Catecholamines in Normal and Abnormal Cardiac Function

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Catecholamines in
Normal and Abnormal
Cardiac Function
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Foreword
When I started my career in cardiovascular research in 1947, von Euler
had just demonstrated from his classic studies on the splenic nerve of the ox,
that norepinephrine was the sympathetic neurotransmitter. The years since
have seen a remarkable unfolding of the extraordinary complex events at the
sympathetic neuroeffector junctions in the heart and blood vessels, whose
outcome dictates the ability of the cardiovascular system to respond appropriately
to the many stresses to which the body is subjected. Indeed so much
information is now available of the factors controlling the release of norepinephrine, its action on alpha! and alpha2 receptors and its metabolism that it is difficult for those not active in the field to encompass and comprehend the current state of knowledge.

Dr. Manger's monograph meets this challenge admirably as befitting his long years of study and contributions to this field. I am proud that my own institution can claim to have stimulated his early interest in the catecholamines. At the time that Dr. Manger commenced his fellowship in the Mayo Graduate School of Medicine, the Mayo Clinic was gaining increasing familiarity with the diagnosis and treatment of patients with pheochromocytoma. Working in the laboratories of Drs. Bollmann, Wakim and Baldes, Dr. Manger developed, in 1953, a technique for the chemical quantitation of epinephrine and norepinephrine in the plasma of patients. In 1977 in association with another colleague from his Mayo years, Dr. Ray Gifford, their classic monograph on pheochromocytoma was published. This provides the most complete account of the morphology, pharmacology and the clinical aspects of this remarkable tumor, and is the hallmark of their broad experience and leadership.

Apart from his own research, Bill Manger's enthusiasm, his ability to communicate effectively with colleagues and his friendly personality have served to stimulate interest worldwide in the sympathomimetic amines. His associations with the most illustrious names in the field, including Julius Axelrod and Ulf von Euler, led to the founding of the Catecholamine Club in 1968. As the secretary-treasurer from the beginning Dr. Manger has been the prime mover in spearheading the meetings which have set the standard for excellence and served so well to advance the science. This year, as a proper recognition of his broad contributions he has been elected President. The National Hypertension Association Inc. which he started in 1977 with its prominent members of its Board of Trustees and its distinguished International Medical Advisory Council serves to unite physicians, scientists and lay public in the continued quest for the better understanding of high blood pressure. This is complimentary to his early interests, since the sympathetic nervous system has the key role in the regulation of blood pressure in normal circumstances, and it is evident that it plays a significant or dominant role in many disorders of circulatory function.

The present book is characterized by lucid and succinct writing, and clear illustrations. His familiarity with the literature has permitted him to focus objectively on the key advances in our knowledge of the role of the adrenergic nervous system and of circulatory catecholamines in governing
the performance of the heart, both in normal and abnormal states. It will serve as a springboard for those young in years from which to formulate new ideas, and put them to the test, and it will serve as a reference for all of us whose memories of particular experiments and concepts need refreshing.

John T. Shepherd, MD, DSc, DSc (Hons) FRCP, Director for Education, Mayo Clinic and Foundation
Dean Mayo Medical School

Dedication

Compassion, concern, sympathy and sensitivity are qualities which are deeply admired by all. The three men to whom this book is dedicated have displayed these qualities to the full limit. Their care for students, associates and their fellow men has been a unique example and remarkable inspiration which will remain always in the memory of those fortunate enough to have known them.

'Almost all noble attributes - courage, love, hope, faith... loyalty - can be transmuted into ruthlessness. Compassion alone stands apart from the continuous traffic between good and evil... within us. Compassion is the antitoxin of the soul' (Eric Hoffer).

There can be no improvement on the statement by Albert Schweitzer that: 'Example is not the most important thing in influencing others; it is the only thing.'

It has been said that the essence of Christianity is: 'To see a need and fill it.' This credo has been central in the lives of Canon Charles Martin, Dr. Howard Rusk and Dr. Shields Warren.

