DISEASES OF CORAL

EDITED BY CHERYL M. WOODLEY, CRAIG A. DOWNS, ANDREW W. BRUCKNER, JAMES W. PORTER AND SYLVIA B. GALLOWAY

WILEY Blackwell

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Cheryl M. Woodley

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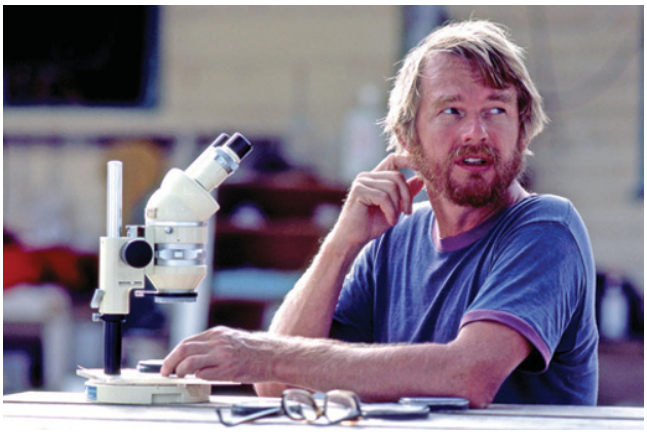
Dedication

Arnfried Antonius



Arnfried Antonius in the early days, preparing for time-lapse recording of black-band diseased corals. *Source:* Photo courtesy of Klaus Ruetzler.

Father of Coral Diseases

Arnfried Antonius, the father of coral diseases, passed away on January 13, 2010 in his 76th year. Arnfried was a highly respected pioneer researcher on coral diseases and a leader in this field. His contributions to the knowledge base for coral reefs were many. His determination, dedication and enthusiasm to his research, and willingness to share his knowledge with eager students and colleagues were but a small token of his passion for coral-reef conservation. As a colleague, strong supporter of my research and a dear friend, his informative and entertaining stories of his field experiences will be sorely missed.

Arnfried was one of the first coral-reef researchers to investigate relationships between biodiversity, community structure and dynamics, and environmental processes and their role in controlling the health of Caribbean coral reefs. While completing a Post Doc through the Smithsonian National Museum of Natural History at the Carrie Bow Cay Field Station, located on a remote barrier reef off Southern Belize, Dr. Antonius discovered one of the most widespread and best known of all coral diseases, black-band disease (BBD). He was the first to use time-lapse photography to characterize BBD processes, and he subsequently identified corals infected with BBD in Puerto Rico, the Florida Keys and other locations in the Atlantic, Red Sea and Pacific Ocean. Even though he was not a scuba diver, his keen interest in coral diseases, his concerns about early warning signs of the degradation of reefs, and his free-diving expertise led to additional discoveries of new coral diseases. For example, he was the first to identify coral diseases in the Indo-Pacific, beginning with reports of a variety of white syndromes (which he called white band disease) from reefs off the coast of Saudi Arabia and the Philippines. He continued his coral research well into his 70s, and trained numerous students who have followed in his footsteps. During the late 1990s, he brought attention to other new syndromes affecting reef-building corals, such as the first protozoan coral killer, a ubiquitous ciliate (*Hallofolliculina corallasia*) infection, which he named skeletal eroding band (SEB). He also highlighted other emerging threats, including cyanobacteria and algae capable of overgrowing and killing corals.

Those who knew Dr. Antonius in the 1970s will remember his dire predictions of the demise of reefs in the Florida Keys. At the time, many colleagues thought he was being overly dramatic. Yet a mere 30 years later, scientists and managers alike are finally recognizing the coral-reef crisis as a real and growing threat. While Arnfried was the first to recognize many of the afflictions affecting stony corals, he also gave us the knowledge and tools to continue in his track, further advancing our understanding of coral diseases and working together to develop realistic solutions to mitigate disease impacts and promote recovery of our precious coral reefs.

In honor of Dr. Antonius, this volume presents an up-to-date compilation of the current state of knowledge of coral diseases. Arnfried will be missed by his family, friends and colleagues, but his dedication to coral-reef conservation and his work on coral diseases will live on.

Andrew W. Bruckner

Contents

Contributors

Greta Smith Aeby
Hawaii Institute of Marine Biology
Kaneohe, Hawaii, USA

Tracy D. Ainsworth
James Cook University
Townsville, Australia

Fuad A. Al-Horani
The University of Jordan
Aqaba, Jordan

Husain Al-Sayegh
University of Miami
Miami, Florida, USA

Luba Arotsker
Ben-Gurion University of the Negev
Be'er-Sheva, Israel

Athena R. Burnett
USDC/NOAA, National Ocean Service
Charleston, South Carolina, USA

Andrew C. Baker
University of Miami
Miami, Florida, USA

Carolina Bastidas
Universidad Simon Bolivar, Sartenejas
Caracas, Venezuela

Patricia L. Blackwelder
University of Miami
Miami, Florida, USA

Thomas Bartlett
USDC/NOAA, National Ocean Service
Charleston, South Carolina, USA

Thomas C. G. Bosch
Christian Albrechts University Kiel
Kiel, Germany

David G. Bourne
Australian Institute of Marine Science
Townsville, Australia

Barbara E. Brown
University of Newcastle upon Tyne
Newcastle upon Tyne, United Kingdom

Andrew W. Bruckner
Khaled bin Sultan Living Ocean Foundation
Landover, Maryland, USA

Robin J. Bruckner
NOAA Fisheries Service
Silver Spring, Maryland, USA

Martina M. Burtscher
Environmental Research Institute
Thurso, Scotland

Aldo Cróquer
Universidad Simon Bolivar
Caracas, Venezuela

Ross Cunning
University of Miami
Miami, Florida, USA

Andrew J. Davies
Bangor University, Menai Bridge
Anglesey, United Kingdom

Simon K. Davy
Victoria University of Wellington
Wellington, New Zealand

Martina A. Doblin
University of Technology
Sydney, Australia

Isabelle Domart-Coulon
Museum National d'Histoire Naturelle
Paris, France

Craig A. Downs
Haereticus Environmental Laboratory
Amherst, Virginia, USA

Richard P. Dunne
West Briscoe, Baldersdale, Barnard Castle Co.
Durham UK

Christine Ferrier-Pagès
Centre Scientifique de Monaco
Principality of Monaco, Monaco

Sylvia B. Galloway
USDC/NOAA, National Ocean Service
Charleston, South Carolina, USA

David Gulko
Hawaii Department of Land and Natural Resources
Honolulu, Hawaii, USA

Pamela Hallock
University of South Florida
St. Petersburg, Florida, USA

Russell A. Harley
Medical University of South Carolina
Charleston, South Carolina, USA

Ross Hill
University of Technology
Sydney, Australia

Fanny Houlbrèque
Laboratoire d'Excellence "CORAIL", Institut de Recherche pour le Développement, ENTROPIE
Nouméa, New Caledonia

Linda A. Hufnagel
University of Rhode Island
Kingston, Rhode Island, USA

Longin T. Kaczmarsky
St. Johns River State College
Palatka, Florida, USA

Gabriele Kass-Simon
University of Rhode Island
Kingston, Rhode Island, USA

Kirsty M. Kemp
Zoological Society of London
London, United Kingdom

Kiho Kim
American University
Washington, DC, USA

Esti Kramarsky-Winter
Tel Aviv University
Tel Aviv, Israel

Ariel Kushmaro
Ben-Gurion University of the Negev
Be'er-Sheva, Israel

Erin K. Lipp
University of Georgia
Athens, Georgia, USA

B. Manikandan
National Institute of Oceanography
Kochi, India

Lisa A. May
USDC/NOAA, National Ocean Service
Charleston, South Carolina, USA

Aaron W. Miller
University of Utah
Salt Lake City, Utah, USA

Elizabeth F. Moses
University of South Florida
St. Petersburg, Florida, USA

Stephen J. Neale
WorleyParsons
Brisbane, Australia

James H. Nicholson
Medical University of South Carolina
Charleston, South Carolina, USA

Gary K. Ostrander
Florida State University
Tallahassee, Florida, USA

Cathie A. Page
James Cook University
Townsville, Australia

Dušan Palić
Ludwig Maximillians University
München, Germany

Esther C. Peters
George Mason University
Fairfax, Virginia, USA

James W. Porter
University of Georgia
Athens, Georgia, USA

C. Raghukumar
National Institute of Oceanography
Dona Paula, India

Peter J. Ralph
University of Technology
Sydney, Australia

Jeyaraman Ravindran
National Institute of Oceanography
Kochi, India

Laurie J. Raymundo
University of Guam
Guam, USA

Bernhard Riegl
Nova Southeastern University
Dania, Florida, USA

Taylor L. Reynolds
John Hopkins University
Baltimore, Maryland, USA

Laurie L. Richardson
Florida International University
Miami, Florida, USA

Riccardo Rodolfo-Metalpa
Laboratoire d'Excellence "CORAIL", Institut de Recherche pour le Développement, ENTROPIE
Nouméa, New Caledonia

