

Contents

Page

ix PREFACE

I HISTORY OF THE RADIATION CHIMAERA

- 4 *The nature of the therapeutic action of haemopoietic cells*
- 6 Humoral hypothesis
- 8 Cellular hypothesis
- 10 Identification of grafted cells

- 15 *Immunological specificity of chimaeras*

II THE PRODUCTION OF RADIATION CHIMAERAS AND THE STABILITY OF THE CHIMAERIC STATE

- 22 *Antigenic differences between the host and the donor*
- 24 Immunological reactivity of the host
- 26 Heterologous chimaeras

- 27 *The radiation dose*
- 28 Radiation syndromes
- 30 Infections
- 32 Bone marrow therapy
- 32 Middlethal radiation dose
- 36 Surviving fraction of the immune system

- 40 *Stability of the chimaeric state*
- 40 Radiation dose
- 43 Host-donor incompatibility
- 43 Mechanism of reversion
- 46 Reversion and theories of haemopoiesis

- 49 *Variations of the irradiation regime*
- 49 Fractionation
- 52 Internal radiation
- 53 Irradiation with neutrons

- 54 *Interval between irradiation and transplantation*

- 57 *Grafting techniques and the nature of the graft*
- 57 Collection and preparation of cell suspensions
- 59 Routes of administration
- 59 Localization of injected cells

Page	
62	Effective cell type
65	Foetal cells
69	Culture of haemopoietic cells
70	<i>Methods of preservation</i>

III SECONDARY DISEASE FOLLOWING BONE MARROW TRANSPLANTATION

79	<i>Recognition of a secondary syndrome</i>
81	<i>Identification of secondary diseases as a graft versus host disease</i>
82	The genetic approach
84	Analogous conditions
85	Direct evidence of anti-host activity
88	Transfer experiments
92	The morphological evidence
92	<i>Description of secondary disease and related syndromes</i>
92	Patterns of secondary disease and mortality
98	Symptoms: diarrhoea and wasting
103	Skin lesions
105	Infectious complications
105	Intensity of graft versus host reaction and secondary disease
108	Secondary mortality in the absence of a foreign graft
110	<i>Pathogenesis of secondary disease</i>
110	Decreased immunological defence
112	Radiation dose
115	<i>Modification of secondary disease</i>
115	Preventive measures
118	Preirradiation of donor marrow
119	Incubation of donor marrow
120	Pooled donor marrow
121	Miscellaneous methods
123	Treatment of secondary disease

IV PATHOLOGY OF THE RADIATION CHIMAERA

127	<i>Introduction</i>
128	<i>The bone marrow syndrome</i>
130	<i>Radiation induced intestinal changes</i>
131	<i>Recovery of haemopoiesis in bone marrow treated animals</i>
131	Bone marrow
132	Lymphatic tissues

Page	
133	Peripheral blood
134	<i>Graft rejection in homologous and heterologous chimaeras</i>
134	The "splenic white pulp reaction"
136	The pathology of graft rejection
137	<i>Secondary disease</i>
137	<i>General pathology and pathogenesis of secondary disease</i>
139	<i>Specific pathology</i>
139	Lymphatic tissues
142	Infectious disease
145	Haemopoiesis
146	Gastro-intestinal tract
150	Liver
152	Jaundice
153	Skin
155	Kidneys
155	Cardiovascular system
156	Other organs
157	<i>The causes of death in secondary disease</i>
158	<i>Comparison of secondary disease with runt disease and homologous disease</i>
160	<i>Graft versus host diseases and auto-immune diseases</i>
161	General features
161	Organ- or tissue-specific features
163	<i>Graft versus host diseases and the immunological deficiency syndromes</i>

V IMMUNOLOGICAL STUDIES WITH RADIATION CHIMAERAS

166	<i>Introduction</i>
167	<i>Reactivity of radiation chimaeras</i>
167	Homograft Reactivity
169	Graft versus host reactivity
172	Reactivity against other antigens
177	<i>Transfer experiments involving radiation chimaeras</i>
177	Transfer of immunity
183	Transfer of immunological tolerance
188	Other data from transfer studies

VI CLINICAL APPLICATIONS OF BONE MARROW TRANSPLANTATION AND RELATED EXPERIMENTS

195	<i>Treatment of Haemopoietic failure following irradiation</i>
-----	--

Page	
195	Homologous bone marrow transplantation
200	Autologous bone marrow reinfusion following irradiation
202	<i>Autologous bone marrow after chemotherapy</i>
202	Experiments with animals
203	Clinical trials
209	<i>Homologous bone marrow after chemotherapy</i>
209	Experiments with animals
209	Clinical trials
214	<i>Whole body irradiation and transplantation of haemopoietic cells in the experimental treatment of leukaemia</i>
215	The effects of irradiation
220	The host-donor combination
220	Attempts at controlling the graft versus tumour reaction
223	Complications of the treatment other than secondary disease
223	The clinical application of bone marrow transplantation in the treatment of leukaemia
227	<i>Treatment of other blood diseases with bone marrow</i>
231	<i>Production of chimaerism as a preparation for organ transplantation</i>
233	REFERENCES
265	ACKNOWLEDGMENTS
267	AUTHOR INDEX
273	SUBJECT INDEX

