Mast cell activation disease and the modern epidemic of chronic inflammatory disease

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A large and growing portion of the human population, especially in developed countries, suffers 1 or more chronic, often quite burdensome ailments which either are overtly inflammatory in nature or are suspected to be of inflammatory origin, but for which investigations to date have failed to identify specific causes, let alone unifying mechanisms underlying the multiple such ailments that often afflict such patients. Relatively recently described as a non-neoplastic cousin of the rare hematologic disease mastocytosis, mast cell (MC) activation syndrome—suspected to be of greatly heterogeneous, complex acquired clonality in many cases—is a potential underlying/unifying explanation for a diverse assortment of inflammatory ailments. A brief review of MC biology and how aberrant primary MC activation might lead to such a vast range of illness is presented. (Translational Research 2016;174:33–59)

Abbreviations: ACI = anemia of chronic inflammation; AD(H)D = attention deficit(/hyperactivity) disorder; ASD = autism spectrum disorder; BMS = burning mouth syndrome; BPAD = bipolar affective disorder; CCS = Cronkhite-Canada syndrome; CFS = chronic fatigue syndrome; CGRP = calcitonin gene-related peptide; CID = chronic inflammatory disease; CKD = chronic kidney disease; CNS = central nervous system; CRH = corticotropin releasing hormone; CSF = cerebrospinal fluid; DM1 = diabetes mellitus type 1; DM2 = diabetes mellitus type 2; ECG = electrocardiographic; EDS = Ehlers-Danlos syndrome; EH = essential hypertension; FM = fibromyalgia; GERD = gastroesophageal reflux disease; GI = gastrointestinal; GWI = Gulf War Illness; H&E = hematoxylin and eosin; HLA = human leukocyte antigen; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; Ig = immunoglobulin; IL = interleukin; IFN = interferon; MC = mast cell; MCAD = mast cell activation disease; MCAS = mast cell activation syndrome; MCRG = mast cell regulatory gene; MCS = multiple chemical sensitivity; MDS = myelodysplastic syndrome; MIST = mast cell immunoreceptor signal transducer; NERD = non-erosive reflux disease; NICM = non-ischemic cardiomyopathy; PCOS = polycystic ovarian syndrome; PCR = polymerase chain reaction; POTS = postural orthostatic tachycardia syndrome; PRCA = pure red cel aplasia; PV = polycythemia vera; RLS = restless leg syndrome; SCA = sickle cell anemia; SM = systemic mastocytosis; SM-AHNMD = systemic mastocytosis with associated clonal hematologic non-mast-cell-lineage disease; TNF = tumor necrosis factor; Treg = T-regulatory cell; TRPV1 = vanilloid receptor type 1; TSH = thyroid stimulating hormone

INTRODUCTION

Much of humanity, especially in developed countries, suffers 1 or more chronic ailments which either are overtly inflammatory in nature (eg, asthma, irritable bowel syndrome [IBS], arthritis) or are suspected to be of a principally inflammatory nature (eg, fibromyalgia [FM], chronic fatigue syndrome [CFS], obesity, diabetes mellitus,

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atherosclerosis), but investigations to date have failed to clearly identify any specific cause of any of these diseases. Allergic rhinitis has been reported to afflict 10%–30% of the global population,[1] asthma in 5%,[2] autoimmune disease of one sort or another in 4%[3] (a figure thought by many to be a significant underestimate), FM in 3%,[4] inflammatory bowel disease (IBD) in 0.5%,[5] and so on. By the millions, such patients suffer adverse quality of life (sometimes to the point of disability) for years to decades on end, often with little to no benefit from older treatments, and newer treatments, typically far more expensive, often offer little clinically significant additional benefit. Furthermore, beyond direct treatment costs, the costs to individual and societal productivity are gargantuan and escalating. A recent estimate of the current annual global total economic cost of obesity—a chronic inflammatory disease (CID) now affecting 30% of the population and estimated to affect 50% by 2030—is $2 trillion.[6]

Any 1 CID would be burdensome enough, but an increasing number of patients are being recognized to have >1 CID.[7] These epidemiologic data thus beg the questions of not only why inflammatory diseases are so prevalent but also why a patient with 1 CID likely bears other CIDs, too. It seems less likely such a patient would be so unlucky as to have coincidentally acquired multiple CIDs, with most or all of them having developed independently of one another, as opposed to there being 1 root problem that is biologically capable of causing, directly or indirectly, most or all the morbidity seen in the patient to date.

Although the common theme of chronic inflammation is readily evident from 1 such patient to the next and thus suggests an underlying unifying mechanism, the heterogeneity of inflammatory polymorbidity across patients—that is, the variability from 1 patient to the next as to the specific set of inflammatory morbidities present and their particular natural courses—seems confounding at first and greatly challenges the clinician to identify a unifying diagnosis in the individual patient, let alone a diagnosis that would unify any cohort of such superficially disparate patients.

The notion that such a unifying process might exist is not new, but the fact that such a process, if it exists, has evaded detection for so long is itself an important clue, that is, if the solution were obvious, it would have been found much earlier. Therefore, perhaps the common etiologic key lies in an area which our accumulated knowledge has given us no reason to suspect harbors the key, that is, an area of rare disease which thus "could not possibly explain" the epidemic proportions of many of the modern CIDs.

And indeed, in just the last few years, new understandings have been emerging in just such an area—mast cell (MC) disease—showing that such disease might in fact be the key to understanding a large swath of modern epidemic noninfectious inflammatory ailments.

The year 2013 marked the sesquicentennial of the discovery of what today remains one of the most underappreciated developments in eukaryotic evolution, the MC. German pathologist Friedrich von Recklinghausen first identified MCs (in frogs),[8] and in 1877, Paul Ehrlich first identified in human connective tissues these same cells, which he termed *Mastzellen*, or well-nourished cells, because of their rich granular content.[9] A decade later, German dermatologist Paul Gerson Unna first associated MCs with human disease in the rare skin disease urticaria pigmentosa.[10] Not until 1949, though, were MCs associated with internal disease in what we today call systemic mastocytosis (SM).[11] Identification of MC products had begun in 1937 with the discovery that the metachromasia of MC granules is due to their heparin content,[12,13] and in 1953, the MC's high histamine content was discovered.[14,15] Ensuing decades saw development of the modern understanding of not only the hematopoietic origin of the normally widely, sparsely distributed MC (now known to be present in all tissues to one degree or another) but also its fundamental function, namely, to produce and release a wide range of molecular signals, generally termed MC mediators and estimated to number from the dozens[16] to perhaps >200,[17] contributing to many processes including defense, growth, healing, and inflammation. In 1987, tryptase was first defined as a highly sensitive and specific marker for MC activation,[18] but in the ensuing quarter century, it has become apparent that serum tryptase levels reflect the body's total load of MCs more than the summative activation state of that load.[19,20]

Insights into the molecular genetic roots of MC disease began emerging in 1993 with identification of the D816V-activating mutation of the kit transmembrane receptor tyrosine kinase, the extracellular portion of which is immunologically recognized as CD117.[21] This mutation later was proved present in most adult SM.[22,23] In 1998, it was shown that the MCs in many cases of SM, unlike any known normal cells, coexpress the aberrant doublet $CD117^+CD25^+$ or $CD117^+CD2^+$, or sometimes even the aberrant triplet $CD117^+CD25^+CD2^+$.[24] In the last 20 years, it has become apparent that MC accumulation in mastocytosis is due more to antiapoptosis than frank proliferation.[25-34]

Long after Unna's first association of MCs with a pathologic state, MC disease (cutaneous or systemic) was still thought to be a disorder of MC proliferation ("mastocytosis") with most clinical consequences

stemming from aberrant mediator release. In 1991, though, John Oates and Jack Roberts of Vanderbilt University hypothesized the existence of a spectrum of disorders of MC mediator release (ie, MC activation) with little to no MC cytoproliferation.[35] Evidence for such MC activation disorders continued to accrue, and 2007 saw the first descriptions in the literature of "monoclonal MC activation syndrome" (MCAS),[36,37] shortly followed by the first formal proposal for diagnostic criteria.[38] That same year, critical insight into the possible cause of the marked clinical heterogeneity of relatively nonproliferative MCAS was provided by German geneticist Molderings et al.[39] Their finding of a large array of mutations in the mRNA for MC KIT (the MC's principal regulatory element) in a cohort of MCAS patients was repeated and extended in another study they reported in 2010 which included healthy controls in whom these mutations were largely absent.[40] (Of note, although these findings have not yet been refuted, they still await independent confirmation). Simultaneously, multiple investigators reported that virtually all cases of mastocytosis, too, harbor multiple mutations (virtually always somatic) across many MC regulatory genes (MCRGs), epigenes, and microRNAs resulting in perturbances of a wide array of intracellular processes.[41-47]

In late 2010, noted MC researchers Cem Akin, Peter Valent, and Dean Metcalfe proposed a fundamentally new conceptualization that all MC diseases first and foremost manifest aberrant MC activation, thus engendering a new top-level designation of "MC activation disease" (MCAD) to describe the full range of (benign and malignant) pathologic MC states.[48] The proliferative diseases of (rare) cutaneous mastocytosis and (even rarer) SM comprise 1 element of MCAD, whereas various forms of the relatively nonproliferative MCAS (suggested by preliminary data as virtually epidemic[49,50] but only rarely demonstrable by presently available testing as monoclonal MCAS) comprise other elements of MCAD. According to this proposal, MCAS could be diagnosed if the patient repeatedly demonstrated symptoms consistent with aberrant MC mediator release, laboratory evidence of such release, absence of any other disease better fitting the entire clinical picture, and at least partial response to therapy targeted at MCs or MC mediators. However, as the mutational heterogeneity of MCAS effects substantial clinical and therapeutic heterogeneity, some felt that a diagnostic criterion for therapeutic response was impractical.[16] A year later, Valent et al[51] published an updated proposal for diagnostic criteria for MCAS in which the diagnostic requirement for therapeutic response was relaxed (ie, desirable but not necessary), and laboratory diagnostic criteria were streamlined to focus on tryptase. However, problematic aspects of this proposal, too, have been identified.[52] Meanwhile, in 2011, Molderings et al[53] published an alternative diagnostic proposal which is structured akin to the World Health Organization 2008 diagnostic criteria for SM,[54] makes diagnostic use of relatively specific MC mediators beyond just tryptase, and does not require demonstration of therapeutic response.