Sebastian Rodríguez
Universidad Simon Bolivar, Sartenejas
Caracas, Venezuela

Alex David Rogers
University of Oxford
Oxford, United Kingdom

Philip Rosenstiel
Christian Albrechts University Kiel
Kiel, Germany

Krystal Rypien
University of California, San Diego
La Jolla, California, USA

Kathryn Patterson Sutherland
Rollins College
Winter Park, Florida, USA

Ann M. Tarrant
Woods Hole Oceanographic Institution
Woods Hole, Massachusetts, USA

Michelle Lisa Taylor
University of Oxford
Oxford, United Kingdom

Michael Thrusfield
University of Edinburgh, Royal School of Veterinary Studies
Roslin, United Kingdom

Maya Vizel
Tel Aviv University
Tel Aviv, Israel

Janet V. Warg
USDA, National Veterinary Services Laboratories
Ames, Iowa, USA

Ernesto Weil
University of Puerto Rico
Mayagüez, Puerto Rico, USA

Bette L. Willis
James Cook University
Townsville, Australia

William H. Wilson
Bigelow Laboratory for Ocean Sciences
West Boothbay Harbor, Maine, USA

Cheryl M. Woodley
USDC/NOAA, National Ocean Service
Charleston, South Carolina, USA

Thierry M. Work
US Geological Survey, National Wildlife Health Center
Honolulu, Hawaii, USA

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We thank the editorial staff of Wiley-Blackwell for agreeing to break with their traditional emphasis on the diseases of commercially important terrestrial vertebrates to include the lower marine invertebrates in this well established veterinary medical series. We also thank the MUSC Department of Pathology and Laboratory Medicine for James Nicholson's contributions in improving many of the graphics throughout this book. We thank Sylvia S. Woodley for the time she volunteered to assist in clerical aspects of this project. We especially would like to express our gratitude to the many anonymous peer-reviewers for taking time to read carefully what was written in these 41 chapters and make constructive comments and corrections that improved this book beyond the ability of the editors.

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Editors' Comment: Recent Changes in Coral Taxonomy

Periodically in systematics, "revisions" occur in nomenclature. In 2012, Ann F. Budd *et al.* published their first monograph in the *Zoological Journal of the Linnean Society* (Budd *et al.,* 2012), which began a revision of scleractinian taxonomy. The goal of these efforts is to integrate the results of molecular analyses with traditional skeletal morphological characters, including recently discovered micro-morphological and micro-structural characters, to resolve confusion in traditional phylogenies (Budd *et al.* 2010). This means that as *Diseases of Coral* goes to press, many of the classical scientific names used herein now have new names proposed for them based on recent genetic and micro-morphometric analysis. For instance Budd *et al.* (2012) propose the following revisions, all of which, if accepted, would change many of the scientific names used in our volume. Please note, however, that most of these taxonomic revisions would change the genus name only, but not the species names used in our book. Below are examples of changes, please refer to the primary references for the complete list of revisions:

- The previous genus *Diploria* has been split into two genera: (i) *Diploria*, which consists only of the species *Diploria labyrinthiformis*, and (ii) a new genus, *Pseudodiploria*, which consists of the species *Pseudodiploria strigosa* and *Pseudodiploria clivosa*.
- The previous genus *Favia* has been split into two genera: (i) *Favia* in the Atlantic (assigned to family Mussidae = clade XXI) and (ii) *Dipsastraea* in the Indo-Pacific (assigned to family Merulinidae = clade XVII).
- The previous genus *Montastraea* has been split into three genera: (i) *Montastraea* in the Atlantic (assigned to family Montastreidae = clade XVI) (*M. cavernosa*), (ii) *Orbicella* in the Atlantic (assigned to family Merulinidae = clade XVII) (*O. annularis*, *O. faveolata*, *O. franksi*, formerly the "*Montastraea annularis* species-complex"), and (iii) Phymastrea in the Indo-Pacific (assigned to family Merulinidae = clade XVII).
- The previous genus *Scolymia* has been split into three genera—*Scolymia* (assigned to the family Mussidae = clade XXI), *Parascolymia* (assigned to the family Lobophylliidae = clades XVIII–XX), and *Homophyllia* (assigned to the family Lobophylliidae = clades XVIII–XX), following the previous usage of Wells (1964).
- *Isophyllastrea rigida* is now *Isophyllia rigida*.

The editors are acutely aware of this rapidly changing scientific landscape. We wish to clarify that the species names used this edition follow classic skeletal morphological form-taxonomic conventions (e.g., Veron 2000). Future editions of this series will publish synonymies, which will allow the reader to move easily between names based on structure and newly assigned names based on morphology and genetics.

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CHAPTER 1

Introduction

James W. Porter

"When the coral shrinks, the economy sinks"
Nora Williams, Mayor, Monroe Co., Florida Keys

Hard Corals = Hard Currency
Bumper Sticker, Montego Bay, Jamaica

Background

The survival of coral reefs is important to humankind. Their survival is not guaranteed.

Coral reefs provide humankind with a dizzying array of goods and services. The total economic value of one small (10 × 20 km) reef in the Philippines tops $38 million USD/year (Cruz-Trinidad *et al.* 2011). Worldwide this number is likely to be in the hundreds of billions (Stoecki *et al.* 2011). This monetary value, however, does not reveal the importance of coral reefs as the major source of irreplaceable protein for many coastal populations in developing nations. The recreational and tourist importance of coral reefs is also exceptional, generating, for instance, more than $4 billion USD annually for the people of the Florida Keys (Riegl *et al.* 2009). Coral reefs also provide shoreline protection. For instance, Indonesian coastal communities with healthy offshore reefs suffered less damage from the devastating southeast Asian earthquake and tsunami in 2009 than communities with degraded reefs offshore (McAdoo *et al.* 2011). Finally, coral reefs have produced a cornucopia of pharmaceutical and bio-products, from cancer-fighting drugs such as prostaglandin and bryostatin to sunscreens that help to prevent cancer (Singh *et al.* 2010; Whalen *et al.* 2010).

Coral reefs are by far the most biologically diverse environments on earth. Whereas tropical rainforests house only eight animal phyla, coral reefs typically have thirty-one of these higher taxonomic groups (Porter and Tougas 2001). Within this diverse assemblage of plants and animals, corals stand out as the primary ecosystem engineers. Unlike terrestrial communities, dominated by trees and other woody vegetation, coral reef communities are built by the limestone skeletons of corals. These skeletons produce topographically complex environments that are home to thousands of other species. Corals are the redwoods of the reef.

Although coral reef assemblages are ancient, successful, and vibrant communities, they exist within a relatively narrow range of thermal tolerances and water-quality parameters. In a globally changing world, these life-giving physical conditions are also changing rapidly. Human activities such as burning fossil fuels are tipping the balance away from environmental conditions that support healthy coral reefs to conditions that do not. For instance, over the next century, rising atmospheric CO_2 concentrations will cause tropical ocean temperatures to rise between 1–3 °C (Hoegh-Guldberg 1999) and surface pH values to fall between 0.1 and 0.5 pH units (Anthony *et al.* 2011). Each of these factors alone is known to affect coral health. We speculate that their combined effect may be devastating (Harvell *et al.* 1999).

Coral Health Perspectives

Successful growth and reproduction require good health. This statement is as true for corals as for any group of organisms. Stress is inimical to health, and pollution, elevated temperature, and ocean acidification are all stressful. While each of these factors alone can cause mortality, their incremental change is also likely to make corals more susceptible to disease than to kill them outright. Stressful conditions may provide proximate causes of death, but as many chapters in this book reveal, disease, not stress, is often the ultimate cause of death. Stress may act to increase susceptibility or lower immunity, but microbes will often finish the job.

Even in 2000, this book could not have been written. There are at least two reasons for this. The first is that we could not study what we did not know was there. A prime example of this scientific lacuna is Joseph Connell's lengthy review in *Science* (1978) on factors controlling coral reef community structure, which never once mentions disease. This study stands in striking

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contrasts with Sinclair and Norton-Griffiths' monograph (1979) on African grasslands, which demonstrates convincingly that disease is one of the major controllers of the Serengeti ecosystem. Coral biologists have simply been slow to catch up; this book is a big step forward.

The second reason is more worrisome. Coral disease is becoming more common than it once was. These kinds of assertions are often dismissed as an artifact of observational intensity: more people are observing coral reefs, so more diseases are seen. The EPA/NOAA Coral Reef Evaluation and Monitoring Program started in the Florida Keys in 1996. It implemented a sophisticated series of timed observations within fixed plots on the seafloor demarcated by stainless steel stakes. Repeated observations within these fixed plots show a statistically significant increase in both the number of stations with disease and the number of different kinds of disease found within their boundaries (Porter *et al.* 2001). Meta-analyses of the disease literature also reveal that several tropical marine organisms have shown disease increases over time (Harvell *et al.* 2004; Lafferty *et al.* 2004). These bibliographic analyses are normalized by the total number of papers published on a specific taxon, helping to control for observational intensity. Chapter 5 in this volume on the history of coral disease corroborates this impression of an increasing number of coral maladies, their prevalence, and, in some cases, their lethality. All of these studies, and many more, point toward increasing illness in the sea (Porter 2001).