William Muir Manger

Acknowledgements

The extraordinarily fine assistance of my research associate, Mildred Hulse, in preparing, editing, and significantly improving this manuscript was invaluable. The assistance of Richard Seides, Richard Sussman, Kirwan Webb, Thomas Brown and Reverend Don Bundy in proofreading, referencing, and editing was also extremely helpful. I am particularly grateful to Drs. Howard B. Burchell, Brian F. Hoffman, Michael P. Kaye, Robert J. Lefkowitz, Raymond Pruitt, Michael R. Rosen, John T. Shepherd for their helpful comments and constructive suggestions regarding the manuscript.

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Rehabilitation Medicine, the Hess Foundation, the Hearst Foundation, and the Northrup Foundation.

Canon Charles Martin

Headmaster and Teacher, 1906

There is no more important endeavor than the molding of the character of youth; these young people are the 'wave of the future' and the course of human events depends on the direction they take. As Headmaster of Saint Albans School, Canon Charles Martin established an unparalleled standard of excellence in his students. To instill worthy ideals and spiritual guidance permits noble dreams which shape the future. By his example, remarkable in every area, Charlie Martin has contributed so much to the lives of so many. For of the most high cometh teaching.

William Muir Manger

Canon Charles Martin XII

Mr. Alfred R. True, formerly Assistant Headmaster and Head of the Lower School at Saint Albans and a modern 'Mr. Chips' in the fullest sense, has been an intimate associate and close friend of Charlie Martin for 33 years. His deep admiration and warm affection for Charlie Martin is expressed in the following:

'Canon Charles Martin has an open and refreshing interest in people and events, and he cares deeply about both. His concern for others and his sensitive involvement in their welfare underlie and explain his 28 years of outstanding success as headmaster of Saint Albans School, where he was greatly beloved, and where he made everyone feel needed in a close school family. Now engaged in other work, he continues to be the cherished friend of all who know him and who count on hearing his warm and reassuring voice.

'Whenever his help is sought or needed, he finds no hour too inconvenient, no day too filled with conflicting obligations, no road to be traveled too long, no task too difficult, in responding. He has given help and solace to countless numbers on countless occasions.

'He has a searching and inquiring mind which leads him to explore and examine all sides of a question, but his ready sense of humor keeps things in perspective. His boundless, restless energy fortifies his widely diverse efforts and sustains his vigorous pursuit of goals. He sets high standards for himself and expects no less of others. In his view, no job is so well performed
that it can't be improved. He reaches for better performance himself and believes firmly that others should be encouraged and pressured to put possible dormant and unchallenged talents to use. His infectious enthusiasm in approaching those whose ability he senses and whose help and participation he wants, overcomes resistance and doubt. Because he is engagingly adept in the art of persuasion, many of his friends and colleagues have learned the joy and satisfaction of succeeding in assignments they were initially reluctant to accept. He has the great gift of stimulating others to useful action, "to their own ultimate benefit", he says, and he has the satisfaction of knowing that he has brightened the days and lightened the burdens of many.'

Mr. John C. Davis, Assistant Headmaster and Head of the Upper School at Saint Albans and a remarkable educator himself, has also been an intimate associate and close friend of Charlie Martin for 33 years. His following remarks reveal something about the nobility of character and the brilliance of leadership which have established Canon Martin's reputation as one of the great headmasters of our time.

Canon Charles Martin XIII

'Among the glories of American private education - and it is a record of such that goes back to the seventeenth century - is the continuing presence of charismatic, dedicated, and innovative individuals.

'Innovative in their desire to propel education from the springboard of the present, dedicated to the mysterious amalgams of the ideals of both this world and the next, and charismatic in their ability to attract, compel, cajole, or bewitch with these ideals the American student of 13-21 years of age, such men and women have been in themselves the history of American education.

'Charles Samuel Martin, Headmaster of St. Albans School in Washington, from 1949 to 1977, is one of these. Born in Philadelphia - that city of schools of quiet distinction - he taught at Episcopal Academy and served for seven years as parish priest in Vermont before embarking on his larger parish of St. Albans School in 1949.

