The MCAS and Covid-19 Theory:

A Multidimensional Epigenetic Phenomenon

Volume One, 2nd Edition

Chapter One: The Host Factor

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.

The MCAS and Covid-19 Theory: A Multidimensional Epigenetic Phenomenon

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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:

Volume One:

SARS-CoV-2, MCAS and the Host Immune Response in Covid-19

Research Index, The MCAS and Covid-19 Theory: Volume One, The Early Chapters

Chapter One: The Host Factor

Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China, Summary of a Report of 72, 314 Cases from the Chinese Center for Disease Control and Prevention, Beijing, China

Pharmacological Treatment Options for Mast Cell Activation Disease

Epigenetics Chapter from Biology: An Illustrated History of Life Science (Ponderables: 100 Discoveries that Changed History)

An Immune Epigenetic Insight to COVID-19 Infection

Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy

Covid-19 Hyperinflammation and Post-Covid-19 Illness May Be Rooted in Mast Cell Activation Syndrome

Potential Association of Mast Cells with Coronavirus Disease 2019

Chapter One: The Host Factor

There are multiple interdependent variables determining outcomes for the Covid-19 patients: the strength of the actual infecting virus, the strength of each person's individual immune response to the virus, and relevant environmental factors impacting both the host and the virus. Our ability to successfully survive an aggressive virus is not based solely upon the powerfulness of the virus, but also upon a person's "host" immune system both before and after viral infection, in addition to the ecological setting in which the infection occurs. As proven by the Institute for Human Genetics at the University of Bonn, mast cell disease is a significant host factor impacting the immune systems of nearly one-fifth of the global population[i] deeming it mandatory for us to consider its potential impact on Covid-19 infectibility, severity and survival.

By comparing the established prevalence statistics of the two diseases, it is clear that roughly the same percentage of the population that suffers from Mast Cell Activation Disease also suffers the harshest bouts of Covid-19. The level of severity in Covid-19 infections are reported to be mild in up to 81% of those infected, whereby up to 19% of those infected experience a far more severe disease presentation, as detailed in a paper published in *JAMA* (*The Journal of the American Medical Association*) on February 24, 2020 from the Chinese Center for Disease Control and Prevention, Beijing, China:

> **Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases from the Chinese Center for Disease Control and Prevention**, (Zunyou Wu, Jennifer M. McGoogan): Most cases were classified as mild (81%; i.e., non-pneumonia and mild pneumonia). However, 14% were severe (i.e., dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[ii]
> https://jamanetwork.com/journals/jama/fullarticle/2762130

Aligning with these Covid-19 severity statistics, MCAS and all Mast Cell Activation Diseases are a group of mutational blood disorders affecting an estimated 17% of the global population yet remain largely undiagnosed and untreated in spite of the discovery of MCAS over a decade ago, as reiterated and classified in the following excerpt published in *Naunyn-Schmiedeberg's Archives of Pharmacology* journal in July of 2016 from the Institute of Human Genetics, University Hospital of Bonn, Bonn; German Center for Neurodegenerative Diseases (DZNE), Bonn; Kreiskrankenhaus Waldbröl, Waldbröl; Gemeinschaftskrankenhaus, Bonn; and, RWTH Aachen University, Aachen- all in Germany; and the Mayo Clinic, Rochester and the University of Minnesota, Minneapolis- both in the Minnesota, USA:

> **Pharmacological Treatment Options for Mast Cell Activation Disease**, (Gerhard J. Molderings, Britta Haenisch, Stefan Brettner, Jürgen Homann, Markus Menzen, Franz Ludwig

Dumoulin, Jens Panse, Joseph Butterfield, Lawrence B. Afrin): Mast cell activation disease (MCAD) is a term referring to a heterogeneous group of disorders characterized by aberrant release of variable subsets of mast cell (MC) mediators together with accumulation of either morphologically altered and immunohistochemically identifiable mutated MCs due to MC proliferation (systemic mastocytosis [SM] and MC leukemia [MCL]) or morphologically ordinary MCs due to decreased apoptosis (MC activation syndrome [MCAS] and well-differentiated SM)…While the prevalence of SM in Europeans ranges between 0.3 and 13 per 100,000, the prevalence of MCAS may be as high as 17 % (in Germany).[iii]
https://link.springer.com/content/pdf/10.1007%2Fs00210-016-1247-1.pdf

