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 Midlethal 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
III SECONDARY DISEASE FOLLOWING BONE MARROW TRANSPLANTATION

79 Recognition of a secondary syndrome
81 Identification of secondary diseases as a graft versus host disease
82 The genetic approach
84 Analogous conditions
85 Direct evidence of anti-host activity
88 Transfer experiments
92 The morphological evidence

92 Description of secondary disease and related syndromes
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 Pathogenesis of secondary disease
110 Decreased immunological defence
112 Radiation dose

115 Modification of secondary disease
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 Introduction
128 The bone marrow syndrome
130 Radiation induced intestinal changes
131 Recovery of haemopoiesis in bone marrow treated animals
131 Bone marrow
132 Lymphatic tissues
CONTENTS

Page 133 Peripheral blood
134 \textit{Graft rejection in homologous and heterologous chimaeras}
134 The “splenic white pulp reaction”
136 The pathology of graft rejection
137 \textit{Secondary disease}
137 \textit{General pathology and pathogenesis of secondary disease}
139 \textit{Specific pathology}
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 \textit{The causes of death in secondary disease}
158 \textit{Comparison of secondary disease with runt disease and homologous disease}
160 \textit{Graft versus host diseases and auto-immune diseases}
161 General features
161 Organ- or tissue-specific features
163 \textit{Graft versus host diseases and the immunological deficiency syndromes}

\textbf{V IMMUNOLOGICAL STUDIES WITH RADIATION CHIMAERAS}

166 \textit{Introduction}

167 \textit{Reactivity of radiation chimaeras}
167 Homograft Reactivity
169 Graft versus host reactivity
172 Reactivity against other antigens
177 \textit{Transfer experiments involving radiation chimaeras}
177 Transfer of immunity
183 Transfer of immunological tolerance
188 Other data from transfer studies

\textbf{VI CLINICAL APPLICATIONS OF BONE MARROW TRANSPLANTATION AND RELATED EXPERIMENTS}

195 \textit{Treatment of Haemopoietic failure following irradiation}
Page
195  Homologous bone marrow transplantation
200  Autologous bone marrow reinfusion following irradiation

202  *Autologous bone marrow after chemotherapy*
202  Experiments with animals
203  Clinical trials

209  *Homologous bone marrow after chemotherapy*
209  Experiments with animals
209  Clinical trials

214  *Whole body irradiation and transplantation of haemopoietic cells in the experimental treatment of leukaemia*
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  *Treatment of other blood diseases with bone marrow*
231  *Production of chimaerism as a preparation for organ transplantation*

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 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.


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