Although it seems likely that any given clinical presentation of MCAD—typically a chronic multisystem polymorbidity of generally inflammatory ± allergic theme—results from a specific set of mutations driving a specific pattern of both aberrant constitutive activation and aberrant reactivity in MCs (because of mutations in the MCs themselves as well as effects on normal and abnormal MCs and other cell lineages likely harboring much the same mutations), at present the range of mutations in MC regulatory elements for which commercial testing is widely available is still very limited (essentially only probing specifically for KIT-D816V). Thus, the question is raised as to whether "primary idiopathic MCAS"[55] might be more accurately termed "MCAS of undetermined clonality." When more readily available, whole KIT (or more extensive) sequencing of isolated MCs will help settle this matter.

It would be absurd, of course, to think that a single disease—MCAD or any other—accounts for all CID, but over the last several years, increasing evidence has been emerging of important, even critical, roles for MC activation in the pathogenesis of a wide array of CIDs. As such, it becomes possible that MCAD—particularly if MCAS is as prevalent and heterogeneously clonal as suggested by available preliminary data—might be a unifying explanation for significant proportions of a number of CIDs. Reviewed here, for sample selections of common, uncommon, and rare CIDs are the data suggesting that MCAD—dominantly MCAS—may be a key process underlying such CIDs.

COMMON INFLAMMATORY AILMENTS

Obesity. Evidence that the epidemic disease of obesity[6] may be rooted in MC disease in at least some portion of the obese population is mounting. MC disease has been clearly associated with obesity.[56] Obesity is now clearly recognized as a chronic systemic inflammatory condition.[57] White adipose tissue has been identified as a reservoir of MC progenitors.[58] Given the intimate involvement of prostaglandin D_2 (produced at much higher levels in the MC than any other known cellular source) and its metabolites in at least 1 key adipose tissue management pathway,[59] it is unsurprising that

overproduction of prostaglandin D_2 is positively correlated with some aspects of adiposity in mice[60] and humans,[61] and it is unsurprising that there is a surfeit of lipid abnormalities in MCAS, too.[62] Elevations in total cholesterol and low-density lipoproteins and decreases in high-density lipoproteins and very low–density lipoproteins are not uncommon.[56] In the author's experience, hypertriglyceridemia, too, is common in MCAD and often is the starkest lipid abnormality.

Diabetes mellitus type 2. Evidence that the epidemic disease of diabetes mellitus type 2 (DM2)[63] may be rooted in MC disease in at least some portion of the DM2 population is mounting. DM2 is now clearly recognized as a chronic systemic inflammatory condition.[57] MC disease has been clearly associated with DM2, and MC stabilization prevents diet-induced DM2 and improves pre-established DM2 in experimental animals and in humans.[64] There may be critical involvement of MC disease in diabetes mellitus type 1 (DM1), too, as MC stabilization delays onset of DM1 in experimental animals,[65] and tyrosine kinase inhibitors, imatinib and sunitinib, have been found capable of preventing and reversing DM1 in nonobese diabetic mice.[66]

Asthma. Increased numbers and heightened activation of MCs in the respiratory tracts of asthmatic patients have long been recognized.[67,68] It is now appreciated that the MC is a pivotal cell in the pathogenesis of not only asthma[69] but also most, if not all, other inflammatory and fibrotic diseases of the respiratory tract.[70]

Interestingly, with respect to the fact that the MC surface bears receptors for all the major sex hormones[71] (progesterone may drive MC maturation and inhibit MC degranulation,[72] whereas estrogen seems to drive MC degranulation,[71] releasing histamine which facilitates endothelial permeability and increases ovarian blood flow during ovulation[73]), it has been observed that 30%–40% of asthmatic women experience worsening of asthma during perimenstrual phases, and prevalence of asthma and other allergic diseases has significantly increased in the last 30 years, possibly related to increasing concentrations of estrogen-like environmental pollutants, mainly in water and food, which can activate MCs.[71]

Atherosclerosis. Given the emerging links between obesity/adiposity and MC disease, potential links between atherosclerosis and MC disease should not be surprising.[56] As with asthma and MCs, the association of atherosclerosis with MCs has been known for decades.[74] MCs are increasingly being understood to be sources of cytokines and other signals that promote atherosclerosis (eg, interleukin [IL]-6 and interferon-gamma [IFN-γ],[75] connexin 43,[76] tryptase,[77,78] chymase,[78] receptor activator of nuclear factor kappa-B ligand,[79] etc.). As such, and again as in asthma, MCs are increasingly coming to be seen as pivotal cells in the development of atherosclerosis.[80-82]

Chronic fatigue syndrome. Also known as myalgic encephalopathy, myalgic encephalomyelitis, or systemic exertion intolerance disease, CFS is a complex disorder characterized by otherwise unexplained debilitating fatigue continuing for at least 6 months, together with a broad range of other constitutional, cognitive, sleep, and inflammatory symptoms.[83] It is a highly prevalent condition, with preponderance among young adults and females.[84,85] MCs and their mediators have been implicated in some common CFS comorbidities, and it has been proposed that proinflammatory cytokine release by activated diencephalic MCs may be pivotal in the development of CFS.[86,87] It also has been proposed that reactivation of various infections could lead to release of corticotrophin-releasing hormone (CRH) resulting (primarily indirectly, including engagement of activating mast cell surface CRH receptors) in many of the symptoms seen in CFS.[88] However, failure to consistently identify such infections in CFS patients and persistence of symptoms despite eventual depletion of CRH suggest that constitutive (abnormal) rather than reactive (normal) MC activation is more likely to be the basal phenomenon, although it is certainly possible that constitutively activated MCs may additionally exhibit abnormal reactivity to CRH.

Fibromyalgia. Yet another prevalent (1%–5%[89]), female preponderant (2–13:1[89]), complex and poorly understood inflammatory condition, with a proteome in cerebrospinal fluid identical to that that in CFS,[90] FM is currently defined as the persistence for 3 months or longer of pain at a certain number of (potentially changing) body points together with certain degrees of a number of other (and, again, potentially changing) multisystem inflammatory symptoms.[91] The symptoms considered in the definition of FM completely overlap with what can be seen in MCAD.[92,93] Increased numbers of activated MCs have been repeatedly found in random skin biopsies in FM patients.[94,95] Especially, given the proximity of neurons to MCs in many sites in the body, it has been proposed that CRH release from MC-proximate neurons in specific soft-tissue sites triggers those local MCs to release proinflammatory and neurosensitizing mediators, yielding much of the symptom burden in FM.[96] Of course, constitutively activated MCs could produce the same phenomenon.

Inflammatory cytokines IL-1 beta, IL-6, and tumor necrosis factor-alpha (TNF-α)—all known products of MCs (and, to be sure, other inflammatory cells)—have been identified in the skin of patients with FM.[97] MC activation has been observed in the thalamus (a critical brain region in the sensation of pain) in FM patients.[98]

Irritable bowel syndrome and inflammatory bowel disease. Evidence has been accumulating for at least a quarter century that MCs are integrally involved in most types of IBD and IBS. Much effort has been expended toward finding correlations between numbers of mucosal MCs and symptoms, and although most of such studies have yielded significant positive results, the magnitude of the differences found between patients vs controls has not been particularly great, and some studies have found no difference, which is perhaps not surprising given the patchiness with which MCs tend to distribute. In a systematic review of the IBS literature in 2011[99] as well as multiple subsequent studies and reviews, the commonest abnormality observed across individual studies was increased numbers of MCs in both the colon and upper gastrointestinal (GI) tract of patients with IBS. The numbers of MCs in close proximity to nerve fibers have been found increased in multiple studies[99,100]; there is a significant correlation between MC proximity to nerve fibers and the frequency and severity of abdominal pain,[99] and degranulated MCs were frequently observed in biopsies from IBS cases.[99] It is unclear from these studies whether MCs activated by proinflammatory substances in the GI lumen are stimulating local nerve fibers or whether it is abnormal activity of the nerve fibers themselves that is causing inappropriate degranulation of MCs.[99] MC stabilizers such as ketotifen[101] and some salicylates (eg, mesalazine[102-104]) have yielded similarly weakly positive results. A more recent key observation has been that it is the degree of activation of MCs that may matter far more than the number of MCs.[105,106] It is interesting, in light of MCs expressing all major sex hormone receptors and degranulating in response to estrogen exposure but not testosterone exposure,[71] that significantly more females than males are diagnosed with IBS.[107] To date, though, despite the accumulated evidence of MC involvement in IBS, including repeated data sets providing preliminary evidence of the etiologic possibility of constitutive MC activation,[39,40] there has been understandable reluctance to identify MC activation as truly a root cause of IBS. As in other CIDs, identification of constitutively activating mutations in MCs in involved tissue may be necessary to confidently attribute the cause of IBS to MC activation.