Significant to the likely relationship between mast cell disease and Covid-19, MCAS can be triggered by mutagenic insults at any point during a person's lifetime resulting in a myriad of chronic, progressive and highly variant symptoms and subset conditions. Notably, SARS-CoV-2 can be a highly virulent and rapidly infective pathogenic exposure with mutagenic capacities inclined to exert a profound epigenetic impact on people with vulnerable mast cells. MCAS represents a marked deviation from how mast cell science has been previously understood and taught for over a hundred years so it is not under consideration by the vast majority of medical science as an influencing factor in the current pandemic. Knowledge of MCAS, with its chronic state of malfunctioning mast cells, assists in elucidating the overall pathophysiology of the Covid-19 infection and decompensation process by factoring in a very real but lesser-known variable in human disease pathology. MCAS is both complex and revelatory; but first, doctors and scientists worldwide need to know that MCAS exists, then they need to factor it into human health in-general and the host immune response to infectious pathogens in-particular.

It is helpful at this point to consider two seemingly opposing schools of thought regarding the etiological aspects of infectious disease: "Germ Theory" and "Terrain Theory" (the latter is also known as "Germ Theory Denialism"). Germ Theory tells us that germs such as bacteria and viruses are either solely or predominantly responsible for the occurrence of infectious disease; whereby Terrain Theory, which is derivative of French scientist Antoine Béchamp's theories of pleomorphism, contends that disease occurrence and severity are determined by the unique immunological landscape of each individual who becomes sick from a pathogen.

The grandstanding 19th century research scientist, Louis Pasteur, and his lesser-known rival, Béchamp, waged their debate acrimoniously in published research forums for decades, with Pasteur's theory ultimately gaining near-exclusive recognition within public health policy and therapeutic development due to the support he received from both the imperialist French government of the day and profit-driven private industry. Corruptive political and financial influencers seemed to find little resistance to their agendas from within Pasteur's shaky ethical framework for he was a man of ruthless ambition whom history has pegged firmly as a plagiarist of mediocre scientific intellect. Pasteur's efforts to control the public health dialogue succeeded, with the scientific community focusing resources ever since almost exclusively on developing methods to attack or control germs rather than working to gain a more comprehensive understanding of how the human body receives and responds to these germs.[iv]

With regard to Germ Theory and Terrain Theory, perhaps it is not a case of one theory being truth and therefore rendering the other theory to be false for science has proven time and again that two or more facts can hold true at once. Often, we simply lack a fuller contextual understanding of how the two facts co-exist and this is where the great complexities of epigenetics come in. In a rare moment of humility, when Pasteur was rumored to have acknowledged in a deathbed realization that, "the germ is nothing, the terrain is everything", he most likely swung his pendulum of self-doubt too far back in the other direction. What is being proposed herein is not an either/or scenario regarding these differing pathobiological theories of infectious disease, but rather a combined theory based upon the dynamics of an epigenetic phenomena whereby multiple factors including the infecting pathogen, the individual's bodily terrain, as well as the environmental influences upon both the germ and the terrain, must all be taken into account.

Before examining how epigenetic alterations are at-play in Covid-19 as well as MCAS, it is important to establish a foundational understanding of Epigenetic science in-general:

> In biology, epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence. The Greek prefix epi- (ἐπι- "over, outside of, around") in epigenetics implies features that are "on top of" or "in addition to" the traditional genetic basis for inheritance…The term epigenetics in its contemporary usage emerged in the 1990s, but for some years has been used with somewhat variable meanings. A consensus definition of the concept of an epigenetic trait as a "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" was formulated…in 2008, although alternate definitions that include non-heritable traits are still being used…[v]
> https://en.wikipedia.org/wiki/Epigenetics

