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Special Issue on Cyclic GMP

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Preface

The chapters in this volume provide up-to-date information on research dealing with regulation of the biosynthesis and degradation of cyclic GMP and with the regulation of physiological systems by cyclic GMP. Research on cyclic GMP, from its inception in the 1960's to the present, has been led by a small number of laboratories concentrated in the United States and Germany. The authors of chapters in this volume, all leaders in the field, have been involved in pioneering research on cyclic GMP in one or more of those few laboratories.

Cyclic GMP was synthesized in H.G.Khorana's laboratory in 1961, well before it was known to exist in biological material. Shortly after synthetic cyclic GMP became available, Ted Rall and Earl Sutherland in Cleveland showed that it had very low potency compared to cyclic AMP in activating liver glycogen phosphorylase. In 1963, Duane Price and his colleagues in New York identified two organic phosphates in rat urine. One was cyclic AMP, which already was known to exist in urine from the work of R. W. Butcher and Earl Sutherland. The other was cyclic GMP. Three years later, James Davis, Sutherland and I confirmed the report by Price and his colleagues and showed that levels of cyclic GMP and cyclic AMP in rat urine changed independently of each other in response to altered hormonal states, implying independent metabolic pathways for the two nucleotides.

During 1969 the existence of cyclic GMP in tissues was reported by Nelson Goldberg and his colleagues in Minneapolis and by Eiji Ishikawa in Sutherland's laboratory in Nashville. The year 1969 also saw the first reports of the discovery of guanylyl cyclase by Ishikawa and me in Sutherland's laboratory, by Arnold White and Gerald Aurbach in Bethesda and by Günter Schultz, Eycke Böhme and Karin Munske in Heidelberg. In 1970, J.F.Kuo and Paul Greengard in New Haven discovered cyclic GMP-dependent protein kinase in lobster muscle. Two years later, Franz Hofmann and Guido Sold in Heidelberg demonstrated the existence of the enzyme in mammalian tissues.

During the 1970's, the properties of guanylyl cyclase were more thoroughly defined by several investigators, including David Garbers and Ted Chrisman in Nashville, Eycke Böhme and Günter Schultz in Heidelberg and by Ferid Murad and his colleagues in Charlottesville. During the 1970s and 80s, Garbers and his colleagues in Nashville and Dallas discovered the family of peptide-regulated, membrane-associated guanylyl cyclases, first in spermatazoa of marine species and then in mammalian tissues. Primarily through the work of Joe Beavo and his colleagues in Seattle, the role of cyclic GMP as a substrate and regulator of multiple isozymes of cyclic nucleotide phosphodiesterase would begin to be clarified during the 1970's and 80's.

Murad and his coworkers observed in the mid-1970's that sodium azide, included in guanylyl cyclase reaction mixtures to retard GTP breakdown, caused an increase in activity of the enzyme and went on to show that this effect was the result of the formation of nitric oxide during the metabolism of azide. Soon thereafter, Böhme, Schultz and their colleagues, Murad and his colleagues, P. A. Craven and F. R. DeRubertis in Pittsburgh and Jack Diamond in Vancouver found that many compounds capable of yielding nitric oxide activate soluble guanylyl cyclase and raise cyclic GMP in tissues. These observations, eventually converging with Rupert Gerzer's discovery in Schultzs laboratory of the heme moiety of soluble guanylyl cyclase, Robert Furchgott's discovery of endothelium-derived relaxing factor and subsequent related work by Louis Ignarro, Salvador Moncada, and Eycke Böhme and their colleagues and others would lead to our current understanding of the role of nitric oxide in signal transduction and the 1998 Nobel Prize in Medicine and Physiology for Furchgott, Murad and Ignarro.

The publication of this volume thus could not have come at a more appropriate time. Over the past decade, some of the most important advances in signal transduction research have involved cyclic GMP. Moreover, the introduction in early 1998 of sildenafil (Viagra), a selective inhibitor of a cyclic GMP phosphodiesterase, for the treatment of erectile dysfunction in men represents the first successful therapeutic

application of an agent designed to alter the activity of a molecular target in a cyclic GMP metabolic pathway. The recent finding by Doris Koesling and Andreas Friebe that YC-1 potentiates the stimulatory effects of nitric oxide and carbon monoxide on cytosolic guanylyl cyclase has stimulated the development of new vasodilators which will have applications different from the commonly used nitric oxide-releasing organic nitrates. There is vigorous research on sildenafil- and YC-1-related drugs in several pharmaceutical companies and rapid growth of information about the involvement of cyclic GMP in the regulation of numerous biological processes. These factors make it likely that there soon will be more new therapeutic agents whose molecular targets will be proteins involved in the metabolism or action of cyclic GMP. Candidates for such molecular targets can be found in each chapter of this volume.

November 1998 Joel G. Hardman

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