Chapter 6

PRESENTATION, DIAGNOSIS, AND MANAGEMENT OF MAST CELL ACTIVATION SYNDROME

*Lawrence B. Afrin**

Division of Hematology/Oncology,
Medical University of South Carolina, South Carolina, US

ABSTRACT

First recognized in 1991 and finally termed such in 2007, "mast cell activation syndrome" (MCAS) is a large, likely quite prevalent collection of illnesses resulting from MCs which have been inappropriately activated but which, in contrast to the rare "mastocytosis," are not proliferating, or otherwise accumulating, to any significant extent. Due to the marked diversity of direct and indirect, local and remote biological effects caused by the plethora of mediators released by MCs, MCAS typically presents as chronic, persistent or recurrent, waxing and waning or slowly progressive multisystem polymorbidity generally, but not necessarily, of an inflammatory theme. Suspected to be of clonal origin in most cases, MCAS usually is acquired relatively early in life via unknown mechanisms; interaction of environmental factors with inheritable risk factors is one possibility. Initial manifestations often occur in childhood or adolescence but are non-specific; in fact, virtually all of the syndrome's manifestations are non-specific, leading to decades of mysterious illness (and incorrect diagnoses often poorly responsive to empiric therapies) prior to diagnosis. A large menagerie of mutations in MC regulatory elements has been found in MCAS patients; most patients appear to have multiple such mutations, with no clear patterns, or genotype-phenotype correlations, yet apparent. Such mutational heterogeneity likely drives the heterogeneity of aberrant MC mediator expression, in turn causing the extreme heterogeneity of clinical presentation. Different MCAS patients can present with polar opposite clinical aberrancies. All of the body's systems can be affected by MCAS. In addition to clinical heterogeneity, diagnosis is confounded by difficulty not only in detecting sensitive and specific biomarkers of primary MC disease but also in finding histologic evidence of a non-proliferative disease wrought by cells capable of great pleomorphism. For example, in contrast to proliferative mastocytosis which usually drives significantly elevated tryptase levels, relatively non-

---
* E-mail: afrinl@musc.edu.

proliferative MCAS usually presents with normal tryptase levels; instead, histamine, MC-specific prostaglandins, and other mediators need to be assessed in evaluations for MCAS. Although the World Health Organization 2008 classification scheme for myeloproliferative neoplasms does not recognize MCAS, proposals for diagnostic criteria have been published recently and generally require presence of symptoms consistent with chronic/recurrent aberrant MC mediator release, laboratory evidence of such release (or of mast cell proliferation not meeting WHO criteria for systemic mastocytosis), absence of any other evident disease which could better explain the full range of findings in the patient, and, ideally but not necessarily, at least partial response to therapy targeted against MCs or MC mediators. Systemic MC disease of any form is not presently curable. Therapies for MCAS generally aim to control and ameliorate the disease by inhibiting aberrant mediator production and release, blocking released mediators, and/or managing the consequences of aberrantly released mediators. Many such therapies are available. Although there presently is no method to predict which set of therapies will best control the individual patient's disease, a methodical, persistent, trial-and-error approach usually succeeds in finding significantly helpful therapy. Lifespan for most MCAS patients appears normal, but quality of life can be mildly to severely impaired absent correct diagnosis and effective treatment.

INTRODUCTION: A NEW CONCEPTUALIZATION OF THE SPECTRUM AND PREVALENCE OF MAST CELL DISEASE

Nearly 150 years ago, German pathologist Friedrich von Recklinghausen was the first to describe mast cells (MCs), reporting in 1863 the observation of these granular cells in frog mesenteries. [1] In 1875 German anatomist Wilhelm Waldeyer reported finding mast cells in a tissue spread of rat dura mater and named these cells "embryonal" or "plasma" cells [2]. Two years later Waldeyer's medical student, Paul Ehrlich, described in his dissertation [3] the discovery in human connective tissues of these same cells, which he termed *mastzellen*, or well-nourished cells, due to their rich granular content evident from unique metachromatic staining properties with aniline-positive dyes. This work contributed to Ehrlich being awarded the 1908 Nobel Prize in Medicine. [4]

Meanwhile, from the clinical perspective, English dermatologist Edward Nettleship and English ophthalmologist Warren Tay described in the *British Medical Journal* in 1869 a rare urticarial skin disease, a symmetric distribution of pigmented maculopapular lesions [5]. A decade later this disease was termed urticaria pigmentosa (UP) by another London dermatologist, Alfred Sangster [6], and another decade later German dermatologist Paul Gerson Unna was the first to associate MCs with human disease, noting the presence of these cells in the lesions of UP. [7] Yet a further six decades passed before, in 1949, Oakland, California county hospital pathologist John M. Ellis first associated MCs with internal disease in an autopsy finding multi-organ involvement in a 1-year-old child who died of cachexia, thereby initially defining systemic mastocytosis (SM). [8] This breakthrough was followed in 1957 with the first report, by Israeli hematologists Pinhas Efrati, Abraham Klajman, and H. Spitz, of a clear case of the most aggressive form of SM, mast cell leukemia (MCL). [9]

Identification of MC products began in 1937 with the discovery by Swedish workers J. Erik Jorpes, Hjalmar Holmgren, and Olof Wilander that the metachromasia of mast cell granules is due to heparin. [10, 11] This work was followed in 1953 by the finding in MCs of "unprecedented" histamine content by Scottish radiotherapist James F. Riley. [12, 13]

Through the remainder of the Twentieth Century there continued to evolve the modern understanding of not only the hematopoietic origin of the normally widely, sparsely distributed MC but also its fundamental function, namely, to produce and release a wide range of molecular signals, generally termed MC mediators, which contribute to the homeostasis of all cells, organs, tissues, and systems in the body. In 1987 Vanderbilt allergist/immunologist Lawrence Schwartz and colleagues defined tryptase as a highly sensitive and specific marker for mast cell activation in mastocytosis. [14] In time, the enormous complexity of the biology of tryptase in its many isoforms would become more apparent [15], and it also would become more apparent that serum tryptase levels reflect the total body load of MCs far more than their activation state. [16, 17]

Molecular genetic insights began emerging in 1993 with Furitsu et al.'s identification of the D816V activating mutation of the KIT transmembrane tyrosine kinase receptor (CD117). [18] This mutation later was proved to be present in most adult SM. [19, 20] Moreover, in 1998 Spanish hematologists Luis Escribano and Alberto Orfao and their team showed that the MCs in many cases of SM, unlike any known normal cells, co-express the aberrant doublet CD117/CD25 or CD117/CD2, or sometimes even the aberrant triplet CD117/CD25/CD2. [21] In 1994 insights began emerging that the accumulation of MCs in mastocytosis may be due more to KIT's effect on anti-apoptosis than frank proliferation [22, 23], and in the last decade this dominance of anti-apoptosis through other factors, too, has been clarified by Gunnar Nilsson's team at the Karolinska Institute [24, 25, 26, 27, 28, 29, 30] and others (as summarized in [31]).

For nearly a century after Unna's first association of mast cells with a pathological state, mast cell disease (cutaneous or systemic) was thought to be a disorder of mast cell proliferation with further consequences from aberrant mediator release. In 1991, though, their clinical observations led pharmacologists John Oates and Jack Roberts of Vanderbilt University to hypothesize the existence of a spectrum of disorders of MC mediator release (i.e., MC activation) with little to no proliferation. [32] Evidence for such "mast cell activation disease" continued to accrue, and the year 2007 saw the first descriptions in the literature of "monoclonal mast cell activation syndrome" [33, 34], shortly followed by the first formal proposal for diagnostic criteria. [35]

In 2007 – coincidentally at the University of Bonn, where Friedrich von Recklinghausen had begun his medical schooling 155 years earlier – critical insights into the causes of the marked clinical heterogeneity of relatively non-proliferative mast cell activation disease were provided by German pharmacologist/geneticist Gerhard Molderings and colleagues. [36] 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 extended further in a follow-on paper in 2010. [37] Given that the range of *KIT* mutations for which commercial testing is available is still very limited, these findings raise the question of whether "non-monoclonal mast cell activation syndrome" (a.k.a. "primary idiopathic mast cell activation syndrome" [38]) might be more accurately termed "mast cell activation syndrome of undetermined clonality." Once whole *KIT* sequencing becomes commercially available, it will be an early order of research business to determine whether the findings by Molderings et al. apply to the general MCAS population.

In 2007 Valent et al. reported the curious affair of two patients who suffered severe hypotension following bee or wasp stings but who had normal tryptase levels and no cutaneous or marrow mastocytosis. However, one patient had one of the minor (clonal)

criteria for SM, and the other had two of the minor (clonal) criteria. They proposed defining such patients as having a "monoclonal mast cell activation syndrome." [39]

At the end of 2010 mast cell researchers Cem Akin (Harvard), Peter Valent (Vienna), and Dean Metcalfe (U.S. National Institutes of Health) published an updated proposal for diagnostic criteria for MCAS. [40] Akin et al. proposed a fundamentally new conceptualization that all mast cell disease first and foremost manifests aberrant mast cell activation, thus engendering a new "top-level" designation of "mast cell activation disease" (MCAD) to describe the full range of pathologic mast cell states. The proliferative (and rare) diseases of cutaneous and systemic mastocytosis would comprise one element of MCAD, while the (increasingly apparently quite prevalent) various forms of the relatively non-proliferative mast cell activation syndrome (MCAS) would comprise the other principal element of MCAD. Akin et al. further ventured that a diagnosis of MCAS would be permitted if the patient demonstrated repeated episodes consistent with aberrant mast cell mediator release, laboratory evidence of such release, absence of any other diseases better fitting the entirety of the clinical picture, and demonstration of at least partial response to therapy targeted at MCs or MC mediators. However, it almost immediately became evident that the mutational heterogeneity of MCAS leads to heterogeneity of not only clinical presentation but also therapeutic responsiveness, rendering the criterion for therapeutic response somewhat impractical. [41] Valent et al. released an updated proposal for diagnostic criteria for MCAS only a year later in which the requirement for therapeutic response was relaxed (i.e., desirable but not necessary). [42] Given the paucity of highly sensitive and specific markers for mast cell disease and the challenges in finding aberrant expression of even those few markers, Valent et al. also proposed a new way to interpret the serum tryptase level. The serum tryptase level, long a staple in diagnosing SM, is virtually always elevated little to none in MCAS, likely due to the relative dearth of MC proliferation in MCAS. Valent et al. thus proposed serum tryptase would now be a marker for MCAS if it rose during a symptomatic attack by at least 20% over the baseline value plus an additional 2 ng/ml. However, it was acknowledged in this proposal that this formula was empiric, that only 80% of the authors had agreed with this element of the proposal, and that validation would be necessary – and which at the time of this writing remains unavailable.

Thus, after roughly one and a half centuries of learning – and teaching successive generations of physicians – that mast cell disease is a rare, proliferative process called mastocytosis, in merely the last five years it has become readily apparent that SM is but the tip of the proverbial iceberg of mast cell disease, with the far more common, relatively non-proliferative MCAS comprising the large bulk of the iceberg, largely unseen/unrecognized for many reasons to be reviewed below. Much research in mast cell biology and disease remains to be done – a challenge at least equaled by the now apparent need to educate the medical community regarding this new conceptualization of mast cell disease.

CLINICAL PRESENTATION OF MAST CELL ACTIVATION SYNDROME

Until 2007, our understanding of the molecular genetic roots of SM was relatively simple: most cases (more than 90%) appeared to be driven by any one of a small set of mutations clustered, for the most part, around *KIT* codon 816, site of one of the molecule's

two kinase (i.e., activating) domains framing the actual enzymatic site. [43] Most mutations in this region seem to cause constitutive activation of the KIT protein. Thus, binding of ligand (stem cell factor) is no longer needed to activate the multiple pathways downstream from KIT which can result in reproduction, anti-apoptosis (which has turned out to be the dominant manner of mast cell accumulation in mastocytosis), differentiation, and mediator production and release. [44]

Poorly explained by this relatively small array of mutations, though, was the marked clinical heterogeneity of mastocytosis. To be sure, certain remarkable features which had long been the clinical hallmarks of mastocytosis – e.g., idiopathic anaphylaxis, odd and copious allergies, spontaneous flushing, vasomotor instability, diffusely migratory rashes and edema – were present in most cases, but many other symptoms and findings were noted, too, with little consistency across this patient population.

In 2007 the seminal findings of Molderings et al. [36] revealed the likely answer for this heterogeneity: a much wider array of (presumably activating) mutations, scattered across all domains of *KIT*, was detectable by whole *KIT* mRNA sequencing in most MCAS patients. In fact, many patients appeared to bear in *KIT* not just one mutation but in fact multiple mutations. These findings were repeated and extended by Molderings et al. in 2010 [37], and other groups simultaneously were identifying activating mutations in other mast cell regulatory elements, too. By 2011 it was readily apparent that the chronic myeloproliferative neoplasms (including mast cell diseases) often bear multiple mutations in the regulatory elements in the neoplastic stem cells, with evolving genomic disruption often heralding clinical progression. [37, 45, 46]

Over the last 70 years our understanding of mast cells' mediator content has dramatically evolved, too. From a time when the known and possible mast cell mediators numbered a mere handful, the body of research to date has identified that in truth mast cells produce and release scores of mediators; modern estimates range from more than 60 [41] to more than 200 [47], many of remarkable potency. Given the mast cell's fundamental role as a vehicle for production and release of these mediators, it is not surprising that mutations in the cell's regulatory elements lead to aberrancies in such production and release. Although most of these mutations investigated to date appear to cause constitutive MC activation leading to increased mediator production and release [48], loss-of-function mutations could be pathologic as well. As all MC mediators are intimately involved in various aspects of homeostasis of all of the body's cells, tissues, organs, and systems, it should not be surprising that either too great or too little production and release of any given mediator likely will have consequences, first at the cellular level and ultimately at the clinical level.

Thus, with any one mutation likely resulting in aberrant production and release of many MC mediators, and with most mast cell diseases harboring multiple mutations across all domains of many or all of the cell's regulatory elements, it should be expected that MCAD will present with an extraordinary degree of clinical heterogeneity to match the extraordinary degree of underlying mutational heterogeneity and resulting heterogeneity of patterns of aberrant mediator expression.

Presented below are the clinical findings, system by system, which have been observed in MCAS patients both in the peer-reviewed literature (cited, as available) and in the author's experience with more than 300 such patients diagnosed since 2008.

Demographic Findings

Although symptoms can initially appear at any age, most commonly it is as an adolescent or child, sometimes even as an infant or neonate, at which symptoms first appear – though due to the non-specific nature of almost every symptom of the disease, the diagnosis often goes unsuspected at the time – and for a very long time thereafter. [48] In the author's and others' experience [48], most patients have been chronically ill for literally decades prior to diagnosis. In fact, because of (1) the multisystem presentation in most patients [49], with symptoms in different systems often presenting at different times, and (2) the general lack of awareness of MCAS in the medical community, at present most MCAS patients live their entire lives without diagnosis, or even suspicion, of the root issue underlying the plethora of problems (many of a generally inflammatory nature) that they often acquire. MCAS patients often are regarded as inexplicably chronically multisystemically ill, perhaps recognized by astute physicians as likely having an underlying systemic inflammatory syndrome, though they don't fit the pattern of any well-known such syndrome, with typical diagnostic testing often yielding negative or "borderline" results, or perhaps results which are mild to moderate in their signal intensity but soon prove to be ephemeral. Though their presenting symptoms in any given system are most commonly subtle to moderate in degree, occasionally MCAS patients will present severe abnormalities (which may have emerged acutely, subacutely, or chronically) in one system or another (e.g., end-stage renal failure [50, 51, 52], refractory diarrhea [53], etc.), with "exhaustive" diagnostic testing failing to reveal a specific etiology. In fact–and as another reflection of its heterogeneity – MCAS can present with polar opposite abnormalities in different patients (e.g., gastrointestinal dysmotility principally mani-festing as diarrhea in one patient vs. constipation in another patient, or dyserythrop-oiesis principally manifesting as erythrocytosis in one patient [54] vs. pure red cell aplasia in another patient [55]). MCAS patients often respond incompletely, or even outright poorly or intolerantly, to therapies targeted at their superficially apparent ailments.

Some MCAS patients have definitively diagnosed inborn or acquired ailments (e.g., sickle cell anemia or obesity) which come to be blamed by many of their physicians for most or all of their symptoms even though it is difficult to explain many of these symptoms based on careful consideration of the biology of the definitively diagnosed ailment. When a patient – particularly a patient with chronic multisystem polymorbidity, generally of an inflammatory theme – presents, it is important for the physician to consider whether the presenting symptoms are typical for the definitively diagnosed ailment or not. If not, it is important to consider the possibility that a co-morbid (and potentially underlying, unifying) illness may be present.

MCAS patients not uncommonly can identify a specific point in their lives – a month, a year, sometimes even a specific date – at which their general health took a distinct turn for the worse. Such points commonly follow – typically by days to weeks but sometimes by several months or mere hours – acute events of either significant psychological or physical stress (e.g., death of a family member, or vehicular trauma) or of significant new antigenic exposure (e.g., travel or relocation). If they have recognized the temporal association between trigger and illness, such patients not uncommonly are quite convinced – even "invested," sometimes for socioeconomic reasons – that the trigger was the cause of the illness. However, careful history-taking virtually always reveals symptoms of MCAS to have been present long before "the turning point" – again, often dating back at least to adolescence and perhaps even to

childhood or infancy. The author typically asks his new patients to present their entire history chronologically (i.e., not merely starting at "the turning point"), starting all the way back at the last point in their lives at which they can remember feeling fundamentally, persistently well for a prolonged period. Even when specifically instructed as such, many patients will not recall some of the MCAS-driven symptoms from the earlier stages of their lives until much later points in the process of reporting their history.

Thus, as will be emphasized again later, it is imperative in the evaluation of a patient thought to possibly have MCAS to take as complete a (life-long) history from the patient as possible, a time-consuming endeavor which further contributes to the diagnostic challenges of MCAS. History-taking must include a complete review of systems as well, as many MCAS patients have been so ill for so long that they have come to accept various aspects of their illness as a baseline "healthy" state for them. Also, after extensive evaluations fail to identify a diagnosis, let alone effective therapy, some patients come to naturally omit certain aspects of their illness when providing their history yet one more time to yet one more physician. For example, the author encountered one patient who had been suffering unpredictable acute non-orthostatic syncopal episodes on virtually a daily basis for 20 years. Extensive evaluation and empiric treatment efforts in the first two years after symptom onset were unproductive. His physicians at the time told him they had nothing further to offer him. The patient continued to suffer his syncopal episodes for the next 18 years (and made substantial adjustments in his life to accommodate his risk for syncope at any unpredictable moment), though he never again mentioned the problem to any of the physicians he newly met over time. Only in an extensive review of systems was this stark symptom revealed. Another patient had suffered near-daily syncope for five years following the birth of her first child but had been told by her obstetrician, upon symptom onset, that post-partum syncope was common and would resolve "in time," so she patiently endured five years of this life-altering symptom without mentioning it to any of her other physicians before an extensive review of systems brought it to light again.

Constitutional Findings

In the author's and others' experience, fatigue/malaise is the most common constitutional complaint of MCAS patients. [40, 48, 49] Most patients remain reasonably functional, though in some this symptom becomes mildly to severely disabling; stories abound about how patients in their 20s act as if they're in their 80s. Chronic fatigue syndrome has been tentatively linked to mast cell disease. [56]

Intermittent elevated temperatures are not uncommon [48] but when present are usually "low-grade" or "feeling hot" (as verbalized by patients) with frank fever (temperature $\geq$ 38°C) an uncommon event which more likely (but not necessarily) signifies infection. Similarly, intermittent shaking chills/rigors are relatively uncommon, but the most common temperature-related complaint by far is a near-constant sense of feeling cold (without necessarily suffering any frank chills). Beyond asking about "fevers or chills," the physician should ask specifically about a sense of feeling cold most of the time, or feeling hot some of the time, since most MCAS patients do not interpret their low-temperature sense as "chills" or their high-temperature sense as "fever."

Unprovoked diaphoresis, not always nocturnal, is another common constitutional complaint of MCAS patients. [48, 49] Some patients manifest this symptom on a circadian basis (e.g., "night sweats"), and, together with the enlarged and/or tender lymph nodes that can be seen in some patients, this symptom can lead to necessary but often fruitless searches for infection (e.g., mononucleosis, tuberculosis) or lymphoma. Of course, given the impact MCAS has on every system in the body, including the immune system [57, 58, 59, 60, 61], secondary infections [49] and malignancies [62] are not uncommon. However, failure of all the symptoms to be easily attributable to the discovered infection or malignancy, or failure of all the symptoms to respond to appropriate therapy for the discovered infection or malignancy, should cause the physician to consider the possible presence of another malady underlying not only the definitively diagnosed ailment but also the other issues seemingly unattributable to the definitively diagnosed ailment.

Some MCAS patients complain of anorexia and potentially even early satiety, which may or may not be accompanied by physically or radiographically detectable splenomegaly. [48] Weight loss is seen in some [63], but far more common is weight gain which often begins subacutely, progresses at a disconcertingly rapid pace, and is without any identifiable correlation to changes in diet or activity. Fluctuating weight in MCAS patients likely is due principally to waxing and waning of edema (usually in a diffusely migratory fashion), but in many MCAS patients with significant, persistently progressive weight gain, usually only a minority of the increased weight is due to edema (or, rarely, ascites or other effusions from MCAS-driven serositis). Instead, gain in adipose tissue usually accounts for the majority of significant, persistent weight gain in MCAS. Some patients may gain more than 50 kg in a year in spite of intensive efforts to diet or exercise and are despondent about their "failure" to control their weight. Again, there often is an identifiable acute stressor within the few months prior to the onset of the weight gain. For some, weight gain quickly becomes their dominant issue, with all other symptoms (e.g., fatigue out of proportion to the weight or any other identifiable factor) being attributed by the patient (and, often, his/her physicians) to the weight gain. Prior to recognition of their underlying diagnosis of MCAS, these patients not uncommonly undergo bariatric surgery (and not uncommonly suffer significant post-operative complications including poor healing) [64, 65] and often lose – at least initially – significant weight. However, other symptoms that accompanied the weight gain often remain unimproved, and often the weight begins to inexplicably, inexorably increase again after achieving nadir.

Pruritus is another common constitutional complaint of MCAS patients. [48, 49] It more commonly is episodic, though in some patients it comes to be a constant discomfort, albeit with waxings and wanings at unpredictable times and without identifiable correlations. In most patients it is a tolerable discomfort which they have felt requires either no treatment or minimal treatment with over-the-counter anti-pruritic agents (most of which are anti-histaminic), but in some patients it becomes a severe, life-altering and -disabling problem. Although sometimes it persists in one specific location, and sometimes it is diffuse (as in an "aquagenic" pruritus triggered in some patients upon a hot shower or bath), more commonly it is a diffusely migratory problem, affecting one area of the skin one minute or hour or day and another area the next minute or hour or day.

MCAS patients also often report prolific – and odd – "sensitivities" (which they may not necessarily interpret as allergies) to assorted drug, food, and environmental provocations. [48, 49] On first consideration, the physician may be inclined to discount reports of anaphylaxis to

acetaminophen, pruritus with levothyroxine, acute malaise from mundane multivitamin preparations, etc. The physician must beware an inclination to reflexively begin wondering about psychiatric disorders in such patients. The physician must also be aware that a drug reaction, whether common or unusual, reported by an MCAS patient not uncommonly is due not to the active pharmaceutical ingredients but instead to the fillers and dyes in the product, i.e., the allegedly inactive ingredients. As such, sometimes simply changing to an alternative commercial formulation of the same drug can eliminate reactions as severe as acute anaphylaxis, while other patients sometimes see improvement with a special formulation of the active ingredient mixed by a compounding pharmacist with a less provocative filler. For example, one of the author's patients eliminated her anaphylaxis to antihistamines such as diphenhydramine and loratadine, and to antibiotics such as sulfamethoxazole/trimethoprim and acyclovir, by compounding these active ingredients with baby rice cereal. Other examples of fillers sometimes used successfully by compounding pharmacists in preparing medications for mast cell disease patients include lactose monohydrate or potato or sometimes even quite simply reconstitution with water at time of use.