Expanding upon this basic understanding in a book entitled *Biology, An Illustrated History of Life Science*, from the *Ponderables, 100 Discoveries That Changed History: Who Did What When Collection*, Epigenetics is eloquently and accessibly described:

> Epigenetics: If an organism's genetic code is thought of as a script outlining which genes should be switched on or off, epigenetics is the study of how this gene expression is regulated by environmental factors. The genetics revolution changed biology, but it also sparked popular confusion. Could we escape our genes? Or was everything about us pre-programmed? Then epigenetics arrived and made it even more confusing. It is a central axiom (or rule) of genetics that inherited genetic material- the DNA that codes our genes- remains unchanged by the body. Whatever you inherited from your parents, you will pass on to your children. That fact underlies everything we know about genes and is the central tenet of some views of evolution, population genetics, and developmental biology (of course, mutations, or mistakes, in genes do occur but this is by accident during copying or by an outside attack altering chemistry of DNA, not through the action of a process started by the body.) So, in other words, all this means that, according to the field of genetics, you only inherit genetic characteristics from your parents. You do not inherit any characteristics they may have acquired during their lives-

things like big muscles from weightlifting, or sore feet from badly fitted shoes. Epigenome: But a new field called epigenetics suggests another element is at work during inheritance. While the genetic axiom still holds firm, the way the body develops and makes use of its genes may be controlled by factors that are acquired in life- and may be passed down from a parent (at least from the mother). Central to this idea is the epigenome. This refers to the army of chemicals, such as histones, that surround, support, and manage DNA inside a cell. (The DNA is called the genome). Experience in life- poor diet, plenty of exercise, even diseases- may alter the epigenome in significant ways. This has the effect of locking some genes away from use by a cell and opening up others that would otherwise be unused. While the genome is passed from parent to offspring unchanged, the epigenome that travels with it might be totally different to the one the parents inherited themselves. Effects of Famine: The strongest evidence for epigenetic effects comes from large-scale studies of families over several generations. One of the biggest followed the Dutch Hunger Winter, a period of famine in The Netherlands at the end of World War II. Babies that were born during or just after the famine form the basis of the study, along with their parents, children, and soon grandchildren, too. It appears that babies born during the famine were generally small and thin in adult life (but perfectly healthy). Those born just after- they were in utero during the famine- grew up to be overweight and prone to mental illnesses. Intriguingly, the children of the two groups share the same characteristics as their mothers. It appears that the effects of malnutrition were felt by the mother, the developing baby, and also the cells inside female babies that would one day become the eggs used to make the next generation. All three generations, mother, child, and grandchild, were impacted by the famine. In a few years, data will be available about the fourth generation. Will the epigenetic effect be passed on that far? ...There are between 2 and 3 meters (roughly 6-9 ft) of DNA in every human cell. Those long, flimsy chemicals need careful storage, a job done by histone proteins, which coil the DNA into ultra-compact units. The structure of the histones and other supporting chemicals forms the epigenome, which is inherited along with the genome…The histones that support and organize the long strands of DNA in a cell were once thought to be purely structural supports. However, epigenetics suggests that they have a role to play in inheritance, at least in the short term.[vi]
https://www.shelterharborpress.com/

Of note, in the upcoming *MCAS* chapter is a review of a newly identified mast cell phenotype generated embryogenically from the yolk sac. Perhaps these ESC-derived mast cells will provide a greater window of understanding into currently unknown epigenetic heritability factors mentioned above.

Leaving Epigenetics for a moment now and returning to the Germ and Terrain Theories, it is worthwhile to review the basic scientific postulations made by Béchamp in his theories of pleomorphism and pathogenic illness, as summarized in a technologically-outdated depiction of infectious disease which demonstrates the predominance of the pro-Pasteurian school of thought, as published on Wikipedia:

> Germ theory denialism is the pseudoscientific belief that germs do not cause infectious disease, and that the germ theory of disease is wrong. It usually involves arguing that Louis Pasteur's model of infectious disease was wrong, and that Antoine Béchamp's was right. In fact, its origins are rooted in Béchamp's empirically disproven (in the context of disease) theory of pleomorphism. Another obsolete variation is known as terrain theory and postulates that diseased tissue attracts germs rather than being caused by it…Béchamp strongly contested Pasteur's view, proposing a competing idea known as the pleomorphic theory of disease. This theory says that all life is based on forms that a certain class of organisms take during stages of their life-cycles and that germs are attracted to the environment of diseased tissue rather than being the cause of it…[vii]
> https://en.wikipedia.org/wiki/Germ_theory_denialism

Contrary to prevailing scientific assumptions, the rapidly advancing field of epigenomics is showing us that both Germ Theory and Terrain Theory have merit, with new technologies confirming the veracity of key aspects of pleomorphic theory on a cellular and sub-cellular basis. Scientists have identified broadly-impacting morphological complexities unique to specific cellular phenotypes which can result from pathogenic insults to certain terrains in certain host cells and tissues. One-hundred and fifty years after Pasteur and Béchamp's era, comes the simultaneous proof of both of their theories: the germ (or the pathogen) infects the host, the proteins within the pathogen strive to reprogram the immune responses of the host, and all of this results in pleomorphic responses in and from both the host and the pathogen; in addition, the particular terrain of each person determines their vulnerability to these infections as well as the severity of the infections. It appears that previous pathogens, in addition to the newly infecting pathogen, can instill alterations in the host terrain to create tissue structures conducive to the establishment of pathogenic reservoirs and future infections.

The pathogens are intentional in their actions, which upholds the Germ Theory; and, the diseased tissues structures within the infected host promote opportunities for further pathogenic infections, which upholds the Terrain Theory. These are interactive factors of evolutionary biology which demonstrate an inherent form of intelligence within the pathogens. Epigenetic mutations ultimately represent adaptive strategies: life seeking life. The host immune response wants the host to survive a pathogenic invasion; and, in the case of Covid-19, the SARS-CoV-2 viral cells want to survive inside the host and the host needs to stay alive in order for the viral cells to stay alive. And so, finally, despite the long-held belief that Béchamp's theories were invalidated by Pasteur, current epigenomic technologies clearly depict modifiable pleomorphic states inherent in the pathogens as well as the host tissues which the pathogens infect and populate. Béchamp's findings have been authenticated, his life's work is vindicated and Pasteur's intentional suppression of an open and spirited scientific debate is shown to have cost the world a hefty price in terms of our lack of understanding of humanity's current burden of illness.

Moving on to a more specific understanding of how SARS-CoV-2 (the germ) is impacting the host immune system (the terrain) via viral-to-host epigenetic pathways, as published in *Future Medicine: Epigenomics* on March 9, 2021 from the All India Institute of Medical Sciences, New

Delhi; Institute of Medical Sciences, Banaras Hindu University, Varanasi; and the National Institute of Immunology, Aruna Asaf Ali Marg, New Delhi- all in India:

