ Transplantation	6
5. "Natural" Lymphocytotoxins	6
6. Immunization of Animals	6
D. Genetics of the HL-A System	7
E. Heterogeneity and Cross-Reactivity of HL-A Antigens	9
F. HL-A, Mixed Lymphocyte Culture (MLC), Cell-Mediated Lympholysis (CML), and Cellular Immunity	10
G. HL-A System and Clinical Transplantation	12
I. Skin Graft Survival	12
II. Kidney Transplantation	12
III. Variability in the Host Immune Response	15
IV. Donor Selection for Kidney Transplantation	17
V. Bone Marrow Transplantation	18
H. HL-A System and Human Diseases	20
I. HL-A and Hematologic Malignant Diseases	20
II. HL-A and Cancer (other than Lymphomas)	22
III. HL-A and Immunopathic Diseases	22
IV. HL-A and Infectious Diseases	23
V. HL-A and Rheumatoid Diseases	24
VI. HL-A System and Various other Diseases	25
I. HL-A System and Blood Transfusion	25
J. HL-A System and Disputed Paternity Cases	26
K. Conclusions	27
References	27
Gene Products of the Major Histocompatibility Complex: Biology and Chemistry. D.A.L. DAVIES and M. HESS. With 19 Figures and 8 Tables	39
I. Introduction	39

2. The MHC in Man and Animals	41
2.1 Similarities	41
2.2 Differences	42
3. Biology of Human MHC Products	43
3.1 HL A Antigens	43
3.2 β 2-Microglobulin (β 2m)	45
3.3 Ir-Region in Man	48
3.4 Association of HL A with Disease	50
4. Additional Information from Animal Studies	52
4.1 Genetics of the H-2 Complex	52
4.2 I-Region Traits and Functions	62
4.3 Donor Specific Prolongation of Transplant Survival	64
5. Chemistry of Human and Mouse MHC Gene Products	68
5.1 Homology	68
5.2 Membranes and Models	68
5.3 Methods	70
5.4 Biochemistry of HL A/H-2 Antigens	76
5.5 β 2-Microglobulin	84
5.6 Immune Response Region Associated Antigens (Ia)	86
6. Concluding Remarks	91
References	92
 Lymphocyte—Defined Components of the Major Histocompatibility Complex. MIRIAM SEGALL. With 7 Figures and 10 Tables	105
A. Introduction. General Principles of MLC	105
B. Technical and Statistical Aspects of Human MLC	106
I. Macro- and Micro-Methods	106
II. Determination of Non-Stimulation	107
1. Controls	107
2. Statistical Analysis	108
3. Quantitation of MLC Results	110
C. Mouse MLC Techniques	114
D. Genetics of MLC in Humans	115
I. Basic Principles	115
II. Correlation of MLC Non-Stimulation in Siblings with Inheritance of the Same HL-A Haplotype	118
III. Exceptional Cases of Stimulation and Non-Stimulation	119
IV. Association of Stimulation with Four-Locus Region	121
V. Minor loci	121
VI. MLC and HL-A Typing in Unrelateds	122
E. Genetics of MLC in the Mouse	126
F. MLC Typing	127
I. Principle of Typing—Use of Homozygous Cells	127
II. Problems in Defining a “Typing” Response	129
G. Cell-Mediated Lympholysis (CML) Reaction	130
I. CML in the Human	130
II. CML in the Mouse	131
III. Relation of CML and MLC	132
H. Correlations of MLC with Grafting	132
I. Conclusion	134
Appendix I. Statistical Definitions	134
Appendix II. Definition of Genetic Terms	135
Addendum	136
References	136