'For a headmaster of a school like St. Albans, this swarming parish of boys and their families does nothing but increase and multiply. Not only did the School's size grow from 364 to 530, but wives, children, and friends were added to the number who came increasingly for advice, help, information, consolation, or simple handholding. Nor was anyone turned away, and a some-time secretary ruefully looked at the dictation that had magically expanded over a holiday weekend and said: "He's the only man I know who ever answered a thank-you note."
'It was by this network of ghostly counsel and support that, both unconsciously and by design, he encouraged his ideals of education. Starting with the practical problems at hand - the academic problem of the student, the marital difficulties of the parents, the loss of the disconsolate, he moved into the spiritual world of character formation, reconciliation, and compassion. He was always aware of the priority of God's jobs to those of Mammon, and if Mammon's were demanding too much time, so much the worse for them. "To the mischief with it!" was his harsh judgement upon them.

'Charlie Martin was not an educational theorist. Although in his time he saw St. Albans among the first to introduce Russian and outdoor survival programs, penology and African studies, social service in the ghetto, or using the media as the educational message, he was eminently pragmatic. He wasted little time on talk, moved at once to action, and once, when he was over 60, he rappelled down a forty-foot wall to show worried mothers that rock-climbing was a safe activity. (They were not convinced.) And when his harried administrators thought they had completed the job at hand and had a program working, there was Charlie Martin off stirring up educational ant hills in another area and wanting to send students to work in the back country of Tanzania or in the Richmond penitentiary. There was no rest for anybody, most of all for him, nor was rest considered desirable.

'Long before politicians had rediscovered the work ethic, Charles Martin was preaching it. In the midst of the late-60s' youth revolution, he grumbled publically about "what they thought was wrong with the Puritan work ethic." In those troubled times when deans and heads of academic institutions were being held hostage in their own offices, Charles Martin was busily anticipating their demands, organizing their reasonable educational expectations into a program, and in essence - keeping miles ahead of them. Imaginative foresight was one of his great gifts.

'His administration at St. Albans was marked by the development of the school structure, the enlargement of the concept of the school community and its social responsibility, and his awareness of the increased role non-academic education should play in the broad practice of instruction. Like the innovative Eliot of Harvard, Dr. Nott at Union, and Hutchins at Chicago, he saw that the present should not be enshrined eternally in an unchanging carapace, for the moment became rapidly the educational past. For him the future of education was like the old comic strip of the frankfurter tied to a stick, in turn tied to the dog's back, so that the animal chased the future hotdog forever. Restless, never satisfied, creating new goals as he pursued his high ideals, Charles Martin made a good school great, and a great ideal

Canon Charles Martin XIV
more capable of realization.

'This he could do because, at the bedrock of his character, he considered the humanity of man important, but not so important as its divine ingredient. When he said once that: "He was not trying to get students into Harvard but into the Kingdom of Heaven," and a bright lad muttered audibly "when is the Director of Admissions going to visit?" Charles Martin only smiled. Perhaps he knew.'

Dr. Howard A. Rusk

Father of Rehabilitation Medicine and Teacher, 1901

Few individuals in a profession have contributed a greater measure to mankind than Dr. Howard Rusk. Through his efforts in rehabilitation medicine, often assisted by his charming and very talented wife, the late Gladys H. Rusk, his influence has been worldwide. The dedication to his work and the devotion to his cause - to understand the handicapped and to help the disabled help themselves - have endeared him to the hearts of all nations. In a true sense he is a champion and a hero of compassion and peace.

William Muir Manger

Dr. Howard A. Rusk XVI

In the following, Dr. Irvine H. Page, an internationally distinguished scientist, has expressed his sense of gratitude and tribute to his long time friend, Dr. Howard A. Rusk:

A Note of Quiet Gratitude

'Howard Rusk is a remarkable fellow. I first heard of him while I was serving on the clinical research committee of the National Research Council during World War II. Repeatedly, Howard Rusk was refered to as an innovator in a field that few thought could be "innovated", i.e. rehabilitation, otherwise known as "physical therapy". It was considered a drab subject. But the Air Force seemed to think differently, chiefly because of this young man, Howard Rusk, a private practitioner from St. Louis. History tells all the rest.