An Immune Epigenetic Insight to COVID-19 Infection, (Bimal P Jit, Sahar Qazi, Rakesh Arya, Ankit Srivastava, Nimesh Gupta, and Ashok Sharma): Introduction: Severe acute respiratory syndrome coronavirus-2 is a positive-sense RNA virus, a causal agent of the ongoing COVID-19 pandemic…Although the current review highlighted the critical epigenetic events associated with SARS-CoV-2 immune evasion, the detailed mechanism is yet to be elucidated…Population genetic analysis revealed that the virus' L-type strain is more aggressive and contagious than the S strain. The genome sequencing approach results indicate that COVID-19 shares 96.2% overall genomic similarity with Bat-CoV-RaTG13 suggests a typical ancestral relationship. According to recent Lancet findings, Acute Respiratory Distress Syndrome is the most common pathological event of COVID-19 characterized by cytokine storm, resulting from the massive secretion of pro-inflammatory cytokines and chemokines during the infection by immune effector cells. Immunocompromised populations associated with several genetic and nongenetic diseases are highly vulnerable to infection and acts as the potential risk factor modulating the clinical severity. Evidence suggests persistent viral attacks associated with altering host epigenetic machinery, thus paving a way to evade and subvert the immune system for a successful infection strategy. Therefore, it is highly crucial to understand the host-cell chromatin dynamics to regulate the expression of specific genes adapted by COVID-19-host confrontation during its infection. Here, we provide a brief insight on possible epigenetic changes associated with coronavirus and other viruses to evade host immunity…Host epigenetic architecture: Despite the Mendelian inheritance, which emphasizes the transmission of genes associated with a particular trait, discovery in several high throughput technologies contributed significant advancement to epigenetics. Epigenetics elucidates gene expression regulation and silencing events without any change in the DNA sequence. Although the changes instigated by this are stable, reversible modifications in the DNA sequences could induce a dramatic change in parent and progeny phenotypes. The consequences may persist for a lifelong period affecting cellular behavior. Deciphering the fine-tuning mechanisms associated with an epigenetic signature could lead to identifying a potential target that will be suitable for identifying severity markers of a particular disease. Understanding the host-viral functional network is crucial to control the virus' pathogenesis and infectivity. More recently, epigenetics has become an emerging field in controlling the host innate and adaptive immune system induced by viral pathogenesis. Being originated by environmental stimuli, the field encompasses two major events, methylation and acetylation, which play a crucial role in altering the chromatin packaging and position of regulatory elements like promoter or enhancers. These methylation and acetylation processes are being carried out by DNMTs (DNA methyl transferases) and HDACs (histone deacetylases), which have varying expression levels in different cells under different conditions. In addition to this, other histone biochemical modifications include phosphorylation, sumoylation, and ubiquitination. Histone modification enzymes portray their role in coordination with other

chromatin regulators like ATP-dependent chromatin remodeling complexes and the contrasting effects of the polycomb group and trithorax group genes. Normal functional cells with transcriptionally active genes are characterized by unmethylated promoter CpG islands, histone hyperacetylation, H3 lysine 4 (H3K4) di- and tri-methylation and H3K79 methylation. In addition to this, the transcriptionally repressed genes are discerned with promoter CpG island methylation, histone hypoacetylation and H3K9, H3K27 methylation…Conclusion: A viral threat to humanity represents a foremost public health concern and accounts for a significant cause of morbidity and mortality for decades. Currently, COVID-19 has raised many scientific and clinical questions. A growing body of evidence indicates that an evolutionary arms race and molecular cross-talk between virus and host epigenetic landscape plays a pivotal role in encouraging the altered immune response. Another question is whether SARS-CoV-2 is evolutionarily adapted to subvert the host replication, transcription and proteome program by modifying the epigenetic machinery, thus evading host immune response. The evidence summarized and discussed here clearly demonstrates that RNA viruses like SARS-CoV-2 are equipped with a molecular entity to evade from host innate immunity by altering epigenetic architecture. Although SARS-CoV-2 modifies the host phenotype by potent epigenetic types of machinery like ACE2R methylation, interfering with host replication machinery, altering antigen presentation and interferon response, innate epigenetic signaling and histone mimicry, however, the mechanistic basis of altered chromatin dynamics and viral antagonism of SARS-CoV-2 is still not thoroughly investigated. Therefore, future studies should explore and generate a more comprehensive map of important epigenetic events in the histone induced by SARS-CoV-2. Integration of the epigenetically technological approach will allow understanding of the epigenetic landscape of immune response induces by SARS-CoV-2 and prediction of a pharmacological target for therapeutic efficacy…Future perspective: …Although cytokine storm seems crucial in modulating clinical severity, however, due to insufficient data and lack of strong evidence until recently, it is unknown whether cytokine storm is the major confounding factor modulating pathological complexity. In contrast, further emerging evidence supports the notion that the phenotype may be manifested due to endothelial dysfunction and systemic inflammatory response. In the battle of nature and host immunity, the role of epigenetics is of tremendous importance elucidating a scientific heft to the current scenario. Although it was previously experienced that the mechanistic underpinnings governing the epigenetic process are highly deterministic in affecting psychological traits like intelligence, personality, sexuality, now it is proved that epigenetics plays a significant role in modulating the infectivity and host-pathogen interaction…Executive summary: Overview: Currently, COVID-19 is the significant public health concern and exhibits a prominent cause of morbidity and mortality worldwide; 1. Viruses have improved several potent mechanisms to efficiently propagate inside the host by fine-tuning the host epigenetic program leading to evasion from innate and adaptive immunity. 2. Both DNA and RNA viruses regulate the epigenetic players like HAT (Histone Acetyltransferases), DNMTs, HDAC culminating into activation and repression of the specific genetic mark in the promoter of innate signaling cascade and thus subvert from host defense. The epigenetic perspective of