Phylogenetic Aspects of Transplantation. EDWIN L. COOPER. With 4 Figures	139
A. Introduction	139
B. Transplantation Reactions in Invertebrates Other than Annelids and Echinoderms	140
1. Organelle Transplantation in Protozoans (Sarcodina, Ciliata)	140
2. Metazoans—Specificity of Reaggregation in Porifera	140
3. Incompatibility in Cnidaria (Hydrozoa, Anthozoa)	141
4. Platyhelminthes and Sipunculida	141
5. Equivocal Incompatibilities in Mollusca (Pelecypoda, Gastropoda, Cephalopoda)	142
6. Arthropoda	143
7. Genetic Control in Urochordata	143
8. Summary of Quasi Immunorecognition	144
C. Transplantation Reactions in Invertebrates that Reveal Primordial Cell-Mediated Immunity	144
I. Short-term Immunologic Memory	144
II. Cell and Tissue Responses that Indicate Self Recognition in Echinoderms	145
III. Transplantation in Asteroidea	145
IV. Short-term Memory	145
V. The Earthworm Model	146
1. First- and Second-Set Allograft Rejection in <i>Lumbricus terrestris</i> and <i>Eisenia foetida</i>	147
2. Rejection of First- and Second-Set Xenografts Exchanged between <i>Lumbricus</i> and <i>Eisenia</i>	147
3. Specificity and Anamnesis	148
4. The Cellular Response	149
5. The Role of Temperature in Earthworm Tissue Graft Rejection	151
6. Summary	151
D. Transplantation Immunity in Fishes	151
I. Introduction	151
II. The Hagfish	151
III. The Lamprey	152
IV. Cartilaginous Fishes	152
V. Bony Fishes (Holosteans; Teleosts)	152
E. Transplantation Immunity in Amphibians	153
I. Adult Apodans	153
1. Introduction	153
2. General Description of Autografts and Allografts	153
3. Histopathology	154
II. Adult Urodeles	155
1. The Latent Phase	155
2. The Rejection Phase	156
3. The Chronic Rejection Response to Xenografts	156
4. Role of the Thymus in Graft Rejection	156
5. Histologic Differences in Skin	157
6. Suppression of Transplantation Immunity	157
III. Anurans	159
1. Larvae	159
2. Bone Marrow Restoration of Transplantation Immunity in Adult Leopard Frogs	161
F. Transplantation Immunity in Reptiles	162
I. Introduction	162
II. The Chronic Response in Turtles	162
III. The Importance of Temperature in Turtles	162
IV. The Mexican Iguana	163
V. The Garter Snake	163
References	164

Ontogenetic Aspects. OSIAS STUTMAN and CATHERINE E. CALKINS. With 3 Figures and 3 Tables	169
A. Introduction	169
B. Ontogeny of Lymphoid Structures	170
C. Ontogeny of Transplantation Immunity	179
D. Ontogeny of Thymus-Dependent Functions	181
E. Concluding Remarks	186
References	187
Humoral and Cell-Mediated Mechanisms of Allograft Rejection. K. THEODOR BRUNNER and JEAN-CHARLES CEROTTINI	195
A. Introduction	195
B. Assay Methods of Cell-Mediated Cytotoxicity (CMC)	198
C. Cytotoxicity Mediated by Specifically Sensitized T-Cells	200
D. In Vivo Formation of Cytotoxic T Lymphocytes	201
E. In Vitro Formation of Cytotoxic T Lymphocytes	202
F. Mechanism of T-Cell Cytotoxicity	203
G. Specificity of Target Cell Destruction by Cytotoxic T Lymphocytes	204
H. Antibody-Dependent Cytotoxicity Mediated by Normal Lymphoid Cells	205
I. Cytotoxicity Mediated by Macrophages	207
K. Relevance of CMC to Allograft Rejection	209
L. The Role of Antibody in Allograft Rejection	210
References	212
Cell Systems Participating in Graft Rejections. J. HAGMANN, M.W. HESS, H.U. KELLER and H. COTTIER	217
A. Introduction	217
B. Lymphocytes	217
I. Development of the Immune System and Lymphocyte Subclasses	217
1. Early Ontogenesis of Lymphoid Organs and Cells	217
2. Postnatal Development of the Lymphocytic Systems	218
3. The Central Role of the Thymus	219
II. Peripheral Lymphocytes	223
1. Lymphocyte Subclasses	223
a) T Cells	223
b) B-cells	226
c) Null Cells	229
2. The Functions of Peripheral Lymphocytes	229
a) Helper and Suppressor Activity	229
b) Cell-Mediated Cytotoxicity	230
c) Mixed Lymphocyte Cultures	232
d) Graft-Versus-Host Reaction (GVHR)	233
C. Macrophages	234
D. Neutrophilic Granulocytes	235
E. Other Cells and Structures	235
References	235
General Tolerance Phenomena. T. HRABA	247
A. Introduction	247
B. Tolerance Phenomena and Other Specific Inhibitions of Immune Reactions	249
I. Inhibition States Classified as Immunologic Tolerance	250