There may even be a connection between the incidence of coral disease and threats to coral reefs from hurricanes. Because warm water supplies more energy to hurricanes, Intergovernmental Panel on Climate Change (IPCC) models forecast an increase in the intensity and frequency of tropical hurricanes and cyclones (Wang and Wu 2011). Recent studies also demonstrate that hurricanes increase both the incidence and severity of coral disease outbreaks (Brandt *et al.* 2013). Rising sea temperatures, therefore, may not only cause coral bleaching and accelerate microbial growth, but also promote hurricane disturbances that increase colony fragmentation and disease susceptibility.

Coral Disease Considerations

It is legitimate to ask, why don't we know more about coral disease. For instance, in the Wiley-Blackwell Disease Series, of which this volume is now a part, *Diseases of Poultry* is already in its 12th edition, with the first edition published 1943. Humans, like all other organisms, explore first what is next to them. Studies of human disease came first, followed by veterinary research, and finally, only recently, investigations on the "ecology and evolution of infectious disease" (as the National Science Foundation's (NSF) and the National Institutes of Health's newest grant programs are called). A recent NSF-sponsored workshop on the *Ecology of Marine Diseases* (Nobel and Porter 2011) reached three major conclusions. First, diseases in the ocean are very important; second, especially as compared to terrestrial diseases, marine diseases are poorly described and little understood; and finally, because of their increasing threat to coral survival, we urgently need to study them. This Wiley-Blackwell Series book, *Diseases of Coral*, is a tangible manifestation of our growing comprehension that disease exerts an important control over the population dynamics of tropical marine organisms such as corals.

Another impediment to progress relates to the complexity of disease etiologies in the marine environment (McCallum *et al.* 2004). The common terrestrial model of one-pathogen, one-disease just does not apply to many of the most pervasive and virulent coral diseases. For instance, in their chapters on colored band diseases, first Raymundo and Weil (Chapter 23) and then Richardson *et al.* (Chapter 24) demonstrate that cyanobacterial associations are causative agents of disease. This finding also highlights a major challenge to investigating and describing coral disease. The "gold standard" of disease investigations occurs through the satisfaction of "Koch's postulates." This occurs when a single species of a disease-causing microbe is successfully (i) isolated from the infection, (ii) grown in pure culture, (iii) reinoculated into a healthy individual, whereupon it (iv) causes the disease. To date, only a few coral diseases—White Plague *Type II* (*Aurantimonas coralicida*, Ch. 15; white plague from Red Sea (*Thalassomonas loyana* Ch. 21); *Acropora* serratiosis (*Serratia marcescens*, Ch. 14); Aspergillosis (*Aspergillus sydowii*, Ch. 16); and vibriosis caused by *Vibrio shiloi* and *Vibrio coralliilyticus* (Ch. 13)—have proven amenable to this kind of deductive reasoning. This leaves the rest (over two dozen more disease syndromes) with much "messier" biologies to investigate. To complicate matters further, some historically well-defined diseases are now exhibiting changing etiologies over time (Joyner *et al.*, 2015), making diagnoses (especially in the field) quite difficult. *Diseases of Coral* addresses this challenge, and begins our quest to understand these complicated etiologies.

Diseases of Coral is organized into five sections. Chapters 1–12 include primers on various topics relating to coral anatomy and physiology, pathology, and immunity. The next two sections include expositions on etiologic diseases (Chapters 13–16) and descriptive diseases (Chapters 17–32). The fourth section (Chapters 33–34) examines biosecurity and permitting issues, which are becoming increasingly important to the study of all infectious agents. Finally, the fifth section (Chapters 35–41) evaluates new methods in coral disease investigation.

More than 25 coral diseases are profiled in this book. This compendium is complete as of 2013, but, unfortunately, new diseases are emerging rapidly, leading to the impression that this will not be the last edition of this book. Whenever possible, an attempt has been made to group diseases either by their signs (e.g., Chapters 21 and 22 on the white syndromes of the Indo-Pacific and Caribbean-Atlantic regions, respectively) or their etiological origins (e.g., Chapters 13 and 19 on bacterial or viral diseases, respectively). Stress responses to elevated thermal and irradiance conditions are also discussed in Chapters 18 and 30.

All of these chapters have several important things in common. They describe the disease, and, to the extent possible,

they define its causative agent(s). High-quality color images are provided throughout the book to present unequivocal diagnostic signs for each disease. A full lexicon of coral diseases and disease terminology is provided at the end of this tome to start the process of developing a descriptive language for these syndromes. Language development is an often overlooked phase of scientific advancement, but it is an especially important part of establishing a new field such as ours.

This book has more than 70 contributing authors. They come from Australia, France, Germany, Israel, India, Jordan, Monaco, Singapore, the United Kingdom, the United States, Venezuela, the Commonwealth of Puerto Rico, and the Trust Territory of Guam. The length of this authorship list, and the diversity of their institutional affiliations, demonstrates how important this field has become. To save coral reefs we must understand the causes for their decline. *Diseases of Coral* begins this process.

Conclusions

While *Diseases of Coral* addresses a specialized topic, a general conservation message emerges from every chapter in the book. Richardson (Chapter 24) and several of her colleagues demonstrate that elevated incidence and severity of disease correlates with elevated pollution. The chapter on acroporid serratiosis (Chapter 14) documents an almost bizarre "reverse zoonosis," delineating a disease transmission from humans to corals (Sutherland *et al*., 2011). Infections of humans by pathogens from wildlife are common, with numerous examples such as bird flu, swine flu, hanta virus, ebola, AIDS, and giardia. Now, however, we know that the human strain of the enterobacterium, *Serratia marcescens*, which causes the nosocomial disease Serratiosis in humans, also kills coral. This is a rare evolutionary triple jump: from terrestrial to marine, from vertebrate to invertebrate, and from anaerobic to aerobic conditions on the reef. This transfer occurs *via* undertreated sewage, and the conservation message is clear. To protect coral, protect water quality.

We freely admit that, in striking contrast to other *Diseases Of …* volumes in this Wiley-Blackwell series, we are unable to provide methods to cure or quarantine any of the diseases we describe. For now, we are bystanders, not naturopaths. As coral reef conservators, however, we feel an urgent need to do more, but we are simply not there yet. By highlighting the gaps in our knowledge, by pointing to what we need to know, we fervently hope that this book will allow us to become healers, and to do so as quickly as possible.

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CHAPTER 2

Pathology

Cheryl M. Woodley, Russell A. Harley, James H. Nicholson and Taylor L. Reynolds

> Disease is the experiment of nature; we see only the results, while we are ignorant of the conditions under which the experiment is performed. Step by step, pathology must unveil these conditions. It progresses from observation to correlation, from correlation to deduction, in order that rational experimentation may accomplish the final synthesis.
>
> *Paul Klemperer, Pathology* (1953)

Introduction

Pathology is the study of disease. The term is derived from the Greek, *pathos*, translated "suffering," and *logos* meaning "science" (*Mosby's Medical Dictionary* 2006). The science of pathology encompasses the detailed study of the disordered changes in the function and structure of an organism, and is concerned with the cause and mechanism of disease (Klemperer 1953; Cheville 1999). "Health" refers to the condition of the organism at a given time, and may refer to a "healthy condition" where morphological and/or functional condition is in a state of soundness or wholeness (Klemperer 1953). The abnormal or disturbed condition that affects the performance of an organism is defined as a *disease*.

The discipline of pathology is divided categorically into *morphological pathology* and *functional pathology* (Klemperer 1953; Cheville 1999; Kumar *et al*. 2005). In pathology, there is a distinction between the manifestation of the disease and the cause of the diseased state. The manifestation of the disease is perceived through its morphological and functional characteristics. For example, in coral, a *sign* of disease can be a gross lesion, but when viewed microscopically, the lesion can be more precisely described as cell death via autophagic cell death formations (morphological pathology) (Downs *et al*. 2009). Signs of disease may also be depicted as changes in function, performance and/or activity; for example, induction of an apoptotic pathway, or depressed levels of glutathione or porphyrin metabolites. *Etiology* is the examination of the causes and origin of a diseased state (see Chapter 3). A number of diseases may show similar signs of dysfunction but the causes of the disease can be manifold. To meet the requisites of the study of a disease, the causative factor and its mechanism must be elucidated. The purpose of pathology in clinical or "field" practice is to provide an investigator with the ability to not only describe and categorize the signs of a disease but to prescribe diagnostic tests relevant to the etiology of a disease, in order to formulate a diagnosis. Understanding the consequences of each of the structural and functional changes within the organism allows a prediction or *prognosis* of the expected outcome.