The physician should be aware that the environmental triggers of flares of mast cell mediator release include not only antigenic stimuli (e.g., drugs, venoms, environmental antigens) but also physical stimuli (e.g., pressure/trauma, exercise, heat, cold, ultraviolet light, and even electrical stimuli (such as electrostatic shocks sometimes suffered when brushing hair) and osmotic stimuli). [48, 66, 67, 68, 69] In the same fashion as how some MCAS patients experience increased frequency and severity of flares of their disease in the spring and fall due to pollen issues, increased difficulty in the summer due to heat and solar ultraviolet exposure is not uncommon in other MCAS patients – who may be some of the same patients who experience flares from pollen. Although exposure to cold (as compared to heat) seems to be a somewhat less common trigger of flares of established mast cell activation disease (with such flares often leading to typically fruitless evaluations for paroxysmal cold hemoglobinuria, cryoglobulinemia, and cold agglutinin disease), the hyperadrenergic experience of acute exposure to severe cold (e.g., from unexpected immersion in cold water from a boating accident) can be the stressor that triggers – days to months later – an escalation of the baseline level of mast cell activation, and diffuse symptoms therefrom, in the (known or yet unrecognized) MCAS patient.

Integumentary Findings

Given that mast cells often are programmed to site themselves at the environmental interfaces, it is not surprising that a wide range of pathology is evident in the integument of patients with aberrant MC activation. [40, 48, 63] Permanent or semi-permanent cutaneous lesions include xerosis, fragility, telangiectasias (including telangiectasia macularis eruptive perstans (TMEP) [70]), and macular or maculopapular freckles. An unpredictable, unprovoked, diffusely migratory, patchy, lightly to moderately erythematous, macular rash is the most common dermatologic complaint. Warts are not uncommon, and problems with spontaneous development of folliculitis [49] and/or small ulcerations – "sores" ranging from as small as 1-2 mm to as large as 2-4 cm and often attributed to diabetes or vascular disease given the lack of any other apparent explanation – are not uncommon and often are long in

healing, sometimes leaving scars (and thus raising the possibility of MCAD underlying idiopathic sclerosing diseases).

As noted previously, pruritus – sometimes localized but more commonly in an unpredictable, unprovoked, diffusely migratory pattern – is a common complaint. [40, 48, 49] Flushing and angioedema – usually episodic but sometimes chronic – are common issues, too. [40, 48, 49] Idiopathically painfully sensitive skin is occasionally seen, usually affecting a region of the body more so than one small site or the entire body.

Proper mast cell function is critical to wound healing [57, 59, 71], and thus it is not surprising that wounds in MCAS patients often heal poorly, taking a concerningly long period of time to close, not uncommonly becoming secondarily infected, and often leaving a more pronounced scar than would be ordinarily expected.

Another very common dermatologic finding in MCAS patients is dermatographism. [48] Sometimes simple removal of clothing makes it apparent, but integrating a simple light scratch test into the physician's standard physical exam is an easy thing to do. The dermatographism of MCAS rarely is so vigorous as to manifest hives; instead, usually only erythroderma is seen in the track of the scratch, arising within 1-30 seconds and often persisting in full splendor for 5, 10, or even 15 minutes or longer.

Alopecia (usually not clinically apparent) is frequently reported by MCAS patients. Interestingly, increased levels of (MC-specific) prostaglandin D_2 are found in alopecic scalps. [367] Onychodystrophies of various sorts, too, are common complaints.

Especially in younger and overweight (but not even necessarily obese) MCAS patients, striae are not uncommonly seen about the trunk, particularly the abdomen, anterior and posterior axillary regions, and even sometimes lower on the back such as in the regions of the costovertebral angles. [72] In the author's experience, striae sometimes resolve with effective MCAS therapy.

Ophthalmologic Findings

The dominant ophthalmologic issues in MCAS patients continue the theme of generally non-infectious inflammation seen in all other systems, too. [48, 49] Irritated ("dry," "sandy," "gritty," "itchy," etc.) eyes are the most common ophthalmologic complaint. Chronic and/or episodic excessive lacrimation, suffusion, scleritis, blepharitis, and conjunctivitis are seen not uncommonly as well. Lid tremors and tics can be bothersome, too; patients sometimes undergo injections of botulin toxin to try to relieve this irksome symptom, and while such treatments often are helpful at first (as with bariatric surgery for MCAS-driven obesity), relapses within a year or so are common.

MCAS patients also complain not infrequently of acute episodes of (typically bilateral) impairment of the ability to focus their vision. These episodes typically last only minutes to hours and often are accompanied by "flares" of many other symptoms such as intense fatigue.

Ophthalmologic evaluations typically are unrevealing; occasionally an incidental finding (e.g., cataracts) is noted, but the ophthalmologist has difficulty attributing the described ophthalmologic symptoms to the ophthalmologic exam findings.

Otologic Findings

The dominant otologic issues in MCAS patients also continue the theme of generally non-infectious inflammation. [49, 73, 74] Otitis externa ("painful" or "itchy" helices and/or canals) is fairly uncommon, while otitis media is more common, especially in children. In patients who suffer this manifestation of mast cell disease, the otitis media often seems oddly frequent in spite of no demonstrable cellular or humoral immune deficiency (with the underlying mast cell disease going unrecognized), and it often seems oddly refractory to antibiotic therapy, though in retrospect this is unsurprising since MCAS-driven inflammation is typically sterile.

MCAS patients also can suffer alterations in hearing (dysacusis). In the same fashion in which the disease, depending on the particular pattern of aberrant mediator expression in the individual patient, can "push" a system to one extreme in one patient and to the opposite extreme in another patient, MCAS patients can suffer hearing loss, tinnitus [49, 63] or hyperacusis [75], and, rarely, both hearing loss and tinnitus (author's experience). Hearing loss presumably is due dominantly to the otosclerosis (of the tympanic membrane and/or the inner ear bones) which has been demonstrated in patients with mast cell disease [76, 77], though degenerating canal hairs or auditory nerve function theoretically are other routes to hearing loss. (Interestingly, in contrast to most gain-of-function *KIT* mutations in mast cell activation diseases, loss-of-function *KIT* mutations have been demonstrated to be at the root of piebaldism, an inborn syndrome of deafness, hypopigmentation, and megacolon. [78]) Tinnitus (which can be unilateral or bilateral or alternating) may be due to release of inflammatory and/or other neuroexcitatory mediators by aberrant mast cells in the vicinity of the acoustic-sensing hair cells in the semicircular canals or the fibers of the auditory nerve. [63] Similarly, the audiologist often finds sensorineural hearing loss of unclear origin.

Other than identifying obvious otitis externa or media (which often is erroneously assumed to be infectious in origin), otologic evaluations typically are unrevealing; occasionally incidental findings (e.g., cerumen) are noted, but the otolaryngologist has difficulty attributing the described otologic symptoms to the exam findings.

Sinonasal Findings

It should be remembered that mast cells tend to position themselves at the body's environmental interfaces. Some of the highest concentrations of mast cells in the body are in the sinonasal cavities and passages. Thus, it is not surprising that a chronic sense of sinonasal congestion, and chronic and/or episodic coryza ranging in degree from mild to severe, is often reported by patients with mast cell disease. [48, 49] Some patients also report intermittent ulcerations, sores, or other focal discomforts in the nasal cavity and passages. Olfactory intolerances are common as well. [49] Intermittent, unprovoked, unpredictable epistaxis, typically minimal and brief in extent but sometimes severe enough to require evaluation and intervention in the emergency room, is also a common finding [48] and presumably is due to acute "flares" of disease leading to increased local release of heparin which further aggravates the already impaired coagulation homeostasis of mucosa rendered chronically friable by chronic inflammation from frequent or continuous aberrant local release of inflammatory mediators.

Oral Findings

Intermittent discomfort or even frank pain in the oral and/or labial mucosa is a common complaint by MCAS patients. [48, 49] It can be focal (and, if so, usually in a migratory fashion rather than persisting in one site) or diffuse, can range from minimal to so severe as to be completely disabling, and may or may not be accompanied by leukoplakia (microbiologic evaluation of which often does not reveal candidiasis), dysgeusia (when present, often of a metallic nature), and/or ulcerations/"sores" which may appear to be herpetic in nature but, if specifically tested, usually are not.

MCAS recently has been associated with burning mouth syndrome (BMS), a diffuse burning discomfort about the macroscopically and microscopically normal oral mucosa for which clear causes such as Sjogren's syndrome and candidiasis cannot be found. [79] BMS often is of acute or subacute onset which, if the patient's history is adequately explored, not uncommonly follows the occurrence/development of a significant stressor in the patient's life. BMS patients have long frustrated the professionals who come to care for this problem – dentists, oral surgeons, and oral pathologists – because of the lack of an identifiable etiology and because of these patients' typically poor responsiveness to empiric therapies including topical and systemic analgesics, anti-depressants, anti-epileptics, and vitamin and other complementary and alternative therapies. Unsurprisingly, psychosomatism or other psychiatric disorders often come to be diagnosed in such patients. At least in some BMS patients, though, MCAS-directed therapy can promptly relieve much or all of the oral burning. Salivary tryptase may be a helpful diagnostic tool in such patients [80], but because this test is not widely available and because the effects of MCAS rarely are limited to just one system, it may be more efficient to pursue evaluation in such patients for systemic MCAS (as described later).

Chronic or intermittent, fluctuating levels of angioedema of the oral tissues – buccal mucosa, tongue, and/or lips – are sometimes seen in MCAS patients. [48, 49] When sufficiently severe to be apparent on physical examination, or when the history is sufficiently consistent with angioedema, evaluations for hereditary angioedema often are pursued, usually revealing normal results but sometimes even more confusingly revealing modestly decreased levels of C1 esterase inhibitor antigen or function which require further assessment by an immunologist to clarify that such patients do not have the severely decreased levels needed for C1 esterase inhibitor deficiency (acquired or congenital) to biologically account for the observed angioedema.

Often less apparent to physicians evaluating MCAS patients, dental decay – typically in spite of good life-long attention to dental hygiene – is common. [81, 82, 83] The fact that such problems are managed by an entirely different health profession, together with the typically slower pace of development of dental problems compared to other MCAS-driven problems, results in the poor awareness by physicians of this aspect of the disease. When this problem is considered at all, MCAS patients – and their physicians and oral care providers – often attribute their oddly advanced-for-age dental decay and early need for dentures simply to "bad luck." Astute physicians who notice the problem and evaluate the patient for humoral (particularly IgA) deficiency usually find normal (or, at worst, only mildly depressed) IgA, IgG and/or IgM levels which cannot account for the decay, particularly in the absence of more noticeable sequelae of immunodeficiency.

In addition to the chronic dental decay seen in some MCAS patients despite good dental hygiene habits, another pattern of onset of dental decay not uncommonly seen is that of the patient with good dentition for decades who then begins suffering subacute significant dental decay despite no change in dental hygiene habits. As with subacute onset of MCAS-driven pathology in other systems despite no apparent change in patient behavior, subacute onset of dental decay often begins to arise in the wake of a significant stressor experienced by the patient. However, due to the slower pace of development and somewhat obscured cosmetic impact of MCAS-driven dental problems compared to problems in many other systems, the connection between the inciting stressor and the subsequent dental problems is often never made.

Pharyngeal Findings

In spite of the physical exam typically finding no pathology whatsoever, pharyngeal symptoms are common amongst MCAS patients, often being described as chronic and/or intermittent, waxing and waning discomfort, irritation, pain, or soreness which often is reflexively diagnosed as infectious (typically viral or Streptococcal) pharyngitis. In other words, the pattern of waxing/waning sterile inflammation seen in the other body sites in MCAS patients is not uncommonly seen in the pharynx as well. [48, 49]

Some MCAS patients deny any frank pharyngeal discomfort – but, when asked specifically on a careful review of systems, immediately endorse a chronic "tickle" in the throat which leads to either a chronic dry cough and/or a chronic sense of a need to clear the throat.

The chronic sinonasal congestion in many MCAS patients sometimes leads to a frank sense of chronic post-nasal drip as the specific cause of the chronic pharyngeal discomfort, but more often the discomfort is present without any clear cause.

The reactions in some MCAS patients to specific drugs, foods, or environmental antigens are sometimes most appreciated by such patients as being localized to the pharynx, causing a prompt escalation of pharyngeal discomfort, or even a frank dyspnea or dysphagia, which often is due to angioedema being one of the components of the reaction. When pharyngeal angioedema is so severe as to cause stridor, emergent intervention is warranted, and patients who suffer such severe pharyngeal reactivity should be advised to always carry epinephrine auto-injectors and should be trained in their proper use.

Lymphatic System Findings

In the author's experience, the most common lymphatic system finding seems to be mild to marked left upper abdominal quadrant discomfort or pain, often aggravated by palpation (and sometimes aggravated even by eating a full meal). Release of inflammatory mediators by aberrant, constitutively activated splenic mast cells may underlie this finding. A modest extent of splenomegaly is radiographically detectable (virtually always showing splenic homogeneity) only in a minority of patients and is even less commonly appreciable on physical examination [48], confusing the examiner as to why the left upper quadrant would be tender.

Somewhat less common in MCAS patients than the complaint of left upper abdominal quadrant discomfort, but by no means infrequent, are complaints of enlargement and/or tenderness of one or more groups of lymph nodes across space and time, i.e., sometimes the adenopathy is tender and diffuse, and sometimes it is non-tender and merely focal. [48] Quite often, too, asymptomatic adenopathy will newly come to light in MCAS patients subjected to radiographic examinations for other reasons. Whether the discovered adenopathy is palpable, symptomatic, or neither, of necessity the physician must consider the entire differential diagnosis for such adenopathy. Certainly there is a wide range of true pathologic processes (infectious, malignant, and otherwise) which are secondary to MCAS and which can cause adenopathy of various characters. When such true pathologies are definitively diagnosed upon proper evaluation of adenopathy, they should be specifically addressed without regard to whether they are primary processes (i.e., coincidental to, and independent of, MCAS) vs. secondary processes, since such distinction, at least at present, is essentially impossible. However, the physician should not be surprised if biopsies of nodes of pathologic size (typically ≥ 1 cm) in the MCAS patient are found by the pathologist to be merely "reactive" or even frankly normal on full histologic and immunophenotypic analysis. Interestingly, even specific pathologic examination with various mast-cell-highlighting techniques (e.g., staining with CD117, Giemsa, toluidine blue, or tryptase, or multicolor flow cytometry for cell surface co-expression of CD117/CD25 or CD117/CD2) typically fails to identify increased (let alone aberrant) mast cells in such nodes, so presumably such reactive adenopathy in MCAS patients is being caused indirectly by mediators released by aberrant mast cells located elsewhere about the body.

Considerably confusing in such situations of histologically/immunophenotypically reactive adenopathy are the occasional findings of T-cell-receptor gene rearrangements or even cytogenetic abnormalities commonly associated with lymphoma, but in the absence of the patient having a clinical course consistent with lymphoma, the physician is well served by caution against diagnosing as lymphoma, much less treating as lymphoma, any "suspicious" lymph nodes which do not meet well-established standard histologic criteria for lymphoma.

Although the adenopathy seen in MCAS patients most commonly (by far) is reactive/ benign adenopathy, it is well established that patients with SM – and, thus, likely any form of MCAD – are at increased risk for hematologic malignancies of all types, including lymphomas. Malignancies in MCAS patients not uncommonly present with somewhat unusual pathologic aspects as well as assorted symptoms (e.g., frequent presyncope) not easily attributable to the readily apparent malignancy; also, such malignancies not uncommonly follow less favorable courses than might be expected. (Interestingly, there are increasing reports of late that monocytosis – which in the author's experience is the single most common hematologic abnormality in MCAS patients – is a statistically significantly independent predictor of poor outcome amongst Hodgkin's and non-Hodgkin's lymphoma patients. [84, 85, 86, 87, 88, 89]) For example, the author has observed a small cohort of patients with the odd constellation of subacutely developing, idiopathic morbid obesity followed within a few years by development of aggressive, highly constitutionally symptomatic angioimmunoblastic T-cell lymphoma, an uncommon form of lymphoma. Evidence of mast cell activation was readily found in these patients, in some even before the lymphoma developed. In light of emerging understanding of the multisystemic effects of mast cell activation disease, it is not an unreasonable hypothesis that MCAS was the underlying

ailment leading to both the odd-character obesity and the relatively unusual form of lymphoma.

Pulmonary Findings

In the upper respiratory tract of many MCAS patients, as previously discussed, one finds predominantly the symptoms of fluctuating levels of sterile inflammation, such as sinonasal congestion, rhinorrhea, painful or merely just discomforting pharyngitis, and sometimes a proximal "dysphagia" which likely is a flaring of inferior pharyngeal and/or proximal esophageal angioedema. [48, 49] Episodic (usually sterile) laryngitis is sometimes experienced, too.

One of the major inflammatory mediators produced by the mast cell, prostaglandin D_2 (PGD_2), is a strong bronchoconstrictor, 10 times more potent than histamine. [90] Thus, it is not surprising that in the lower respiratory tract, the most common complaint by far is an irregularly episodic, seemingly unprovoked, subtle dyspnea, sometimes accompanied by modest wheezing. [40, 48, 49] Even when wheezing is present, it typically is only modest, sometimes appreciable by the patient only with forced respiration. Given that their tidal respiration most times is normal, most MCAS patients with this subtle episodic dyspnea will deny "shortness of breath" on a review of systems, but when alternatively asked whether they ever experience any "discomfort" with breathing, they will admit, "I just can't catch a deep breath like I used to." Dyspneic MCAS patients sometimes consult pulmonologists. Chest imaging and pulmonary function testing often are unrevealing.

Although more typically only a minor complaint in a minority of MCAS patients, idiopathic chronic cough (almost always non-productive) is sometimes the chief complaint. [48, 49] Of course, potentially offending drugs such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers must be excluded, but usually cough-dominant MCAS patients have undergone extensive but fruitless pulmonary evaluations and are labeled simply as having "reactive airways disease," not all that inappropriate a label given the true (but unrecognized) etiology.

MCAS may also be operant in the progression of emphysema and chronic obstructive pulmonary disease [91, 92, 93], especially in patients with minimal to no smoke exposure and those whose lung disease has continued to progress despite cessation of smoking long ago. [94] Mast cell disease has been implicated in pulmonary hypertension, too. [95]

Cardiovascular Findings

Continuing the theme of marked clinical heterogeneity across all systems, the cardiac, vasomotor, and vasculopathic issues in mast cell disease patients occupy virtually the entire spectrum of abnormalities possible in these areas. [40, 48, 49] Palpitations are a very frequent complaint; proven dysrhythmias are less common, but all types are seen. Resting tachycardia (relative or absolute) is quite common [40], though sometimes an idiopathic bradycardia is seen. In contrast to pheochromocytoma, which is hallmarked by episodic tachycardia and hypertension, in MCAS there often are unpredictable, unprovoked episodes of *both* hypertension and hypotension [40], sometimes one following the other quite acutely.

Although most physicians learn early in their schooling that norepinephrine is a potent vasoconstrictor, there generally is little awareness that one of the cellular sources of norepinephrine is the mast cell – and that PGD_2, whose dominant source is the mast cell, is approximately an order of magnitude more potent a vasoconstrictor (in certain vascular beds) than norepinephrine. [96] (Due to different receptor profiles in different tissues, it also can act as a vasodilator in other vascular beds. [97, 98])

While frank syncope fortunately is relatively uncommon amongst MCAS patients, presyncope appears to be quite common. Such episodes often are unprovoked and non-orthostatic, and are variably identified by patients as sudden-onset "lightheadedness," "weakness," "dizziness," or, less commonly, "vertigo." [40, 48] Presyncopal episodes not uncommonly appear to be without provocation (such as orthostatic maneuvers) and manifest at irregular intervals, but average frequencies range from several times daily to as little as once every several months. Patients who characterize their presyncope using one of these terms will often deny the other terms, so it is important in the review of systems to ask patients about all of these sensations. 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 [99, 100]), but MCAS patients treated for POTS (with midodrine or fludrocortisone, for example) typically experience only modest improvement in their presyncopal episodes and little to no improvement in any of their other symptoms.

Some MCAS patients will endorse episodes of frank chest "pain," while others will deny this and only endorse chest "discomfort." [40, 48] Although the physician must always be alert to the symptoms and signs of obstructive coronary atherosclerotic disease, far more often the MCAS patient with chest pain or discomfort provides details which are not consistent with angina and shows no electrocardiographic (ECG) evidence of coronary artery occlusion. The discomfort may be in the left chest or retrosternal, but just as often as not is in the right chest or across the entire chest or is migratory throughout the chest. Radiation of the discomfort is somewhat infrequent, and the associated diaphoresis of angina appears to be quite uncommon.

Although most episodes of chest pain or discomfort in MCAS patients do not show ECG evidence of coronary vasoocclusion, the physician should be aware of two uncommon chest pain syndromes which do show such evidence and which are related to (or suspected to be related to) mast cell activation. First described in 1950, Kounis syndrome (allergic angina or allergic myocardial infarction, with absence of obstructive coronary lesions) clearly is born of mast cell activation and requires identification of an allergic insult as the cause of the coronary vasospasm causing the ECG changes. [101] Kounis syndrome is estimated to be present in 0.002% of all acute myocardial infarctions. [102] Ironically, the incidence of Kounis syndrome may be increasing in step with the increasing use of (allergenic) drug-eluting stents for the treatment of atherosclerotic lesions. [101] It remains unclear whether the mast cell activation in Kounis syndrome is a consequence of allergic provocation of normal mast cells vs. the abnormal (clonal) mast cells thought to underlie MCAS. 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 mid-ventricle and apex, and left ventricular apical ballooning), which is seen in 2% of patients presenting with suspected acute coronary syndrome. [103] Though 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 mast cells), and an increasing number of cases of Kounis syndrome are being reported as having manifested Takotsubo-like left ventricular apical ballooning [e.g., 104]. Takotsubo cardiomyopathy also appears in some patients following idiopathic anaphylaxis [e.g., 105], further increasing suspicion of a connection with MCAS.

MCAS-driven coronary and peripheral atherosclerosis producing true vaso-occlusive pain sometimes can be advanced and aggressive even at relatively young ages. [95, 106, 107, 108] Higher, but still "normal," levels of tryptase may even be a marker for advancing atherosclerosis. [109] The sclerosis and poor healing seen in all other systems in assorted MCAS patients manifest in some patients as non-atherosclerotic vascular anomalies, too, namely, aneurysms, hemorrhoids, and varicosities. [110, 111, 112, 113, 114, 115, 116, 117] Mast cells clearly have a role in angiogenesis as well [118], perhaps also contributing to these vascular anomalies as well as others such as hemangiomas, arteriovenous malformations, telangiectasias, etc. [119, 120, 121]

Although not so often a volunteered complaint, edema frequently emerges on a review of systems taken from an MCAS patient [48], and though mast cell disease appears capable of inducing heart failure [122, 123, 124, 125], the physician should take care to distinguish whether edema in the patient suspected of having MCAS is presenting in a pattern consistent with heart failure or not. The author has identified MCAS in several patients with idiopathic and takotsubo heart failure, but most MCAS patients with complaints of edema have clinically normal cardiac function and manifest a pattern of edema distinct from the classic dependent pitting edema of congestive heart failure. Instead, undiagnosed MCAS patients report a seemingly physiologically inexplicable pattern of unpredictably episodic, diffusely migratory edema. One day the right hand and left foot may be edematous; the next day – or the next week – the left foot and foreleg may be edematous; and the next day edema may only be appreciated in the right periorbital region – all without any appreciable associated rash. MCAS-driven edema more typically is pitting than non-pitting, but with no detectable hypoalbuminemia or impaired cardiac function, the etiology almost always remains unclear as long as the unifying diagnosis of MCAS goes unrecognized.