Proton pump inhibitor-refractory gastroesophageal reflux disease. Gastroesophageal reflux disease (GERD) is epidemic, especially in first world populations. Outside East Asia and Africa, 9%–33% of various populations suffers GERD,[108] and prevalence is increasing, including in East Asia.[108,109] Etiologies for such prevalence are unknown; speculation understandably focuses on obesity, diet, and lifestyle; *Helicobacter pylori* seems a lesser contributor.[108,109] Even more puzzling, half or more of GERD is nonerosive (NERD) and incompletely responsive, or even refractory, to proton pump inhibitor therapy.[110-112] If not the chemical burning of refluxed acid, what is the source of the pain these hundreds of millions of patients suffer? Inflammation—again, the *sine qua non* of MC disease—often causes pain, but most of endoscopic biopsies in GERD patients typically yield readings, from routine pathology processing (ie, staining with hematoxylin and eosin [H&E]), of either benign tissue or, at worst, mild chronic inflammation without obvious cause (eg, absence of *Helicobacter pylori*).[113] However, given the pleomorphism of the MC and its ability to masquerade, on H&E staining, as a lymphocyte, plasma cell, histiocyte, macrophage, or spindle cell,[114,115] it is possible that routine pathologic processing of GI tract biopsies performed to investigate that GERD (and other clinical conditions of GI tract inflammation) may be underappreciating the quantity of MCs in such biopsies, let alone their activation state. (The pathologist, quite reasonably, will only stain for MCs if given a reason to do so, and if the endoscopist has not thought of the possibility of a disease which he was taught [and has experienced] is rare [ie, mastocytosis] and manifests principally as anaphylaxis and flushing, then he will not convey a suspicion of MC disease to the pathologist). Indeed, MC-specific re-examinations of GI tract biopsies declared benign or mildly chronically inflamed on original, H&E-only examinations have identified previously occult increased MCs permitting diagnosis of MCAS and successful treatment,[116,117] although no systematic study has yet been performed to identify what portion of GERD or NERD might be unrecognized MCAS. MCAS almost certainly does not explain all GERDs or even NERD, but even if it accounts for only small portions of such extraordinarily prevalent conditions, millions may find relief through more accurate diagnosis and thus more accurately targeted treatment.

Essential and pulmonary hypertension. Like GERD, essential hypertension (EH), including treatment-resistant forms, is epidemic and increasing in prevalence.[118-122] By definition, the cause of EH is

unknown ("essential"). MC disease has long been recognized as capable of causing acute episodic hypertension, and it has long been recognized that among the MC's mediator repertoire are molecules that directly (eg, norepinephrine[123]) or indirectly (eg, renin,[124] chymase[125]) cause vasoconstriction. MCs preferentially site themselves not only at the environmental interfaces but also at perivascular (blood and lymph) locations.[126] Many MC mediators have very short half-lives and are highly thermolabile, such that their activities may be confined to tissue and leave few to no traces (at least not in easily obtained/analyzed tissue samples [eg, blood, urine]). Given these known aspects of the biology of MCs and their mediators, it is possible that dysfunctional MCs may be key but occult cardiac,[127] renal,[128] and perivascular[129] forces in producing not only acute but also chronic "essential" hypertension. MCs also may be key actors in development of pulmonary and portal hypertension.[130-134] Of course, given the frequent abutment of, and substantial "cross-talk" between, MCs and neurons, it is possible, too, that both perivascular neuron–mediated activation of perivascular MCs and perivascular MC–mediated activation of perivascular neurons may contribute to multifocal and/or systemic arterial vascular tone in EH.[129,135] MCs may influence chronic arterial/arteriolar tone not only by the influence of released mediators on vascular smooth muscle but also by influencing development of atherosclerosis[135,136] and adventitial remodeling.[137] Adipose tissue is a known reservoir of MC precursors,[57,58] and perivascular adipose tissue MCs, too, may play a role in the development of hypertension.[138]

Chronic kidney disease. Chronic kidney disease (CKD) is increasingly epidemic. Prevalence was estimated in 2012 to be 8%–16% worldwide.[139] In the United States, for 2005–2010, prevalence was estimated at 14.0% (43.3 million),[140] and an estimate of prevalence in China in 2012 was 10.8% (119.5 million).[141] Incidence is approximately 50–600 per million population in most developed countries, with Mexico, Taiwan, and the United States suffering the highest rates.[142] Although it is clear that a wealth of pathologies causes CKD, most CKD is of idiopathic etiology other than for association with EH, diabetes, and obesity. Evidence is accumulating that chronic inflammation is a key factor in development of CKD[143-146]; furthermore, diabetes mellitus and obesity are now understood to be inflammatory conditions, and as noted previously, evidence is accumulating that EH, too, is an innately inflammatory condition.[147-149] As acute and chronic hypertension, hyperglycemia, and obesity can all be seen in MC disease,[52] it is possible that MCAD (far more often MCAS than mastocytosis) may be a unifying factor underlying CKD. Renal pathology in CKD is characterized by tubulointerstitial fibrosis with excessive matrix deposition produced by myofibroblasts.[150] Transforming growth factor-beta, a mediator product of several types of cells including the MC, plays a key role in the development of renal fibrosis.[151] The origin of renal myofibroblasts has been a subject of intense investigation. Given that MCs tend to site themselves, among other locations, at perivascular locations, it is interesting that recent data suggest the resident pericyte/perivascular pool is a source of renal myofibroblasts.[150]

Idiopathic nonischemic cardiomyopathy. Nonischemic cardiomyopathy (NICM) is a prevalent problem worldwide[152,153] and is practically as burdensome a problem as ischemic cardiomyopathy.[154-156] There are many identifiable forms of NICM, but the etiologies of many of these forms remain unknown, and the problem remains wholly unclassifiable/idiopathic in many.[153,154] Fibrosis and inflammation, both driven by many MC mediators, are very common pathologies found in NICM (dilated and hypertrophic).[155,157] There is a strong association between asthma and idiopathic dilated cardiomyopathy, suggesting that "hypersensitivity mechanisms may be important in the development of idiopathic dilated cardiomyopathy.[158] In fact, cardiac MCs have been shown to play a causal role in the pathogenesis of adverse myocardial remodeling secondary to sustained elevations in myocardial stress.[159] As part of this response, cardiac MC density increases in a variety of cardiac pathologies including hypertension, myocardial infarction, volume overload, and heart failure, but increased MC activation is clearly at least as much, if not even more, a critical factor in these pathologies than simple increased numbers of MCs.[159] All in all, it would seem that evaluation for MCAD is routinely warranted in patients presenting with idiopathic NICM, and patients with inflammatory myocarditis without apparent specific infectious or noninfectious etiology should not be assumed (as seems often performed in practice) to be suffering viral myocarditis before MCAD is ruled out.[156]

Metabolic syndrome. Metabolic syndrome is an epidemic disease[160] defined as the presence of impaired glucose tolerance or type 2 diabetes mellitus and/or insulin resistance, together with 2 or more of abdominal obesity, hypertension, hypertriglyceridemia and/or low levels of high-density lipoprotein cholesterol, and microalbuminuria.[161] As well

summarized by Zhang and Shi,[161] MCs are clearly involved in the development of obesity, insulin resistance and type 2 diabetes mellitus, hypertension, and dyslipidemia, so it seems not much of a stretch to suspect MC activation is at least "involved" in metabolic syndrome—and may even be causative in at least certain variants of primary MCAD.

Autism spectrum disorders. Collectively, the autism spectrum disorders (ASDs) are now recognized as virtually epidemic, being diagnosed in 1 of 68 children aged 8 years at 11 monitoring sites in the United States in 2010[162]; a recent update suggested that this may have increased to 1 in 45 by 2014.[163] Furthermore, ASDs are roughly 10-fold more common in children with mastocytosis than those without mastocytosis, and perinatal MC activation by a variety of causes typically encountered early in life may contribute to central nervous system (CNS) inflammation and ASD pathogenesis.[164] In a striking similarity to preliminary mutational findings in MCAD,[39,40] *de novo* mutations are commonly found in ASDs.[165]

An initial report of an association of the measles-mumps-rubella vaccine with ASDs[166] was eventually shown fraudulent[167] and retracted,[168] and association between early childhood vaccinations and ASDs in the general pediatric population has subsequently been repeatedly refuted.[169-171] However, cases of various chronic inflammatory illnesses after vaccination have long been reported (eg, the study by Martínez-Lavín et al[172]). In addition, as previously noted, MCs are rarely identifiable with routine (H&E) staining of gastrointestinal tract mucosa, and no studies to date of chronic enterocolitis after vaccination have used MC-specific staining or other testing (eg, the study by Hornig et al[173]), leaving open the possibility that some cases of nonspecific chronic GI tract "lymphocytic" inflammation might actually be cases of chronic GI tract MC-driven inflammation. Therefore, given that (1) stressors of any sort can provoke acute and/or chronic MC activation; (2) vaccination is an immune system stressor; (3) some adult MCAD patients report acute and chronic, local, and systemic reactions to vaccinations consisting of symptoms consistent with MC activation; and (4) MC activation may contribute (as above) to ASD pathogenesis, it is conceivable that vaccination may contribute to ASD pathogenesis in some cases, although perhaps with too small an incidence rate to have been detected in the many recent large reviews in this area. Although vaccinations clearly are safe and effective for the general population, in the same fashion in which some vaccinations are contraindicated in certain subpopulations (eg, immunocompromised individuals), it is possible that some variants of MCAD may confer sufficient immunocompromise or allergic-type reactivity risks to increase toxicity risks from certain vaccinations. Clearly, given the adverse outcomes resulting from the initial report,[174] more carefully designed and executed research will need to be performed in this area if such a hypothesis is to be accurately vetted.