In this chapter, we discuss the evolution of pathology and its role in shaping Western medicine today, and the basic concepts of the discipline. We also consider pathology's role in informing our understanding of organismal and cellular physiology, diagnosis and treatments, with specific emphasis on coral.

A Brief History of Pathology

Evolution of Human Pathology

Interest in disease extends to the earliest civilizations but its documentation began in the seventeenth century BC with Egyptian medicine and the evolution of Western medicine. Although Egyptian dynasties lasted almost 5000 years with recordings of different diseases, there is little evidence in the surviving papyri that they developed any systematic study of the anomalies (Van den Tweel and Taylor 2010). Among peoples living in those distant times, disease was regarded as a living being that existed independently in the body of a patient (Long 1928).

The writings of the Greek medical school at Cos and attributed to Hippocrates (460–370? BC) represent the first complete separation of a systematic medical science from the spiritual and supernatural. They are centered in a conceptual framework known as humoral pathology, which underlies some of our contemporary theories about disease mechanisms. Put simply, humoral pathologists postulated that disease arises from abnormal fluids or "humors." In ancient times, these fluids included blood, phlegm, and yellow and black bile (Long 1928; van den Tweel and Taylor 2010). Although the humoral theory of the nature of disease was later recognized as flawed, records from this time provide clear, accurate descriptions of many disease conditions that have influenced modern science and demonstrated the value of accurate observations (Klemperer 1953).

Diseases of Coral, First Edition. Edited by Cheryl M. Woodley, Craig A. Downs, Andrew W. Bruckner, James W. Porter and Sylvia B. Galloway.

Although the Hippocratic system provided many elegant descriptions, it lacked a connection with anatomy and physiology as we understand them today. For well over a thousand years, there was little progress in medicine. The works of Claudius Galen (129–201 AD), a physician and scientist in Rome, emerged in the second century. His extensive writings, estimated to be over 500 books and treatises, guided medicine for over a thousand years into the Middle Ages (Long 1928; van den Tweel and Taylor 2010). Unfortunately, his works were undisputed in the medical community, leading to little progress in the field of medicine.

In the mid-1500s, the great anatomist and physician Andreas Vesalius at the University of Padua in Italy concluded that Galen's research on anatomy was based on studies of Barbary apes because human anatomy was banned in early Rome. Vesalius published a remarkable seven-volume, beautifully illustrated work, *De Humani Corporis Fabrica* (translated, *On the Fabric of the Human Body*) in 1543 (Long 1928). Studies of normal and abnormal human anatomy (i.e., "pathology") followed in a number of European countries. Galen continued to be studied by medical students into the 1900s; however, the concept of direct observation (autopsy, i.e., to see for oneself) as the best resource for the study of disease had taken firm root. Jean Fernel, a contemporary of Vesalius in Padua, introduced the term "pathology" in his 1554 treatise, *Pathologia*, while at the court of Henry II of France. In the years that followed, the meaning of the term "pathologist" gradually evolved. Two-hundred years after Vesalius and Fernel, Giovanni Morgagni was given the prestigious chair of anatomy and in 1761 published a book that established pathology as a true science: *De Sedibus et causis morborum per anatomem indagatis* (translated as : *On the Seats and Causes of Diseases as Investigated by Anatomy*) (Morgagni *et al.* 1820). This book, which was widely disseminated throughout Europe for the first time, described and depicted diseased organs as a unified anatomic pathology text separate from normal anatomy.

During the Renaissance, fear of the dead was overcome by curiosity involving the human body and the mysteries of life, disease, and death. Although early physicians noted patients' skin color and turgor, pulse, and respiratory rate, methods of physical examination such as auscultation, percussion, and palpation were developed only after pathologic anatomy had shown the actual changes wrought by disease. By the late eighteenth and early nineteenth centuries, pathologists had moved to the front rank in the advance of medicine.

The opening of the nineteenth century saw major political and social change and notable growth of scientific institutions across Europe. Marie-Francois-Bichat brought histology to the practice of pathology (Haigh 1984). James Paget, a British surgical pathologist and physiologist and surgeon to Queen Victoria and Prince Albert, maintained the largest surgical practice in London (Roberts 1989). He was credited with making clinical surgery and pathology more widely available. Pathology was continuing to evolve at the University of Vienna with Carl Rokitansky's introduction of the theory of disease pathogenesis with its basis in humoral pathology (Rokitansky 1855). In Germany, Johannes Müller first used the microscope to analyze cancerous tissues (Olszewski 2010) and published *On the Finer Structure and Form of Morbid Tumors* (Müller 1986) establishing the cellular character of tumors. Mistakenly though, he extrapolated his observations to mean that tumors arose from primitive body fluids by crystallization or *de novo* generation ("blastemas"), but not from other cells (Olszewski 2010). Rudolf Virchow, a physician and pathologist and a student of Müller, disproved this notion using his revolutionary principle *omnis cellula a cellula* meaning "all cells are derived from cells" or in other words, the cell is the smallest unit in which disease can occur. This fundamental concept was revolutionary, leading to an understanding of the organism as composed of continuously developing and interacting cellular units. He went on to introduce other important concepts, such as necrosis. In 1858, he published his seminal work *Die Cellula Pathologie* (*Cellular Pathology),* which included his lectures, observations and experiments (Virchow 1858) and highlighted the potential of diagnosing disease. Virchow went on to co-found the journal *Archiv für pathologische Anatomie und Physiologie und für klinische Medizin* (Metschnikoff 1884) and today is recognized as the father of modern pathology or the father of cellular pathology (Virchow 1858; Long 1928).

Pathology in the Twentieth Century

Medicine in the first part of the twentieth century underwent a sea change with the advent of routine laboratory testing in the diagnosis and treatment of disease. Both clinical laboratories and anatomic pathology were at the heart of the change. Laboratories originally used for research and clinical testing, along with the burgeoning young field of pathology, provided the bridge from the basic sciences to clinical care.

With the marriage of anatomical and clinical pathology, the field began to mature and specialize due to its close and reciprocal collaboration with experimental scientists in the basic sciences (e.g., biochemistry, genetics, cell biology, chemistry, biophysics and bioengineering). Surgical pathology, cytopathology, autopsy pathology, and forensic pathology arose from anatomic pathology. Clinical pathology, also called laboratory medicine, evolved into subspecialties such as chemistry, hematology, microbiology, clinical genetics, molecular pathology, immunology and informatics. As human pathology matured, the fields of veterinary and plant pathology began to grow.

Veterinary Pathology Emerges

Benefitting from the advances in human pathology, veterinary pathology began to emerge in the mid-1800s assisted by Virchow's advocacy of autopsying farm animals as a means of inspecting their meats. In 1870, the first chair of veterinary pathology was established in Berlin (Cheville 1999). However, it was not until 1948 that the American College of Veterinary Pathologists was founded, serving the United States and Canada. The European College of Veterinary Pathologists joined in the

development of veterinary pathology when it was founded in 1995. Today veterinary pathology is evolving specialties that mirror those in human medicine, not only for domestic animals but also in the developing fields of wildlife and aquatic pathology.

The Birth of Coral Pathology

Though the first scientific expeditions exploring the tropical oceans began prior to the American Revolution, explorers like Captain James Cook (Cook 1773) of the Royal Navy and Charles Darwin provide no mention of coral disease lesions as we see today. The closest account of abnormal change in coral comes from the early explorations of Charles Darwin, in which he describes damage from heavy surf, physical trauma, and torrential monsoon rains diluting the saline content of an enclosed lagoon (Darwin 1842).

It was not until 1901, when human and veterinary pathology were relatively mature, that the first suspicion of a coral growth anomaly emerged. Robert Whitfield (1901) described *Meandrina labyrinthica* growing "in combination" with a central colony of *Ctenophyllia*. Shortly thereafter, Vaughn described a specimen of *Madrepora kauaiensis* with an attached polyp with a "different appearance" (Vaughan 1907). The literature is then silent on coral disease until 1965 when Squires examined the skeleton described by Vaughan, and deduced that it was more likely to represent one of three anomalous polyps of the same species "result[ing] from processes similar to those of neoplastic change in higher animals." White *et al.* (1965) challenged Squires' interpretation suggesting that it was probably a hyperplastic response of the coral to a predator attack at three different foci. This began a long and ongoing debate as to the existence and nature of neoplasia in corals (see Chapter 20).

For the 60 years following Vaughan's description, there were no reports of disease in coral, although a better understanding of coral biology was advancing. Thomas Vaughan (1911) performed the first reported physiological studies on gross anatomy, feeding, light exclusion and bleaching. Charles Maurice Yonge made major contributions with his anatomical illustrations and in physiology with biochemical assays of digestive enzymes, studies on the assimilation and excretion of food, emphasizing mesenterial filaments, sedimentation and coral growth (Yonge and Nicholls 1931a) and the structure, function and distribution of zooxanthellae (Yonge and Nicholls 1931b). Importantly, his work included the first histologic description of bleaching, although it was not considered a pathology until the twenty-first century.