Gastrointestinal Findings

Inflammation – usually sterile, occasionally infectious – remains the dominant theme of both the luminal and non-luminal gastrointestinal issues in MCAS. [40, 48, 49, 63, 95] Fibrosing illness is occasionally seen, too. [126]

Aerophagia is common. [49] Esophagitis often manifests as either the aforementioned chest discomfort or "reflux" which frequently is "functional" (i.e., refractory to maximal acid reduction therapy), suggesting the source of the discomfort is not acid. [40]

Gastritis and small and large bowel enteritis are common in MCAS patients and manifest as diffusely migratory abdominal pain as well as diarrhea, constipation, or – most commonly and confoundingly – diarrhea alternating with constipation. [40, 48, 49, 63] Chronic or frequent queasiness, nausea, and vomiting are quite common, too. Partial bowel obstructions are somewhat uncommon but may be due to focally dysfunctional motility and/or focal flares of edema. Irritable/inflammatory bowel syndrome (IBS) is commonly diagnosed by

gastroenterologists consulting on MCAS patients, but upper, lower, and capsule endoscopy and small bowel enteroscopy usually are unrevealing from a macroscopic perspective. Furthermore, routine hematoxylin and eosin staining of random mucosal biopsies virtually always are interpreted as normal or, at most, showing only mild inflammation, more commonly chronic than acute. However, when prompted to investigate further for mast cell disease, the pathologist often finds increased mast cells on staining for CD117 (KIT), Giemsa, toluidine blue, and/or tryptase. (It is important to note that there is no studied consensus as to an upper limit of normal mast cells in various segments of the bowel, but in the author's experience, many pathologists judge more than 20 mast cells per high power field in the gastrointestinal (or genitourinary) tract as increased.) If mast cell disease is suspected in advance of the procedure, tissue samples can be submitted, too, for multicolor flow cytometry, and sometimes the pathognomonic dual cell surface expression signatures of CD117/CD25 or CD117/CD2 can be found. Fresh or fixed tissue can be subjected to polymerase chain reaction analysis for the *KIT*-D816V mutation, though in the author's experience this is seen in the gut as rarely as it is seen in the marrow of MCAS patients.

Somewhat less common than frank inflammatory symptoms, but by no means rare, are assorted selective micronutrient malabsorption syndromes. [40, 48] Amongst such syndromes in the author's experience, iron malabsorption appears most common and usually responds to simple H_1/H_2 histamine receptor blockade. Other observed deficiencies include copper and assorted B vitamins. General protein-calorie malabsorption leads to the expected cachexia but fortunately appears rare.

Pancreatic enzyme supplements appear helpful in addressing various gastrointestinal tract-related symptoms in some MCAS patients (e.g., diarrhea, weight loss, and certain micronutrient malabsorption syndromes), suggesting that pancreatic exocrine insufficiency, perhaps due to MCAS-driven inflammation and/or fibrosis in pancreatic exocrine glands and/or pancreatic ducts, may be yet another manifestation of MCAS. Chronic pancreatitis, too, is a disease of inflammation and fibrosis leading to obliteration of pancreatic ducts; 40% of such cases are idiopathic [127], and an increasing portion of these cases is appreciated to be an autoimmune disease (of unknown origin) directed against the ducts. [128] While the role of mast cells in the etiology of chronic pancreatitis (alcoholic or non-alcoholic) is far from clear, pancreatic mast cell density appears to be 3.5-fold higher in patients with painful chronic pancreatitis than painless chronic pancreatitis. [129]

Evidence of hepatic impact is detectable in about half of MCAS patients. [63] Fibrosis (obliterative portal venopathy) is the most common pathologic finding, but fatty metamorphosis, sinusoidal dilatation, venoocclusive dilatation, nodular regenerative hyperplasia, and cirrhosis are also seen. Sterile hepatitis, with portal triad infiltration by lymphocytes (and smaller numbers of eosinophils) and usually reflected in modest (less than 2- to 3-fold) elevations in transaminases and/or alkaline phosphatase (usually without hyperbilirubinemia), is common. Cholestasis appears uncommon. Portal hypertension, too, appears uncommon but, when present, is reflected as expected in gastroesophageal varices and splenomegaly. [130] Idiopathic ascites also is quite infrequently seen in both SM and in MCAS. [131] It may be seen with or without portal hypertension but, when present, is often massive and difficult to manage. A generalized mast cell-driven peritoneal serositis seems likely to be the cause in cases absent portal hypertension.

Genitourinary Findings

Episodes of sterile inflammation at one or more sites dominate the presentation of MCAS in the genitourinary (GU) tract, though the poor localization of visceral sensation can create diagnostic challenges.

In the author's and others' experience, the most common GU presentation is a dysuric interstitial cystitis [48, 49, 95, 132] which often is mistakenly diagnosed and treated as chronic recurrent urinary tract infections in women and as chronic recurrent prostatitis in men despite failure to find definitive infection. Some women are able to distinguish vaginitis from cystitis, but both can occur in MCAS. Vulvar vestibulitis, with resulting dyspareunia, is sometimes distinguishable, too. [133, 134, 135] Aside from negative or non-diagnostic culture results, another clue that the reported dysuria may be due to sterile MCAS-driven inflammation instead of infectious-driven inflammation is that the symptoms of a true infection typically improve noticeably within 2-3 days of beginning appropriately selected antibiotic therapy. Patients with sterile cystitis, vaginitis, or prostatitis, though, typically report not beginning to notice improvement (if any) until near the end of the extended course of antibiotics which physicians often prescribe for "refractory infection."

More proximally in the urinary tract, some of the mediators released by MCAS can result in non-specific renal inflammation and/or fibrosis [136] leading to organ failure often reflexively attributed to co-morbidities (e.g., hypertension or diabetes) whose severity and duration, upon reflection, do not seem sufficient to cause renal failure. Acute and chronic renal failure can be due to obstructive uropathies, too, but when obstruction is evident on imaging but appears intermittent (even fleeting) and no identifiable stones are identifiable, MCAS-driven obstructive ureteral angioedema should be considered.

Throughout the urinary and genital tracts, inflammatory mediators released by MCAS can cause aching and pain which can be severe and focal but more often are mild to moderate and vague in localization. Chronic low back pain is a common complaint of such patients; flank pain and lower abdominal quadrant pain seem to be less common complaints.

Also likely due to inflammatory and/or fibrogenic mediators, fertility issues, like the aforementioned genital tract and urinary tract issues, are not so rare. [95] In women, luteinizing hormone-stimulated mast cells have long been known to be intimately involved in ovarian function, releasing histamine which stimulates ovarian contractility, ovulation, and follicular progesterone secretion. Also, antihistamines can block ovulation. [137] Thus, it is not difficult to envision that MC dysfunction could result in ovarian dysfunction, but there is little primate *in vivo* data available on this subject thus far. However, aberrant MC activation is a well-recognized primary issue in endometriosis and provides a target for treatment of this significant public health issue which affects 15-20% of women in their reproductive years. [138, 139, 140] The impact of MCAS on gestation is unclear. Miscarriages in MCAS patients, though – especially in the setting of an abnormal prothrombin time or partial thromboplastic time – should prompt consideration of an MCAS-driven anti-phospholipid antibody syndrome, though other hypercoagulable states should be considered as well. In men, 15d-prostaglandin J_2 (a metabolite of (MC-generated) PGD_2) can initiate and maintain sclerosis in the testes. [141] Mast cell blockers can treat oligospermia and result in pregnancy. [142] Decreased libido in both sexes, and erectile dysfunction in men, are common in SM patients [49] and are frequently seen in MCAS as well, likely of multifactorial etiology.

Physicians must be careful not to reflexively attribute all pelvic symptoms in patients with GU tract malignancies to progression of cancer. The author has observed a small number of cases of MCAS confused for recurrence of localized, definitively treated prostate cancer despite a stable normal prostate specific antigen together with numerous local and distant symptoms not expected from locally recurrent or metastatic prostate cancer.

Musculoskeletal and Joint Findings

Although generalized waxing/waning weakness, fatigue, and malaise are some of the most common complaints amongst mast cell disease patients [40, 48, 49], actual myositis, much less frank rhabdomyolysis, appears to be fairly rare, though given the paucity of such cases in which muscle enzymes are measured, and even fewer cases in which muscle is actually biopsied, myositis could be more frequent than is being recognized. However, the author has observed a small subset of MCAS patients who demonstrate substantial elevations (up to ten-fold the upper limit of normal) of creatine kinase and/or aldolase, yet remain asymptomatic. The clinical significance of this finding is unclear.

Premature osteopenia/osteoporosis is frequently found in mast cell disease patients [40, 48, 63, 143] and is usually diffuse but may be focal. Osteosclerosis (usually focal) is seen, too, though much less commonly. [144, 145, 146, 147] Occasional patients may be shown to have both osteopenia and osteosclerosis in different sites. [147, 148] There has been much progress of late in understanding the biology of the excessive bone resorption in osteopenia and osteoporosis. [149] Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa-B) is a DNA transcription regulator found in almost all animal cell types. Osteoclasts express receptor activator of NF-kappa-B (RANK) on their cell surfaces. Osteoblasts secrete RANK ligand. Binding of RANK ligand (RANKL) to RANK leads to upregulation of osteoclast activity (i.e., bone resorption), leading to osteopenia and osteoporosis. Osteopenia and osteoporosis have long been recognized complications of systemic mastocytosis and also seem to be prevalent complications of MCAS. Although the specific mechanism of these conditions in MCAS has not been investigated, no clinical distinction has been identified between osteopenia/osteoporosis in MCAS and osteopenia/osteoporosis in otherwise normal individuals. As such, it seems reasonable at present to presume that the mechanism of these conditions in MCAS likely is the same as in the non-MCAS setting, i.e., excessive RANKL-stimulated osteoclast activity.

MCAS patients commonly report diffuse, and diffusely migratory, aching and pain [40, 48, 49, 95], often acquiring a diagnosis of osteoarthritis, seronegative rheumatoid arthritis, fibromyalgia, and/or polymyalgia rheumatica after evaluation by a rheumatologist fails to identify any more specifically defined rheumatologic disease. These discomforts sometimes seem centered in joints, sometimes in bones (usually without clear association with radiographically identifiable underlying osteopenia or osteosclerosis), and sometimes in soft tissues. Although sometimes the discomfort is quite diffuse and chronic, more commonly the discomfort waxes and wanes as it migrates about various parts of the body. Data exist to suggest mast cell dysfunction may be at the heart of many idiopathic pain syndromes such as chronic low back pain [150] and complex regional pain syndrome. [151] In some patients the migration pattern is limited to a small number of sites (e.g., the legs), while in other patients the migration pattern is quite diffuse.

In addition to pain, another articular issue seen in a small subset of MCAS patients appears to be excessive laxity (i.e., hypermobility), leading some evaluators to diagnose Ehlers-Danlos syndrome (EDS). However, genetic testing in such patients usually rules out all the types of EDS stemming from known mutations, leaving the evaluator to conclude the patient has type III EDS, for which no associated mutations have yet been identified. Curiously, some of these patients also suffer postural orthostatic tachycardia syndrome (POTS, especially the hyperadrenergic form) [152, 153, 154], but careful history sometimes reveals other symptoms attributable not to EDS or POTS but consistent with MCAS, leading to speculation that MCAS may be the root cause of the combined presentation of these disorders in some patients.

Of note, MCAS-driven pain not uncommonly is poorly responsive to traditional analgesics. [155, 156, 157] In fact, traditional analgesics – both non-steroidal anti-inflammatories [158] and narcotics [159, 160] – can trigger flares of mast cell activation and related symptoms in some patients. In such patients, other pharmacotherapy directed against MCs or the direct or indirect effects of their mediators sometimes can be helpful, e.g., antihis-tamines [161, 162], cromolyn [160, 163, 164, 165], bisphosphonates [155], hydroxyurea (Afrin, unpublished data), etc.

Neuropsychiatric Findings

Mast cells are known to be sited not only in proximity to environmental interfaces (mucosa and blood and lymphatic vessels) but also in proximity to nerves. [166, 167] Also, it is becoming increasingly apparent that inflammation – of yet unknown source – is a significant factor in the development of a wide range of neurologic and psychiatric disorders. [168, 169, 170] Thus, it is not surprising that evidence of aberrant MC activation can be found in patients presenting with one or more of a very wide range of peripheral and central neurologic, and psychiatric, findings.

Mast cell disease patients commonly complain of headaches [171], sometimes frequent and severe enough to be disabling. Prior diagnosis of (often seemingly treatment-refractory) migraine headache is common [40], and mast cell degranulation has been implicated in migraine headache. [172]

Episodic dizziness, lightheadedness, weakness, vertigo, and presyncope are common in mast cell disease [40, 48, 49], though in the author's experience frank syncope seems less common in MCAS than in SM. When vasomotor instability is a principal symptom, MCAS patients often are diagnosed as having dysautonomia and/or POTS, though they almost invariably have many other (neurologic and non-neurologic) symptoms which are difficult to attribute to this vague neurologic dysfunction syndrome.

Inflammatory and other neuro-excitatory MC mediators are clearly operant in MCAS, as patients not uncommonly report symptoms of increased sensory and/or motor nerve activity such as tingling/numbness paresthesias and/or tics. [40] Tics tend to remain localized to the limited number of areas in which they initially manifest, whereas paresthesias commonly present as a waxing/waning issue unpredictably migrating about the extremities (more often distal than proximal). Much less commonly, essential resting tremors are seen, and even idiopathic (and sometimes anti-epileptic therapy-refractory) seizure disorders can develop. In

some patients, acute presyncope is mistaken for complex partial epilepsy despite minimal to no abnormal electroencephalographic findings.

Electromyograms and nerve conduction studies not uncommonly are performed in MCAS patients with weakness, tremors, tics, or paresthesias, typically revealing normal or "non-specific" findings. Occasionally, though, distinctive clinical and testing findings compatible with "chronic inflammatory demyelinating polyneuropathy" (CIDP) are found (sometimes accompanied by a modest monoclonal gammopathy of undetermined significance which likely is also MCAS-driven), and if the patient has other (neurologic, or especially non-neurologic) symptoms not easily attributable to CIDP, the possibility of MCAS should be entertained.

MCAS patients with sensory or motor neurologic dysfunction not uncommonly have undergone imaging procedures identifying modest anatomic abnormalities to which their symptoms have been somewhat illogically attributed for lack of any other readily apparent cause. Some patients with symptoms potentially compatible with subacute combined degeneration (SCD) are found to have low-normal, or even slightly low, cobalamin levels and are inappropriately diagnosed with, and treated for, cobalamin deficiency despite complete absence of any of the hematologic sequelae expected in cobalamin deficiency. As discussed in more detail in Hematologic Findings, MCAS-driven copper malabsorption can lead to copper deficiency, clinically mimicking SCD.

There have been tantalizing hints of MC involvement in the development of multiple sclerosis [95, 173, 174] and amyotrophic lateral sclerosis [175]. PGD_2 induces motor neuron loss through demyelination and enhanced astrogliosis [176]; motor neuron PGD_2 receptor blockade can rescue such neurons. [177] There also is growing evidence of MC involvement in Alzheimer's disease. [95]

Given that PGD_2 is the most potent human somnogen known [178, 179], and given that receptors for PGD_2 are known to be present in the human brain's sleep center in or near the pre-optic area [180], it is not surprising that inordinately deep sleep is reported by some mast cell disease patients [181], nor should it be surprising (given other neuroexcitatory symptoms of the disease) that insomnia is commonly reported by these patients. [63, 182] Such patients often report difficulty falling asleep and difficulty staying asleep in spite of their chronic fatigue – which of course may be exacerbated by their sleep disruptions.

Interestingly, obstructive sleep apnea (OSA) seems to be a relatively common problem in the MCAS population and, in the author's experience, seems to be relatively poorly correlated to obesity, raising the possibility of a directly MCAS-driven aberrancy of pharyngeal muscle tone during sleep. Alternatively, MCAS-driven pharyngitis with associated edema may be a factor. [183] Of note, an association between allergic rhinitis and OSA has long been recognized. [184] Regardless of its cause, OSA is relatively easy to treat in most patients, and in the author's opinion, all patients with chronic fatigue and/or disturbed sleep should be evaluated for OSA.

Of potential relevance to consideration of neurologic issues in patients being evaluated for potential MCAS, PGD_2 has a number of known central nervous system effects including osmoregulation, thermoregulation, vasomotor control, neuroendocrine control, and pain perception. [185, 186]

As with the non-psychiatric neurologic issues in MCAS, the psychiatric issues, too, are "all over the map," with ample reports of subtle cognitive disturbances, mood disturbances, irritability, pathologic anger, depression, bipolar affective disease, attention deficit disorder,

anxiety and panic disorders, and even frankly psychotic disorders. [40, 48, 49, 95, 168, 169, 170] Prior diagnoses of idiopathic and often treatment-refractory panic disorders are not uncommon. [187]

In the author's experience, the most common psychiatric issue acknowledged by MCAS patients is episodic cognitive dysfunction recognized either by the patient (who often terms it "brain fog") or, sometimes, a close associate. Such dysfunction tends to affect short-term memory and word-finding more so than other functions. Some patients deny specific areas of cognitive dysfunction but complain that it is simply their overwhelming fatigue that causes a global defect in thinking clearly.

Given that stressful events often trigger acute and chronic flares of MCAS, it is not surprising that post-traumatic stress disorder (PTSD) is not a rare diagnosis in this population. [188] However, it is imperative in taking the history of a patient who is being evaluated for MCAS and who carries a prior diagnosis of PTSD to carefully review the history of the inciting trauma. In the author's experience, such exercises sometime valuably reveal that the long-purported inciting trauma either was trivial or perhaps even never actually occurred, and instead it was another stressor around the time of symptom onset that was the operant inciting factor.

In addition to acute neuropsychiatric issues from MCAS, chronic/developmental issues may exist, too. For example, it has been observed that the incidence of autism is nearly an order of magnitude higher in patients with mastocytosis. [189] Most autism spectrum disorder (ASD) patients have food intolerances and other allergic symptoms indicative of mast cell activation [190], suggesting MCAS may be one possible cause of ASDs. Mast cell activation seems to play an etiological role in a subgroup of children with attention deficit-hyperactivity disorder (ADHD), too. [191]

Endocrinologic/Metabolic Findings

With scores of mediators being released by mast cells, and with each mediator having a wide range of direct and indirect, local and remote effects, the wide range of endocrinologic and metabolic effects that can be seen in assorted mast cell disease patients (both SM and MCAS) is not surprising. [48, 63] It quickly can become impossible to sort out direct from indirect effects – if such sorting could even be said to be useful.

Most of the metabolic "abnormalities" seen in the serum or urine in SM and MCAS are highly non-specific, and the physician is cautioned to consider whether the *clinical* syndrome expected with increase or decrease in any given metabolite or hormone is present before diagnosing, let alone treating, such a syndrome. For example, vitamin D deficiency by laboratory criteria is often present in MCAS [192], though often with no clear correlation to clinical effect such as osteoporosis, and though a low plasma vitamin D level can be corrected by vitamin D supplementation, it is unclear what benefits, if any, are wrought from such supplementation in an individual with normal bone density.

Subtle, typically inconstant abnormalities of basic electrolytes and "liver function tests" (most of which reflect much more than just hepatic function, of course) are *de rigeur*. [62, 63] Most common are minimal to mild elevations in aspartate transaminase and/or alanine transaminase and/or alkaline phosphatase. Severe hypomagnesemia (with attendant

symptoms) is sometimes seen, with no readily apparent cause (e.g., hungry bone syndrome) identifiable.

Hypothyroidism – or at least a modest elevation in thyroid stimulating hormone in the serum – is common and has been linked to increased mast cells in marrow. [193] Hyperthyroidism, too, is seen [194] but in the author's experience appears less common. Either way, anti-thyroid antibodies are often causative and detectable. In a few patients, though, extreme titers of anti-thyroid antibodies are seen without any clinically apparent thyroid disease.

Although ferritin is widely recognized as being secreted by hepatocytes and macrophages, its production by the mast cell [195] is far less appreciated. Hyperferritinemia is quite common in mast cell disease [62], yet often it is misinterpreted as hemochromatosis (even in the absence of an identifiable HFE mutation) or, in the patient who has received red cell transfusions for any reasons, hemosiderosis. [196] It can be tempting to attribute the entirety of the observed hyperferritinemia in an MCAS patient to transfusional hemosiderosis if the patient has any transfusion history, but two clues will suggest that a not insignificant portion of the elevation in ferritin is of inflammatory origin. First, the serum ferritin level often is considerably higher than would be expected purely from the degree of hemosiderosis attendant to the extent of the transfusion history. Second, while the hyperferritinemia of transfusional hemosiderosis marches in relative lockstep with the transfusion history, the hyperferritinemia of inflammation (MCAS-driven or otherwise) is highly variable from one determination to the next.

Mast cell disease has been clearly associated with obesity and with diabetes mellitus (both types) [197, 198]; of note, both obesity and diabetes mellitus (both types) are now clearly recognized as chronic systemic inflammatory conditions. Mast cells have been identified as effector cells in metabolic syndrome, too. [199] Given the intimate involvement of PGD_2 and its metabolites in at least one key adipose management pathway [200], it is not surprising that there is a surfeit of lipid abnormalities in MCAS, too. [63] Elevations in total cholesterol and low-density lipoproteins, and decreases in high-density lipoproteins and very-low-density lipoproteins, are not uncommon. [197] Hypertriglyceridemia, too, is common and often is the starkest lipid abnormality.

Especially in patients without identifiable familial dyslipidemias, statin-refractory lipid elevations – even severe ones – sometimes can be corrected virtually overnight with effective MCAS-targeted therapy. For example, the author observed in one patient, diagnosed with MCAS after four decades of multisystem illness, rapid complete resolution of previously refractory severe hypertriglyceridemia (serum levels approximately 2,000 mg/dl) upon initiation of imatinib.

Hematologic Findings

Perhaps the point of greatest perplexity to physicians attempting to understand mast cell disease (both SM and MCAS) is how a disease that is born of a cell of hematologic origin [167] and is classified as a hematologic disease presents with few to no significant hematologic abnormalities in most cases. [62]

Part of the answer to this conundrum lies in the fact that mast cells spend little of their lifespan in the marrow. Mast cells leave the marrow early, circulate only briefly, and then

enter the peripheral tissues where they reside for the remainder of their relatively long lifespan of several months to a few years. [167, 201, 202] The remainder of the conundrum lies in the recognition that the clinical presentation of MCAS in any given patient is entirely dependent on which mediators are being aberrantly released – and in which amounts, at which times, in which durations, and at which sites – in that patient. Hematologic abnormalities will not be found in patients in whom the aberrant mediator expression patterns do not significantly affect, directly or indirectly, hematopoiesis or blood cell circulation.