Attention deficit/hyperactivity disorder. As with the ASDs, attention deficit disorder and attention deficit/hyperactivity disorder (AD[H]D) is a neurodevelopmental disorder increasingly linked to other disorders in which MCs are increasingly being recognized to play pivotal roles. Atopic disease has now been shown in multiple large studies of the United States, European, and Chinese populations to be strongly associated with AD[H]D, with higher prevalence of AD[H]D in patients with more severe degrees of atopic disease.[175-177] Most of the food-allergic reactions are immunoglobulin E (IgE) mediated, leading to MC degranulation, and there is increasing suspicion that frequent/chronic food-allergic reactions could contribute to AD[H]D.[178] Food dyes, too, have been recognized for decades as capable of causing MC degranulation[179], and dyes are increasingly being recognized as potentially contributory to some cases of AD[H]D.[180] Non-IgE–mediated (eg, IgG mediated) and nonallergic hypersensitivity reactions, too, are thought to trigger AD[H]D symptoms in some children.[181] Children suffering from atopic disease bear increased levels of proinflammatory cytokines such as MC-derived IL-6 and TNF-α which may pass the blood-brain barrier and affect neuroimmune mechanisms involving behavior and emotion. AD[H]D patients have a cerebrospinal fluid (CSF) cytokine profile intermediate between patients with obsessive-compulsive disorder (skewing to proinflammatory cytokines) and schizophrenia (skewing to anti-inflammatory cytokines), with elevated CSF levels of proinflammatory TNF-β and reduced anti-inflammatory IL-4, IL-2, and IFN-γ. In addition, children with AD[H]D are relatively deficient in cortisol, potentially decreasing production of Treg lymphocytes, resulting in a Th2-driven inflammatory state resulting in activation of MCs and other cells contributing to allergy.[181]

Depression. Depression is common in mastocytosis (prevalence ~60%[182]) and in MCAS (prevalence ~72%[183]) in humans—and even in cats[184] and dogs,[185] in which mastocytosis is far more common than that in humans. Depression also has been correlated with other diseases rooted in, or increasingly thought to be rooted in, aberrant MC activation such as IBS and food allergy in some

studies (eg, Addolorato et al.[186], Piche et al.[187], and Yuan et al.[188]).

Depression, such as most major psychiatric disorders, is now understood to have a component of central nervous system inflammation.[189-193] The source of that inflammation has remained unclear, although MCs are increasingly suspected of playing a central role and depression has been associated with other chronic inflammatory disorders (eg, atopic disorders, obesity, autism, chronic pelvic pain) in which MCs have a known role or are increasingly suspected to have a significant role.[164,189,192] Experimentally induced allergy to tree pollen has been reported to induce depressive-like behavior and MC activation in the brain of female rats.[194] Heterocyclic antidepressants (eg, amitriptyline) have been shown to have anti-inflammatory effects mediated in part inhibition of MC degranulation.[195]

Multiple chemical sensitivity syndrome. First described in the medical literature decades ago, multiple chemical sensitivity (MCS) is a syndrome of aberrantly heightened reactivity to a range of chemicals (typically as odors but also by skin or mucosal contact).[196,197] Solvents, pesticides, fragrances, cleaning chemicals, and metals are oft-cited triggers of MCS flares. Onset typically follows a high-level exposure. Thereafter, even very low–level re-exposures can trigger flares, plus the range of sensitivities typically expands over time even without further high-level exposures. The respiratory and gastrointestinal tracts, skin, conjunctivae, and musculoskeletal system are more commonly affected, but potentially any system may be affected. Symptoms usually are consistent with what is commonly seen in MC activation, including flushing.

The very existence, let alone etiology, of MCS has long been debated. The dominant view for decades (persisting in the literature even to the present[198]) has been that MCS is of "psychogenic" origin (notable in that most MCAD patients report being suspected to have psychosomatism long before MCAD is diagnosed as the true root of their symptoms[199]), but more recently an alternative view has been emerging that "neurogenic inflammation," with integral MC involvement, may be at the root of MCS.[196,197,200-203] Compared with healthy controls, the olfactory cortex of MCS patients demonstrates greater fluorodeoxyglucose uptake, consistent with a hypothesis of "CNS hyperreactivity" (ie, neurogenic inflammation) underpinning MCS.[204] In addition of interest, MCs migrate from blood to brain and infiltrate the thalamus within a few hours in response to chemotactic molecules directly released by peripheral sensory afferents.[205] Of course, neurogenic inflammation is now understood to be a common component of the multisystem inflammation that is the dominant feature of MCAD.[199] Increased systemic proinflammatory cytokine levels have been found in MCS, too.[206] The prevalence of MCS has been found to be 10%–15% in the general population,[197] equivalent to that of allergy[207] and asthma,[208] in both of which MCs play integral and perhaps even primary roles. These findings, together with clinical observations that many of the symptoms in MCS flares are consistent with MC degranulation, suggest the possibility that MCs may play an integral and perhaps even primary role in MCS. A rat model believed to be representative of human MCS has shown several similarities in aberrant airway responsiveness to a rat experimental asthma model,[209] and in a small study of MCS patients, 20 of 38 patients showed increased MCs (though not mastocytosis) in skin biopsies.[210] Some of these patients even showed elevated serum tryptase. The investigator hypothesized a disorder of MC activation might underlie MCS.

Anemia of chronic inflammation. Anemia of chronic inflammation (ACI) is estimated to be the second most common cause of anemia worldwide (after iron deficiency).[211] The prevalence of anemia increases with age; 11% of the U.S. population older than 65 years is anemic, and chronic inflammation without CKD is seen in 20% of that anemic population.[212] MCs are central to the initiation of inflammation,[213] and, again, chronic inflammation is the *sine qua non* of MC disease. As such, ACI is common in MC disease—but less common than might be thought, as an analysis of a cohort of 298 MCAS patients found decreases in hematocrit in only 69%.[214] Although it is possible that the overexpression of anemia-driving inflammatory mediators in the dysfunctional MCs in some MCAD patients is too modest to cause anemia, it also is conceivable that constitutive KIT activation in many MCAD patients may result in sufficient activation of proerythropoietic pathways (eg, JAK2) to offset anemia of ACI. (In fact, secondary polycythemia has been reported in a greatly inflamed MCAS patient).[116]

Proinflammatory cytokines such as TNF-α, IL-1, IFN-γ, and IL-6 appear intimately involved in suppression of marrow erythropoiesis by impairing proliferation of erythroid progenitor cells and blunting the erythropoietin response to anemia.[215,216] MCs produce all these proinflammatory cytokines (and many more),[17] providing a pathway by which MCAS of any time (primary, secondary, idiopathic) can contribute to ACI.

Interestingly, in an *in vitro* model, iron supplementation decreased MC granule content, IgE-triggered

degranulation, and production of proinflammatory cytokines after degranulation.[217] Thus, although not yet studied in humans, it is conceivable that iron supplementation in some fashion may be able to help downregulate MC activation and its downstream effects even in an iron-replete state. Until such studies are conducted, though, the relatively high frequencies (up to 47%) of acute and sustained adverse reactions (quite possibly MC/MCAS-driven, judging by the particular symptoms observed including urticaria, rash, and anaphylaxis) to oral and parenteral iron supplementation products[218-222] argue for cautious use of such products in MCAD patients clearly manifesting clinically significant iron deficiency.

Autoimmune disorders. MCs influence initiation and effector phases of potentially any type of autoimmunity via many mechanisms including directing T-cell differentiation, promoting dendritic cell maturation and migration to secondary lymphoid organs, and orchestrating migration of T cells and other immune cells to sites of inflammation. The impact of MCs on development of autoimmunity can be related to the activating stimulus, tissue site, proximal target cells, and genetically determined variability in mediator production.[223]

In clinical experience, a very wide range of autoantibodies and autoimmune diseases have been seen in association with MCAD (eg, autoimmune thyroiditis, autoimmune nephritis, autoimmune dermatitis, antiphospholipid antibody syndromes, multiple sclerosis [specifically discussed later, etc.]). Interpretation of autoantibody titers in MCAD can be challenging since some patients manifest detectable titers, ranging from minimal to marked, of certain autoantibodies without manifesting any symptoms or signs of the autoimmune diseases classically associated with those autoantibodies, and autoantibody titers in such patients often vary substantially (even sometimes temporarily disappear altogether) from one determination to the next, in contrast to more stable trends commonly seen in patients truly manifesting the expected associated autoimmune disease (own unpublished experience). (In similar fashion, confoundingly highly variable reactivity to the same set of allergens from 1 skin patch testing to the next just weeks later is also not uncommonly seen in MCAD [own unpublished experience]). The finding of such an "ineffective" autoantibody raises the possibility that what is being detected is a mimicking, or "off-target," antibody (erroneously generated via MCAD-driven immune dysfunction) with sufficient specificity to react with probes for that autoimmune disease–associated antibody but not sufficiently specific to cause the classically associated disease. In the setting of MCAD, diagnosis of autoimmunity should not be based solely on discovery of the presence of an autoantibody, no matter the titer, and rather should carefully adhere to established diagnostic criteria for the given autoimmunity. Even then, given the common overlap of MCAD symptoms and autoimmune disease symptoms, diagnosis of autoimmunity must be considered cautiously given the often profound therapeutic decision-making consequences.