As the twentieth century progressed, studies of the anatomy and physiology of individual coral animals became increasingly sophisticated, with major contributions by Libby Hyman (1940) and Thomas Goreau Sr. (Goreau and Bowen 1955). Hyman's (1940) zoological descriptions and accurate anatomical diagrams of many invertebrate species have been incorporated into a treatise on Anthozoa that are used today by coral pathologists for morphologic anatomy and terminology as a foundation for their practice (Hyman 1940; Fautin and Mariscal 1991). Goreau (Goreau and Bowen 1955) conducted many pioneering studies of various aspects of coral physiology, among which was demonstrating the kinetics of calcium uptake of coral from its seawater medium.

Squires' report of growth anomalies on Pacific coral was soon followed by descriptions of black-band disease (Antonius 1973), white plague type I (Dustan 1977) and white-band disease (Antonius 1981). In 1981, Peters first applied histology to studies of oil toxicity in stony coral (Peters *et al.* 1981) and then examined the histology of diseased and sediment-stressed corals on the reefs of St. Croix, USVI and Puerto Rico (Peters 1984). For the next 30 years, coral disease reports exploded with the description of over 40 syndromes, placing the field of coral pathology equivalent to the descriptive/observational stage of human pathology in the Middle Ages. However, the budding field had the opportunity to take advantage of the foundations already laid by human and veterinary pathology to help accelerate its maturation.

Efforts to align coral disease studies with medical and veterinary fields, reduce ambiguities in disease descriptions based on *in situ* appearance, and establish a systematic vocabulary among coral disease researchers were formalized in 2002 with the establishment of the Coral Disease and Health Consortium (Woodley *et al.* 2003). Quickly others joined the effort to establish standards in terminology for describing lesions to support morphologic diagnosis (Galloway *et al.* 2007; Work and Aeby 2006), adapting clinical laboratory tests to corals (e.g., Chapters 35–41 this volume), and providing genomic resources for development of next-generation diagnostics (Meyer *et al.* 2009; Sunagawa *et al.* 2009; Shinzato *et al.* 2011).

Using these foundations the next generation of coral-disease researchers should be better equipped to advance our understanding of disease processes, discern the roles that physical, chemical and biological factors play in coral disease etiology and pathogenesis, and help conservation managers to devise better strategies to minimize disease impacts on coral reefs for the future.

General Pathology: Key Concepts for Coral Disease Studies

General pathology is a wide-ranging and multifaceted discipline. It draws on numerous specialty areas in basic and clinical science to understand the mechanisms of injury—to cells, tissues and the organism—and how the organism responds to these changes. Applying these principles and tools to coral health and disease, however, is only the beginning. Many of these concepts apply as well to coral as they do their human, animal, and plant counterparts (e.g., cell injury and death, cellular adaptive responses, DNA damage, metabolic disorders); others do not (e.g., diseases of adaptive immunity, disorders of organ systems).

The following sections attempt to introduce some key concepts of pathology that relate to coral and the search for the

causes and mechanisms of their diseases. Cellular and subcellular responses to adaptation, injury and death are given greater emphasis because they are the most common bridge to understanding coral pathology. At this level it is also inevitable that disease begins, and it is changes at this level that result in the functional alterations expressed in the individual that ultimately affect populations. The remaining sections highlight several key topics of general pathology.

Lethal Injury

Death as a Process

Health, disease, dying and death form a continuum that exists in all life. At one end, *absolute health* has all system functions operating optimally within their normal levels. As an organism's functions become destabilized (homeostasis compromised) by physical, chemical or biological agents, *illness* ensues with characteristic changes in the system's structure and functions (Engelberg 1997). With continued breakdown of physiologic feedback controls, the variables governing homeostasis move further and further away from their normal ranges. This sets in motion the disappearance of the organism's stabilizing ability, resulting in a state of dying (Engelberg 1997).

The process of dying is complex, involving the shutdown of multiple systems that are networked into an integrative matrix of signal transduction and feedback loops, and which can mask or supersede the primary causative agent and pathogenesis (Cheville 1999). The objective of pathology is to recognize these complex internal and external factors driving disease processes and their action and interactions, then integrate and interpret these pieces of evidence to determine the true underlying cause (Klemperer 1953; Cheville 1999). At the other end of the spectrum is death. This occurs when the organism's functions are irreversibly compromised to the degree that all systems collapse and life cannot continue (Engelberg 1997; Cheville 1999; Wobeser 2006). The slope and timing of this continuum are governed by the degree of functional impairment suffered and the dynamics of the disease process. Death can occur abruptly by destroying major pathways in the network that supports the integration of cells forming a multicellular organism without initially killing or injuring any cells. Conversely, death can be a slow, insidious process, beginning at the cellular level, with dysfunction of subcellular systems affecting their homeostasis (Engelberg 1997). If left unchecked the process will cascade, affecting other cells, tissue and ultimately the organism.

Cell Death

Cell death can be a normal and critical physiological process to maintain the health and vitality of multicellular organisms or can be a signature of disease. It occurs during embryonic development and morphogenesis for maintenance of tissue integrity and as a defense to remove redundant, damaged or infected cells (Vaux and Korsmeyer 1999; Smith and Yellon 2011). The modes of cell death are classified morphologically, according to enzymatic criteria, functional aspects or by immunological characteristics throughout the literature, leading to confusion and imprecision in the field (Kroemer *et al*. 2009). The Nomenclature Committee on Cell Death recently updated guidelines (Kroemer *et al.* 2009) for terms to be used in describing modalities of cell death. Emerging from this group are three principal forms of cell death: autophagy, apoptosis, and necrosis. A fourth term, necroptosis, was recently proposed (Galluzzi and Kroemer 2008) and is included in the discussion below.

Autophagy

Autophagy or "self-digestion" is an intracellular process involving pathways that most often sequester cytoplasmic materials into an autophagosome. This structure then fuses with lysosomes (animals) or vacuoles (algae, yeast, plants) for degradation and recycling the components into cellular building blocks (Mizushima and Komatsu 2011). Generally, this process is considered a survival mechanism that is induced by conditions such as infection, starvation, hypoxia, and/or energy deprivation (Smith and Yellon 2011), but also occurs during development and differentiation (Mizushima and Komatsu 2011). Morphological characteristics of cells undergoing autophagy are (i) absence of chromatin condensation, (ii) massive cytoplasmic vacuolization, (iii) accumulation of double-membrane autophagic vacuoles, and (iv) little or no *in vivo* uptake by phagocytic cells (Kroemer *et al*. 2009).

Three types of autophagy have been described: macroautophagy, microautophagy and chaperone-mediated (or selective) autophagy (Mizushima and Komatsu 2011; Smith and Yellon 2011; Shaid *et al*. 2013). Macroautophagy is generally considered the predominant type and involves degradation of bulk materials such as protein aggregates or organelles. To achieve this, cytoplasmic materials are sequestered by an isolation membrane, which forms the autophagosome. This then fuses with the lysosome (or vacuole in plants) where degradation occurs. Microautophagy does not require a membrane intermediate as the lysosome itself endocytoses the material to be degraded (Smith and Yellon 2011). Chaperone-mediated autophagy occurs when heat shock cognate 70 and co-chaperones recognize certain proteins and transport them into the lysosome through a translocation complex (Mizushima and Komatsu 2011).

Defects in the autophagic process have differing consequences and resulting pathologies, depending on the step(s) that are affected. For example, failure of autophagosome formation would result in the persistence of damaged or toxic material within the cytoplasm promoting protein aggregation, high cellular content of abnormal organelles (i.e., mitochondria), and/or increase in lipid content (Wong and Cuervo 2010). Other conditions arise when certain components are not recognized for loading into the autophagosome. In other instances, the autophagosome is not cleared of its contents because of decreased fusion or decreased degradation in altered lysosomes (Wong and Cuervo 2010). If fusion is successful but the autophagosome persists, they can become leaky, releasing lysosomal enzymes and activating other cellular-death pathways.

Apoptosis

Apoptosis was originally used to describe specific morphological features that occurred during a type of cell death originally called "shrinkage necrosis." It occurs normally during development and acts to maintain cell populations in tissues as well as providing defense when cells are damaged (Elmore 2007). It is a genetically programmed process for cell elimination and has been associated with the activation of caspases (cysteine-dependent aspartate-specific proteases). It should be noted that it is distinct from "programmed cell death" as there are other forms of programmed cell death that can occur with nonapoptotic features (Elmore 2007).