SARS-CoV-2: ACE2R methylation determines SARS-CoV-2 entry into the host cell: 1. ACE2 gene methylation across three CpG sites (cg04013915, cg08559914, cg03536816) in lung epithelial cells is of paramount importance SARS-CoV-2 infection; 2. SARS-CoV-2 may regulate ACE2 expression by controlling the SIRT1 and KDM5B activity. SARS-CoV-2 epigenetically alters antigen presentation and Interferon response: 1. SARS-CoV-2 significantly delayed interferon-stimulated gene expression; 2. SARS-CoV-2 may regulate Type I and III IFN response by modulating H3K27me3 and H3K4me3 histone mark; 3. Monocyte and macrophage-mediated inflammatory response associated with COVID-19 are induced by acetylation and deacetylation of histones. Histone mimicry as a basis for modulation of gene expression and immune evasion: 1. SARS-CoV-2 protein with bromodomain and protein E mimics bromodomain histones and evades from host immune response; 2. However, there is a paucity of literature pertinent to this field. Coronavirus modulates innate epigenetic signaling: 1. SARS-CoV-2 may regulate NF-κB signaling by p65 chromatin recruitment; 2. However, very few works have been conducted in this field; 3. SARS-CoV-2, 2'-O MTases mimics the host's cap1 structure and plays a vital role in immune evasion; 4. Coronavirus uses Hsp90-mediated epigenetic process to hijack the infected cells. Epigenetic tools to study the evasion strategy of SARS-CoV-2: 1. Several technological approaches have contributed to the understanding of nuclear architecture and chromatin network substantially; 2. Advancement in the single cell-based chromatin analysis approach; microscopy-based single-molecule real-time imaging for chromatin dynamics, epigenome microarray, chromatin immune precipitation with next-generation sequencing, will be highly beneficial to understand the dynamism of host chromatin and virus interaction. Conclusion and future perspective: 1. **Although the current review highlighted some of the critical epigenetic events associated with SARS-CoV-2 immune evasion, the detailed mechanism is yet to be elucidated**; 2. Future studies should focus on the novel paradigm involved between host and SARS-CoV-2 and the epigenetic basis of immune evasion to predict pharmacological targets and therapeutic interventions.[viii]
https://www.futuremedicine.com/doi/full/10.2217/epi-2020-0349

While an epigenetically-driven pathophysiology of Covid-19 is clearly stated above, it is also clearly stated that the mechanism(s) by which this occurs remain inadequately defined. It has been emphasized in an ever-expanding number of research publications since early in the pandemic onward that Mast Cell Activation Syndrome, a blood disorder impacting almost one-fifth of the global population, is facilitating the epigenetically-driven course of infective disease from SARS-CoV-2.

In an early response to Covid-19, an identification of mast cells as a contributor to the multi-systemic inflammatory responses present in Covid-19 has been detailed in the following paper published in the *Journal of Biological Regulators and Homeostatic Agents* on February 4, 2020 from the Aristotle University of Thessaloniki, Macedonia, Greece; Clinica dei Pazienti del Territorio, Fondazione Policlinico Gemelli, Rome, Italy; University of Camerino, Camerino, Italy; University of Ferrara, Ferrara, Italy; University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA, USA; University of Chieti, Chieti, Italy:

Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy, (S. K. Kritas, G. Ronconi, Al Caraffa, C. E. Gallenga, R. Ross, P. Conti): …Coronavirus is interspecies and can also be transmitted from man to man, with an incubation ranging from 1 to 14 days. Human coronavirus infections can induce not only mild to severe respiratory diseases, but also inflammation, high fever, cough, acute respiratory tract infection and dysfunction of internal organs that may lead to death. Coronavirus infection (regardless of the various types of corona virus) is primarily attacked by immune cells including mast cells (MCs), which are located in the submucosa of the respiratory tract and in the nasal cavity and represent a barrier of protection against microorganisms. Viral activate MCs release early inflammatory chemical compounds including histamine and protease; while late activation provokes the generation of pro-inflammatory IL-1 family members including IL-1, IL-6 and IL-33. Here, we propose for the first time that inflammation by coronavirus may be inhibited by anti-inflammatory cytokines belonging to the IL-1 family members…Coronaviruses often have highly pathogenic activity in animals, but today it has been seen that, with their particular pathogenic proteins, they can cause more or less serious respiratory diseases both in adults and children…Therefore, human coronavirus infections can induce not only mild to severe diseases, but also systemic inflammation, high fever, cough, acute respiratory tract infection and dysfunction of internal organs that can lead to death. Coronavirus is classified as a RiboNucleic Acid (RNA) virus, with a genome that can often escape the innate immune system, especially if it is malfunctioning. Regardless of the various types of coronaviruses, the entry of the virus into the organism activates innate immunity, which intervenes in the first instance to engulf the invader. The severity of the disease lies in the ability of the innate immune cells to stem viral infection. The stronger the innate immune system, the less the ability of the virus to replicate itself, suppress the immunity and, therefore, to induce the pathological state. In the case of innate immune suppression by the virus, adaptive immunity is also inhibited. The coronavirus is capable of producing viral enzymes and proteases that damage the immunity and inhibit the signaling pathways of type 1 interferon (IFN), along with nuclear factor-xB, facilitating innate immune evasion…MCs are involved in innate and adaptive immune systems, playing a role in autoimmunity, infections, tissue damage, and inflammatory signals…When biologically activated, MCs generate biologically active substances including chemokines and cytokines without degranulation. MCs are responsible for allergic reactions, but also participate in inflammation and defend the body against bacterial helminthic and viral infections. MCs can be activated by IgE and specific antigen, but also by bacteria and viruses.[ix]
https://www.biolifesas.org/biolife/2020/02/04/mast-cells-contribute-to-coronavirus-induced-inflammation-new-anti-inflammatory-strategy/

Much suspicion regarding an interrelational co-morbid disease process occurring between mast cells and SARS-CoV-2 in symptomatic and severe Covid-19 has been generated amongst mast cell experts, with several research papers having reached publication including an admonitory theory published in the *International Journal of Infectious Diseases* on September 10, 2020, as summarized below with further elaboration in *Chapter Six: Covid-19, MCAS and the*

Compromised Immune System, from the AIM Center for Personalized Medicine, Purchase, New York, USA; Washington University, St. Louis, Missouri, USA; and, the Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany:

Covid-19 Hyperinflammation and Post-Covid-19 Illness May Be Rooted in Mast Cell Activation Syndrome, (Lawrence B. Afrin, Leonard B. Weinstock, Gerhard J. Molderings): Highlights: 1. Much of Covid-19 hyperinflammation is consistent with mast-cell-driven inflammation; 2. Prevalence of severe Covid-19 is similar to that of mast cell activation syndrome (MCAS); 3. Drugs inhibiting mast cells (MCs) and their mediators show promise in Covid-19; 4. None of the authors currently treated MCAS patients with Covid-19 had severe forms or mortality; and, 5. The dysfunctional MCs of MCAS may underlie severe acute and chronic Covid-19 illness. (Abstract) Objectives: One-fifth of Covid-19 patients suffer a severe course of Covid-19 infection; however, the specific causes remain unclear. Mast cells (MCs) are activated by SARS-CoV-2. Although only recently recognized, MC activation syndrome (MCAS), usually due to acquired MC clonality, is a chronic multisystem disorder with inflammatory and allergic themes, and an estimated prevalence of 17%. This paper describes a novel conjecture explaining how MCAS might cause a propensity for severe acute Covid-19 infection and chronic post-Covid-19 illnesses. Methods: Observations of Covid-19 illness in patients with/without MCAS were compared with extensive clinical experience with MCAS. Results: The prevalence of MCAS is similar to that of severe cases within the Covid-19-infected population. Much of Covid-19's hyperinflammation is concordant with manners of inflammation which MC activation can drive. Drugs with activity against MCs or their mediators have preliminarily been observed to be helpful in Covid-19 patients. None of the authors' treated MCAS patients with Covid-19 suffered severe infection, let alone mortality. Conclusions: Hyperinflammatory cytokine storms in many severely symptomatic Covid-19 patients may be rooted in an atypical response to SARS-CoV-2 by the dysfunctional MCs of MCAS rather than a normal response by normal MCs. If proven, this theory has significant therapeutic and prognostic implications.[x]
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7529115/