'Howard combines in a remarkable fashion many talents, chief of which are knowledge, ability, compassion and charm. He is a first-rate doctor, a pretty good research worker, and a topnotch speaker and organizer. He sought the ear of everyone to further his unselfish objective, and got it. Much
is made of his friendship with celebrities, but I can testify after having known him for 30 years that his personal warmth is given to all who approach him. Unlike many, he has created and developed what he promised. Although he has been showered with honors, his life will have left a more permanent heritage in the form of rehabilitation of the handicapped. His past achievement would be enough for most of us but Howard will never give up and rest on his laurels. For that we all bless him.'

Dr. Shields Warren

Pathologist and Teacher, 1898-1980

Dr. Shields Warren was revered and loved by all who knew him. His scientific brilliance combined exceptional ingenuity and boundless energy with rigid objectivity and inflexible integrity. His charm, humility and warmth made it pure delight to be in his presence; his concern and compassion for his fellowmen was no less than magnificent. He was a man for all seasons. A statement made by Sir Dominic J. Corrigan in 1829 so perfectly describes the life-long attitude of Shields Warren that it is included in this dedication:

Dr. Shields Warren XVIII

'Whether my observations and opinions be disproved or supported, I shall be equally satisfied. Truth is the prize... and, in the contest, there is at least this consolation, that all the competitors may share equally the good attained.'

William Muir Manger

The following tribute to Dr. Shields Warren was expressed by Dr. John Z. Bowers, a close friend and former research associate.

Shields Warren - A Tribute

'Few men have had as deep and varied an influence on American medical science as Shields Warren. He can be described as a "universal genius". Yet at the same time he was a remarkably kind, gentle, and self-effacing man, everyone's friend, and without an enemy. Those of us who enjoyed a personal as well as professional association with Shields admired and benefitted from his infinite capacity for hard work. 'The fact that his grandfather, William Fairfield Warren, a Methodist
cleric, was the founding president of Boston University, and his father, William Marshall Warren, served for many years as professor and dean of the College of Liberal Arts, influenced Shields to enroll at the university for his undergraduate studies. After graduation in 1918 and a year of "hoboing" across America, Shields studied medicine at mighty Harvard. In that period all students were required to conduct and report a sanitary survey. Shields selected Rochester, New Hampshire, and had as his collaborator a fellow student at Boston University, Alice Springfield, from the same community. The selection of Rochester introduced a romantic note for not long there-after she became Alice Springfield Warren, his charming wife, helpmate, and the mother of two lovely daughters.

'After training in pathology, then the queen of the basic sciences, with Frank Burr Mallory at Boston City Hospital, Shields joined the Harvard faculty and 2 years later became head of pathology at the "Deac", the New England Deaconess Hospital. He worked closely with Elliot P. Joslin, deemed by many the world's leading expert on diabetes mellitus. This association resulted in Shields' magisterial book, The Pathology of Diabetes Mellitus. Thyroid tumors became another of his areas of expertise when Shields took over Surgical Pathology for the Lahey Clinic. The clinic was dominated by excellent surgeons led by Frank Lahey and Richard Cattell. (Perhaps Cattell's greatest hour came when he was lecturing in London and was called in consultation on Anthony Eden who had suffered a torn common bile duct during biliary surgery. Cattell had been successful in repairing a number of such cases, and he agreed to operate on Eden but stipulated that this could only be done at a New England hospital. Rumor has it that Winston Churchill tried to persuade Cattell to perform the surgery in London, but Cattell insisted on Boston, and became victorious.)