1. The Sulzberger-Chase Phenomenon	250
2. Immunologic Paralysis	250
3. Tolerance to Heterologous Serum Proteins	251
4. Tolerance to Other Antigens	253
II. Other Antigen-Induced States of Specific Inhibition of the Immune Response	253
1. Immunologic Enhancement	253
2. Immune Deviation	254
C. Mechanisms of Immunologic Tolerance	254
I. The Relation of Antibody-induced Suppression to Immunologic Tolerance	254
II. Cellular Processes in Immunologic Tolerance	256
III. Suppressor Cells	258
IV. Transplantation Tolerance	260
V. Mechanism of Unresponsiveness to Self Components	262
D. Conclusions	264
References	265

Transplantation of Cells: Experimental and Clinical Observations. GERHARD R.F. KRUEGER. With 44 Figures and 3 Tables	275
A. Introduction	275
B. Historical Notes	276
C. Cell Types Used for Transplantation and Indications for the Respective Procedure	278
I. Experimental Transplantation	278
II. Human Transplantation	284
1. Indications for Transplantation of Blood and its Components	284
2. Indications for Transplantation of Bone Marrow	284
D. Techniques of Cell Transplantation	287
I. Details of Patient Selection	287
1. Selection of the Host	288
2. Selection of the Donor	288
II. Preevaluation and Pretreatment of Host and Donor	288
1. Pretreatment of the Donor	288
2. Pretreatment of the Recipient	289
III. Procurement of Bone Marrow Cells	294
IV. Cell Grafting	296
V. Cells other than Bone Marrow Cells used for Transplantation in Man	296
VI. Posttransplant Clinical Investigation of Bone Marrow Recipient	297
E. Demonstration and Localization of Engrafted Cells	300
F. Graft-Host Interactions	311
I. Microenvironmental Influences	311
II. Graft Rejection	312
III. Graft-Versus-Host Reaction (GVHR)	318
IV. Therapeutic Intervention of Postengraftment Disease	320
G. Conclusions	321
References	322

Skin Grafts in Animals and Man. ZOLTAN J. LUCAS. With 4 Figures and 3 Tables	329
A. Introduction	329
B. Operational Definition of Transplant Antigens	330
C. Morphologic Changes Occurring in Skin Allografts	332
I. Sequential Changes in Gross and Microscopic Appearance	333
II. Characterization and Quantitation of the Infiltrating Cells	335
III. Comparison of Morphologic Events in the Homograft Reaction and in other Hypersensitivity Reactions	335