There appear to be only a few mutations (most centered around *KIT* exons 8 and 9, particularly codon 816) which drive proliferative mast cell disease (i.e., mastocytosis) resulting in increases in marrow mast cells (systemic mastocytosis). In one study, random marrow biopsies missed this patchy infiltrative disease approximately one-sixth of the time [203], so a second marrow biopsy may be helpful if there is clinical suspicion of mastocytosis but an initial biopsy is unrevealing. Alternatively, the clinician and patient can consider bilateral biopsies in a single session. Mast cells in the marrows of mastocytosis patients are typically organized in small clusters and appreciated to have aberrant (often spindled) morphology and immunophenotype. [20, 37, 204, 205, 206] However, such diseases, born of rare mutations, are themselves rare. [207]

In contrast, MCAS is a relatively non-proliferative disease in which there also seems to be relatively little of the anti-apoptotic forces that account for the majority of the mast cell accumulation in mastocytosis. [208] As such, in MCAS patients there seldom are readily detectable increased numbers, abnormal morphologies, abnormal immunophenotypes, or *KIT* codon 816 mutations in marrow mast cells. [37, 48]

As it is now appreciated that the serum tryptase level is more reflective of the total body load of mast cells and less reflective of their activation state [16, 17], patients suspected of harboring systemic mast cell disease but who have serum tryptase levels less than twice the upper limit of normal (i.e., the lower limit for diagnosis of systemic mastocytosis as specified in the 2008 World Health Organization consensus criteria [209]) do not necessarily require marrow examination during the diagnostic evaluation given the low yield of this procedure. Again, given that MCAS is a relatively non-proliferative disease, most patients in this population present with normal serum tryptase levels [48], even during symptomatic flares of disease; a minority of patients will manifest slightly elevated levels (below the twice-upper-normal limit in the WHO criteria), and an occasional patient will manifest a level which is inconstantly slightly above the threshold in the WHO criteria. As previously noted, a recent consensus proposed recognizing modest elevations in serum tryptase during symptomatic flares (20% above baseline, plus an additional 2 ng/ml) as demonstrative of mast cell activation, but the validity and clinical utility of this calculation have not been specifically studied. [42]

Many MCAS patients present with 100% normal complete blood counts, leukocyte differentials, and, when examined, bone marrow aspirates and biopsies. [48] However, a large minority of MCAS patients present with (typically subtle, but sometimes severe) abnormalities in blood or marrow which may be significant clues to the presence of the disease. In the author's experience, the most common abnormality in the peripheral blood of MCAS patients is a monocytosis on the leukocyte differential. This monocytosis is much more commonly a relative monocytosis rather than an absolute monocytosis, and it is usually subtle enough (1-5 absolute percentage points above the upper limit of normal of about 10%) that most physicians give little thought to the possibility that such a finding may be

diagnostically significant. This monocytosis is usually not seen across all of a patient's serial blood counts but usually is seenoften enough across the series to be provocative, suggesting at a minimum some sort of inflammatory state is present. Similarly patterned elevations in eosinophils (in degree and persistence) are seen in somewhat fewer MCAS patients than who manifest a monocytosis. Similarly patterned basophilia is seen in even fewer patients but, as with a fairly persistent relative or absolute monocytosis or eosinophilia which cannot be attributed to any other evident disease, can be a clue to the presence of MCAS. Also, a similar pattern of "reactive lymphocytes" is sometimes seen on the leukocyte differentials, but identification of such requires the physician to order a manual differential, as routine automated differential rarely distinguish such cells.

Aside from these subtle and often missed or ignored abnormalities in the leukocyte differentials, minor abnormalities in any or all of the blood cell counts are common in MCAS. As is the case with the many other systems affected by the disease, the heterogeneity of these hematologic abnormalities across the MCAS patient population is likely due to the mutational heterogeneity of the disease which drives heterogeneity in aberrant patterns of mediator expression, thereby heterogeneously affecting hematopoiesis and blood cell trafficking.

Independent of the above-noted common abnormalities in the leukocyte differential, there may be a leukocytosis or leukopenia which, if present, is usually modest in degree but on occasion can be severe and seemingly idiopathic despite intensive investigation. [210]

Similarly, thrombocytosis or thrombocytopenia may be present (for the same reason, i.e., mutational heterogeneity leading to mediator expression heterogeneity) and is typically modest in degree. However, platelet count abnormalities in MCAS are sometimes severe and engender diagnoses of essential thrombocytosis or immune thrombocytopenia. In cases of thrombocytosis, analysis for any of the mutations in Janus kinase 2 (JAK2) typically associated with the classic BCR/ABL-1-negative chronic myeloproliferative neoplasms (MPNs, including polycythemia vera, essential thrombocytosis, and myelofibrosis, for the most part) may be positive or negative. Even when positive, though, such mutation analysis does not necessarily rule out underlying, or at least co-morbid, MCAS when there are findings in the presentation which cannot be easily attributed to the apparent MPN. Given the propensity of MCAD patients to develop hematologic malignancies of potentially any type [204], it is possible for a JAK2-positive MPN, too, to have developed secondary to mast cell disease (including SM and MCAS). [211, 212]

With regard to red cells, too, MCAS patients may present with increased or decreased numbers. Erythrocytosis – presumably due to "paraneoplastic" release of erythropoietic mediators either directly by mast cells or indirectly by other cells being driven by aberrant MC mediator release – is typically modest and without JAK2 mutations, but such patients not uncommonly are nevertheless mistakenly diagnosed with, and treated for, polycythemia vera (it is unknown what portion of the 2% of JAK2-wild-type polycythemia vera patients have underlying, or at least co-morbid MCAS) – and unsurprisingly show little symptomatic improvement with phlebotomy. [54] (Such patients treated with hydroxyurea may show more symptomatic improvement since this drug can help control some aberrant mast cell populations.) Some MCAS patients also suffer obstructive sleep apnea (an etiologic role for uvular mast cells has been postulated [213]), and the physician must be careful to rule out chronic, or at least nocturnal, hypoxemia as a cause of an erythrocytosis that can be anywhere from mild to severe in degree.

The erythrocytosis of MCAS usually is mildly macrocytic; it is unclear whether this reflects more a reticulocytosis driven by aberrant erythropoietic mediator release vs. dysplastic erythropoiesis. MCAS-driven erythrocytosis rarely is of such a degree as to consume iron in excess of the ability to ingest and absorb iron, but on occasion true iron deficiency is seen in MCAS patients (whether due to bleeding lesions or iron malabsorption) and inevitably results in the expected microcytosis.

To be sure, although erythrocytosis is seen in some MCAS patients, anemia is the far more common erythrocytic abnormality seen in these patients. As with the erythrocytosis of MCAS, anemia is typically mild to moderate in degree but sometimes, with a marrow shown to be empty of red cell precursors, can be severe and mistaken for parvovirus B19-negative pure red cell aplasia (PRCA) which typically does not respond well to classic therapies for PRCA. [55]

An exemplar of the heterogeneity of MCAS all in itself, anemia in MCAS is typically mild but can be moderate or severe, and it can be normocytic, macrocytic, or microcytic. As MCAS virtually always causes the patient to have a "chronic inflammatory state," normocytic anemia is never surprising. As with MCAS-driven erythrocytosis, when MCAS-driven anemia is macrocytic, it is usually modest (mean corpuscular volume (MCV) approximately 100 fL); again, it is unclear whether reticulocytosis or dyserythropoiesis is dominant. It is possible that some cases of the recently defined idiopathic dysplasia of uncertain significance, and perhaps even the recently defined idiopathic cytopenia of uncertain significance, may be MCAS, but this has not been studied. [368] When the anemia is moderate to severe, or the macrocytosis is more pronounced (MCV approximately 105-110 fL), marrow examination to rule out a true myelodysplastic syndrome (whether a coincidental primary lesion or an MCAS-driven secondary lesion) is essential. The most severe macrocytoses (MCVs in excess of 115 fL, often together with red cell distribution widths (RDW) in excess of 25) immediately raise the question of cobalamin or folate deficiency. Of these two abnormalities, cobalamin deficiency is the more common and may or may not be associated with subacute combined degeneration, and it is imperative to identify whether pernicious anemia (PA, due either to anti-intrinsic factor antibodies or anti-parietal cell antibodies) is present, as PA can be associated with autoimmune thyroid disease and gastric malignancy and requires surveillance for both). Folate deficiency is less common and, in the absence of obvious alcohol abuse or an inborn hemolytic condition such as sickle cell anemia, immediately begs the question of an acquired chronic autoimmune hemolytic anemia as one of the potential autoimmune consequences of MCAS. Non-immune ("Coombs-negative") chronic hemolytic anemia may be due to paroxysmal nocturnal hemoglobinuria (PNH), an ultra-orphan disease (estimated 5-10 cases per million) whose "root" deficiency of the glycophosphatidylinositol (GPI) cell-surface-protein-anchor (due to acquired mutations in the PIG-A gene) explains both the susceptibility of affected erythrocyte to complement-mediated lysis and the effectiveness of the anti-complement-factor-5 monoclonal antibody therapy eculizumab in managing the hemolytic aspects of this disease, but the many other symptoms often found in PNH patients which are not readily attributable to hemolysis, and the much more variable response of such symptoms to eculizumab, may suggest an underlying MCAS which eventually results in PNH via a PIG-A mutation akin to how MCAS may result in, say, acute leukemia via a chromosome 7 mutation affecting a myeloid growth factor (or growth factor receptor) gene or myeloma via a chromosome 13 mutation.

A steadily worsening microcytic anemia in the MCAS patient is most commonly due to iron deficiency, though a deficiency in copper is possible, too. Confoundingly, though, anemia in copper deficiency is sometimes normocytic or even moderately macrocytic. [369]

Iron deficiency in such patients usually is due to an MCAS-driven selective iron malabsorption (and often corrects with simple H_1/H_2 histamine receptor blockade), but it remains imperative to rule out chronic bleeding from the gastrointestinal and genitourinary tracts. Presuming upper, lower, and capsule endoscopy and urinalysis find no source of bleeding, a simple oral iron absorption test can be easily conducted in the office (regardless of whether the patient is presently receiving iron supplementation by any route) to identify whether iron malabsorption is present. Many different versions of the oral iron absorption test have been described but have faced assorted challenges including radiation exposure and poor reproducibility. A more recently developed approach which addresses some of these problems involves first obtaining a blood sample to be tested for baseline plasma iron concentration, then administering a 100 mg dose of sodium ferrous citrate, and then determining another plasma iron concentration two hours later. An increase of less than 50 μg/dL is consistent with malabsorption. [214]

Iron malabsorption in MCAS can be due to a variety of causes. Although classically taught as a macrocytic anemia, pernicious anemia [215, 216] can present with microcytosis and iron deficiency resulting from MCAS-driven immune dysfunction leading to anti-parietal cell antibodies which in turn cause gastric achlorhydria, impeding absorption of non-heme dietary iron every bit as much as can be seen with iatrogenic achlorhydria. Iron malabsorption has been found in up to half of patients with inflammatory bowel diseases, many of which are increasingly suspected to be due to mast cell disease. [217, 218] The expression of the master regulator of iron homeostasis, hepcidin, whose upregulation leads to downregulation of transfer of absorbed iron from the duodenal enterocyte into the circulation, is induced by various inflammatory cytokines including interleukin-6 [219], one source of which is the mast cell. [220] Tumor necrosis factor alpha, too, interferes with this transfer and is produced by various cellular sources including the mast cell. [281] Iron malabsorption is sometimes seen with gastric acid suppression therapy, too (though it is much more commonly seen with proton pump inhibitors than H_2 receptor blockers). Such therapy is used to treat the gastritis and gastroesophageal reflux symptoms of MCAS and can inhibit acid production so effectively that there remains insufficient acid to convert ingested non-heme iron from the poorly soluble, poorly absorbed ferric state to the much more soluble and absorbable ferrous state. [221, 222, 223] Thus, sometimes discontinuation of the proton pump inhibitor (or at least a change from proton pump inhibitor therapy to H_2 receptor blockade therapy) is all that is required to restore adequate iron absorption.

Copper deficiency in MCAS patients usually is a result of a selective copper malabsorption (via yet undetermined specific mediator aberrancies), but the physician must be alert to the possible presence of zinc toxicity (which can cause copper deficiency), as some MCAS patients take excessive quantities of over-the-counter zinc preparations which are advertised to improve some of the constitutional issues suffered by MCAS patients. Also, the dental issues in MCAS patients can lead to early need for dentures, and overuse of zinc-based denture adhesives can lead to zinc toxicity which in turn can cause copper deficiency with its expected hematologic and (cobalamin-deficiency-mimicking) neurologic consequences. [224, 225]

Hypothyroidism is an uncommon cause of microcytic anemia [226], but it is a common consequence of MCAS. [48] Simple history or inexpensive testing usually can exclude hypothyroidism as a contributor to microcytosis in anemic MCAS patients.

All of these pointers regarding microcytic anemia having been stated, the physician is cautioned to carefully review the long-term trends in hemoglobin and MCV before setting off down the potentially long and expensive path of evaluating for iron or copper deficiency. It is *worsening* anemia and microcytosis that signal *pathologic* micronutrient deficiency. However, some MCAS patients, in spite of all of their symptoms, manifest *stable* anemia and microcytosis, and thalassemia should be considered in such patients who are of at-risk ethnicities; congenital or acquired sideroblastic anemia, too, should be considered. Of course, other (not necessarily microcytic) inborn hemoglobinopathies can also co-exist with MCAS and sometimes (such as in the oft-symptomatic sickle cell anemia patient) may obscure recognition of co-morbid MCAS.

An occasional MCAS patient will manifest low serum iron and ferritin concentrations ordinarily suggestive of iron deficiency – yet the MCV and red cell distribution width will be virtually normal, clearly ruling out iron deficiency. It is hypothesized that such patients may harbor MCAS-driven aberrant mediator expression patterns which alter iron transport in the circulation but not utilization in the marrow. Such isolated findings of low serum iron and ferritin do not in themselves call for treatment.

The marrow in MCAS patients usually is normal, with cytogenetic studies usually showing normal karyotypes or culture failures. The most common abnormal pattern in the marrows of MCAS patients is a non-specific, mild myeloproliferative/myelodysplastic appearance [54] (often seen in SM, too [227]) which the pathologist is reluctant to definitively label as either a myeloproliferative disorder or a myelodysplastic syndrome (MDS), yet the appearance of the word "dysplasia" in the report often leads the clinician to diagnose the patient with, and treat the patient for, MDS. When the marrow in MCAS appears less than definitively dysplastic and the karyotype is normal (and other molecular probing for MDS-associated mutations is negative), and/or the patient responds poorly to MDS-targeted therapy, the physician who is considering MDS in the differential diagnosis should also consider MCAS.

Regardless of whether the marrow in an MCAS patient is reported as normal or as the above-noted mild non-specific abnormality, it is rarely the case that increased mast cells, or aberrant mast cell morphology or immunophenotype or *KIT* codon 816 mutations, are identified. Again, this is in distinct contrast to what is expected in SM. Given that there are no known differences in prognosis or therapy for MCAS vs. indolent SM (which comprises the greatest fraction of SM cases [204]), some investigators feel that if the serum tryptase is elevated little to none (signifying likely absence of a proliferative mast cell disease) and there are no other clinical or laboratory suggestions of non-mast-cell-lineage hematologic malignancy, it is reasonable to omit a marrow examination from the evaluation of patient suspected of having MCAS. [48, 370]

Coagulopathic Findings

Excessive clotting and/or bleeding issues are not rare in MCAS patients. While it is possible for virtually any bleeding disorder to be present as a coincidental co-morbidity in an

MCAS patient, the bleeding typically seen in those MCAS patients who do manifest "easy" bleeding or bruising may be due to flares of disease which elaborate heparin (the first discovered mast cell mediator [10, 11]) into local tissues which also may be primed for bleeding due to a friable state induced by chronic release of inflammatory mediators by the mast cell disease. In the author's experience, the bleeding most commonly seen in MCAS patients is a history of "easy bruising" and/or an intermittent unprovoked epistaxis which is typically mild and does not require professional intervention, but more severe bleeding (nasal and elsewhere) is certainly possible. Curiously, although menorrhagia can be a presentation of MCAS, many female MCAS patients who report easy bruising and/or epistaxis report normal menses, perhaps underscoring the importance of (in)appropriate localization of aberrant mast cells in producing some of the symptoms and findings in the disease. Some MCAS patients only present with abnormal bleeding in the context of surgical and non-surgical trauma, in which the bleeding is confined to the traumatized site and often leads to extensive, but perplexingly normal, coagulation studies. In some such cases, modest coagulation study abnormalities lead to inappropriate diagnoses of rare coagulopathies such as certain rare subtypes of von Willebrand disease based on only modest abnormalities in specific testing for such disorders. Absent highly abnormal results on highly specific tests for uncommon coagulation disorders, hematologists should be careful to consider the possibility of underlying mast cell disease when evaluating puzzling bleeding or thrombotic coagu-lopathies, especially when localized.

When local elaboration of heparin due to mast cell disease (SM or MCAS) is identified as the definitive or likely cause of an odd, clinically significant local bleeding pattern, mast cell-targeted therapy (e.g., H_1/H_2 histamine receptor blockade) often is helpful. Occasionally in more severe cases, local administration of protamine, if feasible, may be warranted, and in the most severe cases, systemic thrombolysis inhibitors (tranexamic acid or aminocaproic acid) may become necessary.

Thromboembolism is not a rare event in MCAS patients and sometimes occurs without any coagulation system abnormality being identifiable. However, many such cases manifest subtle abnormalities (high or low) of prothrombin time (PT) and/or partial thromboplastin time (PTT) which are not readily attributable to their present anticoagulation therapy (e.g., an elevated PTT in a patient whose only anticoagulant is warfarin), and in such cases the physician must consider the possibility of an anti-phospholipid antibody syndrome. Eval-uation in such cases for beta-2-glycoprotein-1 antibodies, anti-cardiolipin antibodies, and lupus anticoagulant (even in patients who have abnormal PTTs but normal PTs) is warranted. When such antibodies are identified and persist for more than 12 weeks, diagnosis of an anti-phospholipid antibody syndrome and chronic anticoagulation (initially with warfarin, to an INR of 2.0-3.0) are appropriate. [228, 229, 230] The utility of testing for anti-prothrombin antibodies remains controversial. Although the use of aspirin might seem tempting given its dual effects of inhibiting platelet function and certain mast cell functions, aspirin appears to be inferior to warfarin in reducing the risk for anti-phospholipid antibody-associated thromboembolism. [231, 232]

MC heparin has recently been shown to interact with the coagulation system in manners other than just activating anti-thrombin III. MC heparin activates Factor XII, leading to activation of the rest of the "intrinsic" clotting cascade, perhaps another mechanism by which MCAD can promote thrombosis. Also, heparin released from MCs initiates, in a Factor XII-dependent manner, formation of bradykinin which engages endothelial kinin-b2 receptors

resulting in vascular dilation and leakage, i.e., a non-histamine-mediated route by which MCAD can cause angioedema and potentially even hypotension or presyncope. [371]

Immunologic Findings

A review of the immunologic consequences of mast cell disease is beyond the scope of this chapter. For present purposes it must suffice to say that both cellular immune deficiencies and humoral immune abnormalities are common in MCAS, leading to impairments of any or all of the primary functions of the immune system which in turn lead to increased susceptibility to infection, increased development of autoimmune conditions, impaired healing, and increased risk for malignancies of all types (especially hematologic malignancies). [58, 233, 234]

Hypersensitivity reactions of all types (I, II, III, and IV) can be seen in mast cell disease [58], and many such patients report multiple and/or odd hypersensitivity reactions. [48] The physician must be alert to hypersensitivity reactions which can occur not only in acute fashion but also subacute or delayed.

MCAS patients often have increased difficulties with infection [58, 235], both more frequent infections than previously experienced (at common and uncommon sites, and with common and uncommon organisms) and oddly prolonged infectious episodes in spite of known correct antibiotic therapy. This is, in one sense, a manifestation of the known propensity for poor healing in patient with dysfunctional mast cells.

An increased risk for hematologic malignancy (of potentially any type, but more commonly myeloid) is well established in mast cell disease [204], but suggestions are emerging of increased risk for a wide range of other malignancies as well. [234] Whether this risk is due to direct involvement of aberrant mast cells in the development of cancer-causing mutations and/or due to mast cell disease-driven suppression of immune surveillance creating a permissive environment for carcinogenesis is unclear. Mast cell involvement in peritumoral angiogenesis is well established, as is the common presence of increased mast cells in a variety of solid tumors. [236] Whether tumor-associated mast cells are normal (i.e., mast cells recruited both in support of angiogenesis as well as in an effort to repair the tissue damage done by malignancy) or whether there might be a subpopulation of such mast cells whose aberrant activation (i.e., MCAS) serves as a primary provocation of such tumors is unknown.

The activated mast cell controls the key events in wound healing: triggering and modulation of the inflammatory stage, proliferation of connective cellular elements, and final remodelling of newly formed connective tissue matrix. Surplus or deficit of degranulated mediators impairs repair by causing exuberant granulation tissue, delayed closure, and chronic inflammation. [233]

Mast cells influence initiation and effector phases of autoimmune diseases via many mechanisms including promoting dendritic cell maturation and migration to secondary lymphoid organs, directing T cell differentiation, and orchestrating the migration of T cells and other immune cells to the sites of tissue inflammation. Variable effects of mast cells are related to the activating stimulus, tissue site, proximal target cells, and genetically determined variability in mediator production. [58]

Distinction of MCAS-induced inflammation and autoimmunity from inborn autoinflammatory syndromes (usually identified relatively early in childhood) is challenging and requires a high index of suspicion and expensive genetic testing.

DIAGNOSTIC APPROACHES TO MAST CELL ACTIVATION SYNDROME

Diagnosis of MCAS is often difficult for many reasons, principally the cognitive challenge it poses to the diagnostician. The average physician is capable of considering only a handful of clinical elements at a time when attempting to recognize diagnostic patterns of presentation (e.g., fever, night sweats, and hemoptysis suggest a possibility of tuberculosis). [237] Temporal factors are important to human cognition, too. The human mind is increasingly challenged at recognizing patterns when events occur with less temporal regularity and less temporal proximity to one another. Furthermore, repetition of presentation is key for diagnostic efficiency. The physician who repeatedly sees the same set of elements present in the same temporal pattern will be able to recognize the same pattern more efficiently in the future. [238]

MCAS, though, seems almost artificially engineered to confound diagnosticians. Its great menagerie of underlying activating mutations, combined with the mast cell's normal function of producing and releasing a cornucopia of highly potent mediators (each with multiple direct and indirect, local and remote effects) [47], ensures a tremendous range of clinical presentations. Once a full history is obtained, it is evident that the average MCAS patient presents with a large number of symptoms and findings, and many of these presenting elements wax and wane over time periods ranging from minutes to years, often with no clear temporal relationship to one another. Though the general motif of the clinical presentation of MCAS is chronic multisystem polymorbidity of a generally inflammatory theme, many elements of the presentation are not clearly "inflammatory" (e.g., electrolyte abnormalities, osteoporosis, migratory edema, etc.). Moreover, many other elements, while discovered relatively recently to be inflammatory in nature, still are not understood by most physicians to be inflammatory phenomena (e.g., atherosclerotic vascular disease, obesity, psychoses).

All of these factors, of course, conspire to ensure that the key element of repetition is nearly absent from the MCAS landscape. Even the physician who is highly attuned to the general theme and heterogeneity of MCAS presentations may make the diagnosis in dozens of patients before finding one whose presentation is relatively similar to any of the others already diagnosed.

Yet another confounder is the disincentivization by the typical modern health care system to invest the substantial time often needed to make the diagnosis. [239, 240, 241] At present, most MCAS patients live a life of chronic unwellness, accruing over time more and more diagnoses often of unclear etiology and suboptimally responsive to therapy. Those who are diagnosed with MCAS typically have seen many physicians over many years and have undergone many tests and empiric therapies. The complexity of the typical MCAS presentation requires the diagnostician obtain a complete (often life-long) history, carefully review often quite voluminous past records, perform a thorough physical examination, order several laboratory tests which require careful education of the patient and laboratory staff, and

review results which often are not available until weeks later. However, many modern health care systems do not compensate physicians for such an extent of work.