As MCAS-driven inflammation can initially be seen as early as the immediate postnatal period, distinction of MCAS from inborn autoinflammatory syndromes (usually identified relatively early in childhood) is challenging and requires a high index of suspicion (fostered by emergence early in infancy of chronic multisystem inflammation) and presently expensive genetic testing. Such distinction is further confounded by increasing recognition that some autoinflammatory syndromes (eg, cryopyrin-associated periodic syndrome, in which mutations silencing NLRP3 expression result in upregulated expression of IL-1β and its downstream inflammatory consequences[224]) are principally operant in MCs,[225] essentially rendering such syndromes just assorted specific (if rare) variants of MCAS. Again, appropriate genetic testing is needed in cases of very early emergence of chronic multisystem inflammation, but access to such testing may be limited by third-party payer systems (some of which require genetic counseling before approving coverage of the costs of such tests). Nevertheless, such diagnostic considerations are important given that for some autoinflammatory syndromes (whether variants of MCAS or not), orphan drugs exist (eg, IL-1β antagonists such as anakinra or canakinumab for cryopyrin-associated periodic syndrome[224]) which well target the molecular lesion or its principal consequences, affording the patient substantial benefit without necessarily also having to engage more classic MC-targeted therapies.

Endometriosis. The often chronically painful condition of endometriosis is an epidemic problem, estimated to be present in 2.2%–7.5% of the general U.S. female population at age-based risk,[226] with far higher prevalence rates in more select populations (eg, approximately 2 of 3 young women with chronic pelvic pain[227] and 30%–45% among women undergoing surgery for sterility, chronic pelvic pain, fibroids, or ovarian cysts[228]). Worldwide, endometriosis is costly in terms of direct costs of care[229,230] and lost productivity.[231] Interestingly, about two-thirds of women with chronic pelvic pain also have chronic bladder pain,[232] for which interstitial cystitis (strongly associated with MC activation and associated with other neuropsychiatric

disorders potentially driven by MC activation[233]) is a major cause.

Aberrant MC activation, with release of assorted inflammatory mediators, is a well-recognized primary issue in endometriotic tissue and provides a target for treatment of this significant public health issue.[234-237] MCs and degranulating MCs are more abundant in endometriotic tissue than those in other pelvic tissues, and deep infiltrating lesions of endometriosis bear significantly more MCs and activated MCs and show closer physical proximity of MCs to nerves, than is seen in peritoneal or ovarian endometriosis—an interesting finding given that women with deep infiltrating lesions report more pain than women with peritoneal or ovarian endometriosis.[235] Interestingly, a high density of activated MCs has been found in endometrial polyps, too (mean 113/mm^2 [constant across menstrual cycle phases] vs 38/mm^2 in adjacent endometrium [ranging significantly from highest {68/mm^2} in menstrual phase to lowest {29/mm^2} in secretory phase] and 16/mm^2 in normal endometrium).[238] Critically, the frequency of primary MCAD in endometriosis (as in most conditions now recognized to overlap with, and possibly be attributable to, MCAD) remains unstudied. Identification of primary MCAD as a frequent driver just of endometriosis alone would be a clarion call for substantially increased research in MCAD.

Polycystic ovarian syndrome. Like endometriosis, polycystic ovarian syndrome (PCOS) is a prevalent female morbidity associated with chronic low-grade inflammation and a number of other comorbidities which themselves are being increasingly recognized as chronic low-grade inflammatory issues (eg, type 2 diabetes mellitus and insulin resistance, dyslipidemia, etc.).[239] In a rat model, it was found that MCs may be involved in induction of ovarian cysts.[240] The possibility that increased numbers of MCs in PCOS may be a more systemic than ovarian-localized phenomenon was suggested in another experimental PCOS rat model in which increased MC infiltration in the soft palate was found in PCOS rats vs controls.[241]

Celiac disease and nonceliac gluten intolerance. Celiac disease is a T-cell–mediated small bowel enteropathy induced by gluten in genetically predisposed individuals; symptoms classically include abdominal pain, bloating, diarrhea, nausea, vomiting, fatigue, and weight loss.[242] However, the disease is not exclusively effected by T cells, and involvement of MCs, releasing twice as much histamine in the jejunum of celiac patients in response to a gliadin challenge as compared with healthy controls, was clear 3 decades ago,[243] although findings of whether the number of MCs in celiac-affected small bowel mucosa is increased or decreased compared with normal mucosa have radically varied.[244,245] Although certain human leukocyte antigen (HLA) variants (DQ2 and DQ8) have long been known to be highly associated with (but not causative of[246]) celiac disease, more recently variants in IL-1 receptor-related protein ST2 (IL-1RL1, the receptor for IL-33, an alarmin which is released on structural cell damage and leads via IL-1RL1 to Th2 lymphocyte, MC, and basophil activation) also have been identified as susceptibility markers for celiac disease, further raising questions of whether primary MCAS might have some involvement in the development of celiac disease.[247] At other inflammasome axes, mutations in NLRP3 leading to constitutive inflammasome activation (critically operant in MCs[225]) have also been found to be associated with celiac disease (and other autoimmune/inflammatory diseases),[248,249] and polymorphisms of the proinflammatory cytokine TNF-α, too, have been associated with celiac and other autoimmune/inflammatory diseases.[246,250] Increased intestinal epithelial permeability is a key pathologic feature of celiac disease (and IBD), and mice deficient in MCs or even just MC chymase demonstrate significantly decreased basal small intestinal permeability.[251] Assorted inflammatory cytokines (for most of which the MC is a known source, eg, IFN-γ and TNF-α[17]) increase acutely in intestinal tissue of celiac patients exposed to gluten[252,253] (IFN-γ is a key to damaging enterocytes, as blocking antibodies prevent such damage[254]), but the specific cellular source(s) of each such cytokine remains unclear. Maiuri et al found such rapid ($\leq$1 hour) activation of enterocytes by a gliadin challenge in duodenal-jejunal flexure biopsies from celiac patients that T-cell activation seemed an unlikely explanation for this early phase of response as no markers of lymphocyte activation were seen, and it was noted that on antigen challenge, T lymphocytes secrete cytokines only after many hours and do not have a store for rapid release. Instead, release of preformed mediators, such as from MCs as seen in asthma, seemed more likely.[255] Other diseases likely originating in, or closely involving, dysfunctional MC activation (eg, chronic urticaria,[256] asthma[257]) have been seen in association with celiac disease and sometimes do not improve even when a gluten-free diet improves intestinal symptoms.[258,259] Idiopathic chronic urticaria does not appear to convey risk for celiac disease.[260] If MCAS is as prevalent (and primary) as suspected in work to date,[39,40,49,50] it is likely that a significant fraction of the celiac population coincidentally bears MCAS, potentially leading to erroneous attribution of some symptoms to celiac disease instead of (likely unrecognized) MCAS. Although it is unknown whether the principal T-cell–

centered molecular pathogenetic processes in the small bowel in celiac disease cause the extraintestinal symptoms sometimes seen in the disease (eg, hematologic, psychiatric, endocrine, hepatic, renal, neurologic, rheumatologic/autoimmune, dermatologic, oral mucocutaneous, skeletal, cardiovascular),[242] it is of note that most or all such symptoms are seen in MCAD.

Furthermore, gluten intolerance (of unknown mechanism[s]) is also seen in many patients without celiac disease[261]; many of these patients are also diagnosed with "functional bowel disorders" such as IBS in which MCs increasingly are being suspected of playing a pivotal role (though still unclear whether primary or secondary).[262] Primary MC disease has long been suspected as a potential etiology in celiac disease and a variety of other inflammatory and functional gastrointestinal ailments,[263] but the only specific investigations of the presence of primary MC disease in such diseases have focused exclusively on markers of SM[264,265] and have not sought other evidence of MC clonality suggested recently to be present in most cases of MCAS.[39,40]

Migraine headaches. Migraines are yet another CID with significant prevalence, estimated to affect 6%–8% of men and 15%–25% of women in the Western population.[266,267] Suspicions that many migraines may be rooted in MC activation date back at least half a century.[266,268,269] Several studies have shown elevations in MC mediators such as histamine in the plasma of migraine patients compared with controls both during and between attacks.[267] Evolution of research in this area has come to focus on a central role for dural and brain MCs, abutting vessels, and neurons (especially in the dura), thereby primed to be activated by signaling (calcitonin gene–related peptide [CGRP], neurotensin, pituitary adenylate cyclase–activating peptide, substance P, etc.) resulting from trigeminal or other nervous stimulation and in turn activating dural nociceptors via yet another array of signals (eg, histamine, nitrous oxide, TNF-α, vasoactive intestinal peptide, serotonin, prostaglandin I_2, bradykinin, vascular endothelial growth factor).[266,267,270-274] Furthermore, several of these mediators trigger further CGRP release from MCs, driving a positive-feedback loop. As such, blockades of these signals may be beneficial to migraineurs. Histamine H_1 receptor antagonists and prostaglandin antagonists (ie, nonsteroidal anti-inflammatories) help some,[267,275] sumatriptan helps some (presumably via its inhibition of nociceptor release of CGRP[267] which directly relaxes vascular smooth muscle[276]; other CGRP blockers, including small molecule receptor antagonists and monoclonal antibodies, are showing promise, too[267,277,278]), renin-angiotensin axis inhibitors help some (presumably due to inhibition of vasoconstriction driven by renin from MCs),[279] capsaicin helps some (Frydas et al.[280]; presumably via activation of vanilloid receptor type 1 [TRPV1] expressed on neurons[281] and MCs[282]), and histamine H_3 receptor agonists may help some, too.[283]

Interestingly, migraines are associated with a number of other CIDs in which MCs increasingly are thought to play pivotal roles (eg, endometriosis,[284] asthma,[285] and cardiovascular disease[279]). In addition of interest, there are suggestions that the histamine H_3 receptor agonist class potentially useful in migraines may also be helpful in obesity and diabetes mellitus,[286] yet other diseases in which MCs appear to have some involvement as discussed previously.