Apoptosis is characterized by rounding-up of the cell, pseudopod retraction, membrane blebbing, cell shrinkage, reduced cellular and nuclear volume (pyknosis), DNA fragmentation (karyorrhexis), minor changes of organelles and clearance by phagocytes (Kroemer *et al*. 2009; Smith and Yellon 2011). Pathologies from abnormalities in apoptosis are found in many diseases (e.g., cancer, degenerative diseases) and can arise from conditions of insufficient or excessive apoptosis (Elmore 2007).

Necrosis

The term "necrosis" originates from the Greek, *nekros,* meaning "dead body." Necrosis is generally viewed as an unregulated or accidental type of cell death that is induced by some nonspecific and overwhelming stress from external (e.g., chemicals, toxins, infections, trauma) (Galluzzi and Kroemer 2008), or internal factors (e.g., oxidative stress, DNA damage, calcium overload, hypoxia, irradiation). Multiple viruses and certain bacterial and parasitic infections (Vanlangenakker *et al.* 2012) also can induce necrosis. It is characterized morphologically by an increase in cell volume (oncosis), swelling of organelles, plasma membrane rupture and loss of cytoplasmic contents, and moderate chromatin condensation (Kroemer *et al*. 2009; Smith and Yellon 2011). Rather than the contained processes of apoptosis or autophagy, necrosis results in cell lysis and an uncontrolled release of cellular contents. These include hydrolytic enzymes moving into intracellular spaces, which can evoke inflammatory responses and injury to surrounding cells and tissues, and buildup of cell debris (Proskuryakov *et al*. 2003). There are no specific biochemical biomarkers to diagnose necrosis, so typically light and electron microscopy are used to provide morphological evidence of necrotic cells (Vanlangenakker *et al.* 2012).

Necrosis, under certain circumstances, is regulated and mobilized by specific signal transduction mechanisms (Smith and Yellon 2011) indicating that necrosis can be programmed as a regulated nonapoptotic cell death mechanism (Galluzzi and Kroemer 2008). Evidence for programmed necrosis is that: (i) cell death with a necrotic appearance can contribute to embryonic development and tissue homeostasis, (ii) it can be induced by ligands binding to specific membrane receptors, and (iii) it can be regulated by genetic, epigenetic and/or pharmacological factors (Galluzzi and Kroemer 2008). Experimentally, cell death processes can shift features morphologically from apoptosis to a mixture of necrotic and apoptotic features by inactivation of caspases, indicating that these different pathways can cross regulate each other. This further suggests that necrosis is a default cell death pathway (Galluzzi and Kroemer 2008).

Necroptosis

Necroptosis is a recently characterized specific form of programmed necrosis or regulated nonapoptotic cell death with classical necrosis morphology (Galluzzi and Kroemer 2008). It depends on the serine/threonine kinase activity of RIPK1, a cytoprotective agent and is mediated by an extensive network of genes (Galluzzi and Kroemer 2008). The necroptosis program initiation can occur with various signals such as death receptors, tumor necrosis factor receptor (TNFR), members of the pathogen recognition receptor (PRR) family, and pathogen-associated molecular patterns (PAMPs), with TNFR1 being the most extensively studied pathway (Vandenabeele *et al*. 2010).

Though this new area of exploration is young, being able to dissect and decipher the signals in these cell death pathways will provide new insights into mechanisms of pathology, etiologies and importantly, ways to interrupt these pathways for treatments or prevention.

Sublethal Injury

Virtually all pathologies start with molecular, functional and/or structural changes at the cellular or subcellular level. Tissues are an organization of different cell types within an extracellular matrix that interact with each other to carry out specific functions and similarly, organs are a higher level of organization formed with varied tissue types. Physical and chemical interactions among subcellular components are important factors that govern the responses of cells, tissues, organs and ultimately the individual, to injury or disease.

Normal cells are generally constrained within a narrow range of functional and structural parameters (i.e., nominal range) by their genetic program of differentiation and specialization, availability of metabolic substrates, contact inhibition by neighboring cells and detoxification systems (Boorse 1977; Engelberg 1997; Kumar *et al*. 2005; Gallagher 2009). Each cell is a dynamic system of subcellular structures interplaying with multiple processes; many are key metabolic pathways that govern the cell's behavior, function, specialization and homeostatic responses. The behavior of these components and processes define the cell's physiologic condition (cellular integrity and homeostatic responses—for example, genomic integrity, metabolic condition, detoxification, membrane integrity) and consequently changes in these behaviors indicate changes in their physiological condition (Engelberg 1997; Downs 2005; Gallagher 2009). Normal cells have a dynamic range within which their subcellular processes and components operate (i.e., steady-state rates or levels of the various components) without changing their phenotype. This range is referred to as the cellular resiliency or

the cellular stress capacity (Downs 2005). Steady-state rates or the kinetics of these subcellular processes (e.g., genomic integrity maintained by DNA replication and repair pathways or protein metabolism) can be altered by numerous factors (e.g., toxicants, infections, hormones, growth factors). It is at this cellular level that virtually all forms of pathology begin, and can manifest at tissue, organ and organismal levels. The degree to which steady-state rates are altered will determine the cell's response to the new conditions, such as hyperplasia (increase in cell numbers), hypertrophy (increase in individual cell size), or atrophy (decrease in cell size) in order to regain an equilibrium, though often at a new steady state. If the limits of the cellular stress-response capacity are exceeded and it results in a condition that affects performance or function, cell injury occurs. Cell injury is actually a continuum between reversible injury and the point at which the damage or pathology is irreversible (Wobeser 2006).

Tissue Regeneration and Repair

Corals, like higher organisms, exhibit wound-healing behavior. However, unlike higher organisms, corals have the ability to reproduce asexually by fragmentation, as well as the ability to dedifferentiate their tissues and regenerate new polyps from tissue explants. These processes along with wound healing have been described through gross observation and experimental manipulation of scleractinian corals; however, the mechanisms and processes that govern them have not been well described at the cellular, developmental or biochemical levels. These processes are detailed and referenced in Chapters 7, 35 and 36 of this volume.

Cellular Adaptations

As physiologic stress or pathologic factors increase their demand on cells, the cellular steady state is altered. When the capacity of normal cellular responses is exceeded, cells can modulate their responses in order to survive or prevent injury. The type of adaptive response often depends on the stimuli and cell types involved. Classical responses consist of hypertrophy, hyperplasia, atrophy or metaplasia (Kumar *et al*. 2005).

Hypertrophy is the increase in cell size due to an increase in structural components as opposed to swelling. Primary triggers for this adaptation have been attributed to mechanical and/or hormonal factors. This condition can occur under normal or pathological conditions (Kumar *et al*. 2005). A distinct but often related process is *hyperplasia* and involves an increase in the number of cells. It is often a result of abnormal hormone or growth factor stimulation of cells, but also has been linked to certain viral infections (Kumar *et al*. 2005). In contrast, *atrophy* is the decrease in cell size, loss of structural components, and diminished function. It is often associated with reduced nutrients or stimulation, or pathological conditions (Kumar *et al*. 2005). Biochemically, atrophy is marked by increased protein degradation via lysosomes or the ubiquitin-proteosome pathway and is often accompanied by autophagic vacuoles.

A fourth adaptation is *metaplasia,* in which one cell type is converted into another. This can occur through a process called transdifferentiation, which occurs when there is conversion of one differentiated cell type into another. This process may or may not involve cell division. Metaplasia also encompasses stem cells, which are undifferentiated cells that can divide and ultimately develop into a specific cell type (Tosh and Slack 2002). Toma *et al*. (2001) showed that, in some circumstances, a fraction of stem cells can generate cells from a different embryonic lineage. Regardless of the change in cell type, the process of metaplasia at a molecular level arises from changes in expression of key developmental (i.e., homeotic) genes (Tosh and Slack 2002).

Cellular Injury

Cell injury can result from physical, chemical and/or biological stressors or deficiencies of critical substrates (e.g., ATP, oxygen, glucose) (Cobb *et al*. 1996). Physical insults can come from radiation, temperature extremes, mechanical trauma, and, for corals, excessive light, and salinity extremes.

Chemical factors causing injury can be toxins, pollutants (toxicants) or pharmaceuticals. These factors can act directly by interfering with biochemical pathways, or binding to organelles or membranes. Other chemicals can be metabolically converted through cellular detoxification systems from nontoxic to reactive toxic compounds. Often chemical exposure may not create overt tissue injury (acute effects), but may cause delayed effects (chronic effects) or affect cellular functions in ways that increase susceptibility to other types of damage (Orrenius *et al.* 2011). A cell's proliferative state, repair capacity, and ability to produce proteins that promote or inhibit cell death processes often determine a cells fate (Orrenius *et al.* 2011).