D. The Immune Responses Induced by Skin Grafting	339
I. Afferent Phase—Antigen Recognition	341
II. Central Phase—Clonal Proliferation, Yielding both Memory and Differentiated Effector Cells	344
III. Effector Phase—the Expression of Immunity	344
1. Specific Immune Cytotoxic Mechanisms	344
2. Recruitment of Nonsensitized Effector Cells by Lymphokines Secreted by Sensitized T-Cells	346
3. Local Activation of the Host's General Inflammatory Response	347
4. Correlation of Immunologic and Pathophysiologic Events with Clinical Skin Graft Rejection Syndromes	348
IV. Autoregulatory Phase	349
1. Complete or Partial Tolerance	350
a) Conditions Affecting Induction, Maintenance, and Reversal of Immunologic Tolerance	350
b) The Absence of Reactive Cells or the Presence of Nonreactive Cells	351
c) The Presence of Immunologically Active Lymphocytes Blocked by Serum Factors	351
d) Other Alternatives: Suppressive or Regulatory Events Mediated by Lymphocytes on Immune Reactions	352
2. Immunologic Enhancement	352
a) General Features of Graft Survival	352
b) Relationship Between Organ Vascularity and Immunologic Enhancement	353
References	354
 Transplantation of Connective Tissue. M. JÄGER and C.J. WIRTH. With 16 Figures	359
A. Introduction	359
B. General Section	360
I. Anatomic Structure of Connective-Tissue Types as it Affects Suitability for Transplantation	360
II. Viability and Nonviability: Denaturation of the Graft as it Affects Primary Healing and Restructuring	361
III. Biological and Mechanical Merits of Auto-, Homo-, and Heterologous Transplants	362
IV. Changes with Age in Connective Tissue as they Affect Transplantation	365
V. Immune Reactions in the Transplantation of Living and Preserved Connective Tissue	367
VI. Preservation	368
VII. Healing	377
C. Specific Section	380
I. Tendon	380
II. Cutis	382
III. Fascia	384
IV. Dura	385
D. Future Prospects	392
References	393
 Transplantation of the Cornea in Man and Animal. E.N. HINZPETER and G.O.H. NAUMANN. With 11 Figures and 9 Tables	403
I. Introduction and Historical Background	403
II. Basic Principles of Keratoplasty	404

A. Terminology	404
B. Indications for Keratoplasty	405
C. Criteria for Donor Material and Storage	407
1. General	407
2. Donor-Cornea Evaluation (Laboratory and Clinical)	408
3. Storage	409
D. Surgical Techniques in Keratoplasty	411
E. Factors Determining Prognosis of Keratoplasty	412
1. Quality of the Donor-Cornea	412
2. State of the Recipient Cornea	413
3. Other Ocular Disease	414
4. Quality of Surgery	415
F. Healing of the Corneal Wound in Keratoplasty	415
G. Fate of Donor Cells in Keratoplasty	416
III. Unsuccessful Keratoplasty	417
A. Nonimmunologic Factors for Graft Failure	418
B. Immunologic Reasons for Graft Failure	421
IV. Experimental Keratoplasty and Heterografting	431
References	432

General Pathology of the Transplantation Reaction in Experimental and Clinical Organ Grafts.

CHRISTOPH R. JERUSALEM and PAUL H.K. JAP. With 61 Figures 439

A. The Many Facets of the Transplantation Reaction	439
I. Introduction	439
II. Terminology	440
1. Donor-Recipient Relationship	440
2. Chronologies of Rejection	441
III. Elements of the Transplantation Reaction	442
1. Dichotomy of the Immune Response	442
2. T-Helper Cell Mechanisms	446
3. Effector Mechanisms of Cell-Mediated Cytotoxicity	447
a) Autonomy of T-Lymphocyte Cytotoxicity	448
b) Mediators of the Cellular Immune Reaction	449
c) Cell-Mediated Cytotoxicity Independent of Thymus	451
IV. Humoral Factors Involved in Graft Rejection	456
B. Effector Cells and the Target Cell Injury	457
I. Morphology of Infiltrating "Lymphoid Cells"	457
1. Small Lymphocytes	458
2. Medium-Sized Lymphocytes	458
3. Atypical Lymphocytes	458
4. Large Lymphocytes	459
5. Transformed Lymphocytes	459
6. Lymphoid Killer Cells	460
7. Monocytes	460
8. Macrophages	461
II. Morphology of the Cell-Mediated Target Cell Destruction <i>in vitro</i>	464
1. Membrane Contact	464
2. Morphology of Cell-Mediated Target Cell Lysis	465
3. Morphology of Antibody-Dependent Cell-Mediated Cytotoxicity	466
4. Other Mechanisms of Cell-Mediated Target Cell Destruction	467
III. Features of Antibody-Mediated Injury	467
1. Morphology of the Complement-Dependent Immune Cytolysis	468
2. Relationship Between Immune Complexes and Clotting	468
3. Pathogenesis of Tissue Injury Mediated by Immune Complexes	469