Neurogenic pain syndrome. MCs can cause pain, including "neurogenic" pain, via a wide variety of pathways, the details of which are beyond the scope of this article but which have been extensively reviewed elsewhere.[205,287,288] As such, MCAD may be an underlying cause of neurogenic pain syndrome in some patients.

Restless leg syndrome. Restless leg syndrome (RLS) is another prevalent condition (estimated 5%–20%[289]) whose etiology is unknown. A review of conditions reported to be associated with RLS found that 95% of the 38 identified highly associated conditions (eg, many neurologic conditions suspected to be caused at least in part by MCAS,[199] IBS, celiac disease, FM, diabetes mellitus, obesity, sleep apnea, sarcoidosis, chronic obstructive pulmonary disease, pulmonary hypertension) were themselves associated with inflammatory/immune changes, suggesting that RLS itself may be mediated through such mechanisms.[290]

Schizophrenia. Schizophrenia is a chronic brain disorder with various structural and functional anomalies found in assorted cortical and subcortical compartments causing both positive and negative emotional and motivational symptoms and cognitive deficits. Its pathogenesis and pathobiology remain poorly understood, but dysregulations in dopamine, histamine, and other neurotransmitter axes (eg, possibly neurotensin,[291] serotonin,[292] prostaglandin,[293] etc.) seem important in its development, and H_3 receptor antagonists are showing some activity in trials in schizophrenia and may come to play at least an adjuvant role in management of the disease.[294-296]

Like most other major psychiatric morbidities, schizophrenia is now understood to have a neuroinflammatory component,[297] and although the source(s) of such inflammation remain far from clear, MCs increasingly are being suspected of playing a key role[298]—thus

creating a possibility that certain forms of primary MCAS might be drivers of such illnesses.[199] It has been pointed out that MCs can cross the intact blood-brain barrier and they are the only cells which can arrive at the site of brain injury already armed to initiate acute inflammation by release of preformed/stored mediators (eg, TNF-α) after appropriate stimulation, whereas other types of inflammatory cells either cannot cross the intact blood-brain barrier or require time to synthesize and then release assorted inflammatory mediators which contribute to a wide range of processes such as blood-brain barrier disruption, nociceptor activation, recruitment of other inflammatory cells, and so forth.[298] A possible association between a TNF-α polymorphism and schizophrenia has been identified.[299] Schizophrenia, such as MCAD (far more MCAS than mastocytosis), appears highly heritable.[300] Schizophrenia is associated, too, with other chronic inflammatory illnesses in which MCs increasingly are thought to play pivotal roles (eg, IBS[301,302]; an assortment of anxious, depressive, and attention disorders[303,304]; diabetes mellitus, hyperlipidemia, cardiovascular disease, obesity, malignancy, osteoporosis[305]; migraine, asthma, psoriasis/eczema[302]; interstitial cystitis, inflammatory disease of the ovary, menstrual disorders, arthritis[306]; etc.), further suggesting that a systemic MC activation disorder may be the unifying diagnosis in some cases of schizophrenia.

Bipolar affective disorder. Bipolar affective disorder (BPAD), such as schizophrenia, is a costly (in all the meanings of the word), prevalent disease (each afflicts 1% of the world's population[307]) which has come to be recognized as having a neuroinflammatory component of unclear source.[291] In fact, there are emerging suspicions and data that BPAD may be just 1 component of a multisystem inflammatory disorder, possibly involving the innate immune system and blood-brain barrier disruption and expressing many proinflammatory cytokines for which the MC is a known source.[17,308-320] Systemic MC activation has been seen in BPAD,[321] and cognitive dysfunction (as is also very commonly seen in MCAD) and serum and CSF markers of neuroinflammation are seen even in the euthymic state of BPAD.[322,323] A possible association between a TNF-α polymorphism and BPAD has been identified,[299] and a possible linkage between BPAD and the NLRP3 inflammasome (critically operant in MCs[225]) has been identified.[324] An identified association of infections (and autoimmune diseases) with BPAD[325] is provocative in view of a key aspect of the natural history of MCAD being stepwise escalations in morbidity shortly after major stressors.[93] BPAD has been associated with certain single nucleotide polymorphisms in the 4p15-16 region of genome; curiously, the nearest gene to 1 intronic area of interest is MIST (MC immunoreceptor signal transducer).[307] Interestingly, the mainstay of BPAD therapy—lithium—is now thought to have some anti-inflammatory effect.[326] Novel potential therapies for BPAD have been reported useful in MCAD, too.[327]

LESS COMMON INFLAMMATORY AILMENTS

Fibrosing diseases (including multiple sclerosis). MCs have potential, via many of their expressed mediators (eg, transforming growth factor-beta[17,328]), to drive fibrosis. MCs have been observed to drive, or at least be associated with, fibrosis in many sites in the body including skin,[329] heart,[127,330,331] lung,[332] kidneys,[333,334] liver,[335] pancreas,[336] retroperitoneum,[337] marrow,[338-340] and all stages of vascular atherosclerotic plaques.[334] MCAS has been seen in association with sclerosing mediastinitis.[341] MCs have long been known to play an important role in the development of multiple sclerosis,[342,343] and exacerbations of inflammation in the meninges (a rich source of MCs) have been correlated with clinical exacerbations of multiple sclerosis,[344] leading some to posit the meninges as new therapeutic targets in the disease.[345] MCs have been found to induce systemic sclerosis in mice.[346] It has been suggested that MCs may be instrumental in development of fibrosis,[347] but no investigation into whether primary MCAS might account for some portion of the cases of fibrosing diseases has been performed. It may be reasonable to consider the diagnostic possibility of MCAD when fibrosis is found.

Normal karyotype myelodysplastic syndrome. Increases or decreases in all peripheral blood cell counts have been seen in MCAD (including MCAS), and in MCAS, a mild macrocytosis is not uncommonly seen, too.[214] Unsurprisingly, myelodysplastic syndrome (MDS) is suspected in many such cases, yet marrow examination finds an MDS-associated recurrent cytogenetic abnormality in 40% of cases of diagnosed primary MDS.[348] Of note, marrow examination in MCAS, by the very limited testing for MC clonality presently available in the clinical laboratory (KIT-D816V mutation analysis by polymerase chain reaction [PCR], and flow cytometry for a $CD117^{+}$[$CD25^{+}$ and/or $CD2^{+}$] signature), rarely finds cytogenetic or other evidence of clonal disease. The marrow in MCAS usually shows only normal trilineage hematopoiesis, but the most common abnormal pattern in MCAS (own unpublished data) is a vague/nonspecific myeloproliferative and/or myelodysplastic appearance,

sometimes leading to an erroneous clinical diagnosis of MDS. With further systematic study of the appearance of the marrow in MCAS and further systematic study of the presence of MCAS in MDS and idiopathic cytopenias and cytoses, it may become reasonable to routinely consider MCAS in the differential diagnosis of these diseases, particularly when only modest marrow dysplasia is found.

Idiopathic iron-deficiency anemia. Most iron deficiency is of physiologic (menstrual) origin; pathologic iron deficiency usually is due to blood loss (gastrointestinal or urinary tracts or dysfunctional uterine bleeding). Malnutrition leading to iron deficiency is usually identifiable on history, as is iatrogenic medical or surgical achlorhydria leading to iron malabsorption, but autoimmune achlorhydria (pernicious anemia) and small bowel inflammation causing iron malabsorption can be virtually clinically silent. In cases of idiopathic iron-deficiency anemia in which small bowel biopsies appear normal on routine H&E staining, specific examination for MCs (preferably with CD117 immunohistochemical staining targeted at omnipresent MC KIT, which performs better than histochemical stains targeted at MC granules or their contents which may be difficult to detect after degranulation[349,350]) to identify otherwise occult MCAD is warranted.

Kounis syndrome. First described >60 years ago, Kounis syndrome (also known as allergic angina or allergic myocardial infarction, with absence of obstructive coronary arterial lesions) clearly is born of MC activation and requires identification of an allergic insult as the cause of the coronary vasospasm causing the electrocardiographic (ECG) changes.[351] Kounis syndrome is estimated to be present in 0.002% of all acute myocardial infarctions.[352] Ironically, the incidence of Kounis syndrome may be increasing in step with the increasing use of (allergogenic) drug-eluting stents for the treatment of atherosclerotic lesions.[351] Kounis syndrome has now been observed in cerebral and mesenteric arteries, too,[353] and given the perivascular presence of MCs in all vascular beds, presumably the same phenomenon is possible at other sites. It remains unclear whether the MC activation in Kounis syndrome is a consequence of allergic provocation of normal MCs vs the abnormal (clonal) MCs thought to underlie MCAS.