The modern trend toward subspecialization of the physician work force [242, 243] also works against the MCAS patient. Subspecialists tend to limit the range of clinical elements they consider in forming a differential diagnosis to the elements commonly involved with the systems they commonly manage. The cardiologist gives more consideration to palpitations, less to diarrhea; the gastroenterologist, *vice versa*. MCAS, though, is a prototypical multisystem disease, and failure by the diagnostician to consider the full range of presenting elements (forgetting or ignoring in practice the maxim of Occam's Razor learned in training) virtually guarantees failure to recognize MCAS. MCAS patients typically are not so special, so uniquely unlucky, as to have acquired 20 problems all independent of one another; rather, it is much more likely that they have but a single problem which is biologically capable of causing all of the observed findings.

Even absent extensive experience with MCAS, though, the diagnostician can be aided in suspecting MCAS by remembering just a few simple tips:

(1) As mentioned above, the general presenting motif of MCAS is chronic multisystem polymorbidity, generally of an inflammatory theme and with assorted elements waxing and waning over time, sometimes in synchronization with one another but more often cycling with different periods and amplitudes.

(2) When there are symptoms and findings not classically expected with, or not easy to attribute to, the patient's established diagnoses, alternative diagnoses must be entertained to account for these "leftover" elements, and given the universal truth of Occam's Razor, it becomes more likely that the same diagnosis that accounts for the leftover elements also accounts for the established diagnoses.

(3) The range of mast cell mediators and their effects is so great that "unusual" presentations actually become *de rigeur*. That is to say, although any given unusual presentation remains unusual, the full set of unusual presentations constitutes a large fraction of the total set of presentations. Thus, when the clinician recognizes an "unusual," "odd", "weird", "bizarre," or "strange" element in the patient's presentation–e.g., "allergies" to typically innocuous medications, migratory rather than dependent edema, severe and highly variable hyperferritinemia not attributable to the patient's transfusion and chelation history, etc. – his "MCAS radar" should go on alert. The presence of an unusual element in the presentation by no means establishes a diagnosis of MCAS, but it sometimes can be the first spark toward lighting a fire of recognition.

Thus, the largest impediment to diagnosing MCAS may simply be suspecting it. Once MCAS has been suspected, though, how should the diagnostic evaluation proceed?

Given that MCAS has come to be recognized only recently, and given its heterogeneity, it is not surprising that there is not yet a definitive consensus regarding diagnostic criteria.

In late 2010 Akin et al. proposed the diagnosis be permitted if a patient met all of the following four criteria: (1) symptoms consistent with aberrant mast cell mediator expression, (2) laboratory evidence of aberrant mast cell mediator expression, (3) absence of any other evident disease better explaining the full range of findings in the patient, and (4) at least partial response to therapy targeted controlling mast cells or blocking mast cell mediators.

[40] Objections voiced to these criteria included the limited range of validated mediators of mast cell activation vis-à-vis the large number of mast cell mediators. [41] Also, that the mutational heterogeneity (and corresponding heterogeneity of mediator expression) would virtually ensure heterogeneity of therapeutic response was recognized in a modified proposal published in early 2012 by Valent et al. [42]

In 2011 Molderings et al. proposed a set of two major and four minor criteria (modified from the World Health Organization 2008 consensus diagnostic criteria for systemic mastocytosis) [48]:

Major criteria:

(1) Multifocal or disseminated dense infiltrates of mast cells in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (CD117-, tryptase-, and CD25-stained)
(2) Unique constellation of clinical symptoms secondary to a pathological increase in mast cell activity (mast cell mediator release syndrome)

Minor criteria:

(1) Mast cells in bone marrow or other extracutaneous organ(s) show abnormal morphology (>25%) in bone marrow smears or on histological examination
(2) Mast cells in bone marrow express CD2 and/or CD25
(3) Detection of genetic alterations in mast cells from blood, bone marrow, or extracutaneous organs, which have been confirmed to result in an increase in the activity of affected mast cells.
(4) Evidence of a pathological increase in mast cell activity through detection of an elevated level of at least one sensitive mast cell-derived mediator, i.e., tryptase, heparin, histamine, PGD_2, chromogranin A, leukotrienes (and their assorted metabolites) in blood and/or urine

Molderings et al. proposed that MCAS be diagnosed if both major criteria are present (with or without any minor criteria) or if the second major criterion and at least one minor criterion are present.

In early 2012 Valent et al. proposed a modification of the Akin et al. criteria. The requirement for demonstrating at least partial response to mast cell- or mast cell mediator-targeted therapy was relaxed to a preferable but not required criterion. [35] Also, the range of mediator aberrancies supportive of the diagnosis was expanded to include an increase in serum tryptase, during a flare of symptoms, of 20% over the baseline serum tryptase level plus an additional 2 ng/ml. It was noted that this algorithm has not yet been validated.

Clearly, the diagnostic criteria for MCAS have been rapidly evolving, and given the increasing pace of research in this area, continued rapid evolution should be expected.

In the author's opinion, an initial laboratory survey for evidence of MCAS should include a complete blood count with manual differential, a comprehensive metabolic panel, serum magnesium, quantitative immunoglobulin profile if the patient has had frequent problems with infection, prothrombin time (PT) and partial thromboplastin time (PTT) if the patient has had easy bruising or bleeding or thromboembolic events, serum tryptase, serum chromogranin

A, plasma histamine, chilled plasma PGD_2, stat chilled plasma heparin (in patients not on exogenous heparin products), and chilled urine for PGD_2 and *N*-methylhistamine.

Tryptase has been well established as a highly specific mast cell mediator. [14] Its biology is complex; many isoforms with different behaviors and functions have been elucidated. [15] It is heat-labile [244, 245] and has a relatively short half-life *in vivo* (from 6-8 minutes in healthy subjects to 1.5-2.3 hours in patients with hypersensitivity reactions), longer (~4 days) in separated serum. [246] The WHO 2008 diagnostic criteria for mast cell disease call only for the measurement of total serum tryptase, setting a threshold of 20 ng/ml as the minimum level consistent with a diagnosis of systemic mastocytosis. [209] It is unclear whether measurement of specific isoforms of tryptase would be beneficial in diagnosing MCAS, and thus at present the measurement only of total serum tryptase can be recommended in the evaluation of a patient suspected of having MCAS. Although the serum tryptase level usually is not elevated in MCAS [37, 48] due to the relatively non-proliferative nature of the mast cells in this disease, an elevated level can be found in a minority of MCAS patients, and any elevation at all can help buttress a diagnostician's suspicions of mast cell activation being involved in the patient's illness.

Elevated serum levels of chromogranin A (another known mast cell product [47, 247] which appears quite heat-stable [248]) can be helpful toward diagnosing MCAS, but other potential causes (heart failure, renal insufficiency, proton pump inhibitor (PPI) use, and neuroendocrine cancer) should be excluded. Changes in serum chromogranin A level in response to initiation or cessation of PPI therapy are fairly reliable and rapid (within 5 days [249]) but highly variable in magnitude [250, 251], likely due to multiple mechanisms including pharmacogenomic polymorphisms (largely in cytochrome p450 isoenzyme 2C19 [252]) and increase in density of chromogranin A-secreting enterochromaffin cells (especially in gastric tissue) in response to gastric acid reduction. [253]

Although it was the first mast cell mediator to be discovered [10, 11] and is a highly sensitive and specific indicator of mast cell activity [32, 254], heparin is difficult to measure in the clinical setting. Heparin has a short half-life and decomposes rapidly even at chilled temperatures. [254] Seidel et al. [254] reported an upper limit of normal of 0.02 anti-Factor Xa units/ml, but the utility of assessing the plasma heparin level for evidence of MCAS is limited by many commercially available assays having a lower limit of detectability of 0.10 anti-Factor Xa units/ml. Still, an occasional MCAS patient will manifest a level of 0.10 anti-Factor Xa units/ml or greater.

Histamine is slightly less specific for mast cell disease than tryptase in that histamine is also released by basophils. Histamine is not heat-labile [255] and has a short half-life *in vivo* [256, 257] (estimates have ranged from 1 minute to 1 hour and may vary based on increased histaminase activity during anaphylaxis [258]), but it appears stable in separated plasma at room temperature for at least 48 hours [259]. Its major metabolite, *N*-methylhistamine, has a longer half-life *in vivo* [257], which is why it is a preferable measure over histamine, especially when a sample cannot be collected during or immediately after a flare of symptoms.

Although also produced in macrophages [260, 261, 262, 263], Langerhans cells [264], liver endothelium [263], platelets [265], Th2 helper T cells [266], stimulated osteoblasts [267], and possibly adipocytes [268], prostaglandin D_2 appears to be far dominantly produced in mast cells [269, 270], yielding attractive specificity for clinical detection of MCAD. In patients with MC activation producing increases in urinary *N*-methylhistamine, the fold

increase in urinary PGD_2 is substantially greater than seen for the histamine metabolite. [271] However, PGD_2 appears to have an even shorter half-life than histamine (on the order of 1-30 minutes in various studies). [272, 273, 274] In fact, PGD_2 is metabolized so rapidly that its measured levels may substantially underestimate its total production. [275] Some PGD_2 metabolites, though, are more stable than the parent compound (e.g., $9\alpha,11\beta$-PGF_2 [269]), leading some to preferentially test such metabolites over PGD_2. ($PGF_{2\alpha}$, too, is a more stable metabolite of PGD_2, but far more $PGF_{2\alpha}$ comes from reduction of PGH_2, and even some from PGE_2, which are produced by a range of other types of cells [276], making the value of $PGF_{2\alpha}$ as a marker for mast cell activity somewhat unclear.) Assays of levels of histamine and prostaglandin metabolites are further complicated by the need of many laboratories to ship samples to a reference laboratory for measurement. Care must be taken by the patient and laboratory staff to maintain the samples (particularly for heparin and PGD_2) in chilled condition throughout collection, transport, storage, and shipment until final processing. Non-steroidal anti-inflammatory agents, which inhibit cyclooxygenase and thus limit prostaglandin production, can result in low PGD_2 levels in the blood and urine. It is unclear whether urinary PGD_2 is exclusively the product of the kidneys [277] or dominantly a filtering of plasma PGD_2 [269]. If the former is true, a low urinary PGD_2 could be due to renal disease – though certainly patients with renal disease due to activated infiltrated mast cells can manifest elevated urinary PGD_2 levels. Therefore, renal insufficiency is not a reason to forego testing of the urinary PGD_2 level.

A 24-hour urine collection is preferred over a spot/random collection given the evanescence of mediator flares and the short half-life of many mediators makes spot urine samples and blood samples somewhat less likely to catch (often transiently) elevated levels of mediators.

Elevated levels of mast cell mediators not uncommonly are not detectable unless the patient is markedly symptomatic. If the history is consistent with MCAS but an initial laboratory screen for elevated mast cell mediators is normal, repeat screening is warranted when the patient is more symptomatic, most preferably when symptoms are acutely flaring. If possible, hourly determinations of serial levels of serum tryptase, chilled plasma PGD_2 and histamine, and chilled spot urinary PGD_2 and *N*-methylhistamine should be pursued at baseline and over the next 2-3 hours as a flare of symptoms evolves.

Given the heterogeneity of mast cell disease and the above-noted challenges in detecting elevated levels of mast cell mediators, it should not be surprising that some patients present with histories which are classic for MCAS but screens for the most sensitive and specific mast cell mediators which are normal. When repeated efforts to identify aberrant mast cell activity using the above-described screen fail, consideration can be given to screening for aberrant expression of less specific mast cell mediators such as Factor VIII [278, 279], plasma free norepinephrine [280], tumor necrosis factor alpha [220, 281, 282, 283, 284, 285, 286, 287, 288], and interleukin-6. [220] In the author's experience, the first two of these are elevated in MCAS more commonly than the rest. Plasma free norepinephrine is often ordered as part of a plasma free catecholamine profile; the author has observed in many MCAS patients a pattern of elevated norepinephrine, low-normal or low epinephrine, and sometimes elevated dopamine.

Although commercial testing (whether through local or reference laboratories) is not yet widely available, levels of mast cell mediators leukotriene B4 and cysteinyl leukotrienes C4, D4, and E4 have been reported to be elevated in patients with systemic mastocytosis as

compared to healthy controls. [289] Plasma and urinary leukotrienes also increase with acute attacks of asthma [290], a disease increasingly suspected to originate in aberrantly active mast cells [291] and thus perhaps a form of MCAS. However, leukotriene expression has not been specifically studied in the MCAS population. Furthermore, leukotrienes are synthesized in a variety of myeloid cells (and epithelial cells as well) [292, 293], so the specificity of elevated leukotriene metabolite levels for mast cell disease is unclear and may depend substantially on the presence of a clinical history compatible with mast cell disease. Whether elevated leukotriene levels are related more to mast cell load (and thus useful primarily in systemic mastocytosis and perhaps also in a limited range of MCAS presentations in which increased numbers of mast cells can be found in anatomically relevant sites (such as in airway smooth muscle in asthma patients [291]) or to mast cell activity (and thus useful in MCAS in general) remains to be determined. However, if the clinical history is best explained by mast cell activation but abnormal levels of the previously discussed biochemical markers cannot be identified, it would not be unreasonable to also examine levels of plasma and urinary leukotriene metabolites if commercial assays of such are accessible.

If the prothrombin time or partial thromboplastin time, or both, are abnormal (increased or decreased), a survey for anti-phosopholipid antibodies (anti-cardiolipin antibodies, beta-2-glycoprotein-1 antibodies, and lupus anticoagulant) should be pursued; the utility of anti-prothrombin antibodies remains controversial as discussed above. Although the presence of anti-phospholipid antibodies without a history of thromboembolism does not merit a diagnosis of anti-phospholipid antibody syndrome, let alone prophylactic anticoagulation with its attendant risks, foreknowledge of the presence of such antibodies when patients enter high thrombotic risk scenarios can be helpful both proactively and reactively should thrombosis occur.

Because MCAS is a relatively non-proliferative mast cell disease, none of the recent proposals for diagnostic criteria for MCAS absolutely requires histologic detection of increased numbers, or aberrant immunophenotypes or genotypes, of mast cells. In fact, neither the Akin et al. 2010 criteria [40] nor the Valent et al. 2012 criteria [42] make any mention of histologic detection. However, histologic detection of quantitative or qualitative mast cell aberrancy can be used, per the Molderings et al. 2011 criteria [48], to support the diagnosis. As mast cells typically reside at the environmental interfaces [166, 167], histologic evidence of disease sometimes can be found in biopsies of rashes and other skin lesions, gastrointestinal tract mucosa, and respiratory tract mucosa. Less commonly, but also in keeping with the known biology of their development and function, increased and/or aberrant mast cells can be found in biopsies of marrow and lymphovascular structures.

Due to the relatively non-proliferative nature of MCAS and the fact that mast cells spend little of their early formative time in the marrow [167, 201, 202], MCAS is rarely detectable – histologically, immunophenotypically, or genotypically, using present commercially available techniques – in marrow. [48, 370] As such – and in distinct contrast to the evaluation for systemic mastocytosis which can be suspected when serum tryptase levels are consistently greater than twice the upper limit of normal – marrow examinations presently do not seem to be useful enough to warrant being mandatory components of evaluations for MCAS. It of course remains possible that a small portion of cases of systemic mastocytosis as defined per the WHO 2008 criteria [209] may be missed by not examining the marrow of MCAS patients with serum tryptase levels below 20 ng/ml, but the largest portion of systemic mastocytosis patients fall into the category of indolent systemic mastocytosis [62, 204], whose prognosis

and treatment presently are not known to be significantly different than seen and applied in MCAS. Furthermore, the more morbid (and often more proliferative) forms of systemic mastocytosis warranting more aggressive (often cytotoxic) treatment – SM with associated clonal hematologic non-mast-cell-lineage disease (AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL) – present normal tryptase levels even more rarely than indolent systemic mastocytosis. SM-AHNMD, ASM, and MCL also typically present aggressive clinical features, such as obvious hematologic malignancy or hepatic failure, which quickly engenders biopsy and histologic identification of the true diagnosis. Thus, although it is important to distinguish SM-AHNMD, ASM, and MCL from MCAS, the likelihood of confusing these entities with MCAS is very low.

Mast cell disease sometimes can be detected in biopsies of gastrointestinal tract mucosa, commonly performed in patients with symptoms of inflammation of the upper and/or lower segments of the gastrointestinal tract. "Mastocytic enterocolitis" is often the diagnostic label assigned when increased mast cells are found on biopsy of intestinal tissue [294], but the overlap of this label with MCAS is inescapable. Interestingly with regard to the upper segment of the gastrointestinal tract, 40% of the tens of millions of patients in merely the United States alone who have chronic "gastroesophageal reflux disease" are refractory to therapy with maximal doses of proton pump inhibitors (PPIs). [295, 296, 297, 298, 299, 300] In keeping with the severe suppression of acid production effected by PPIs, these PPI-refractory "functional dyspepsia" patients have been demonstrated to have no significant remaining acid production, yet they remain symptomatic. Because they do not produce any acid to be refluxed, it is not acid reflux causing their symptoms. Instead, there must be another cause of the pain and discomfort they are sensing. Most such patients have undergone esophagogastroduoenoscopy, often with random mucosal biopsies taken. These biopsies – typically subjected only to routine staining with hematoxylin and eosin, and possibly also Steinert staining for *Helicobacter pylori* – are usually read as showing either normal tissue or, at worst, mild to moderate chronic inflammation (and even occasionally with a modest increase in eosinophils, too). Infection of any type at any site, certainly including *H. pylori* in gastric tissue, often provokes local reactive (i.e., normal) activation and proliferation of mast cells. [301, 302, 303] However, it has been established that gastric mucosal mast cells are increased in H. pylori-negative functional dyspepsia, too [301, 304], raising the possibility that functional dyspepsia is another manifestation of MCAS. Indeed, it has been the author's experience, too, that re-staining of the *H. pylori*-negative biopsies from PPI-refractory functional dyspepsia patients for mast cell markers (e.g., CD117, Giemsa, toluidine blue, tryptase) not uncommonly reveals increased numbers of mast cells. On occasion, such a finding may be the only detectable laboratory evidence of mast cell disease.

Unprovoked, transient, diffusely migratory rashes are common in MCAS, but in the author's experience biopsies of such rashes rarely reveal increased mast cell populations.

Although the presence of increased mast cells in airway smooth muscle tissue in asthmatic patients has long been known [305], and though it stands to reason (given, again, the normal role of mast cells in human biology) that the respiratory tract is a site where abnormal mast cells ought to be detectable in MCAS patients, there are no studies published yet of the incidence of quantitatively and/or qualitatively abnormal mast cells in respiratory tissue specifically in MCAS patients. Should full sequencing in the future of *KIT* in the mast cells of asthmatic patients reveal the prevalent and heterogeneous clonality seen in MCAS

patients [36, 37], it may become more apparent at that point that biopsy of respiratory tract mucosa, or perhaps simple bronchoalveolar lavage, can be useful in diagnosing MCAS.

The recent discovery that aberrant mast cells are detectable, via mutation-specific polymerase chain reaction (PCR) testing, in the peripheral blood of most patients with indolent systemic mastocytosis [306] raises the question of whether the same holds true in MCAS patients. Once full genomic sequencing (or at least full *KIT* sequencing) becomes routinely, economically available from certified commercial clinical laboratories, such testing may become the most direct route for demonstrating the presence of clonal mast cell disease in patients clinically suspected of having MCAS.

The ability to detect laboratory evidence of mast cell disease likely will advance rapidly in the coming years. The greater challenge will remain sparking the initial suspicion of the diagnosis in the mind of the clinician limited both by human cognitive capacity and by the brief time typically available to evaluate the patient. Validated symptom questionnaires completed by the patient (e.g., [63, 307]) can help the clinician clarify the likelihood of the patient having MCAS, but engagement of such tools necessarily first requires that initial "spark" in the clinician's mind that MCAS may be in the differential diagnosis. In the future, computer-aided diagnostic tools built into electronic clinical information systems may be able to assist clinicians in recognizing morbidity patterns potentially consistent with MCAS.

MANAGEMENT OF MAST CELL ACTIVATION SYNDROME

Mast cell activation syndrome (MCAS) is, like systemic mastocytosis, a disease of aberrant mast cell activation. Unlike systemic mastocytosis (SM), though, MCAS is relatively non-proliferative. Therefore, at present the general therapeutic approach to MCAS is identical to that used for decades now for systemic mastocytosis except there is little to no role for the substantially cytotoxic therapies typically reserved for the more aggressive and proliferative forms of SM as previously discussed, namely, SM-AHNMD, ASM, and MCL. Management of indolent SM has been discussed at length in the literature (e.g., [68, 204, 308]) and, as such, will only be summarized here. Drug dosages listed are for adults; suitable pediatric pharmacology resources should be consulted regarding dosages for children.

Avoidance of triggers, desensitization therapy (when specific unavoidable environmental triggers can be identified), and prophylactic therapies (e.g., bisphosphonate therapy for osteoporosis) help limit morbidity from MCAS.

Symptoms and other clinical consequences (e.g., blood count abnormalities) in MCAS and indolent SM result virtually exclusively from the consequences (direct or indirect) of aberrant mediator release. It should be remembered, too, that because of potential circulation of released mediators, and because of potential interaction of released mediators with elements of the nervous and hormonal/endocrine systems, the dysfunctional mast cells releasing the operant mediators may or may not be located proximately to the clinically affected site. Thus, therapies for MCAS and indolent SM primarily aim to (1) reduce mast cell production and release of mediators, (2) interfere with released mediators, and (3) counter unavoidable effects of released mediators.

The clinician who assumes responsibility for identifying effective therapy in an MCAS patient must keep in mind that the extreme underlying mutational heterogeneity of the disease

almost certainly leads to extreme heterogeneity of aberrancy in patterns of mediator production and release, in turn leading to extreme heterogeneity of both clinical presentation and responsiveness to therapeutics. With the exception of classic histaminic symptoms, at present it is virtually impossible to deduce an effective therapeutic strategy for the individual MCAS patient based on the presenting symptoms and findings. Most MCAS patients are able to eventually identify a regimen which helps them feel significantly better at baseline, though chronic or acute flares of disease activity often persist. In order to have the best chance at finding optimal therapy for the individual MCAS patient, the clinician must practice – and counsel his patient to practice – patience, persistence, and a methodical approach to trying assorted therapies.

Thus, in each patient being treated, each medication tried should be dosed appropriately for the disease and should be given an appropriate period, in accordance with its pharmacokinetics and pharmacodynamics, to demonstrate efficacy. Ineffectiveness of one medication of a given class does not necessarily preordain that all other medications of that class will be ineffective, and it is not at all unreasonable to try at least one or two other medications of a class if the initial medication tried of that class proves ineffective or intolerable. Medications which have clearly demonstrated tolerability and efficacy by the end of a suitable trial period should be continued; medications not achieving such criteria should be stopped (or, if necessary (such as with high doses of glucocorticoids), weaned). Once the effectiveness of a tolerable therapy has been identified, consideration should be given to trying to identify the lowest effective dose and frequency of the therapy.

In view of the innate complexity of the disease and its inherent propensity to react adversely to potentially any new exposure, it is critically important to try to make only one change in the MCAS patient's regimen at any given time. [309] There certainly are times when the severity of one or more symptoms justifies multiple simultaneous interventions, but if multiple therapeutic changes are made simultaneously and the patient either improves or worsens, it is impossible to identify – without further subtractive experiments – which therapeutic change(s) resulted in which clinical change(s). Thus, polypharmacy can emerge rapidly without a patient, appropriately contemplative approach to medication management in the MCAS patient.

Clinicians also must remain aware that when it is stated that MCAS patients can react adversely to potentially any new exposure, the emphasis is on the "any." Environmental antigens (including smoke [310, 311, 312, 313]), ordinarily innocuous microbes, food or drink (especially alcohol), and medications can be offensive to MCAS patients via touch, inhalation, or ingestion. However, reactivity patterns appear to be fairly unique to each patient.

