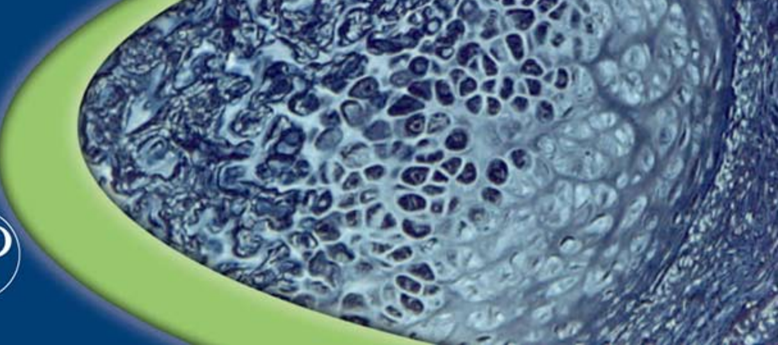
Principles of REGENERATIVE BIOLOGY

Bruce M. Carlson



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To the memory of Richard J. Goss, who stimulated me and many others to probe into the mysteries of regeneration.*

*As a student about to graduate from a small midwestern college, I was wandering through the library and ran across the first issue of the *Journal of Experimental Zoology* that the library had subscribed to. In it was an article by Richard Goss and Martha Stagg (Regeneration in lower jaws of newts after excision of the intermandibular regions. *J Exp Zool* 137:1–12, 1958). Even though I had already signed up to do graduate work on fish taxonomy at Cornell, that article affected me almost like a religious conversion, and I knew instantly that regeneration would be my ultimate field of endeavor. Although my interest in fish has not abated, I have never regretted the decision to switch to regeneration research, and it has led me down some fascinating pathways.

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Preface

Regeneration is one of the most fascinating phenomena in biology, but it is also one of the most complex. Virtually all species, from protozoa to humans, have the capacity to regenerate, but the extent of their regenerative ability varies greatly. Planaria, starfish and some worms can regenerate most of their body, whereas many other species are able to regenerate only parts of specific tissues. Among the vertebrates, urodele amphibians are the best adapted for regeneration; they can regenerate limbs, tails, jaws, eyes and a variety of internal structures.

For much of the twentieth century, mammals, including humans, were considered to have a poor capacity for regeneration. This was particularly true up to the late 1950s, when I first began to explore the literature on regeneration. A research visit to the Soviet Union during 1965–1966 exposed me to many new ways of looking at mammalian regeneration. Perhaps the most striking to me was the emphasis on *uslovie* ("conditions") of regeneration that abounded in the Russian regeneration literature of the 1960s. The essence of this concept was that the success of regeneration often is a function of the environment in which the regenerative process is taking place. I was initially inclined to attribute this emphasis to the waning influence of Lysenkoism, which still permeated the Russian biology of the time. This element was certainly present, but during my several decades of research on regeneration since that time, I have come to appreciate how important the environment is in supporting or failing to support regenerative processes in mammals.

With the explosion of knowledge from molecular biology and the burgeoning interest in generating or regenerating tissues or organs through various tissue engineering or stem cell approaches, many scientists and students have shown a renewed interest in the phenomenon of regeneration. Because relatively few have had the luxury of being able to approach the phenomenon of regeneration from a broad biologic perspective, I thought that it would be useful to write a short book that outlines some of the fundamental biologic principles of regeneration. As the book has evolved, the contents have focused principally on regeneration in vertebrate systems, but when certain points are best illustrated by examples taken from the very diverse universe of invertebrate regeneration, they are included, as well. In order to manipulate regenerative processes, it is important to understand the underlying principles of regeneration. Laying these out is what this book is all about.

It is often said that science progresses by stepping on the shoulders of one's predecessors. My hope is that this book will place in focus enough intellectual shoulders of pioneers in regeneration research to provide sufficient stepping stones for the next generation of researchers in this fascinating field.

Bruce M. Carlson

Acknowledgments

This book was made possible through the sharing of information over many years with colleagues and students all around the world. I am particularly indebted to those who have generously provided me with reprints, not only of their own work, but hard-to-locate reports from often quite obscure sources. The present book grew out of an earlier one (Carlson, BM. 1986. Moscow: *Regeneratsiya,* Nauka), which was published only in Russian, and I thank Dr. Victor Mitashov for suggesting that I write that one.

