

# PREFACE

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*“Man’s mind stretched to a new idea, never goes back to its original dimensions.”*

**Oliver Wendell Holmes**

The latter part of the 20<sup>th</sup> century has seen an amazing change in how we view and synthesize endocrinology. Prior to the 1980s, we understood endocrine disorders and the field of endocrinology through patients with genetic mutations, protein purification, physiological experiments in humans and whole animals, tissue culture cells, and radio-immunoassays. Little did we know that the field of endocrinology (and all of genetics) would move by leaps and bounds because of a simple mammalian model—a mouse that grew twice as fast as its fellow littermates. As students at the time, we were fascinated by these mice, glorified by their appearance on the 1982 and 1983 covers of *Nature* and *Science*. These transgenic mice, created by Drs. Ralph Brinster and Richard Palmiter and colleagues, were the first endocrine models created by genetic manipulation—mice carrying a mouse metallothionein I promoter driving the expression of either rat growth hormone (1982) or human growth hormone (1983). The expression of the foreign growth hormone genes (transgenes) resulted in “gigantic mice” because of the growth hormone excess. Clearly, for our field and all of biology, the phrase “a picture is worth a thousand words” rang true on those autumn days in 1982 and 1983 and generated a movement that revolutionized our thinking. Little did we realize that a second revolution was already evolving that would take hold of the field in the decade to follow.

In the early 1980s, Dr. Martin Evans’ laboratory first isolated cell lines from the inner cell mass of mouse blastocysts that could be propagated in culture, maintain their pluripotency, and contribute to the germline. These so-called embryonic stem (ES) cell lines, first used with retroviral infection in an attempt to model the human Lesch-Nyhan syndrome, became valuable genetic conduits to mimic and better understand endocrine disorders and systems. In parallel with the development of ES cells, Oliver Smithies and colleagues showed in 1985 that they could achieve homologous recombination to correct a mutation in the human  $\beta$ -globin locus in mammalian tissue culture cells. Although this was heralded as a major breakthrough for the possible correction of human genetic diseases, it more importantly suggested that germline mutations of endogenous mammalian genes could be created. Homologous recombination in ES cell lines along with the so-called positive–negative selection strategy developed in the laboratory of Dr. Mario Capecchi, laid the foundation for “knockout” technology with more far-reaching implications than were envisioned at the early stages. The first knockout models were subsequently created with great excitement in the early 1990s including mice lacking the endocrine factors insulin-like growth factor II (1990), transforming growth factor- $\beta$ 1 (1992), and inhibin (1992). As you will see in the following chapters, thousands of transgenics have been created to study and manipulate the endocrine system. Some of these models have given expected results, whereas analysis of the phenotype of others has revealed novel functions for these endocrine factors. Clearly, transgenesis has given endocrinologists a new tool for understanding structure/function relationships in vivo.

In closing, we graciously thank all of the authors of *Transgenics in Endocrinology* for accepting our challenge to write state-of-the-art chapters on their specific topics. Writing

reviews of ever-changing fields is not an easy task, but we honestly believe each chapter to be a work of art. Because all of the authors are experts in their respective areas, it has been a pleasure to read these bodies of work and to be part of the editorial process. We would also like to thank Michael Conn for having enough confidence in us to edit this volume of diverse topics, the first of its kind for the three of us. A great deal of thanks also goes to Ms. Shirley Baker who coordinated the correspondences with the authors and incorporated all of our editorial scribbles. Lastly, to all of the readers of this book, enjoy the chapters and the immense body of literature that has been published in the field of transgenics and endocrinology over the last two decades. We hope that *Transgenics in Endocrinology* will instill much excitement and insight into your endocrine research endeavors in the 21<sup>st</sup> century.

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