When prescribing or recommending medications, clinicians should keep in mind that virtually all commercial medications, whether prescription or over-the-counter products, contain not merely the active ingredient(s) but also "fillers" (or "binders") and dyes which are inert in most patients but in MCAS patients can be as offensive as active ingredients can be. When an MCAS patient reacts unfavorably and intolerably to a commercial form of a medication deemed important for the patient, sometimes the problem can be resolved by switching to an alternative commercial formulation (e.g., an alternative brand-name formulation, or an alternative generic formulation). Many off-patent medications are formulated by multiple manufacturers into generic products which commonly are visually indistinguishable from one another, and as a result the patient often is unaware not only of the

specific manufacturer of the product being taken but also when one formulation is substituted for another by the patient's local or mail-order pharmacy. Even when a substituted generic product is visually distinguishable from the product previously being provided to the patient, many patients are unaware that different manufacturers use different fillers and dyes in formulating ostensibly the same medication. The stabilized MCAS patient who becomes destabilized soon after switching one of his medications to a different formulation may simply be reacting to one of the fillers or dyes in the new product. Switching back to the prior formulation may be all that is necessary to restabilize the patient. Of course, such an event also is an opportunity to investigate the formulation of the offending product and identify potential offending ingredients for which a future program of active avoidance may prove beneficial.

Furthermore, the active ingredients of many commonly used medications are available in relatively purified form from pharmaceutical manufacturers. For the relatively rare patient who reacts to a very broad range of fillers and dyes, it is possible to have a compounding pharmacist obtain purified active ingredient and package it either into dye-free gelatin capsules or compound it into liquid or tablets using innocuous carrier fluids or agglutinating substances known to be tolerated by the patient (e.g., baby rice cereal, potato, lactose monohydrate, etc.). In the author's experience, even "well-established" anaphylactic reactions sometimes can be completely abrogated by providing the patient such custom-compounded formulations. Some patients, too, succeed with this "compounding" approach simply by reconstituting active ingredient with water immediately prior to ingestion.

Given the rarity of systemic mastocytosis, together with how recently MCAS has come to be recognized, there are no large controlled studies of any intervention for mast cell disease. The absence of such data, together with the great underlying mutational heterogeneity of mast cell activation disease, means that at present the clinician treating MCAS has no way to know in advance which medications are most likely to benefit the patient. Most clinical and laboratory consequences of the disease can arise via multiple mechanisms. As such, there presently are no symptoms or laboratory findings which can reliably foretell effectiveness of any given therapy, and absent such foreknowledge of effective therapy, an economics-based strategy for determining the order in which to try assorted therapies is a reasonable approach, starting with the most inexpensive therapies and escalating in cost as necessary. Such an approach is often appreciated by patients who, due to chronic disability from the disease, are underemployed or unemployed and may face difficulties affording health care. Fortunately, in many MCAS patients the disease is easily controlled with one or two inexpensive therapies – but there also are many patients who require moderately and even stratospherically expensive medications. Clinicians treating MCAS often are asked by their patients to write letters supporting application for disability qualification. Dialogues with third-party payers may be necessary, too, to help insured patients who are being denied coverage of prescribed treatments due to insufficient understanding of MCAS by the payer. MCAS patients also sometimes require their clinicians' assistance in enrolling in drug manufacturer assistance programs to access unaffordably expensive therapies.

Largely due to how recently awareness of MCAS has dawned on the medical community, there have not yet been any clinical trials (of either diagnostic approaches or therapeutics) in MCAS. However, in light of the increasingly apparent prevalence of the disease, trials – particularly of newer, better targeted (and often more expensive) therapies – are greatly needed.

Glucocorticoids can be helpful in controlling MCAS chronically and emergently [68], and certainly are inexpensive, but the rafter of well-known toxicities from chronic use render them less preferable in that setting.

The most inexpensive sustainable therapies for MCAS (and indolent SM) generally include histamine H_1 and H_2 receptor blockers (addressing such receptors on end organs as well as mast cells themselves) [48, 68], benzodiazepines (also addressing such receptors on end organs as well as mast cells themselves) [314, 315, 316, 317, 318], and non-steroidal anti-inflammatory drugs (NSAIDs, including aspirin). [48, 68]

Antihistamines typically are first-line therapies for chronic control of MCAS and often are highly useful in the emergency management of the disease, too. To minimize histamine-mediated mast cell activation, most MCAS patients should try a histamine H_1 receptor blocker in combination with an H_2 receptor blocker.

Diphenhydramine is the prototypical histamine H_1 receptor blocker and is highly effective in many MCAS patients suffering flares of symptoms, but its principal side effect of sedation is undesirable in patients who regularly work or operate heavy machinery and in patients whose disease causes chronic fatigue. In the United States, approved non-sedating histamine H_1 receptor blockers include loratadine, fexofenadine, cetirizine, and levocetirizine, but unlike diphenhydramine, none of these drugs is commercially available for intravenous administration, making diphenhydramine the histamine H_1 receptor blocker of choice in the emergency management of MCAS. Loratadine may have fewer drug-drug interactions than the other products. Loratadine may be effective at the recommended over-the-counter dosing of 10 mg daily, but many patients respond to it better when it is taken every 12 hours. Some patients even can identify further improvement when dosing is increased from every 12 hours to every 8 hours. Higher individual doses of 20 or even 30 mg sometimes provide more benefit, too. However, some MCAS patients on multiple daily doses of loratadine complain of excessive sinonasal dryness, constipation, or urinary hesitancy, and in such patients it may be more beneficial (with respect to sustaining control over the dysfunctional mast cells) to try decreasing the individual dose (e.g., 5 mg, still taken 2-3 times daily) rather than the frequency (e.g., 10 mg taken daily).

Dosing strategies for fexofenadine, cetirizine, and levocetirizine are similar to those used with loratadine. In MCAS, reasonable initial dosing for fexofenadine typically is 180 mg every 12 hours; for cetirizine, 10 mg every 12 hours; and for levocetirizine, 5 mg every 12 hours.

Although cimetidine and ranitidine are effective histamine H_2 receptor blockers, famotidine and nizatadine have fewer drug-drug interactions. [319, 320, 321] Unlike the non-sedating histamine H_1 receptor blockers, most of the H_2 blockers are commercially available for intravenous administration if necessary. As with the H_1 blockers, the H_2 blockers sometimes are optimally effective in providing what control they can over mast cell activation when taken just once daily. However, many patients respond better to twice-daily use of H_2 blockers. Famotidine often is begun at 20-40 mg every 12 hours, while ranitidine is begun at 75-150 mg every 12 hours. Nizatadine can be used at 150-300 mg every 12 hours. Cimetidine is less preferable because of its rafter of drug-drug interactions but, when necessary, can be tried starting at 400 mg every 12 hours.

Given recent recognition of the involvement of inflammation in the development and evolution of a wide range of psychiatric morbidities, it is an open question as to whether benzodiazepine-driven inhibition of mast cell activation gives rise (directly or indirectly) to a

significant portion of the anxiolytic effect seen with these drugs in diseases such as panic and anxiety disorders. Benzodiazepines also are helpful in some patients with inflammatory bowel disease, again raising the question of whether it is enterocyte benzodiazepine receptors or mast cell receptors that are more operant in this benefit. Benzodiazepine therapy in MCAS patients certainly can result in a wide range of other improvements, too (i.e., beyond neuropsychiatric and enteric effects), likely underscoring what can be accomplished solely from blocking mast cell benzodiazepine receptors.

Other inexpensive antihistaminic drugs can be helpful in controlling MCAS, too. Doxepin, ketotifen, tricyclic antidepressants, phenothiazine antiemetics, and the atypical antipsychotic quetiapine all have histamine H_1 receptor blocking effects, and such drugs not uncommonly provide benefit even if the patient is already on a classic H_1 blocker such as diphenhydramine or loratadine. The author begins a trial of doxepin at 10 mg twice daily (though some patients find optimal dosing at just 6 mg once or twice daily) and asks the patient to escalate the dose weekly in increments of 10 mg twice daily until the point of maximal efficacy or tolerance, whichever is reached first. Many patients have difficulty tolerating the grogginess often seen with doses exceeding 50 mg twice daily. Ketotifen is not approved in the United States as a commercial oral preparation, but active ingredient can be legally obtained by pharmacists for compounding into oral forms. The author begins his patients on trials of ketotifen at 1 mg twice daily and asks patients to escalate weekly in increments of 1 mg twice daily to the point of maximal efficacy or tolerance, which rarely exceeds 6 mg for the individual dose. Frequency, too, can be increased over time to as often as every 6 hours. The drug's (reversible) common toxicities include headache, conjunctivitis, and upper airway inflammation.

Many MCAS patients have long suffered symptoms of major depressive disorder and are already taking selective serotonin reuptake inhibitors (SSRIs) which, like benzodiazepines, can impact not only neurons and enterocytes but also mast cells via cell surface serotonin reuptake transporters (SERTs). [372, 373] However, addition of antihistamines to SSRIs increases the risk for development of potentially life-threatening serotonin syndrome, for which the clinician must remain alert; onset of this syndrome of increased central nervous system serotonergic activity causing mental status changes, autonomic hyperactivity, and neuromuscular abnormalities requires immediate cessation of the offending drugs and institution of aggressive benzodiapine therapy (such as lorazepam, initially dosed at 2-3 mg 3-4 times daily).

Like antihistamines, benzodiazepines often are useful not only in chronic management of MCAS but also in emergency management of the disease. Although benzodiazepines with longer half-lives such as diazepam can be helpful, most MCAS patients who benefit from benzodiazepines use shorter half-life drugs such as lorazepam, clonazepam, or alprazolam, typically dosed every 8-12 hours. Although dose-finding experiments initially should use the same dose given at regular intervals, many patients report eventually discovering optimal benefit from benzodiazepines upon using slightly different doses at different times of the day possibly involving slightly irregular intervals; the shorter half-life benzodiazepines obviously are more amenable than the longer half-life benzodiazepines to such personalization of therapy. The author typically asks his patients to begin lorazepam, clonazepam, or alprazolam at 0.25 mg every 12 hours, escalating weekly as tolerated in increments of 0.25 mg twice daily (e.g., 0.5 mg every 12 hours, 0.75 mg every 12 hours, etc.) until either maximal efficacy is achieved or it becomes apparent (typically at a total daily dose of about 4-8 mg) the drug

will not be effective at a tolerable dose. Experimenting with increased frequency (e.g., every eight hours) can be pursued after the patient comes to understand the drug's effects at twice-daily dosing. Flunitrazepam is another benzodiazepine reported to be useful in mast cell disease but has a longer half-life; dosing is typically 0.5-2 mg daily [315], more convenient for some patients but allowing less of the intraday variability in dosing and response appreciated by other patients.

Imidazopyridines such as zolpidem also target the benzodiazepine receptor and sometimes are useful in treating MCAS. In the author's experience, the likelihood for benefit from imidazopyridines seems independent of whether benzodiazepines are already being used and whether they are proving beneficial. Imidazopyridines seem to help somewhat with the insomnia frequently seen in MCAS, but unlike benzodiazepines, beneficial impacts on other MCAS symptoms are not often seen with these drugs. Also unlike benzodiazepines, currently available imidazopyridines do not seem to have any role in the emergency management of MCAS.

Non-steroidal anti-inflammatory drugs (NSAIDs) can be very helpful in some MCAS patients – but the physician needs to be aware that these drugs (and many narcotic analgesics, too) can trigger flares of mast cell activation, even to the point of anaphylaxis, and even at ordinarily trivial doses. [48, 322, 323, 324] Aspirin is the least expensive NSAID. Patients who report prior intolerance of aspirin sometimes can gain tolerance by being started on very low doses (e.g., 1-10 mg, which may require the services of a compounding pharmacist) and doubling as often as every 6 hours as tolerated, with full precautions in place for managing anaphylaxis. [322, 325] Patients who report prior tolerance of aspirin typically can be started at 325 mg twice daily. Recent data suggest non-enteric-coated aspirin may be absorbed better than, and is tolerated as well as, coated aspirin. [374] Patients who are unaware of any prior exposure to aspirin (somewhat unusual given the wide range of products into which aspirin is integrated) may be best served by starting with a dose of 40-80 mg and doubling as often as every 6 hours as tolerated. Once tolerance of lower doses (e.g., 325 mg twice daily) is demonstrated, dosing can be escalated as often as daily until target dosing is reached. Some patients respond quite well to just 325 mg twice daily and do not require higher doses, but many patients do not clearly respond until dosing reaches 650-1300 mg twice daily. The need to dose aspirin as high as 1300 mg four times daily (felt to be sustainable with maximal ulcer prophylaxis in place) in order to achieve a desired therapeutic salicylate level of 20-30 mg/dl has been reported [322], but in this author's experience, failure to observe at least some response by a total daily dose of 2600 mg strongly suggests higher doses will be no more helpful. It has been questioned, too, whether doses exceeding 500 mg twice daily provide additional benefit. [375] Patients embarking on a trial of aspirin should be counseled regarding potential toxicities. Patients who benefit from aspirin at total daily doses of 650 mg or higher need to consider methods to improve their ability to tolerate chronic use of the drug. Concomitant use of histamine H_1 and H_2 receptor antagonists is helpful and probably should be the first therapy to be considered for ulcer prophylaxis; consideration can also be given to addition of a proton pump inhibitor to the regimen, though the clinician should recognize that marked acid suppression can interfere with reduction (by gastric hydrochloric acid) of non-absorbable (dietary and supplemental) ferrous iron to absorbable ferric iron.

If aspirin is intolerable or ineffective, other NSAIDs can be tried. If renal insufficiency or thrombocytopenia are present, use of a COX2-selective NSAID such as celecoxib (typically 100-400 mg twice daily) can be considered, though this drug appears to confer a small but

statistically significantly increased risk (as compared with placebo) for cardiovascular disease. [326]

Leukotrienes are synthesized and released by mast cells and clearly drive a wide variety of events categorized as inflammatory in nature. [289] As such, it is not surprising that the selective leukotriene receptor antagonists such as montelukast (10 mg 1-2 times daily) and zafirlukast (20 mg twice daily) are clearly helpful in some forms of MCAS. [48, 68] Montelukast and zafirlukast dosing should be curtailed in patients with significant hepatic impairment.

Cromolyn has long been recognized for its mast-cell-stabilizing activity in some patients [48, 68], and though its specific mechanism of action remains unclear, it has recently been discovered to be a potent agonist of the G-protein-coupled receptor 35, whose expression in human mast cells, eosinophils, and basophils is upregulated upon challenge with IgE antibodies. [327] It is an expensive drug, its half-life is quite short, and it is very poorly absorbed. However, it can be effective in stabilizing the mucosal mast cells with which it comes in contact. It is not available for intravenous administration. Patients with systemic mast cell disease generally use nebulized cromolyn (20 mg 2-4 times daily) and/or oral cromolyn (100-200 mg 2-4 times daily, typically in commercial liquid form but also compoundable into capsules). It also is available commercially in the U.S. as an eyedrop and nosedrop, and it can be compounded as a cream as well. Due to an initial flare of mediator release, some patients experience a flare of symptoms in the first few days of exposure to cromolyn before seeing symptoms reduce to well below their prior baseline.

Pentosan is another "mast cell stabilizer" [48] whose mechanism of action remains unknown. Its activity seems far greater against mast cells in the urinary tract than elsewhere. It has been used for many years to treat interstitial cystitis, which has increasingly come to be recognized as a form of MCAS. [132] Pentosan is typically dosed at 100 mg every 8-12 hours.

Quercetin, the principal bioflavonoid in human diets (sources include apples, onions, berries, red grapes, citrus, broccoli, and tea [328]), is poorly absorbed [329] but has a range of properties potentially useful in mast cell activation disease. Among other mechanisms of action, it is thought to inhibit lipoxygenase and cyclooxygenase, resulting in reduced production of inflammatory mediators (e.g., leukotrienes and histamine). [330] It may also serve as an inhibitor of tyrosine kinases [331] and other regulatory proteins of interest in activated mast cells (e.g., heat shock proteins, RAS, etc.). [330] Quercetin seems to provide general anti-inflammatory effects and seems to impede PGD_2-driven flushing. [332] Dosing typically is in the range of 500-2000 mg per day given in 2-4 divided doses. A more recently developed water-soluble form, quercetin chalcone, is dosed as 250 mg thrice daily. [329]

Pancreatic enzyme supplements are helpful in some MCAS patients whose symptom complexes include features of (painful or painless) chronic pancreatitis such as chronic diarrhea, weight loss, and certain micronutrient malabsorption syndromes.

Allergen-driven cross-linking of multiple IgE molecules bound to mast cell-surface IgE receptors (FcεRI) is a major route of mast cell activation. [166] Omalizumab is a humanized monoclonal antibody which reversibly binds to the Fc portion of IgE, thereby sterically hindering IgE binding with its FcεRI mast cell-surface receptor. [333] As with all monoclonal antibody therapies, omalizumab is expensive. Omalizumab (typically dosed at 150-300 mg subcutaneously every 2-4 weeks) has been reported to be effective in controlling MCAS in a small number of patients [333, 334], but in contrast to the 2-8 weeks it typically requires to

identify effectiveness for most of the agents patients try in attempting to control their MCAS, a trial of omalizumab should be pursued for at least 3-4 months before judging its efficacy. From the very small amount of data presently available, responsiveness of MCAS to omalizumab seems independent of pre-treatment serum IgE levels.

As demonstrated by Molderings et al. [36, 37], most MCAS patients harbor one or more clonal mutations in mast cell *KIT*, and most of these mutations lead to constitutive activation of the KIT protein. [37] Activation of KIT in turn leads to activation of, among many pathways, the Janus kinases (JAK1, JAK2, JAK3, Tyk2), which in turn lead to activation of Signal Transducer and Activator of Transcription (STAT), which then migrates to the cell nucleus, where it binds to DNA and promotes transcription of genes responsive to STAT. [335] It is well demonstrated that upregulation of STAT leads to increased production and release of a number of inflammatory cytokines. [336] In view of these biological insights, the tyrosine kinase inhibitors of KIT and the Janus kinases can be predicted to be useful in some forms of mast cell disease. Imatinib is less useful in systemic mastocytosis, as most cases of SM harbor mutations in the region of *KIT* codon 816 which are resistant to imatinib binding. [337] However, imatinib can also inhibit constitutive activation of KIT caused by mutations at certain other sites in *KIT* (such as the juxtamembrane region), and via mechanisms not yet clear, even some systemic mastocytosis patients with the *KIT*-D816V mutation can respond to imatinib. [338] Underscoring the "mutational overlap" between SM and MCAS, responses to imatinib have been reported in MCAS. [54, 55, 210] In contrast to the dosing typically used in chronic myelogenous leukemia, lower dosing has appeared sufficient thus far in MCAS patients who respond to tyrosine kinase inhibitors. The author typically begins a trial of imatinib in an MCAS patient at 100 mg daily, escalating after a week, if tolerated but without improvement, to 200 mg daily, then observing for the rest of the first month. In the author's MCAS patients, doses greater than 200 mg daily have not appeared more efficacious. Similarly, when trying dasatinib, dosing as little as 20 mg daily – far less than then 100 mg/d typically used for chronic myelogenous leukemia – can be effective, and doses greater than 40-50 mg/d rarely appear necessary or more beneficial. As compared to imatinib, dasatinib targets a wider spectrum of tyrosine kinases, has additional immunosuppressive/ anti-inflammatory effects, and may be the better initial choice in patients with renal insufficiency, but it may have a greater propensity for clinically significant pulmonary complications; a few responses have been reported in systemic mastocytosis patients thus far [338, 339], but there have been no reports thus far of the use of this drug in MCAS patients. Nilotinib has a far greater affinity than imatinib for KIT's kinase domain. It has a somewhat different toxicity spectrum than imatinib and dasatinib and requires somewhat closer electrocardiographic and laboratory monitoring; a few responses have been reported in systemic mastocytosis patients thus far [338], but there are no reports yet of use of this drug in MCAS patients. Janus kinase inhibitors, too, have not yet been reported to have been used in any form of MCAD. The tyrosine kinase inhibitors uniformly are very expensive. No generic formulations are presently available.

Tumor necrosis factor (TNF) alpha is a well-established mast cell mediator product [281], and TNF-alpha antagonists such as etanercept, adalimumab, and infliximab are approved for use in a variety of systemic inflammatory diseases increasingly suspected to be of aberrant mast cell origin (such as rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease). Thus, there is reason to suspect such drugs would be useful in ameliorating TNF-alpha-derived symptoms in some patients with MCAS, but no data regarding the use of

any of these drugs in MCAS have been published and there are no reports of such trials in progress or development.

There is hardly an interleukin which is known to not be produced and released by the mast cell. [47] Thus, there is reason to suspect that interleukin-1 antagonists (e.g., anakinra) and interleukin-1-beta antagonists (e.g., canakinumab) may be helpful in some forms of MCAS, but, again, no data regarding the use of any of these drugs in MCAS have been published and there are no reports of such trials in progress or development. Similarly, given the impact of MC heparin on bradykinin generation [371], kinin-b2 receptor blockers (approved for hereditary angioedema) may eventually prove useful in MCAD, but there are no case reports, let alone clinical trials, of such use yet.

Along with calcium and vitamin D supplementation, bisphosphonates are proven helpful for conditions of excessive bone resorption. A small case series demonstrated that concurrent use of interferon alpha and pamidronate in patients with systemic mastocytosis led to significantly increased bone mineral density which was subsequently maintained with pamidronate alone. [340] However, no controlled trials have been performed, and interferon can be substantially toxic. New anti-RANKL monoclonal antibody therapy such as denosumab has demonstrated efficacy in certain osteopenic/osteoporotic situations equal to or better than bisphosphonate therapy. [149] In theory, such antibody therapy should be useful in ameliorating the osteopenia/osteoporosis of MCAS. No controlled clinical trials regarding the use of any of these bone-protecting therapies in MCAS have been performed, but use of any therapy approved or generally recommended for osteoporosis/osteoporosis seems reasonable in MCAS patients also found to have osteopenia/osteoporosis. Osteonecrosis of the jaw (ONJ) is a topic that must be considered when contemplating use of the bisphosphonates or anti-RANKL therapy. ONJ is a rare but serious complication of such therapies. It is known to be more prevalent in cancer patients than osteoporosis patients, but it has not been reported in mast cell disease patients receiving these therapies. Nevertheless, it seems prudent to practice with mast cell disease patients the preventive measures advised for other populations receiving these drugs including pre-treatment dental evaluation, good dental hygiene, and suspension of therapy in the period surrounding invasive dental therapy.

Interferon-alpha is a well recognized modulator of the chronic myeloproliferative neoplasms including systemic mastocytosis. [341, 342] Its activity in MCAS has not been specifically investigated, but it seems reasonable at present to presume it would have similar activity (as in systemic mastocytosis) in downregulating aberrant mediator production and release. However, interferon alpha therapy is expensive and associated with many toxicities which not infrequently lead to patient withdrawal from therapy. Use of the pegylated form appears to decrease toxicity, and pegylated interferon treatment of chronic myeloproliferative diseases in general appears to require lower doses than needed with non-pegylated interferon. A case of systemic mastocytosis with secondary osteoporosis successfully treated with pegylated interferon has been reported [343], but use of the pegylated product has not been specifically investigated in any form of mast cell disease.

Tryptase inhibitors remain in the early stages of clinical development (generally, pre-clinical development and Phase 1 clinical trials).

Hydroxyurea is an oral RNA synthetase (a.k.a. ribonucleotide reductase) inhibitor useful chronically and acutely in a wide range of hematologic malignancies. [344, 345, 346, 347] It also has been recommended for essentially lifelong use in sickle cell anemia patients. [348] A modest degree of efficacy has been reported with hydroxyurea in SM [342]. The author has

observed some symptomatic responses to hydroxyurea in MCAS but recommends initiation of therapy be monitored more cautiously in patients with mast cell disease, as in this population the drug not uncommonly causes far more rapid and severe cytopenias than seen in other populations. Starting hydroxyurea at 500 mg daily, monitoring blood counts weekly for the first month and weekly for another month after each dose escalation, seems appropriate. As limited by cytopenias or other toxicities, the daily dose can be escalated in 500 mg increments as often as monthly. Daily doses greater than 2000 mg are seldom needed, and many responding patients do well with only 500-1000 mg daily. It is possible that the early intolerance sometimes seen with this drug even at low doses may be a consequence of reaction to fillers or dyes in a particular formulation; in such cases, transitioning the patient to another formulation can result in improved tolerance and good efficacy.