Biological agents can include external agents such as microbes, parasites or viral infections. Infectious bacterial agents often produce enterotoxins that can kill host cells or induce other types of cell death (Lin *et al*. 2010). Viral infections can cause cytolytic or cyopathic injury that, depending on the host cell and virus, may result in cell lysis, cytoskeletal damage, cell fusions or inclusion bodies that contain virions or viral proteins (Netherton and Wileman 2011). Still other viruses are oncogenic causing cellular proliferation and tumors (Tamm 1975). Intrinsic factors such as alterations in function or availability of growth factors, hormones, enzymes, cell signaling molecules, reduced oxygen supply (hypoxia), genetic alterations (e.g., chromosomal abnormalities, mutations) or nutritional imbalance are also biological factors that can cause cell injury (Kumar *et al*. 2005).

The most common causes of cellular injury are related to loss of cell membrane integrity, depletion of ATP due to mitochondria dysfunction, oxidative stress, and loss of genomic integrity (Kumar *et al.* 2005).

Cell Membrane

The plasma membrane is a phospholipid bilayer with proteins, which acts as a barrier between the cell's cytosol and the extracellular environment. Loss of membrane integrity can result from decreased synthesis of phospholipids or increased breakdown by phospholipases, injury from reactive oxygen species (ROS), or cytoskeletal damage from increased calcium activating proteases (McNeil and Steinhardt 2003; Petit-Zeman 2004). Disruption of the membrane creates an uncontrolled influx of calcium from the extracellular environment and a concomitant efflux of cytoplasmic elements and loss of osmotic balance (Kumar *et al*. 2005). The rise in intracellular calcium concentration can initiate structural and biochemical processes leading quickly to cell death (Draeger *et al*. 2011).

ATP Depletion

Depletion of ATP has widespread effects on multiple, critical cellular systems and is often associated with chemical toxicity (e.g., cyanide or carbon monoxide poisoning) or hypoxia (Cobb *et al*. 1996). The cell's main energy source, ATP, is required for most anabolic and catabolic processes within the cell such as protein and DNA synthesis, membrane transport, maintaining ion gradients across membranes, and lipid and carbohydrate biosynthesis. Interference with ATP production can lead to increased membrane permeability, dissolution of chromatin and mitochondrial damage.

Mitochondria are key targets for most agents of cell injury and their dysfunction compromises energy production in many ways. Their damage can affect oxidative phosphorylation, calcium homeostasis, oxidative stress levels, and reduce protein activity or turnover. Reduced levels of ATP synthesis can alter protein synthesis and degradation, result in less effective DNA repair, and have other chronic effects that cumulatively increase signals for cell death pathways (James and Murphy 2002). Normally, cellular calcium concentrations are controlled tightly with slight concentration changes signaling cellular response pathways. Mitochondria regulate cytoplasmic calcium either indirectly, by pumping it out of the cell by calcium-dependent ATPases to storage sites, or directly through a mitochondrial membrane potential that causes uptake of calcium into the mitochondria via a calcium uniporter (James and Murphy 2002). Disruption of these homeostatic processes can interrupt calcium-mediated signaling pathways or initiate a cell death pathway. The mitochondrial respiratory chain produces significant amounts of superoxide, a type of damaging reactive oxygen species (ROS), that under normal conditions is removed by antioxidant defenses such as superoxide dismutase, glutathione peroxidase, or cytochrome *c* (James and Murphy 2002). When production and scavaging of ROS is out of balance, damage to mitochondrial membranes, DNA, and proteins can occur, leading to mitochondrial dysfunction and breakdown.

Oxidative Stress

Cellular processes such as respiration, enzymatic activities and photosynthesis require molecular oxygen, but these processes also can generate ROS (Lesser 2006). The most common ROS are singlet oxygen ($^1O_2$), superoxide radicals (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($^{\bullet}OH$) (Halliwell and Gutteridge 1999; Lesser 2006; Ryter *et al*. 2007). Nitric oxide (NO) and its derivatives (e.g., nitrogen monoxide) are also produced intracellularly and are considered a subclass of ROS (Ryter *et al*. 2007). Intracellular ROS production is modulated by metabolic processes, and also can be increased by a multitude of xenobiotics, toxicants, and environmental factors (Ryter *et al*. 2007).

Reactive oxygen species can serve in normal cellular functions such as gene expression, growth and apoptosis, but also can cause cellular damage or death (Lesser 2006). Levels of ROS that exceed a cell's ability to detoxify or use them will cause modification or degradation of lipids, proteins, DNA and carbohydrates (Lesser 2006; Ryter *et al*. 2007). Lipid peroxidation is one of the most prevalent cellular injuries, and targets prominent membrane constituents, polyunsaturated fatty acids (PUFA). Oxidation of PUFAs can affect membrane fluidity (Halliwell and Gutteridge 1999) and in mitochondrial membranes, PUFAs can affect ATP production and multiple enzyme activities. Degradation products of lipid peroxidation include 4-hydroxynonenal, malondialdehyde, epoxides, ketones and various hydrocarbons that in turn may cause further toxicity (Halliwell and Gutteridge 1999; Lesser 2006).

A wide array of proteins is susceptible to oxidative damage or degradation. The consequences of protein damage not only affect enzyme activity but also major cellular processes involving receptors, transport proteins, generation of electrical charges (i.e., neuronal activity), and maintenance of ion gradients (e.g., Na+/K+) (Halliwell and Gutteridge 1999).

Protein damage can occur through oxidation of amino acid side chains, protein-protein crosslinking, protein fragmentation and peptide bond cleavage from ROS attack of glutamyl, aspartyl or prolyl side chains (Bertlett and Stadtman 1997). Although all amino acids are susceptible to ROS oxidation, sulfur containing amino acids, cysteine and methionine, are particularly sensitive. Aromatic amino acids are also susceptible to ROS attacks, and are readily oxidized into various hydroxyl derivatives (Bertlett and Stadtman 1997).

Carbonyl formation is another type of protein damage from oxidation events. Carbonyl groups can be produced by direct oxidation of lysine, arginine, proline or threonine side chain residues but also by reactions with aldehydes from lipid peroxidation or from active derivatives generated from the reaction of reducing sugars or their oxidation products with lysine (glycation and glycoxidation) (Bertlett and Stadtman 1997; Dalle-Donne *et al*. 2003). Because protein carbonyl formation can be achieved through many different types of reactions and its accumulation has been associated with aging, oxidative stress and several disease states, it has become a commonly used

biomarker for protein oxidation (Bertlett and Stadtman 1997; Dalle-Donne *et al.* 2003).

Genomic Integrity

The cell's DNA is naturally a stable molecule that experiences various types of damage from spontaneous chemical decomposition (e.g., apurinic sites, deamination of cytosine to uracil), ROS species (e.g., strand nicks or breaks, oxidation of purines or pyrimidines), or ultraviolet irradiation (e.g., pyrimidine dimers). Under normal metabolic conditions, cells are equipped with a DNA repair system composed of several different repair pathways that are activated depending on the type of damage in need of repair (Halliwell and Gutteridge 1999; Hansen and Kelley 2000). Several DNA repair enzymes can reverse damage. This includes photolyase, which breaks pyrimidine dimers, DNA ligase that joins single strand breaks, and O^6-methyl-DNA-alkyltransferase, which accepts the alkyl group from O^6-methylguanine, an oxidative DNA damage product (Hansen and Kelley 2000). Bulky lesions (e.g., DNA adduct) are repaired by the nucleotide excision repair (NER) complex, which cuts the DNA on both sides of the lesion and DNA polymerase then fills in the gap, using the undamaged opposite strand for fidelity. The base excision repair (BER) pathway, repairs damage to single bases caused by oxidation, alkylation, hydrolysis or deamination by removing the base from its sugar-phosphate backbone with a DNA glycosylase, leaving DNA AP sites (apurinic/apyrimidinic) (see Chapter 41). The mismatch repair (MMR) pathway functions during DNA replication by a "proof-reading" complex that excises incorrect bases and then allows DNA polymerase to fill the single strand gap.

The extent to which mutation accumulation or cell injury occurs from oxidative damage ultimately depends on the chromatin conformation, contiguous base sequences, efficiency of repair enzymes, and the dose of ROS to the cell (Halliwell and Gutteridge 1999; Lesser 2006). If ROS/RNS exceeds antioxidant capacity, genetic material will experience oxidative stress. The excess ROS not only directly damages DNA but also in so doing affects other processes such as signal transduction, cell proliferation, and cellular communication. The ROS also can unleash components that activate endonucleases and interfere with repair (Halliwell and Gutteridge 1999). When repair systems are overwhelmed or fail, mutations and chromosomal aberrations eventually lead to one or more types of pathologies.

Genetic and Developmental Pathology

Abnormalities in chromosomes or accumulation of errors in the genetic code affecting important genes or developmental programs can be inherited during sexual reproduction, resulting in genetic diseases (Kumar *et al.* 2005; Kahn and Solomon 2007). These genetic errors can result in morphological defects, developmental anomalies, metabolic disorders or malignant tumors.

To date, no heritable genetic disorders have been reported for coral.