In the late 1920s Shields began his pioneering and classical research on the effects of ionizing radiation on living tissues. This culminated in his selection as Commander Warren to lead a navy team to Nagasaki in September 1945 for elucidation of the medical effects of the atomic bomb. Influenced by his months at Nagasaki, Shields became a key figure in the creation of the Atomic Bomb Casualty Commission for long-term studies of the effects of the weapon. In 1946 he prepared a statement proposing such a commission; it was drafted by Navy Secretary James Forrestal and submitted to President Harry S. Truman. With Truman's prompt endorsement, the ABCC came into full flower in the spring of 1947 while Shields was renewing his studies at Nagasaki. He continued as its advisor and by invitation returned to Japan on a final visit in 1975 when the ABCC became the
Radiation Effects Research Foundation under Japanese leadership but with financial support from both governments.

'Shields never retired from active service; he continued to be involved in governmental medicine and radiation, international studies, and directorships of such major companies as Mallinckrodt. The walls of his office in the Shields Warren Radiation Laboratory at Harvard were covered with pictures of his disciples and a world map adorned with innumerable flags representing the homes of his devoted students.

'He loved the sea and was an ardent and excellent sailor. A "radioactive flag" showing an atomic nucleus surrounded by electron shells flew from the mast of his boat. Shields was truly a man for all seasons, mourned and beloved by hosts of people around the world.'

Dr. Bowers concluded a eulogy to Dr. Warren with the following:

'Shields was constantly on the lookout for new vistas, new challenges, and new intellectual horizons. He was the epitome of the intellectual explorer. As Rudyard Kipling wrote in his poem, The Explorer:

"- On one everlasting Whisper day and night repeated - so:
Something hidden. Go and find it. Go and look behind the Ranges -
Something lost behind the Ranges. Lost and waiting for you. Go!"

Author's Remark

Knowledge of the importance of the adrenergic system in normal and abnormal cardiac function has expanded rapidly and remarkably within the past two decades. It therefore seemed justifiable to review and concisely compile this information into one volume so that it is readily accessible. This monograph briefly presents our understanding of catecholamine metabolism, adrenergic receptors and responses, and neural regulation of the heart. It also describes some of the current concepts of involvement of the adrenergic system and circulating catecholamines in cardiac pathophysiology.

William Muir Manger

Introduction

In his textbook on medical anthropology from the end of the 18th century, J.e. Loder comments upon the possible function of the suprarenals in the following words (translated from the Swedish edition, Lund, 1799): 'In the adult they may contribute to give the blood in the lower caval veins some sharpness, in order better to stimulate the heart to contraction...'.

That this surmise was closer to the truth than the author could anticipate was proven some 100 years later by the dramatic effects of suprarenal
extracts on cardiovascular activity, observed by Oliver and Schafer in 1895. This discovery made instantly clear that the heart could be subject to the potent regulatory effects of certain naturally occurring agents, later identified as catecholamines.

The accelerating effect of sympathetic heart nerve stimulation demonstrated some 20 years earlier by M. and E. von Cyan, and at about the same time by Bever and von Bezold, hardly evoked the interest it deserved, in part probably due to lack of understanding of the mechanism governing this effect.

At the turn of the century it was thus known that the heart could be excited by nerve stimulation as well as by suprarenal extracts. An integration of these two effects was achieved when Elliott in 1904 proposed his famous hypothesis that the chromaffin cell hormone adrenaline served as chemical neurotransmitter. This was followed by the genially simple experiments of Loewi in 1921 providing the final solution to a problem which had occupied physiologists for so long.

Continued experimental work along these lines revealed that adrenaline was not the only member of the catecholamine family endowed with powerful regulatory properties in the heart, but had to share this important action with the primary amine dopamine, and its beta-hydroxylated congener, noradrenaline.

In the past decades the role of the catecholamines for heart function in normal and diseased states has become the subject of intensive studies, to a large part based on new and improved techniques, both with regard to

Introduction XXII

evaluation of the manifold catecholamine effects on the heart and with regard to the formation and metabolism of the active amines. These problems are extensively dealt with by the author, whose own interest in and contributions to this field extend over several decades. In a systematic and engaging way the author presents and discusses the main areas in which the catecholamines influence cardiac function.