Cyclophosphamide, a DNA alkylator, seems to have little activity in human mast cell disease [68] but nevertheless can be helpful sometimes in management of steroid-refractory cases of the autoimmune disease which can emerge from the milieu of mast cell disease. The drug can be given as a daily oral dose (100 mg) or as pulse intravenous dosing (1000 mg/m^2 every 3-4 weeks for 3-4 cycles). Although such regimens are considered to be relatively low dosing and tend to be tolerated well, DNA alkylator therapy inevitably conveys some increased risk for secondary malignancy.

Other single- and multi-agent cytotoxic drug regimens have been used in systemic mastocytosis (e.g., taxanes, nucleoside analogs, etc.). Though durable responses are rare, cladribine may be the best performer to date. [68] The rationale for use of cytotoxic drugs in the relatively non-proliferative MCAS seems weak, and there are no reports of the use of such drugs in MCAS patients.

Similarly, there are scarce reports of other immunosuppressive agents (e.g., cyclosporine, azathioprine, methotrexate, alemtuzumab, daclizumab, etc.) being used with widely varying degrees of success in systemic mastocytosis (as summarized in [68, 309, 349] and others), but no reports of the use of these drugs in MCAS have been published yet. The same can be said for inhibitors of the mammalian target of rapamycin (mTOR), another target of activated KIT.

Allogeneic hematopoietic stem cell transplant therapy in theory might be curative but has been used in systemic mastocytosis only rarely to date (the largest study was of three patients who all relapsed by 39 months [350]). This approach seems to be used most in the setting of associated refractory hematologic malignancy [68] (sometimes with the mast cell disease being recognized only in post-transplant retrospect) and generally (but not always, e.g. [351]) failing to eradicate the mast cell disease component [68], providing little reason *a priori* to consider using this approach for MCAS patients without associated refractory hematologic malignancy.

Secondary issues in MCAS – e.g., inflammation, infection, autoimmunity, malignancy, coagulopathy, osteopathy, etc. – not uncommonly come to clinical attention first, but regardless of whether such issues present prior or subsequent to diagnosis of mast cell disease, they warrant standard therapy and may fare better when the mast cell disease is concomitantly specifically addressed, such as can be seen in the setting of SM-AHNMD. [308]

Many patients with mast cell activation disease suffer pain. [48, 49] Sometimes the pain is diffuse, while sometimes it is focal at any given time and diffusely migratory over time. It often is described as a deep-seated muscular, bony, or marrow-based "aching" rather than a distinct "pain." Narcotic and non-narcotic analgesics often are ineffective. (In fact, in a

fashion similar to how NSAIDs can trigger flares of mast cell disease, so, too, can narcotics.) Sometimes other classes of mast-cell-targeted agents not expected to have analgesic effect are nonetheless effective at achieving such (e.g., antihistamines seem to help reduce chronic migraine headaches in some MCAS patients).

Patient with mast cell activation disease often suffer presyncopal events (frank syncope seems somewhat less common). [48, 49] When hypotension can be demonstrated during such events, and when the trigger appears to typically be postural change, medications such as fludrocortisone (0.1-0.4 mg daily), midodrine 5-20 mg 3-4 times daily, and pyridostigmine 15-60 mg 2-3 times daily can be helpful. [100, 352, 353] Salt loading, too, occasionally is helpful.

Emergency and perioperative management of severe flares of mast cell disease has been amply discussed in the literature (e.g., as reviewed in [68, 354]), and such information is available publicly, too. [355] In general, in addition to epinephrine for anaphylaxis, glucocorticoids, histamine H_1 and H_2 receptor antagonists, and benzodiazepines form the core of the therapeutic attack at such a problem. Also, patients susceptible to anaphylaxis should be prescribed epinephrine autoinjectors and should be counseled to call for help and fully recline before using the device to prevent trauma from falls should dysrhythmias or other complications develop to further weaken a patient likely already weakened from the flare.

Some MCAS patients are highly reactive to a wide assortment of foodstuffs. Elimination diets such as described for the eosinophilic esophagitis population [356, 357, 358, 359] may be helpful, but efforts to control the underlying mast cell disease probably are the best approach.

In spite of the substantial fatigue and malaise many MCAS patients experience, and in spite of their many physical sensitivities (e.g., heat, cold, ultraviolet radiation, exertion, etc.) and antigenic sensitivities (e.g., pollen, perfumes, etc.), MCAS patients should be strongly encouraged to regularly exercise – but only to the usual individual limit of tolerance each patient likely has learned from experience, as, again, exertion clearly can trigger a flare of mast cell activation in some patients. At the same time, although the mechanism likely is complex and remains quite unclear, exercise can help many patients with chronic inflammatory diseases improve both subjectively and objectively, acutely and chronically. [360, 361, 362, 363]. Brief (15-30 minute) periods of exercise of mild-to-moderate intensity may be more helpful, at least subjectively, than longer periods and high intensity of exercise. [364, 365] Also, some workers in the field have observed that activities causing frequent sharp abdominal motion (e.g., jogging, tennis, soccer, etc.) may be more prone to provoke flares of mast cell activation than less abdominally provocative activities (e.g., bicycling); a potential mechanism for this difference may be aberrantly heightened response of constitutively activated gastrointestinal tract mast cells to physical force.

Perhaps the single most important aspect to successful management of mast cell disease is identification of a local "physician/partner" who will help the patient not only access local health care resources as needed for tactical management of acute issues with the disease but also access remote resources which may be able to help determine strategic management of chronic issues. Absent an effective local physician/partner (which can be challenging to identify for many reasons), the MCAS patient often faces great difficulty gaining initial control over the disease even after consulting remote expertise which for many reasons cannot provide care for acute issues with the disease.

At present the prognosis of MCAS patients remains unstudied. However, the experience with indolent systemic mastocytosis (ISM) may serve as a guide. It has been estimated that if ISM patients survive the first three years of symptomatic disease, they appear to enjoy undiminished survival relative to the age- and sex-matched population. [62, 68, 166, 322] Quality of life, however, may be diminished as symptoms persist and progress, especially if the root cause remains undiagnosed and untreated.

Table 1. Symptoms and findings in mast cell activation disease

System	Potential manifestations of mast cell disease
Constitutional	Fatigue, malaise, asthenia, "chronic fatigue syndrome," subjective and/or objective hyperthermia and/or hypothermia, "sense of feeling cold much of the time," sweats/diaphoresis (not always nocturnal), flushing, plethora or pallor, increased or decreased appetite, early satiety, weight gain or loss, pruritus, environmental sensitivities (often odd)
Integumentary	Rashes and lesions of many sorts (classic urticaria pigmentosa, "freckles," telangiectatic/angiomatous lesions, xerosis, warts, tags, folliculitis, ulcers, diffusely migratory but sometimes focally persistent patchy erythema), pruritus (often diffusely migratory, sometimes aquagenic), flushing, angioedema, striae, dermatographism, poor healing, alopecia, onychodystrophy
Ophthalmologic	Irritated eyes, increased or decreased lacrimation, suffusion, conjunctivitis, difficulty focusing, lid tremor/tic, solar sensitivity, infectious or sterile inflammation
Otologic	Infectious or sterile otitis externa and/or media, hearing loss or hyperacusis, tinnitus, otosclerosis
Oral/oropharyngeal	Pain (sometimes "burning"), leukoplakia, fibrosis, lichen planus, ulcers, sores, angioedema, dental decay, dysgeusia, throat tickle/discomfort/irritation/pain, post-nasal drip
Lymphatic	Adenopathy, usually sub-pathologic and often waxing/waning in size, sometimes asymptomatic but not uncommonly tender, sometimes focal, sometimes migratory, pathology usually shows a reactive lymphocytosis or sometimes an atypical non-specific lymphoproliferative disorder; left upper quadrant discomfort (likely from release of mediators from splenic mast cells with or without detectable splenomegaly)
Pulmonary	Rhinitis, sinusitis, pharyngitis, laryngitis, bronchitis, pneumonitis (often confused with infectious pneumonia), cough, dyspnea (often low-grade, inconstant, "I just can't catch a deep breath" despite normal pulmonary function tests), wheezing, obstructive sleep apnea, pulmonary hypertension
Cardiovascular	Presyncope (lightheadedness, weakness, dizziness, vertigo) and/or syncope, hypertension and/or hypotension, palpitations, dysrhythmias, chest discomfort or pain (usually non-anginal in character), coronary and peripheral arterial atherosclerosis/spasm/infarction, aneurysms, hemorrhoids, varicosities, aberrant angiogenesis (hemangiomas, arteriovenous malformations, telangiectasias), migratory edema (often non-dependent and in spite of normal cardiac and renal function)

Table 1. (Continued)

System	Potential manifestations of mast cell disease
Gastrointestinal	Aerophagia, angioedema in any segment of the luminal tract, dysphagia (often proximal, possibly due to pharyngeal angioedema), pain/inflammation (often migratory) in one or more segments of the luminal tract (from esophagitis to proctitis) and/or one or more solid organs (e.g., hepatitis, pancreatitis), queasiness, nausea, vomiting, diarrhea and/or constipation (often alternating), malabsorption (more often selective micronutrient malabsorption than general protein-calorie malabsorption), ascites either from portal hypertension and/or peritoneal serositis; gastroesophageal reflux disease (often "treatment-refractory") and inflammatory/irritable bowel syndrome are common pre-existing diagnoses
Genitourinary	Inflammation (often migratory) in one or more segments of the luminal tracts (ureteritis, cystitis, urethritis, vaginitis, vestibulitis) and/or one or more solid organs (e.g., nephritis, prostatitis), chronic kidney disease, endometriosis, chronic low back pain or flank pain or abdominal pain, hydronephrosis (likely from ureteral angioedema), infertility, erectile dysfunction, decreased libido; in the appropriate setting of multisystem morbidity, miscarriages should prompt consideration of antiphospholipid antibody syndrome potentially due to MCAS
Musculoskeletal	Clinical myositis, often diffusely migratory (fibromyalgia is a common pre-existing diagnosis), subclinical myositis (i.e., asymptomatic elevated creatine kinase not otherwise explained), arthritis (typically migratory), joint laxity/hypermobility, osteoporosis/osteopenia, osteosclerosis, sometimes mixed osteoporosis/osteopenia/osteosclerosis; MCAS-driven musculoskeletal pain not uncommonly is poorly responsive to non-steroidal anti-inflammatory drugs and narcotics
Neurologic	Headache (especially migraine), presyncope and/or syncope, peripheral (usually distal) sensory and/or motor neuropathies including paresthesias, tics, tremors (typically resting), chronic inflammatory demyelinating polyneuropathy, seizure disorders (can be "treatment-refractory")
Psychiatric	Mood disturbances (e.g., anger, depression), bipolar affective disorder, attention deficit-hyperactivity disorder, post-traumatic stress disorder, other anxiety and panic disorders, psychoses, memory difficulties, word-finding difficulties, other cognitive dysfunction, wide variety of sleep disruptions
Endocrinologic/ Metabolic	Abnormal electrolytes (including magnesium) and liver function tests, delayed puberty, dysmenorrhea, endometriosis, osteosclerosis and/or osteoporosis, hypothyroidism, hyperthyroidism, dyslipidemia, hyperferritinemia, selective vitamin and/or other micronutrient deficiencies, weight change, possibly diabetes mellitus
Hematologic/ Coagulopathic	Polycythemia or anemia, leukocytosis or leukopenia, chronic (usually mild) monocytosis or eosinophilia or basophilia, thrombocytosis or thrombocytopenia, arterial and/or venous thromboembolic disease, aberrant bruising and bleeding; in MCAS the marrow usually does not show increased or even flow-cytometrically aberrant mast cells and marrow histology is often interpreted as normal or as unspecified myelodysplastic/myeloproliferative syndrome; standard cytogenetic studies are almost always normal or show culture failure
Immunologic	Type I, II, III, and IV hypersensitivity reactions, increased risk for malignancy, autoimmunity, impaired healing, increased susceptibility to infection, elevated or decreased levels of one or more isotypes of immunoglobulin; modest monoclonal gammopathy of undetermined significance not uncommon

Most are chronic, low-grade; some are persistent but many are either episodic or waxing/waning.

Table 2. Diagnostic approach to mast cell activation syndrome

A	History: Chronic multisystem polymorbidity, generally (but not necessarily) of an inflammatory theme, often suboptimally responsive to therapy.
B	Physical examination findings (see Table 1).
C	Rule out other diseases potentially explaining the full range of findings on history and exam.
D	Laboratory testing:

	1	Complete blood count with manual differential.
	2	Comprehensive metabolic panel (including serum magnesium).
	3	Quantitative immunoglobulin profile if the patient has had frequent problems with infection
	4	Prothrombin time (PT) and partial thromboplastin time (PTT) if the patient has had easy bruising or bleeding or thromboembolic events.
	5	Serum tryptase.
	6	Serum chromogranin A.
	7	Plasma histamine.
	8	Chilled plasma PGD_2.
	9	Stat chilled plasma heparin (in patients not on exogenous heparin products).
	10	Chilled urine (24-hour preferred over spot) for PGD_2 and N-methylhistamine.
	11	If available, plasma and urine levels of mast cell mediators leukotriene B4 and cysteinyl leukotrienes C4, D4, and E4 can be assessed, too.

If possible, non-steroidal anti-inflammatory drugs should be avoided for several days prior to specimen collection.

If tests are normal (or PGD_2 levels are below normal), check whether specimens require chilling were handled properly and consider repeat testing (possibly waiting until patient is having a flare of symptoms).

If repeat testing is still normal, Factor VIII, plasma free norepinephrine, tumor necrosis factor alpha, and interleukin-6 may provide some support for the diagnosis. Other causes of elevations of these mediators should be excluded if possible.

If blood and urine testing is persistently negative, histologic and immunohistochemical (and, if possible, flow cytometric) studies of old and fresh gastrointestinal mucosal biopsies and/or marrow biopsies and aspirations may be helpful. Immunohistochemical studies should include at least CD117 staining, possibly also Giemsa, toluidine blue, and/or tryptase staining. Multi-color flow cytometric studies on fresh tissue should look for dual expression of CD117/CD25 or CD117/CD2 (occasionally triple expression of CD117/CD25/CD2, too, will be seen). Polymerase chain reaction testing for *KIT* mutations as commercially available (at least *KIT*-D816V) can be considered in old and fresh tissues.

If the prothrombin time or partial thromboplastin time are abnormal (increased or decreased), a survey for anti-phospholipid antibodies (anti-cardiolipin antibodies, beta-2-glycoprotein-1 antibodies, and lupus anticoagulant) should be pursued; the utility of anti-prothrombin antibodies remains controversial.

E	Proposed diagnostic criteria (as per Molderings et al. [48]; can also consider proposals of Akin et al. [40] and Valent et al. [42])

Major criteria:

	1	Multifocal or disseminated dense infiltrates of mast cells in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (e.g., gastrointestinal tract biopsies; CD117-, tryptase- and CD25-stained).
	2	Unique constellation of clinical complaints as a result of a pathologically increased mast cell activity (mast cell mediator release syndrome)

Minor criteria:

1. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) in bone marrow smears or in histologies
2. Mast cells in bone marrow express CD2 and/or CD25
3. Detection of genetic changes in mast cells from blood, bone marrow or extracutaneous organs for which an impact on the state of activity of affected mast cells in terms of an increased activity has been proved.
4. Evidence of a pathologically increased release of mast cell mediators by determination of the content of
   a. tryptase in blood
   b. *N*-methylhistamine in urine
   c. heparin in blood
   d. chromogranin A in blood
   e. other mast cell-specific mediators (e.g., leukotrienes, PGD_2)

Table 3. Management of mast cell activation syndrome

A	Inhibition of mediator production	
	1	Non-steroidal anti-inflammatory drugs
	2	Steroids (not for long-term use if possible)
	3	Rarely: immunomodulatory drugs (e.g., thalidomide)
B	Inhibition of mediator release (mast cell stabilization)	
	1	Benzodiazepines
	2	Cromolyn (oral and/or inhaled)
	3	Ketotifen (oral)
	4	Pentosan
	5	Tyrosine kinase inhibitors
	6	Alpha interferon (pegylated or non-pegylated)
	7	Omalizumab
	8	Quercetin
	9	Rarely: hydroxyurea, immunosuppressants
C	Blockade of released mediators	
	1	Histamine H_1/H_2 receptor blockers
	2	Leukotriene antagonists
	3	Bisphosphonates
	4	Rarely: TNF-alpha antagonists, IL-1/-1β antagonists
D	Treatment of secondary issues (see Table 1)	
E	No defined role for cytotoxic therapy absent advanced tissue mastocytosis	
F	No defined role for cellular (transplantation) therapy	

CONCLUSION

Mast cell activation syndrome (MCAS) is a recently recognized, prevalent, relatively non-proliferative whose underlying mutational heterogeneity leads to marked clinical heterogeneity which can be quite confounding from diagnostic and therapeutic perspectives. While not diminished in duration compared to the general population, MCAS patients' lives

often are diminished in quality until the disease is diagnosed and treated. With patience, persistence, and a methodical approach, most MCAS patients are able to eventually identify a therapeutic regimen which helps them feel significantly better most of the time. Although such efforts may require trials of many medications consuming months or even years, many MCAS patients have been ill for far longer periods of time prior to diagnosis and, in simply having finally identified a diagnosis and prognosis, are bolstered to willingly endure the present "trial-and-error" approach to identifying effective therapy.

Research into improved diagnostic and therapeutic approaches for MCAS is needed, but an equally great challenge lies in the domain of medical education. The longstanding, and still universally valid, paradigm of diagnosis is pattern recognition: specific symptom A + specific physical exam finding B + specific test result C = specific diagnosis D. MCAS, however, presents with extreme clinical heterogeneity, at least superficially appearing to break this standard diagnostic paradigm. The clinician will face a series of MCAS patients, most of whom will present as chronically unwell, though the details will differ so substantially across patients as to make the underlying pattern – chronic multisystem polymorbidity of a generally inflammatory theme, with other potential etiologies of known non-mast-cell origin ruled out – very difficult to see. How is the clinician to recognize the unifying theme within the individual patient, let alone across multiple patients? A further complication is the increasing discovery of evidence of underlying mast cell disease in (typically inflammatory) diseases long of unknown origin. For example, given the increasingly apparent involvement of aberrant mast cell activation in rheumatoid arthritis (RA) [366], is there a role for diagnostically and/or therapeutically addressing not only RA but also MCAS in RA patients (with an eye toward how SM-AHNMD patients fare better with treatment for both SM and AHNMD [308])? Clearly, in addition to researchers continuing efforts to identify the full spectrum of mast cell disease, medical educators increasingly will need to collaborate with cognitive scientists to identify effective methods for training clinicians to recognize the chameleon that is MCAS.

REFERENCES

[1] von Recklinghausen F. Ueber eiter – und bindegewebskörperchen. *Virchows Arch.* 1863;28:157-197.

[2] Waldeyer W. Ueber Bindegewebeszellen. *Arch. Mikrosk. Anat.* 1875;11:176-194.

[3] Ehrlich P. Beiträge zur Kenntnis der Anilinfärburgen und ihrer Verwendung in der Mikroskopischen Technik. *Arch. Mikrosk. Anat.* 1877;13:263-277.

[4] Nobel Foundation. All Nobel Laureates in Physiology or Medicine. Available at http://www.nobelprize.org/nobel_prizes/medicine/laureates/ (accessed December 16, 2012).

[5] Nettleship E, Tay W. Rare forms of urticaria. *Brit. Med. J.* 1869;2:323-330.

[6] Sangster A. An anomalous mottled rash, accompanied by pruritus, facticious urticaria and pigmentation, 'urticaria pigmentosa'? *Trans. Clin. Soc. London* 1878;11:161-163.

[7] Unna P. Beiträge zur Anatomie und Pathogenese der urticaria simplex und pigmentosa. *Monatschrift der praktischen Dermatologie* 1887;6:9-18.

[8] Ellis JM. Urticaria pigmentosa. *Arch. Pathol.* 1949;48(5):426-435.

[9]   Efrati P, Klajman A, Spitz H. Mast cell leukemia? Malignant mastocytosis with leukemia-like manifestations. *Blood* 1957 Oct 1;12(10):869-882.

[10]   Holmgren H, Wilander O. Beiträge zur Kenntnis der Chemie and Funktion der Ehrlichschen Mästzellen. *Z. Mikroskop. Anat. Forsch.* 1937;42:242-278.

[11]   Jorpes E, Holmgren H, Wilander O. Über das Vorkommen von Heparin in den Gefässwänden und in den Augen. *Z. Mikroskop. Anat. Forsch.* 1937;42:279-300.

[12]   Riley JF. Histamine in tissue mast cells. *Science* 1953;118:332-333.

[13]   Riley JF, West GB. The presence of histamine in tissue mast cells. *J. Physiol. (Lond)* 1953;120:528-537.

[14]   Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N. Engl. J. Med.* 1987;316:1622-1626.

[15]   Hallgren J, Pejler G. Biology of mast cell tryptase: an inflammatory mediator. *FEBS* 2006 May;273(9):1871-1895.

[16]   Schwartz LB, Sakai K, Bradford TR, Ren SL, Zweiman B, Worobec AS, et al. The α form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. *J. Clin. Invest.* 1995;96:2702-10.

[17]   Borer-Reinhold M, Haeberli G, Bitzenhofer M, Jandus P, Hausmann O, Fricker M, Helbling A, Müller U. An increase in serum tryptase even below 11.4 ng/mL may indicate a mast cell-mediated hypersensitivity reaction: a prospective study in Hymenoptera venom allergic patients. *Clin. Exper. Allergy* 2011 Dec;41(12): 1777-1783.

[18]   Furitsu T, Tsujimura T, Tono T, Ikeda H, Kitayama H, Koshimizu U, Sugahara H, Butterfield JH, Ashman LK, Kanayama Y, Matsuzawa Y, Kitamura Y, Kanakura Y. Identification of mutations in the coding sequence of the proto-oncogene c-*kit* in a human mast cell leukemia cell line causing ligand-independent activation of c-*kit* product. *J. Clin. Invest.* 1993;92:1736-1744.

[19]   Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, Metcalfe DD. Identification of a point mutation in the catalytic domain of the protooncogene c-*kit* in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. *Proc. Natl. Acad. Sci. USA* 1995 Nov;92: 10560-10564.

[20]   Garcia-Montero AC, Jara-Acevedo M, Teodosio C, Sanchez ML, Nunez R, Prados A, Aldanondo I, Sanchez L, Dominguez M, Botana LM, Sanchez-Jimenez F, Sotlar K, Almeida J, Escribano L, Orfao A. *KIT* mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood* 2006 Oct 1;108(7):2366-2372.

[21]   Escribano L, Orfao A, Díaz-Agustin B, Villarrubia J, Cerveró C, López A, Marcos MAG, Bellas C, Fernández-Cañadas S, Cuevas M, Sánchez A, Velasco J, Navarro JL, San Miguel JF. Indolent systemic mast cell disease in adults: immunophenotypic characterization of bone marrow mast cells and its diagnostic implications. *Blood* 1998 Apr 15;91(8):2731-2736.

[22] Iemura A, Tsai M, Ando A, Wershil BK, Galli SJ. The c-*kit* ligand, stem cell factor, promotes mast cell survival by suppressing apoptosis. *Am. J. Pathol.* 1994 Feb; 144(2): 321-328.