Environmental Pathology

Environmentally related diseases fall in two general categories, physical injury and chemical injury. For corals, this is one of the most relevant areas of pathology. Physical agents of injury are by far the most studied aspect in coral and can occur via several mechanisms. For example, mechanical injury can occur through the blunt force of boat groundings, fracture and crushing by excavation for development, or lacerations from predation by fish or snails (see Chapter 17). Because corals thrive in oligotrophic waters with little tolerance for change in water quality parameters, they are also subject to physical injury from changes in sea surface temperature, excessive sedimentation, nutrient input and salinity. The most well recognized thermal pathology in coral is "coral bleaching" (see Chapters 18 and 30). In this condition, corals lose their symbiotic algae or the algal chlorophyll is degraded, leaving only the transparent tissue covering white skeleton. In the case of coral bleaching, however, the gross lesions can be elicited by many different physical changes to the coral's environment (detailed in Chapters 18 and 30, this volume) as well as bacterial infections (detailed in Chapter 13, this volume) and by itself does not provide a clear diagnosis.

Chemical injury or toxicity is by far the most diverse and pervasive group of agents affecting coral health and fitness, and possibly the most amenable to management actions, compared to agents of physical injury or infectious disease agents (Bellwood *et al.* 2004; Rotchell and Ostrander 2011). Toxicology involves the study of harmful effects of toxins, xenobiotics or other damaging agents (Rotchell and Ostrander 2011). A range of pollutants are commonly found in reef environments. These include personal care products (Danovaro *et al.* 2008), heavy metals from antifoulant paints (Downs and Downs 2007), plasticizers (e.g., phthalates, Thurén 1986; bisphenol-A, endocrine disruptor, Crain *et al.* 2007), agricultural chemicals (Glynn *et al.* 1984; Lewis *et al.* 2009), sewage (Liu *et al.* 2012), fuel and other hydrocarbons (Rougée *et al.* 2006), and natural toxins (Golubic *et al.* 2010). The degree of toxic injury depends on the inherent structure and properties of the chemical, its availability for uptake by the receptor organism, its dose, and the way an organism metabolizes it (Kumar *et al.* 2005; Kahn and Solomon 2007). Some toxicants have direct modes of action (e.g., nitroaromatics, cadmium, PAHs), others act indirectly (e.g., DDT, PCBs) (Sullivan and Krieger 2001). Cells are equipped with a detoxification system, referred to as phase I (Cytochrome P450 monooxygenase system) and phase II reactions. In phase II, compounds may be metabolized or undergo conjugation for better solubility and elimination (e.g., glutathione) (Sullivan and Krieger 2001; Kumar *et al.* 2005). Detoxification systems in corals are a relatively recent line of exploration (Downs *et al.* 2010; Rotchell and Ostrander 2011). There are, however, metabolic reactions that render some compounds more toxic through the generation of toxic metabolites. Depending on the chemical, adverse effects can be mutagenic, carcinogenic or may impair reproduction and overall fitness.

Pathology of Neoplasia

The term *neoplasia* means "new growth" and characterizes conditions of abnormal cell proliferation and maturation in which normal regulatory controls have failed. The resulting growth is a *neoplasm* (Kumar *et al.* 2005; Kahn and Solomon 2007) and has become synonymous with the term *tumor.* Tumors arise by a series of genetic alterations in the genome of a single cell and are inherited by each new progeny of the neoplasm, creating a clonal population of cells.

Neoplasms fall into two major categories, benign and malignant. Benign tumors are usually confined to the site of origin; they have well defined margins, expand slowly and rarely cause impairments to the organism (Kahn and Solomon 2007). Conversely, malignant tumors have poorly defined margins; the genetic change results in transformation of the cells that allow the tumor to grow by local invasion of surrounding tissues, destroying normal tissue in the process and when unchecked can proliferate away from their site of origin (Kumar 2005).

It is clear that corals exhibit growth anomalies with distinct lesions that differ markedly from the surrounding tissue and skeleton (reviewed in Chapter 20, this volume). Some causes of growth anomalies are known and relate to a well known reaction of the coral to encapsulate invading organisms, such as algae, fungi (Morse *et al.* 1977; Le Campion-Alsumard *et al.* 1995) or trematode metacercaria (Aeby 1998; see Chapter 28). Most etiologic agents of these abnormal growth forms are unknown. There is growing evidence, as more careful histological examinations are conducted, that is suggestive of neoplasia in some cases; in others the morphologies may be atypical hyperplastic lesions—pseudotumors—rather than neoplasia. The picture of the true nature of growth anomalies is still unclear. Discerning the pathogenesis of these will require understanding more about the developmental program and controls of skeletogenesis as well as closer inspection of genetic changes that partially define true neoplasms (see Chapter 20).

Pathology of Infectious Diseases

The field of microbiology is well developed in human and veterinary medicine. The research pioneers, Louis Pasteur and Robert Koch, established microbes as etiologic agents of infectious disease, and modern microbiology has expanded our knowledge based on molecular genetics. From this rich history, precepts such as Koch's postulates and Evans' rules (see Chapter 3 for detailed discussion) emerged to guide infectious disease investigations and form the building blocks for the modern understanding of infectious disease pathogenesis.

We now know that infectious agents belong to a wide range of taxa, which span from prions that have abnormal protein forms with no nucleic acids to viruses as small as 20 nm with a variety of types and forms of nucleic acids (see Chapter 19; Kumar *et al.* 2005) to bacteria, fungi, protozoa and helminths. The most prominent group of infectious agents among coral diseases is the bacteria (reviewed in Chapters 13–15 of this volume), and include diseases associated with *Vibrio* spp., *Serratia marcescens* and *Aurantimonas coralicida.* Only one fungal pathogen has been described for coral, *Aspergillus sydowii*, affecting seafans (Smith *et al.* 1998; see also Chapter 16). Corals are also affected by protozoan infections by ciliates resulting in brown-band disease and skeletal eroding disease (reviewed in Chapters 23 and 26 of this volume).

For an infection to be productive, the infectious agent must be able to overcome the host's defenses, propagate and disseminate (Kumar *et al.* 2005). As a result of this process, cells and tissues are damaged. For corals, this can occur in three primary ways: (i) direct cell death, (ii) release of toxins that kill cells or enzymes that degrade tissues, or (iii) collateral damage from inducing the coral's innate immune system during the process of neutralizing the disease agent. The best characterized mechanisms of cell and tissue damage in coral by infectious agents are related to *Vibrio* infections (reviewed in Chapter 13 this volume). Both toxin and enzyme release have been described in these infections. For most of the presumptive infectious coral diseases, the routes of spread and dissemination are unknown. There are however a few examples in which evidence for vectors or intermediate hosts exists, such as a marine fireworm that served as a winter reservoir and summer vector of a *Vibrio* pathogen (Sussman *et al.* 2003) or sewage disseminated *Serratia marcescens* that infects *Acropora palmata* (Sutherland *et al.* 2011; reviewed in Chapter 14).

Identifying and showing causality or mechanisms of pathogenesis has been difficult in coral as it is for most wild populations. For most coral diseases, the etiologic agent resides in the unknown category.

Conclusions

Understanding in all science begins with observation and description, and coral pathology is no different. A complete understanding of the origins, impacts, control measures or conservation goals cannot be achieved if study of disease stops with, or is confined to, observation and description.

Pathology provides a roadmap to navigate from exacting observations to insights of the inextricable structure-function relationships that govern all life. Changes in these relationships, under the influence of a complexity of external and internal factors, ultimately determine disease occurrence.

The successful practice of pathology requires an integrated knowledge of the alterations in structure and function, coupled with a mindset that guides the investigator from precise observations to a correlation of the facts. This leads to deductive reasoning in order to discover the pathologic mechanisms of infectious diseases, spontaneous disease or disease as a result of toxic insult. Pathologists use their expertise in host–pathogen interactions, molecular pathogenesis, diagnostic pathology and parasitology, plus new and evolving investigative technologies in immunohistochemistry and diagnostic imaging to understand emerging diseases and to develop a deeper understanding of known diseases.

Thus, each disease is an experiment that can be studied and can teach. Careful attention to detail, careful records, and thought and discussion lead to discovery. This was true a hundred years ago, remains so today, and applies equally to coral disease as to human diseases.

Summary

- Pathology is the study of abnormal changes in the function and structure of an organism, discovery of its underlying cause(s), and understanding the events and processes involved in the development of disease.
- The abnormal or disturbed condition that affects the performance of an organism is defined as a *disease*.
- The discipline of pathology is divided into morphological pathology and functional pathology, which merge into specialties based on methodology or system, for example histopathology, clinical pathology, forensic pathology, cytopathology, experimental pathology, chemical pathology and genomic and genetic pathology.
- The purpose of pathology in clinical or "field" practice is to not only describe and categorize the signs of a disease, but to prescribe diagnostic tests as to the etiology of a disease.
- Dissecting and understanding the cellular and molecular mechanisms, genetic programs, cell switches and signals that govern cell injury and death is an avenue with diagnostic, prognostic and therapeutic applications to the study of coral disease.

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