The recognition of specific receptors in the heart, and the discovery of numerous agonists and antagonists, some of which possess a high degree of specificity, has made possible precision and effectiveness in the treatment of disturbances in heart function which in their turn have become increasingly better understood and identified. This applies to coronary circulation as well as to the mechanical and metabolic processes in the myocardium. The mode of action of a variety of cardiac drugs, in later years elucidated at chemical and physiochemical levels, are exemplified by the mechanisms of action of adenylate cyclase-stimulating and catecholamine-depleting drugs. The
unique arrangement of the contractile tissue in the heart and its nervous control offer special conditions for intervention by the highly active catecholamines. Still many unanswered challenging questions and problems remain as regards the fine regulation and reflex control of cardiac function. The rapid and impressive advances in diagnosis and treatment of cardiac dysfunctions during recent years have increased the needs for textbooks covering this multifaceted field. The present volume gives a highly readable and critical evaluation of the role of the catecholamines in heart function, not only for the benefit of those who have the responsibility of giving a scientifically based treatment to the heart patient, but also for those more directly engaged in cardiological research. The logical pursuit of the numerous manifestations of catecholamine actions in the heart allows the reader to obtain an integrated view of the present knowledge in this central sector of medicine.

Ulf Svante von Euler, Stockholm
Emeritus Professor of Physiology
Karolinska Institute
1970 Nobel Prize Laureate in Physiology

Preface

In this book Dr. Manger has drawn upon his longstanding interest in the effects of catecholamines on the heart and circulation to provide a remarkably complete and clear summary of our current understanding of the biochemistry, physiology and pharmacology of adrenergic transmitters, the autonomic regulation of cardiac electrical and mechanical activity and the role of adrenergic transmitters in causing cardiovascular pathology. The text is admirably illustrated and throughout the author has provided clear and meaningful tables to summarize the most important information and relationships.

The short historical background highlights a number of the major findings during the past 60 years and emphasizes the manner in which understanding of biological processes and systems grows in parallel with technological advances. The next section provides a lucid exposition of the current understanding of the synthesis, storage and release of catecholamines in nerve terminals and chromaffin cells, a detailed consideration of the regulation of these processes and a clear picture of the relative importance of the different mechanisms in relation to physiological control and drug action. This section is followed by a detailed consideration of adrenergic receptors and the responses that result from their activation. The introductory material summarizes in tables the typical responses of most tissues to
activation of \(\alpha\) and \(\beta\)-receptors, the commonly employed \(\alpha\) and \(\beta\)-agonists and antagonists and finally the effects of circulating epinephrine and norepinephrine. The reader then is given a concise description of current knowledge of the types of adrenergic receptors in the myocardium and coronary circulation and the effects of their activation. For each case evidence is presented fully and interpreted fairly and an adequate number of appropriate references is provided to permit the reader to clarify points of particular interest. This background permits a detailed description of the neural regulation of the heart. The interactions between sympathetic and vagal effects are described as are the major cardiac reflexes and the role of intracranial and spinal neural mechanisms. A consideration of the effects of neural mediators on cardiac electrical activity and the coronary circulation and the changes that result from denervation then permits a full exposition of the known and expected effects of autonomic influences on the ECG and cardiac rhythm. This material benefits from the author's understanding of both basic physiology and clinical cardiology. The final section considers the important involvement of the autonomic nervous system in cardiac pathology and pathophysiology. The problem of infarction is given prominence as is the role of the adrenergic nervous system in ischemia and infarction and the associated disturbances of rhythm. There are interesting treatments of the changes in adrenergic physiology in heart failure and the role of the sympathetic nerves in causing hypertrophy. The final topic, a consideration of the effects of excessive adrenergic activity and excessively high circulating levels of catecholamines, demonstrates the author's long interest in and many studies on pheochromocytoma. The book will be of interest to a wide variety of readers. For the clinician and cardiologist it tells clearly and precisely what is and what is not known about the subject and identifies the major areas of clinical interest. For the basic investigator it emphasizes many intriguing problems which remain to be solved and many important clinical applications of what is known about adrenergic physiology and pharmacology. It represents a very major effort and undoubtedly will make a most significant contribution to all who read it. Even though information will continue to accumulate and ideas to change, this work will surely stand the test of time.

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