In addition to the previous MCAD/Covid-19 paper authored by Afrin, Weinstock and Molderings, another early pioneer in mast cell research has weighed in on the strong likelihood of a co-morbid disease process transpiring between mast cell disease and Covid-19. Dr. Theoharis Theoharides, the pre-eminent Neuro-Immunologist in the field of Mast Cell Activation Diseases, has offered valuable insights into the possible correlation between MCAS and persistent Covid-19 cases which are currently referred to as Adult and Children's Multisystem Inflammatory Syndromes (aka Long-Covid), as introduced in the following excerpt which is also revisited again in this work in *Chapter Six: Covid-19, MCAS and the Compromised Immune System*, as published in T*he Annals of Allergy, Asthma and Immunology* on November 6, 2020 from Tufts University School of Medicine, Boston, Massachusetts:

Potential Association of Mast Cells with Coronavirus Disease 2019, (Theoharis C. Theoharides): …Many recent reports indicate that a considerable number of patients who received positive test results for SARS-CoV-2 are asymptomatic or have mild symptoms. However, increasing anecdotal evidence suggests that many patients who either recovered from or had mild symptoms after COVID-19 exhibit diffuse, multiorgan symptoms months after the infection prompting the Centers for Disease Control and Prevention to name it adult multisystem inflammatory syndrome. These symptoms include malaise, myalgias, chest tightness, brain fog, and other neuropsychiatric symptoms that are quite similar to those presented by patients diagnosed as having mast cell activation syndrome (MCAS). It is, therefore, critical that MCAS (International Classification of Diseases, Tenth Revision code D89.42—idiopathic mast cell activation syndrome, not systemic mastocytosis) be suspected, evaluated, and addressed in any patient with COVID-19 who experiences chronic multiorgan symptoms. Given the abovementioned discussion, it would be prudent to consider blocking mast cells and the action of their mediators both prophylactically and symptomatically during the COVID-19 pandemic…In conclusion, mast cells could contribute to the pathogenesis of COVID-19 and any postinfectious inflammatory syndromes through the release of proinflammatory, fibrotic, or thrombogenic mediators. Hence, it is reasonable to consider their inhibition at least for prophylaxis if not symptomatic treatment of patients diagnosed as having COVID-19 with mild symptoms...[xi]
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7644430/

In previous, pre-pandemic efforts to try to improve clinical care options for a highly-distressed patient population, a major challenge was to figure out how to most effectively explain the vast and variable importance of MCAS to the world. Specifically, the hurdle was how to widen the lens people are looking at mast cell disease through in order to demonstrate how one root disease process can cause such diverse and widespread illness. At a devastating cost, Covid-19 may have overcome this obstacle. With more people now ready to accept the concept that a large segment of the population has a common and foundational immunological deficiency which can dictate the host immune response to pathogens, this work will attempt to explain what is known about MCAS from experience and research to date. Understanding how mast cell-related host factors are determining Covid-19 outcomes is essential to reducing further catastrophic loss and overcoming our current circumstances. The hope is for others to build on this information in order to expand our armamentarium of appropriate and effective global solutions.

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