Takotsubo cardiomyopathy. In contrast to Kounis syndrome, no allergic insult appears to precede onset of Takotsubo syndrome (acute stress–induced cardiomyopathy with a hyperkinetic cardiac base, hypokinetic midventricle and apex, and left ventricular apical ballooning), which is seen in 2% of patients presenting with suspected acute coronary syndrome.[354] Although a clear connection between Takotsubo cardiomyopathy and MCAS has not yet been identified, 75% of Takotsubo cases manifest elevated plasma catecholamines (known products of several types of cells including MCs), and an increasing number of cases of Kounis syndrome are being reported as having manifested Takotsubo-like left ventricular apical ballooning.[355] Takotsubo cardiomyopathy also is appearing in some patients after idiopathic anaphylaxis,[356] further increasing suspicion of a connection with MCAS.

Burning mouth syndrome. Although prevalence varies dramatically in assorted select populations, approximately 1% of the general population reports chronic burning oral discomfort and meets established diagnostic criteria for burning mouth syndrome (BMS).[357] Although BMS is often secondary to infections, autoimmune disease, and other readily identifiable pathologies, many cases remain idiopathic. The author has reported several cases of BMS associated with a definable MCAS (and responsive to MCAS-directed therapy)[117] and since the time of that, report has seen and successfully treated (with MC-directed therapies) many additional cases (unpublished data).

Postural orthostatic tachycardia syndrome. Frank syncope fortunately is relatively uncommon among MCAS patients, but presyncopal episodes appear to be quite common. They often are unprovoked and nonorthostatic and are variably identified by patients as sudden-onset "lightheadedness," "weakness," "dizziness," or, less commonly, "vertigo." Sometimes, the matter will come to the otolaryngologist for evaluation, and the patient will be diagnosed with "vertigo." Tilt-table testing by the cardiologist may or may not be found consistent with postural orthostatic tachycardia syndrome (POTS, particularly the hyperadrenergic variant, which has been associated with MCAS[358,359]), but MCAS patients treated for POTS (eg, with midodrine or fludrocortisone) typically experience only modest improvement in their presyncopal episodes and little to no improvement in any of their other symptoms. If clinical history of a patient diagnosed with POTS reveals other (non-POTS) symptoms suggestive of MC activation, evaluation for an underlying MCAS is warranted.

Dysautonomia. Dysautonomia is a relatively nebulous diagnostic term encompassing a wide range of aberrant autonomic nervous system manifestations such as instability of blood pressure, pulse, or temperature. Dysautonomic patients sometimes manifest seizure and/or pseudoseizure behavior, too. In its typically episodic

behavior, dysautonomia mimics flares of MCAD, and MCAD (particularly MCAS) has now been found in many dysautonomic patients.[199] MC-directed therapy can reduce dysautonomic symptoms in some MCAD patients (eg, Afrin[360] [online supplement 2, case 5],[361]).

Glomerulonephritis. MCs have been found to be involved in various forms of glomerulonephritis including focal segmental[362] and crescentic,[363] raising the possibility that primary MCAS could be an underlying cause in some cases of glomerulonephritis.

Idiopathic hypercoagulable syndrome. MCs produce a number of procoagulant mediators (eg, Factor VIII[364,365]), and a tentative association between atopic diseases and venous thromboembolism has been identified.[366] Furthermore, MCAD is a fundamentally inflammatory disease, and the association between inflammation and thrombosis has been long known. As such, evaluation of the idiopathically hypercoagulable patient for MCAD may be warranted.

Difficult-to-control hypothyroidism. In classic simple hypothyroidism, a given thyroid hormone supplementation dose provides stable normalization of thyroid function, but many patients with hypothyroidism frustrate their physicians by their "failure" to maintain a stable normal thyroid-stimulating hormone (TSH) level in response to a given dose of thyroid hormone. This pattern of instability is common in patients with MCAS who also are diagnosed with hypothyroidism (typically long before their diagnosis with MCAS, an unsurprising phenomenon given the overlap in symptoms between the 2 diseases and the only recent recognition of MCAS). Many such patients, in fact, have manifested only modest TSH abnormalities not correlating well with the severity of their symptoms (not to mention the presence of some symptoms [eg, allergy] which hypothyroidism cannot easily explain), and yet they are diagnosed with hypothyroidism for lack of any other apparent unifying diagnosis. An association between thyroid autoimmunity and putatively MC-driven diseases such as chronic urticaria and idiopathic angioedema has long been known.[367,368] Interestingly, it has been found in rats that thyroid MCs, on stimulation by TSH, participate in the process of thyroid hormone secretion[369] and that rat thyroid MC numbers, exocytotic activity, histamine, and serotonin content vary in relation to circadian activity of the thyroid gland.[370] These findings raise the possibility that the dysfunctional, constitutively activated MCs may impact thyroid function.

Gulf War illness. Although obviously essentially nonexistent among the civilian population, Gulf War illness (GWI) actually is quite common among veterans of Western forces who have served tours of duty in the Middle East. Approximately 40% of the >2 million U.S. veterans who have served in Kuwait, Iraq, and Afghanistan have developed GWI, typically within 1–2 years of returning to the United States. Despite >20 years and $1B of research by the U.S. Departments of Defense and Veterans Affairs, not a single cause has been identified for this nebulous, heterogeneous entity whose general theme appears to be chronic multisystem inflammation; the specific symptom complexes observed are well within the realm of what MCAD can cause. Interestingly, ground forces (perhaps more at risk for exposure to novel environmental antigens) develop GWI at higher rates than naval or air forces. Furthermore, the development of symptomatic GWI soon after return from a zone of armed conflict also well fits the observed natural history of MCAD in which escalation of symptoms often soon follows a major stressor (physical or psychological).

Poor-phenotype sickle cell anemia. Sickle cell anemia (SCA), the first monogenic disorder discovered, results from a single base-pair substitution in the gene for beta globin resulting in a variant hemoglobin which is less soluble than normal in hypoxic conditions. The resulting poorly deformable, sickled erythrocytes cause microvascular obstruction and the clinically well recognized pain crises of SCA. It has long been observed, though, that there seem to be 2 broad subpopulations of SCA patients, a large majority in whom the disease seems to cause relatively few complications and relatively little morbidity, and a minority in whom the disease causes far more complications and substantially greater morbidity. Efforts to identify the factors distinguishing these subpopulations have yielded no greatly satisfying explanations to date. Recently, MC activation was identified as the dominant cause of pain in a mouse model of SCA,[281] and a case series of poor-phenotype SCA patients was reported in whom MCAS was found in all.[360] Furthermore, some of these patients proved transformable into good-phenotype SCA patients on identifying effective treatments for their MCAS. Somewhat different treatments were found helpful in different patients, in keeping with the clinical heterogeneity (perhaps born of mutational heterogeneity?) of the syndrome. Although the wide range of complications associated with poor-phenotype SCA suggests other primary comorbidities, too, likely are present in various proportions across the poor-phenotype SCA population, primary MCAS of one form or another may be a key comorbidity in this challenging group of patients. Another group now has identified modest, but statistically significant,

increases in tryptase in SCA patients with chronic pain compared with SCA patients without chronic pain.[371] Tyrosine kinase inhibitors have been proposed as potentially useful adjuvants in SCA.[372]

RARE INFLAMMATORY AILMENTS

JAK2–wild-type polycythemia vera. Approximately 98% of patients meeting diagnostic criteria for polycythemia vera (PV) bear a mutation in JAK2, most commonly the V617F substitution—but ~2% do not. MCs can produce erythropoietic factors (eg, activin A[17]). The author has reported a case of MCAS-driven polycythemia[116] and since then has seen many others. Interestingly, imatinib has seemed more helpful in absolutely or relatively erythrocytotic MCAS patients than anemic MCAS patients (own unpublished data), perhaps due to stabilization of constitutively activated KIT and thus downregulation of not only erythropoiesis-driving JAK2 but also inflammation-driving JAK1 and JAK3. As such, when other causes of benign erythrocytosis have been excluded, MCAD should be considered before a diagnosis of JAK2–wild-type PV is made by default. Furthermore, in individuals who obviously are severely chronically inflamed and yet manifest hemoglobin and hematocrit levels in the normal range (let alone elevated), it has to be considered whether a relative polycythemia due to an occult erythropoietic force that can be seen in the presence of severe inflammation—potentially MCAD—is present.

Idiopathic pure red cell aplasia. Similar to the case of misdiagnosed PV in whom MCAS was discovered and successfully treated, the author has reported a case of idiopathic pure red cell aplasia (PRCA) which appeared to be due to MCAS and which was responsive to MC-directed therapy[373]—and since then has seen several similar cases (unpublished data). Consideration of MCAD may be warranted in otherwise idiopathic PRCA.

Drug-induced agranulocytosis. Similar to the cases of misdiagnosed PV and PRCA in whom MCAS was discovered and successfully treated, the author has reported a case of sulfasalazine-induced agranulocytosis which proved resistant to multiple therapies until MCAS was recognized and treated. Both imatinib and aspirin proved helpful.[374] Consideration of MCAD may be warranted in drug-induced and idiopathic agranulocytosis—and, in fact, any relatively acute drug-induced reaction not attributable to another apparent mechanism. Potential for (aberrant) MC reactivity to drug excipients must be considered, too, especially when the drug in question ordinarily is well tolerated.

Idiopathic aplastic anemia. As noted previously, MCAD can drive anemia to the point of PRCA and granulocytopenia to the point of agranulocytosis. Severe pancytopenia may be possible, too, and although careful assessment for all other known causes of course must be pursued in the patient with aplastic anemia, evaluation for MCAD may be warranted, too.

Idiopathic thrombocytosis. Thrombocytosis not attributable to a known cause such as infection, iron deficiency, a clearly identifiable inflammation, or a myeloproliferative neoplasm may be due to the sometimes less clearly identifiable inflammatory disorder that is MCAD.