Thanks to the University of Michigan's retirement furlough program, this is the first book that I have been able to write during the daytime hours. Special thanks also to my wife and colleague, Jean, for her continuous support of my book-writing projects.

The present book has benefited greatly from the many fine original illustrations that were prepared by Shayne Davidson, with whom I had previously worked on a number of smaller projects. It's always a pleasure to work with a true professional. Thanks are also due to Jasna Markovac and Tari Broderick at Elsevier for accepting the manuscript and supporting the actual writing. Fran Levy skillfully and cheerfully guided the transformation of the manuscript into a book. To her, many thanks are due.

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List of Abbreviations

cAMP	Cyclic adenosine monophosphate
ANG	Angiopoietin
AP	Activator protein
ARIA	Acetylcholine receptor inducing activity
BDNF	Brain-derived neurotrophic factor
BHH	Banded hedgehog
BMP	Bone morphogenetic protein
CAM	Cell adhesion molecule
CNS	Central nervous system
CNTF	Ciliary neurotrophic factor
DHKA	Dictyostelium histidine kinase
DNA	Deoxyribonucleic acid
DOB	Devoid of blastema—a zebrafish mutant
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EPH	Ephrin
ERK	Extracellular signal-regulated kinase
ES	Embryonic stem cells
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
G	Gap, with respect to the mitotic cycle
GAP-43	Growth-associated protein
GDNF	Glial cell–derived neurotrophic factor
GFP	Green fluorescent protein
GRHL	Homolog of *Drosophila grainy head* gene
GTPase	Guanosine triphosphatase
HB-EGF	Heparin-binding epidermal growth factor
HGF	Hepatic growth factor, also known as scatter factor
HIF	Hypoxia-inducible factor
HOX	Homeobox-containing transcription factor
HSP	Heat shock protein
IGF	Insulin-like growth factor
IHH	Indian hedgehog

KGF	Keratinocyte growth factor
KROX	A gene that regulates hindbrain development
L1	A cell adhesion molecule (NgCAM)
LF	A transcription factor downstream of WNT
M	Mitosis—component of the cell cycle
MAG	Myelin-associated glycoprotein
MAP	Microtubule-associated protein
MDR	A surface antigen found on hematogenous stem cells
MEIS	Homeobox genes activated by retinoic acid
MMP	Matrix metalloproteinase
MPS	A mitotic checkpoint kinase
MRF	Myogenic regulatory factor
MRL	Strain of mouse with a high regenerative capacity
MSX	Ortholog of *Drosophila* Msh (muscle segment homeobox)
MYF	A myogenic regulatory factor
MYOD	A myogenic regulatory factor
NGF	Nerve growth factor
NGFR	Nerve growth factor receptor
NGR	Nogo receptor
NK	Natural killer cells
NKX	A transcription factor regulating heart development
NO	Nitric oxide
Nogo	An antigen from myelin degeneration products that inhibits axonal growth
NT	Neurotrophic factor
NVTBOX	*Notophthalmus viridescens* T-box gene
OCT	Octa box—a small transcription factor
OMGP	Oligodendrocyte-myelin glycoprotein
PAX	Paired homeobox-containing transcription factor
PDGF	Platelet-derived growth factor
PNS	Peripheral nervous system
PROD	An ortholog of CD59, part of the complement group
PRX	Called Mhox earlier; a member of group of Aristaless-like homeobox genes
RAF	A serine/threonine kinase
RAS	A small GTPase
Rb	Retinoblastoma
RGD	Arginine-glycine-asparagine sequence of importance in cell adhesion
RHO	A cytoplasmic regulatory protein
RNA	Ribonucleic acid
S	Synthesis (DNA) phase in the mitotic cycle
SCA	An antigen found on stem cells
shh	Sonic hedgehog
SIS	Small intestine submucosa—a natural tissue substrate

SOX	An HMG box-containing transcription factor
SPARC	Secreted protein rich in cysteine—an extracellular matrix protein
T	T cell—a lymphocyte that matured through the thymus, involved in cellular immunity
TBX	T box transcription factors
TGF	Transforming growth factor
THY	Thymidylate synthase complementing protein
TIMP	Tissue inhibitor of matrix metalloproteinase
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor