The MCAS and Covid-19 Theory:

A Multidimensional Epigenetic Phenomenon

Volume One, 2nd Edition

The Introduction

by, Diane M. Kane

talkMCAS.com is an independent science platform dedicated to
mast cell research, education and advocacy for the betterment of global health.
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This book is dedicated to all those who have suffered from mast cell disease unaided, to all those who have lost their lives or had their lives impaired by disease processes yet to be understood by medical science, and to the healthcare practitioners who have assisted these patients without turning them away.

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This current draft of *The Early Chapters* is a work-in-progress, with publishing and editorial notes below:

Publishing notes: *The MCAS and Covid-19 Theory* will eventually be published in four separate volumes, each containing extensive research excerpts from relevant medical journal publications. Volume One, which will serve as a Synopsis version with greater accessibility for the lay reader, may also serve as an introductory overview for scientists. Due to the current global health crisis, the author will work in an open-book format sharing Research Editions which will be made available in PDF form to all healthcare stakeholders who inquire via **info@talkmcas.com**, with the agreement that all copies printed in paper-form or shared online will be used for research purposes and not for financial gain. It is hoped that this document will be shared far and wide.

All scientists are encouraged to extrapolate from this body of work and publish independently on these findings for the purpose of helping the sick. Highlights, summaries and updates of *The MCAS and Covid-19 Theory* will be posted on the MCAS research hub: **www.talkMCAS.com**, providing direct access to all who seek to expand their knowledge, advance medical science and improve global health.

Please submit any new publications to be considered for entry into the final draft of the work to the above-mentioned email address. For all of those who authored publications contained in this catalog of investigational research, please note that the publisher of *The MCAS and Covid-19 Theory* will respect all appropriate copyright agreements and will seek all necessary reprint permissions prior to publication. This current iteration of the document is intended to assist the medical community in meeting the challenges that are upon us with Covid-19.

Editorial notes: The author is presenting this work from a layperson's perspective, seeking a platform for the patient's voice within global healthcare. Support for the patient community from the authors of the work contained herein is respectfully sought. The research excerpts contained in this book have been extracted from a wide variety of peer-reviewed publications from credentialled scientific journals, as well as several valuable magazine and book entries.

For the sake of continuity, the bibliographic footnotes contained within the original publications have been removed and the formatting structures have been unified and abbreviated for the benefit of consolidating the research into a single work. It is hoped that the authors of the individual publications will appreciate the need to present these complex findings as accessibly and effectively as possible.

About the Author: Diane M. Kane, an American born in 1964, was diagnosed with MCAS in 2017 at Cedars-Sinai Medical Center in Los Angeles after a lifelong struggle with an unidentified chronic illness. As a recovering MCAS patient and a suspected SARS sufferer from a 2003 trip to Vietnam, Diane is advocating for appropriate care for other MCAS patients and for all global citizens who may be impacted by Covid-19, MCAS or both.

As a researcher, writer and MCAS patient-advocate, Diane is sharing her knowledge of MCAS and its complex epigenetic relationship to infectious disease from both a scientific perspective and a place of hard-earned personal experience. After travelling throughout the United States, Europe and Asia for several decades in search of a greater understanding of her complex health challenges, the author reveals through this work that previously elusive explanations now appear to be within grasp for the many doctors and patients who are struggling with these perplexing and often debilitating illnesses.

It is hoped that the hypothesis of interrelated co-morbidity presented in this book will encourage all who read it, especially medical scientists worldwide, to seek a more comprehensive and translational understanding of the epigenetic etiologies of Mast Cell Activation Syndrome and Covid-19, as well as MCAS and many other acute and chronic illnesses. Although this book may ultimately pose more questions than answers, the stimulation of a robust dialogue regarding mast cell disease and pathogenic infections will, in itself, be a major victory on the road to global wellness. Together, we can walk forward in hopeful expectation that the answers to these questions will soon bring great healing to many and better protections to all.

The MCAS and Covid-19 Theory, Complete Four Volume Table of Contents:

Introduction

Thank you for your time and attention. Respectfully to all, it is an imperative for the medical community to consider a highly-prevalent yet rarely diagnosed blood disorder known as Mast Cell Activation Syndrome, or MCAS (em-kass), as an underlying diagnosis unifying the people most severely impacted by Covid-19. It will be demonstrated herein that a multidimensional epigenetic phenomenon is occurring by which SARS-CoV-2 is instigating the acquisition of novel mast cell mutations while also exacerbating inflammatory tissue structures established by previously acquired mast cell mutations in vulnerable people who possess a genetic predisposition to mast cell disease.

A growing number of mast cell experts in the world have published research papers detailing a suspected co-morbidity between Mast Cell Activation Disease and Covid-19, and still their warnings remain unheard and unheeded. For the sake of the world and all who are suffering, please review the following research with the open-minded respect that is owed to the many dedicated experts whose detailed pursuit of scientific truth has contributed most substantially to this body of work. By identifying how mast cell disease may be dictating the immune responses of people most severely impacted by Covid-19, medical science could determine: who is most vulnerable to severe infection and how to best protect them; how to best treat those who have already been infected including the growing number of Long-Covid cases; and, how to reduce community persistence of Covid-19 and improve overall global resilience to future infectious disease outbreaks.

Also of great significance is a further revelation that came from this research endeavor. It is clear that SARS-CoV-2 is not the only pathogen interacting in an interrelational disease process with dysfunctional mast cells. With prolific evidence of causal correlations to a wide variety of catastrophic health challenges including Covid-19, this body of work will elucidate how mast cell mutations have been instrumental in severe infection and refractory syndromic illness in many communicable and noncommunicable diseases worldwide for a very long time. Through a review of the research, it is shown that aberrantly-behaving mast cells are implicated in the patho-epigenetic inception and proliferation of many diseases including acute infections such as HIV, Tuberculosis, Malaria, Influenza, Polio and Dengue Fever, in addition to their involvement in progressive conditions such as Chronic Fatigue Syndrome, Autoimmunity, Atherosclerosis, Fibrosis and other Cardiovascular, Metabolic, Gastrointestinal and Neurological disorders. Acting in a conjunctive relationship with pathogens, dysfunctional mast cells appear to be linking episodic infectious disease to long-term chronic illness through a latency of infection enabled by the mast cell mutations.

Seeking foundational aspects of disease through a Systems Perspective, which employs the comprehensive investigational methodologies of Systems Biology and Systems Chemistry, will generate a more accurate map of a person's immunological landscape than what is currently provided through the narrow window of Biomedical Reductionist practices. Upstream genomic and epigenomic truths articulate a more exacting blueprint of etiological factors of disease than can be provided by downstream deductive theories, always. And with the certainty of

widespread epigenetic mutations laying at the heart of the current pandemic, these are hard upstream truths to share. Yet they are vital truths to know in order to achieve improved outcomes.

It is not all bad news though. Hidden in the dark cloud of disease that has been hanging over the world since the pandemic struck lies a silver lining of scientific advancement that is almost unfathomable in scope. As will be shown in the research chapters ahead, the epigenetically-acquired mast cell mutations appear to allow pathogens to instill host immune deficiency factors in Covid-19 as well as many other acute and chronic diseases. In this era of rapidly advancing microscopy, epigenetic mutations and the morphological alterations which these mutations conduct at a sub-cellular level are now viewable in real-time. Issues of cell lineage, cell differentiation and cell fate are being shown to be far more complex than hematopoietic science has previously estimated.

The emergent science demonstrates an extramedullary myelopoietic production of a unique inflammatory myeloid tissue comprised of unique myeloid cell phenotypes unbeknownst by science until recently. Important to these unique myeloid cells is the recent finding that not all hematopoietic blood cells, including mast cells, are derived from hematopoietic stem cells (HSCs). There is an HSC-independent process of hematopoiesis that is generated from Embryonic Stem Cells (ESCs); and, the ESCs come into existence prior to the formation of HSCs and the cells produced by the ESCs, including unique mast cell and macrophage phenotypes, are long-lived, renewable throughout adulthood and differently functioning than other known mast cell and macrophage phenotypes.

In addition to the identification of a new pathway for hematopoietic cell and tissue formation, as well as the growing knowledge regarding the existence of inflammatory microenvironments comprised of unique myeloid tissue structures within the human body, it is also important to note several other recent groundbreaking discoveries which include the identification of two new organ systems: the Interstitium and the Glymphatic System. Quite simply, we don't know everything that we think we know about anatomical biology. Previously held certainties are not certain at all. With this new scientific information at-hand, it is imperative to determine how Epigenetics plays a role in imposing or exacerbating structural morphologies and behavioral alterations at cellular and subcellular levels, especially since these factors greatly impact human health in ways not previously conceptualized. Knowledge is ever-evolving and we cannot overcome today's pandemic with yesterday's science, although the incorporation of some long-suppressed science may help illuminate where we went wrong and what we can do to correct our current course.

While the world at-large seems to grasp the usefulness of identifying genetic determinants of disease, we remain largely unenlightened as to epigenetic determinants. In addition to seeking the potential in-born, genetically-dictated causal factors of disease, we must also pursue a greater understanding of the epigenetic alterations which we can acquire throughout the course of our lifetimes anytime from immediately post-conception up until the final moments of life. Recent findings depicting lipid raft structures provide a remarkable and profound window of knowledge into the intentional implementation of epigenetic alterations by pathogens within the

cellular landscape of the human body. These epigenetically-acquired molecular modifications can and will result in altered host immune responses, as transpires in Covid-19.

Astonishingly, with the development of new investigative technologies, scientists have been able to confirm the existence of lipid rafts which are transient nanoscale molecular docking stations located within the lipid-based membrane structures of cellular walls. It is within the lipid rafts within the membrane walls of cells rich in a cholesterol precursor called 7-Dehydrocholesterol (7-DHC) that SARS-CoV-2 most effectively gains entry into the host cell. The virus then, for its own replicative and survival purposes, hijacks our lipid rafts and assumes control of our epigenetic machinery in order to reprogram our innate and adaptive immune responses. This lipid raft mechanism of infection, along with the resulting complexity of viral and host protein interactions known as the interactome, are significant factors in many if not all infectious diseases. The acute episode of infection from a pathogen, defined as a communicable disease, can result in pathogenic reservoirs within the host which are capable of causing a variety of chronic and progressive noncommunicable disease states; and latent, reservoir-resident pathogens may in-fact be capable of re-emergence.

In consideration of these paradigm-shifting findings, and the many more heretofore unknown aspects of human biology which continue to be revealed at a rapid pace, humility needs to be summoned and hope can be fostered. It is within the current realm of scientific knowledge to establish a greater understanding of the overall pathophysiology of Covid-19 than that which is currently being presented. Most urgently, a more diverse epidemic response plan is needed than the one currently being deployed and this requires a broader and more open dialogue than what is currently being conducted or permitted. While vaccines may meet a significant need, they do not meet every need created by Covid-19 nor any other catastrophic infectious disease event.

With respect to vaccination programs, both current and historical, this work represents a proposed augmentation of those policies and not a rebuttal of them. However, vaccine safety and efficacy issues will need to be strenuously reevaluated in light of the avalanche of novel scientific findings being brought to light. Although there are still a great many unknown scientific variables left for the world to unravel, there are also several undeniable facts which must now be weighed into the human immunological equation. Increased knowledge of the potential epigenetic functions of lipid rafts, the identification of novel ESC-derived mast cell and macrophage phenotypes, as well as the potentiality of widespread DHCR7 mutations, are all revolutionary immunological findings. And, in science as in life, more will always be revealed.

Factoring epigenetic disease determinants into the Covid-19 pathophysiologic profile will enable us to more accurately assess who is at-risk for a symptomatic course of infective disease. With a deeper look at the facts, it is clear that not everybody is at-risk for infection; and, of those who are at-risk, not everybody is at the same level of risk. It has also become apparent through extensive doctor and patient accounts that not everybody who has been infected by SARS-CoV-2 can fully clear the virus from their system and many are suffering persistent symptoms with a wide range of ongoing debilitations. People are struggling to manage infections and yet we are not implementing all of the potential tools in our toolbox to assist them. Mast cell stabilizers and other applicable therapeutics could aid the Covid-19 population immediately, and perhaps

immensely. Hopefully the findings herein will demonstrate the wide array of therapeutic options which, unfortunately and to the point of negligence, remain largely untapped.

This hypothesis will be presented in four parts, with Volume One setting the stage by introducing the epigenetic events involved in the differing host immune responses to SARS-CoV-2, with an emphasis on why these scientific variables absolutely *must* be factored into our understanding of Covid-19, without delay. The U.S. Center for Disease Control (CDC) issued a *CDC Community Mitigation Strategy* document for hospitals early in the pandemic which listed the medical conditions known to confer increased vulnerability to Covid-19 and this research project was borne from that list. Volume Two of this work presents a comparative review of how Covid-19 is impacting the organs systems of people infected by SARS-CoV-2 vs. the known impacts from mast cells within those same organ systems, insofar as science has identified these facts; and an interrelational co-morbid disease process is clearly revealed. Volumes Three and Four provide a contextual understanding of these often noncanonical research findings with a concluding emphasis on actionable and stabilizing solutions.

Through an open process of collaborative research, the intention is for this theory of co-morbidity between Covid-19 and mast cell disease to continue to be expanded and shared publicly and globally, for we are more effective together than alone. *The MCAS and Covid-19 Theory* shares scientific findings from a diversified collection of research conducted by investigators committed to seeking biological truths for the purpose of sustaining global health. It is an honor and a privilege to present excerpts from over 300 peer-reviewed medical research publications from clinical and laboratory researchers in hospitals and academic institutions worldwide. Each paper is well-worth reading in its entirety for its own merits and cyber links are provided in the hope that readers will venture further into the intended science beyond its application within this hypothesis. With deep gratitude and respect for this shared science and its many authors, this overall body of work represents a universal effort of mutual support.

Most importantly, thank you to the families who permitted autopsies for the advancement of science following the loss of loved ones to Covid-19. Equal respect is also paid to the courageous pathology teams who performed the autopsies amid highly stressful and uncertain circumstances. It is with deep reverence and respect that these reports have been included within this compendium of research. In recognition of the great tidal wave of loss that has washed over the world, may we offer our condolences for all those who were swept away from us too soon and may we better support all of those who are willing to assume frontline positions in the fight for global wellness. May we persevere on the road to scientific discovery and may the lessons we learn honor the depth of the sacrifice.

The paramount goal of this work is to inspire medical researchers and healthcare practitioners, from one end of the earth to the other, to further interpret and expand upon the findings presented within this wide-reaching collation of scientific findings. The world is in desperate need of scientists, doctors, public health officials, political leaders, pharmaceutical company executives and investors, and health-focused philanthropists, who will rigorously pursue the epigenetic factors imposed upon the host immune system by SARS-CoV-2 and mast cell disease. We will continue to flounder in scientific darkness until such a time. For all who read this, please

take the batons of investigational science that are being passed to you here and help the world to prevail over these complex challenges.