Hypermobility/hyperflexibility-type Ehlers-Danlos syndrome. Although Ehlers-Danlos syndrome type III (EDS-III) is the most common type of EDS (approximately 40% of all EDS), it is the only one of the many types of EDS for which a highly recurrent (and presumably causative) mutation has not been found. The author has observed (unpublished data) a substantial minority of MCAS patients to also bear hypermobility-type (ie, Type III) EDS-III, and others have begun reporting an association of EDS-III with MCAS and/or POTS (which is also suspected of being rooted in MCAS in some cases).[375-380] The possibility is raised that EDS-III is a result of abnormal assembly of normal connective tissue proteins into a weak matrix under the influence of chronic inappropriate MC mediator release. Assessment for an underlying/comorbid MCAS may be warranted in patients diagnosed with EDS-III and particularly those also diagnosed with POTS.

Cronkhite-Canada syndrome. Cronkhite-Canada syndrome (CCS) is a rare disorder of nonfamilial polyposis typically associated with diarrhea, hypogeusia, onychodystrophy, and alopecia. Clinically significant malabsorption is common, too. Hints of potentially significant MC involvement have been raised repeatedly in the small body of literature on CCS, including observations of MC infiltrates in colonic mucosal biopsies and association of CCS with BMS.[117,381,382] Treatment directed against MCs or their mediators has been reported to help CCS.[383,384]

Hypersensitivity vasculitis. Vasculitides, by definition, are inflammatory disorders. Most are of unknown case. Given that MCs preferentially site themselves at the environmental interfaces and at perivascular locales, and given that with routine H&E staining MCs usually masquerade as certain other types of inflammatory cells, MCAD may be worth considering in the differential diagnosis in the patient with vasculitis—especially a clinically apparent hypersensitivity vasculitis—in which the history reveals issues difficult to attribute

Fig 1. Spectrum of mast cell (MC) activation disease. In recognition of the fact that all MC disease is, first and foremost, disease of inappropriate MC activation, Akin et al.[48] have proposed a new umbrella term of MC activation disease to describe the full spectrum of MC disease. SM-AHNMD, systemic mastocytosis with associated clonal hematologic nonmast cell lineage disorder.

(whether by type of symptom and/or time course) to the vasculitis.

Tachy-brady syndrome. Tachy-brady syndrome can be viewed as a dysautonomia and, as such, might be attributable to MCAD in some patients.

DISCUSSION

After roughly 150 years of medical orthodoxy that MC disease is principally only a rare, cytoproliferative process called mastocytosis, in merely the last few years it has become readily apparent that mastocytosis is but the tip of the proverbial iceberg of MCAD (Fig 1), with the far more common, but relatively nonproliferative, MCAS comprising the large bulk of the iceberg, largely unseen/unrecognized for many reasons as reviewed elsewhere.[93] As suggested by genetic investigations to date in both mastocytosis and MCAS, the MCAD iceberg may include a great assortment of mutationally based syndromes all sharing the common features of aberrant constitutive MC mediator expression and aberrant MC reactivity, both of which lead to multitudinous (largely "inflammatory" ± "allergic") downstream consequences. A relatively few variants in this assortment additionally feature significant MC neoplasia leading to clinical disease recognized as "mastocytosis" of one form or another. It almost goes without saying, too, that the mutations underlying MC misbehavior in primary MCAD (whether mastocytosis or primary MCAS) must be rooted in a hematopoietic stem cell (or a pluripotent progenitor), and thus although the end clinical effects in what we now call MCAD seem dominantly driven by the actions of those mutations in the patient's MCs, it is likely that the same mutations drive at least some constitutive and reactive aberrancies in other hematopoietic progeny (eg, lymphocytes, macrophages, etc.), too, which of course not only further expands and amplifies the full scope of the observed clinical syndrome in the individual patient but also calls into question whether diagnostically labeling such illnesses as assorted variants of "MCAD" might be as misleading as our thinking has been for the last century about the presumed rarity of MC disease. Although we are urged to not judge books by their covers, titles (ie, diagnostic labels) nevertheless strongly influence not only our thoughts about what lies within but also then our resulting actions. Thus, it may be necessary to develop a library of specific leukocyte activation syndrome terms beyond the MCAD/syndrome and macrophage activation syndrome presently in the literature, to include natural killer cell activation syndrome, Treg lymphocyte activation syndrome, eosinophil activation syndrome, basophil activation syndrome, and so forth, depending on the type of inflammatory cell in which the activating mutations are dominantly operant. Unknown for now is whether it will be possible to clinically distinguish one of these from another without leukocyte genome sequencing being routinely clinically available, thus raising the question of whether the more cytologically inclusive "leukocyte activation syndrome" label should be applied in spite of the obviously greater challenge of deducing how to treat a more general disorder than a more specific disorder. Of equal terminologic importance, too, will be a system for labeling variants of each specific leukocyte activation syndrome based on their mutational underpinnings which surely will soon come to be routinely identified as sequencing technology rapidly becomes more readily available in the clinical laboratory.

For now, though, MCAD is the label for the collection of illnesses which seem to manifest dominantly via excessive activation of MCs, and we have presented here a brief review of evidence suggesting how MCAD (far more commonly MCAS than mastocytosis) might be the critical diagnosis not only underlying many common, uncommon, and rare inflammatory ailments (mostly chronic, but sometimes acute) but also unifying the co-presence of such ailments in any given polymorbid patient into a single, cohesive diagnosis.

The rough concordance of the overall global prevalence of CIDs with preliminary estimates of the prevalence of MCAD may or may not be a coincidence. The same can be said of the familial penetrance of MCAD vs the long-recognized familial penetrance of CIDs.

The rarity of mastocytosis precludes any possibility of that disease underlying any significant fraction of the population with any given, prevalent CID, but if

the true prevalence of MCAS is relatively close to current estimates of epidemic prevalence, it becomes possible that certain variants of MCAS may underlie certain CIDs. It would be difficult, though, to conduct an adequately powered trial in a cohort of MCAS patients large enough to permit identifying potential recurrent mutational patterns present in given variants of MCAD (principally MCAS) leading to 1 particular CID or another. Instead, a practical strategy for probing the potential rooting of various CIDs in MCAS would be to conduct a range of pilot studies across a range of CIDs, each accruing a small number of patients with a given CID (and sociodemographically matched healthy controls) and pursuing an evaluation for MCAD (including sequencing and mutation analysis of a panel of MCRGs). Each such study would be able to not only tentatively identify what portion of the population with that CID also harbors MCAD/MCAS but also hopefully identify 1 or more recurrent MC mutational patterns in that CID, laying groundwork for further research probing for a potential causative association and the molecular mechanisms that would underlie such causation. (For example, it might be predicted that POTS patients would manifest 1 set of mutational patterns in the MCRGs, whereas an EDS-III cohort would manifest another set of such patterns—and that the mutational patterns found in a cohort featuring both POTS and EDS-III would be a "blend" of the findings in the POTS-only and EDS-III–only cohorts). Better understanding of the molecular genetic roots of the specific variant(s) of MCAD underlying 1 CID or another may facilitate identification of more effective, CID-specific therapies and significantly shortcut the present long, laborious, expensive "trial-and-error" personalized medicine process of finding helpful therapy for the individual MCAD (and CID) patient.

Before a concerted effort to pursue this strategy is launched, though, the current controversy about whether most MCAS patients harbor clonal MCs (even if not bearing mutations familiar in mastocytosis) must be settled. Studies seeking to independently confirm the repeated findings of high rates of clonality in the general MCAS population reported by the University of Bonn[39,40] must fully sequence not only KIT (on which the studies from Bonn exclusively focused) but also a host of other MCRGs which have been found in recent years to be routinely mutated in mastocytosis. Furthermore, it needs to be established whether conducting this sequencing work in the general peripheral blood mononuclear cell population is sufficient or whether this work must be focused in the MC population (approximately 0.01% of the mononuclear cell population). This latter determination will be especially important as efforts are made to shift the diagnostic process for primary MCAS in the clinical laboratory from a focus on the technically (and even logistically) challenging process of measuring MC mediators to a focus on MCRG sequencing and mutation analysis. In addition, given the long-known heterogeneity of MCs in various tissues (eg, tryptase-expressing MCs vs chymase- and-tryptase-expressing MCs), it may become necessary to determine whether MCs isolated from peripheral blood will be sufficient for routine diagnostic work or whether tissue biopsies will still be needed.

A clearer understanding of the mutational roots across the CID landscape may facilitate, too, an understanding of the epidemiologic concerns in this area. There is at least a sense (and, in some CIDs, proven) that the incidence of CIDs has been rising, that is, the rising incidence and prevalence of various CIDs is not simply a matter of improved clinical recognition and diagnosis. Especially given the great human costs, let alone great financial costs, of the CIDs, the importance of identifying the root causes of these diseases is obvious. An ounce of prevention usually is a better approach than a pound of cure, but in a disease, or system, as complex as MCAD, cause needs to be understood before effective prevention can be designed.

In summary, although the extreme heterogeneity across the many trees in the CID forest argues that substantial genetic and environmental heterogeneity is present, the many common features found across these diseases, and simply the great prevalence of CIDs overall, argues for a "shared soil." MCAD, particularly MCAS, seems a good candidate to be that soil, or at least a substantial constituent of that soil. Research is needed to confirm whether MCAS truly is mutationally rooted in most patients, and on such confirmation, extensive further research will be needed to understand how specific variants of MCAS drive specific CIDs—and how specific MC-directed therapies might be more effective in controlling (perhaps even curing?) such CIDs.

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