Preface

The discovery of haematopoietic chimaerism, resulting from the intravenous administration of bone marrow cells into a lethally irradiated animal, has opened new ways to investigate numerous problems in the fields of immunology, haematology and tissue transplantation. In fact, radiation chimaeras have become such accepted tools for studies in these areas that there is now a tendency to neglect the original object of bone marrow transplantation as a cure for lethal exposure to ionising radiation. In addition, the outcome of clinical trials involving bone marrow transplantation in the treatment of disorders of the haematopoietic system, mainly leukaemia, has been disappointing; also insurmountable difficulties have been encountered in attempts to facilitate organ transplantations by inducing haematopoietic chimaerism in human patients. These factors have caused many investigators to abandon the idea that bone marrow transplantation can ever become a valuable asset to clinical medicine. It is our opinion that these failures have occurred mainly because the clinical applications were undertaken too soon, most of them before even the minimum of basic knowledge required to bridge the gap between mouse and patient had been obtained.

A particularly unexpected complication has arisen because of the immunological reaction of the lymphoid cells present in the transplanted marrow against the new host. This has confronted investigators with the formidable problem of identifying a completely new syndrome (generally called secondary disease) as well as with the task of unravelling its pathogenesis and devising methods for its prevention and treatment.

Many errors in extrapolation from the laboratory experiment to the patient have been made and much time was lost before it became evident that the graft versus host reaction in primates, including man, is incomparably more violent than in rodents. One of the main objects of this monograph is to present an exhaustive review of the comparative pathology of the immunological complications which occur after transplantation of foreign bone marrow, and to analyse the causes of the clinical failures in the light of the available experimental data.

This work has been greatly facilitated by our long-standing co-operation with the group led by George Mathé in Paris. Apart from being one of the pioneers in bone marrow transplantation, he has been the only clinician to conduct careful clinical trials whenever new experimental results seemed to require them. Because his clinical approach has always taken into full account the data obtained from experiments by his own group and by others, his accumulated clinical material represents by far the most important source of information on this aspect.

It is as yet impossible to predict what therapeutic advantages will eventually be gained from the vast amount of research that has been

invested in radiation chimaeras. Quantitative evaluation of the current methods for storage of bone marrow, and the development of more appropriate freezing techniques, certainly warrant new clinical trials of autologous bone marrow transplantation. Recent advances in the control of secondary disease by treatment with cytotoxic and antimetabolic drugs, the new prospects offered by the introduction of anti-lymphocyte serum and the steady progress that is being made towards the identification of transplantation antigens in leucocytes as a method for the selection of compatible donors, all seem to provide grounds for a more optimistic outlook concerning the future of homologous bone marrow transplantation. Whatever the chances are, the stakes are so high that a continuation of the investigation of homologous bone marrow transplantation, both experimental and clinical, appears to be more than justified.

This monograph has been written for specialists and workers in related fields. We have made no special attempt to prepare a complete review of the literature on radiation chimaeras, but have preferred to discuss trends and ideas emerging from various lines of research, from our personal point of view.

Throughout the book we have employed the original terminology of transplantation, mainly because we did not consider it practical to change these terms so soon after their derivatives became established in the scientific language of the various European countries, including our own, where transplantation immunology is a relatively new addition to medical research. For those readers who have already forgotten the "old" terminology, we should say that isologous, homologous and heterologous are used here in place of syngeneic, allogeneic and xenogeneic respectively.

Acknowledgments are given on page 265.

The critical readers for whom this monograph is obviously intended are referred to four recent monographs which deal in different ways with the same subject: *Transplantatsionnyi immunitet i radiatsionnye khimery (Transplantation Immunity and Radiation Chimaeras)* by R. Petrov and Yu. Zaretskaya, Atomizdat, Moscow (1965); *L'Aplasia myelo-lymphoide de l'irradiation totale* by G. Mathé, J. L. Amiel and L. Schwarzenberg, Gauthier-Villars, Paris (1965); *Tissue Grafting and Radiation* by H. S. Micklem and J. F. Loutit, Academic Press, New York and London (1966); *Bone Marrow Transplantation* by D. E. Pegg, Lloyd-Luke, London (1966).

We feel confident that these volumes contain all the information that we have omitted or neglected in the present one.

Rijswijk
October 1966

D. W. VAN BEKKUM
M. J. DE VRIES