[23] Metcalfe DD, Mekori JA, Rotten M. Mast cell ontogeny and apoptosis. *Exp. Dermatol.* 1995 Aug;4(4):227-230.

[24] Ekoff M, Lyberg K, Krajewska M, Arvidsson M, Rak S, Reed JC, Harvima I, Nilsson G. Anti-apoptotic Bfl-1 is the major effector in activation-induced human mast cell survival. *PLoS ONE* 2012;7(6):e39117, doi:10.1371/journal.pone.0039117.

[25] Karlberg M, Xiang Z, Nilsson G. FcγRI-mediated activation of human mast cells promotes survival and induction of the pro-survival gene Bfl-1. *J. Clin. Immunol.* 2008;28(3):250-255.

[26] Möller C, Xiang Z, Nilsson G. Activation of mast cells by immunoglobulin E-receptor cross-linkage, but not through adenosine receptors, induces A1 expression and promotes survival. *Clin. Exp. Allergy* 2003 Aug;33(8):1135-1140.

[27] Ekoff M, Strasser A, Nilsson G. FcεRI aggregation promotes survival of connective tissue-like mast cells but not mucosal-like mast cells. *J. Immunol.* 2007 Apr;178: 4177-4183.

[28] Möller C, Alfredsson J, Engström M, Wootz H, Xiang Z, Lennartsson J, Jönsson J-I, Nilsson G. Stem cell factor promotes mast cell survival via inactivation of FOXO3a-mediated transcriptional induction and MEK-regulated phosphorylation of the proapoptotic protein Bim. *Blood* 2005 Aug 15;106(4):1330-1336.

[29] Möller C, Karlberg M, Abrink M, Nakayama KI, Motoyama N, Nilsson G. Bcl-2 and Bcl-XL are indispensable for the late phase of mast cell development from mouse embryonic stem cells. *Exp. Hematol.* 2007 Mar;35(3):385-393.

[30] Ullerås E, Karlberg M, Westerberg CM, Alfredsson J, Gerondakis S, Strasser A, Nilsson G. NFAT but not NF-κB is critical for transcriptional induction of the prosurvival gene A1 after IgE receptor activation in mast cells. *Blood* 2008 Mar 15; 111(6):3081-3089.

[31] Liu C, Liu Z, Li Z, Wu Y. Molecular regulation of mast cell development and maturation. *Mol. Biol. Rep.* 2010;37(4):1993-2001.

[32] Roberts LJ, Oates JA. Biochemical diagnosis of systemic mast cell disorders. *J. Invest. Derm.* 1991;96:19S-25S.

[33] Sonneck K, Florian S, Müllauer L, Wimazal F, Födinger M, Sperr WR, Valent P. Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: Monoclonal mast cell activation syndrome. *Int. Arch. Allergy Immunol.* 2007;142:158-164.

[34] Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, Metcalfe DD. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. *Blood* 2007;110:2331-2333.

[35] Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, Castells M, Sperr WR, Kluin-Nelemans HC, Hamdy NA, Lortholary O, Robyn J, van Doormaal J, Sotlar K, Hauswirth AW, Arock M, Hermine O, Hellmann A, Triggiani M, Niedoszytko M, Schwartz LB, Orfao A, Horny HP, Metcalfe DD. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur. J. Clin. Invest.* 2007;37:435-453.

[36] Molderings GJ, Kolck UW, Scheurlen C, Brüss M, Homann J, Von Kügelgen I. Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. *Scand. J. Gastroenterol.* 2007; 42:1045-53.

[37] Molderings GJ, Meis K, Kolck UW, Homann J, Frieling T. Comparative analysis of mutation of tyrosine kinase Kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics* 2010;62:721-7.

[38] Akin C, Metcalfe DD. Chapter 15: Mastocytosis and mast cell activation syndromes presenting as anaphylaxis. In: Castells MC, ed., *Anaphylaxis and Hypersensitivity Reactions*, Springer, New York, 2011, pp. 245-256.

[39] Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome. *Int. Arch. Allergy Immunol.* 2007;142(2):158-164.

[40] Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic Criteria. *J. Allergy Clin. Immunol.* 2010;126:1099-1104e4.

[41] Molderings GJ, Homann J, Raithel M, Frieling T. Toward a global classification of mast cell activation diseases. *J. Allergy Clin. Immunol.* 2011 May;127(5):1311.

[42] Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, Castells M, Escribano L, Hartmann K, Lieberman P, Nedoszytko B, Orfao A, Schwartz LB, Sotlar K, Sperr WR, Triggiani M, Valenta R, Horny H-P, Metcalfe DD. Definitions, criteria, and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int. Arch. Allergy Immunol.*2012;157: 215-225.

[43] Longley BJ, Reguera MJ, Ma Y. Classes of c-*KIT* activation mutations: proposed mechanisms of action and implications for disease classification and therapy. *Leuk. Res.* 2001 Jul;25(7):571-576.

[44] Akin C, Metcalfe DD. The biology of Kit in disease and the application of Pharmacogenetics. *J. Allergy Clin. Immunol.* 2004;114:13-19.

[45] Tefferi A, Vainchenker W. Myeloproliferative neoplasms: molecular pathophysiology, essential clinical understanding, and treatment strategies. *J. Clin. Oncol.* 2011 Feb 10;29(5):573-582.

[46] Klampfl T, Harutyunyan A, Berg T, Gisslinger B, Schalling M, Bagienski K, Olcaydu D, Passamonti F, Rumi E, Pietra D, Jäger R, Pieri L, Guglielmelli P, Iacobucci I, Martinelli G, Cazzola M, Vannucchi AM, Gisslinger H, Kralovics R. Genome integrity of myeloproliferative neoplasms in chronic phase and during disease progression. *Blood* 2011 Jul 7;118(1):167-176.

[47] Ibelgaufts H. "Mast Cells" in COPE: Cytokines and Cells Online Pathfinder Encyclopaedia, 2012. Available at http://www.copewithcytokines.de/cope.cgi?key= mast%20cells (accessed December 16, 2012).

[48] Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *J. Hematol. Oncol.*2011;4:10-17.

[49] Hermine O, Lortholary O, Leventhal PS, Catteau A, Soppelsa F, Baude C, Cohen-Akenine A, Palmérini F, Hanssens K, Yang Y, Sobol H, Fraytag S, Ghez D, Suarez F, Barete S, Casassus P, Sans B, Arock M, Kinet JP, Dubreuil P, Moussy A. Case-control

cohort study of patients' perceptions of disability in mastocytosis. *PLoS ONE* 2008;3(5):e2266, doi:10.1371/journal.pone.0002266.

[50] Kondo S, Kagami S, Kido H, Strutz F, Müller GA, Kuroda Y. Role of mast cell tryptase in renal interstitial fibrosis. *J. Am. Soc. Nephrol.* 2001;12:1668-1676.

[51] Welker P, Krämer S, Groneberg DA, Neumayer HH, Bachmann S, Amann K, Peters H. Increased mast cell number in human hypertensive nephropathy. *Am. J. Physiol. - Renal Physiol.* 2008;295(4):F1103-F1109.

[52] Barczyk M, Mysliwiec M, Kalinowski M, Rowinski M, Brzosko S. Mast cell tryptase in patients after renal transplantation. *Transplant. Proc.* 2008 Dec;40(10):3437-3439.

[53] Guilarte M, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, Martínez C, Casellas F, Saperas E, Malagelada JR. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut* 2007 Feb;56(2):203-209.

[54] Afrin LB. Polycythemia from mast cell activation syndrome: lessons learned. *Am. J. Med. Sci.* 2011;342:44-49.

[55] Afrin LB. Mast cell activation disorder masquerading as pure red cell aplasia. *Int. J. Hematol.* 2010;91:907-908.

[56] Theoharides TC, Papliodis D, Tagen M, Konstantinidou A, Kempuraj D, Clemons A. Chronic fatigue syndrome, mast cells, and tricyclic antidepressants. *J. Clin. Psychopharmacol.* 2005 Dec;25(6):515-520.

[57] Kumar V, Sharma A. Mast cells: emerging sentinel innate immune cells with diverse role in immunity. *Mol. Immunol.* 2010 Nov-Dec;48(1-3):14-25.

[58] Sayed BA, Christy A, Quirion MR, Brown MA. The master switch: the role of mast cells in autoimmunity and tolerance. *Annu. Rev. Immunol.* 2008;26:705-739.

[59] Rao KN, Brown MA. Mast cells: multifaceted immune cells with diverse roles in health and disease. *Ann. NY Acad. Sci.* 2008;1143:83-104.

[60] Arock M, Valent P. Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives. *Expert Rev. Hematol.* 2010 Aug;3(4):497, http://dx.doi.org/10.1586/ehm.10.42.

[61] Heib V, Becker M, Taube C, Stassen M. Advances in the understanding of mast cell function. *Brit. J. Haematol.* 2008;142:683-694, doi:10.1111/j.1365-2141.2008.07244.x.

[62] Lim K-H, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, McClure RF, Li C-Y, Pardanani A. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009;113:5727-5736.

[63] Alfter K, von Kügelgen I, Haenisch B, Frieling T, Hülsdonk A, Haars U, Rolfs A, Noe G, Kolck UW, Homann J, Molderings GJ. New aspects of liver abnormalities as part of the systemic mast cell activation syndrome. *Liver Int.* 2009 Feb;29(2):181-186.

[64] Albino FP, Koltz PF, Gusenoff JA. A comparative analysis and systematic review of the wound-healing milieu: implications for body contouring after massive weight loss. *Plastic Reconstructive Surg.* 2009 Nov, 124(5):1675-1682.

[65] D'Ettorre M, Gniuli D, Iaconelli A, Massi G, Mingrone G, Bracaglia R. Wound healing process in post-bariatric patients: an experimental evaluation. *Obes. Surg.* 2010;20:1552-1558.

[66] Sarchio SNE, Kok L-F, O'Sullivan C, Halliday GM, Byrne SN. Dermal mast cells affect the development of sunlight-induced skin tumours. *Exper. Dermatol.* 2012 Apr;21(4):241-248.

[67]   Johansson O. Disturbance of the immune system by electromagnetic fields—A potentially underlying cause for cellular damage and tissue repair reduction which could lead to disease and impairment. *Pathophysiol.* 2009 Aug;16(2-3):157-177.

[68]   Escribano L, Akin C, Castells M, Orfao A, Metcalfe DD. Mastocytosis: current concepts in diagnosis and treatment. *Ann. Hematol.* 2002;81:677-690.

[69]   Gulliksson M, Palmberg L, Nilsson G, Ahlstedt S, Kumlin M. Release of prostaglandin D2 and leukotriene C4 in response to hyperosmolar stimulation of mast cells. *Allergy* 2006 Dec;61(12):1473-1479.

[70]   Watkins CE, Bokor WB, Leicht S, Youngberg G, Krishnaswamy G. Telangiectasia macularis eruptiva perstans: more than skin deep. *Dermatol. Rep.* 2011;3:e12, pp. 23-30, doi:10.4081/dr.2011.e12.

[71]   Kennelly R, Conneely J, Bouchier-Hayes D, Winter D. Mast cells in tissue healing: from skin to the gastrointestinal tract. *Curr. Pharmaceut. Design* 2011 Nov;17(34): 3772-3775.

[72]   Sheu HM, Yu HS, Chang CH. Mast cell degranulation and elastolysis in the early stage of striae distensae. *J. Cutan Pathol.* 1991;18:410-416.

[73]   Berger G, Hawke M, Ekem JK, Johnson A. Mast cells in human middle ear mucosa in health and in disease. *J. Otolaryngol.* 1984;13(6):370-374.

[74]   Ebmeyer J, Furukawa M, Pak K, Ebmeyer U, Sudhoff H, Broide D, Ryan AF, Wasserman S. Role of mast cells in otitis media. *J. Allergy Clin. Immunol.* 2005 Nov;116(5):1129-1135.

[75]   Clemis JD, Mastricola PG, Schuler-Vogler M. Sudden hearing loss in the contralateral ear in postoperative acoustic tumor: three case reports. *Laryngoscope* 1982 Jan;92(1):76-79.

[76]   Bretlau P. Otosclerosis in the lateral semicircular canal. *J. Laryngol. Otol.* 1968;82:65.

[77]   Lerner MR, Lerner AB. Urticaria pigmentosa with systemic lesions and otosclerosis. *Arch. Dermatol.* 1960;81(2):203-204.

[78]   Roskoski Jr RR. Signaling by Kit protein-tyrosine kinase -- the stem cell factor receptor. *Biochem. Biophys. Res. Comm.* 2005;307:1-13.

[79]   Afrin LB. Burning mouth syndrome and mast cell activation disorder. *Oral Surg. Oral Med. Oral Pathol. Oral Radiology Endodontol.* 2011;111(4):465-472.

[80]   Borelli V, Marchioli A, Di Taranto R, Romano M, Chiandussi S, Di Lenarda R, Biasotto M, Zabucchi G. Neuropeptides in saliva of subjects with burning mouth syndrome: a pilot study. *Oral Diseases* 2010 May;16(4):365-374.

[81]   Afrin LB. Sclerosing mediastinitis and mast cell activation syndrome. *Pathol. Res. Pract.* 2012 Mar 15;208(3):181-185.

[82]   Farnoush A. Mast cells in human dental pulp. *J. Endodontics* 1984 Jun;10(6):250-252.

[83]   Raslan N, Wetzel W-E. Exposed human pulp caused by trauma and/or caries in primary dentition: a histological evaluation. *Dental Traumatol.* 2006 Jun;22(3):145-153.

[84]   Gandhi MK, Hertzberk MS, Han E, Seymour JF, Hicks R, Gill DS, Keane C, Crooks P, Radford K, Vari F. Monocytes are associated with impaired T-cell immunity and residual interim-PET/CT avidity after 4 cycles of CHOP-R in patients with high-risk DLBCL. *Blood* 2011;118(21):1570.

[85]   Porrata LF, Ristow K, Habermann TM, Ozsan N, Dogan A, Macon W, Colgan JP, Witzig TE, Inwards DJ, Ansell SM, Micallef IN, Johnston PB, Nowakowski GS, Thompson C, Markovic SN. Absolute monocyte/lymphocyte count prognostic score is

independent of immunohistochemically determined cell of origin in predicting survival in diffuse large B-cell lymphoma. *Leukemia Lymphoma* 2012 Nov;53(11):2159-2165, doi:10.3109/10428194.2012.690605.

[86] Porrata LF, Ristow KM, Colgan JP, Habermann TM, Witzig TE, Inwards DJ, Ansell SM, Micallef IN, Johnston PB, Nowakowski GS, Thompson CA, Markovic SN. Peripheral blood lymphocyte/monocyte ratio at diagnosis and survival in nodular lymphocyte-predominant Hodgkin lymphoma. *Brit. J. Haematol.* 2012 May; 157(3): 321-330.

[87] Porrata LF, Ristow KM, Colgan JP, Habermann TM, Witzig TE, Inwards DJ, Ansell SM, Micallef IN, Johnston PB, Nowakowski GS, Thompson CA, Markovic SN. Peripheral blood lymphocyte/monocyte ratio at diagnosis and survival in classical Hodgkin's lymphoma. *Haematologica* 2011;96,doi:10.3324/haematol.2011.050138.

[88] Wilcox RA, Ristow K, Habermann TM, Inwards DJ, Micallef INM, Johnston PB, Colgan JP, Nowakowski GS, Ansell SM, Witzig TE, Markovic SN, Porrata L. The absolute monocyte count is associated with overall survival in patients newly diagnosed with follicular lymphoma. *Leukemia Lymphoma* 2012 Apr;53(4):575-580.

[89] Tadmor T. Absolute monocyte count identifies high-risk patients with lymphomas: "absolutely" simple and "counts" mean a lot! *Leukemia Lymphoma* 2012 Apr; 53(4):519.

[90] Hardy CC, Robinson C, Tattersfield AE, Holgate ST. The bronchoconstrictor effect of inhaled prostaglandin D_2 in normal and asthmatic man. *New Engl. J. Med.* 1984;311: 203-13.

[91] Mortaz E, Folkerts G, Redegeld F. Mast cells and COPD. *Pulm Pharmacol. Therapeut.* 2011 Aug;24(4):367-372.

[92] Chi DS, Lin T-C, Hall K, Ha T, Li C, Wu ZD, Soike T, Krishnaswamy G. Enhanced effects of cigarette smoke extract on inflammatory cytokine expression in IL-1β-activated human mast cells were inhibited by Baicalein via regulation of the NF-κB pathway. *Clin. Mol. Allergy* 2012;10:3.

[93] Kalenderian R, Raju L, Roth W, Schwartz LB, Gruber B, Janoff A. Elevated histamine and tryptase levels in smokers' bronchoalveolar lavage fluid. Do lung mast cells contribute to smokers' emphysema? *Chest* 1988;94:119-123.

[94] Rutgers Sr, Postma DS, ten Hacken NHT, Kauffman HF, van der Mark TW, Koëter GH, Timens W. Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000;55(1):12-18.

[95] Anand P, Singh B, Jaggi AS, Singh N. Mast cells: an expanding pathophysiological role from allergy to other disorders. *Naunyn-Schiedeberg's Arch. Pharmacol.* 2012 May, in press, doi:10.1007/s00210-012-0757-8.

[96] Nakagomi T, Kassell NF, Sasaki T, Lehman RM, Torner JC, Hongo K, Lee JH. Effect of removal of endothelium on vasocontraction in canine and rabbit basilar arteries. *J. Neurosurg.* 1988 May;68(5):757-766.

[97] Beasley CRW, Hovell CJ, Mani R, Robinson C, Holgate ST. The comparative vascular effects of histamine, prostaglandin D_2 and its metabolite $9\alpha11\beta$-PGF_2 in human skin. *Br. J. Clin. Pharmacol.* 1987;23:605-606.

[98] Giles H, Bolofo ML, Lydford SJ, Martin GR. A comparative study of the prostanoid receptor profile of $9\alpha11\beta$-prostaglandin F_2 and prostaglandin D_2. *Br. J. Pharmacol.* 1991;104:541-549.

[99]   Shibao C, Arzubiaga C, Roberts II LJ, Raj S, Black B, Harris P, Biaggioni I. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension* 2005;45:385-390.

[100] Raj SR. The postural tachycardia syndrome (POTS): pathophysiology, diagnosis and management. *Indian Pacing Electrophysiol. J.* 2006 Apr-Jun;6(2):84-99.

[101] Kounis NG, Hahalis G, Manola A, Kourelis T, Theoharides TC. Chapter III: Kounis syndrome (allergic angina and allergic myocardial infarction). In: Gallo AP, Jones ML, eds., *Angina Pectoris: Etiology, Pathogenesis and Treatment*, Nova Science Publishers, Happauge, NY, 2008, pp. 77-150.

[102] Biteker M. Current understanding of Kounis syndrome. *Expert Rev. Clin. Immunol.* 2010 Sep;6(5):777+, doi:10.1586/eci.10.47.

[103] Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur. Heart J.* 2006, 27(13): 1523-1529.

[104] Yanagawa Y, Nishi K, Tomiharu N, Kawaguchi T. A case of takotsubo cardiomyopathy associated with Kounis syndrome. *Int. J. Cardiol.* 2009 Feb 20, 132(2): e65-e67.

[105] Vultaggio A, Matucci A, Del Pace S, Simonetti I, Parronchi P, Rossi O, Maggi E, Gensini G, Romagnani S. Tako-Tsubo-like syndrome during anaphylactic reaction. *Eur. J. Heart Failure* 2007, 9(2):209-211.

[106] Forman MB, Oates JA, Robertson D, Robertson RM, Roberts LJ, Virmani R. Increased adventitial mast cells in a patient with coronary spasm. *N. Engl. J. Med.* 1985 Oct 31;313:1138-1141.

[107] Atkinson JB, Harlan CW, Harlan GC, Virmani R. The association of mast cells and atherosclerosis: A morphologic study of early atherosclerotic lesions in young people. *Human Pathol.* 1994 Feb;25(2):154-159.

[108] VanderLaan PA, Reardon CA. Thematic review series: the immune system and atherogenesis. The unusual suspects: an overview of the minor leukocyte populations in atherosclerosis. *J. Lipid Res.* 2005 May;46:829-838.

[109] Deliargyris EN, Upadhya B, Sane DC, Dehmer GJ, Pye J, Smith Jr. SC, Boucher WS, Theoharides TC. Mast cell tryptase: a new biomarker in patients with stable coronary artery disease. *Atherosclerosis* 2005;178:381-386.

[110] Anvari MS, Boroumand MA, Mojarad EA, Karimi A, Abbasi K, Shirzad M, Omran AS, Movahedi N, Shirani S, Goodarzynejad H. Do adventitial mast cells contribute to the pathogenesis of ascending thoracic aorta aneurysm? *Int. J. Surg. Pathol.* 2012 Oct;20(5):474-479, doi:10.1177/1066896912440820.

[111] Tsuruda T, Kato J, Hatakeyama K, Kojima K, Yano M, Yano Y, Nakamura K, Nakamura-Uchiyama F, Matsushima Y, Imamura T, Onitsuka T, Asada Y, Nawa Y, Eto T, Kitamura K. Adventitial mast cels contribute to pathogenesis in the progression of abdominal aortic aneurysm. *Circ. Res.* 2008;102:1368-1377.

[112] Ishibashi R, Aoki T, Nishimura M, Hashimoto N, Miyamoto S. Contribution of mast cells to cerebral aneurysm formation. *Curr. Neurovasc. Res.* 2010 May;7(2):113-124.

[113] Zhang J, Sun J, Lindholt JS, Sukhova GK, Sinnamon M, Stevens RL, Adachi R, Libby P, Thompson RW, Shi G-P. Mast cell tryptase deficiency attenuates mouse abdominal aortic aneurysm formation. *Mol. Med.* 2011;108:1316-1327.

[114] Taweevisit M, Wisadeopas N, Phumsuk U, Thorner PS. Increased mast cell density in haemorrhoid venous blood vessels suggests a role in pathogenesis. *Singapore Med. J.* 2008;49(12):977-979.

[115] Yamada T, Tomita S, Mori M, Sasatomi E, Suenaga E, Itoh T. Increased mast cell infiltration in varicose veins of the lower limbs: a possible role in the development of varices. *Surgery* 1996 May;119(5):494-497.

[116] Yamada T, Yamamoto H, Ogawa A, Miyazaki K, Tokunaga O, Itoh T. Ultrastructural demonstration of mast cells in varicose veins of lower limbs: presence of mast cell-mediated mechanism. *J. Cardiovasc. Surg. (Torino)* 1997 Oct;38(5):443-446.

[117] Sayer GL, Smith PDC. Immunocytochemical characterisation of the inflammatory cell infiltrate of varicose veins. *Eur. J. Vasc. Endovasc. Surg.* 2004 Nov;28(5):479-483.

[118] Ribatti D, Crivellato E. Mast cells, angiogenesis, and tumour growth. *Biochim. Biophys. Acta Mol. Basis Dis.* 2012 Jan;1822(1):2-8.

[119] Glowacki J, Mulliken JB. Mast cells in hemangioma and vascular malformations. *Pediatrics* 1982;70(1):48-51.

[120] Meijer-Jorna LB, van der Loos CM, de Boer OJ, van der Horst CMAM, van der Wal AC. Microvascular proliferation in congenital vascular malformations of skin and soft tissue. *J. Clin. Pathol.* 2007;60(7):798-803.

[121] Wahrman JE, Honig P. Hemangiomas. *Pediatr. Rev.* 1994 Jul;15(7):266-271.

[122] Kolck UW, Alfter K, Homann J, von Kügelgen I, Molderings GJ. Cardiac mast cells: implications for heart failure. *JACC* 2007 Mar 13;49(10):1106-1108.

[123] Batlle M, Pérez-Villa F, Lázaro A, Garcia-Pras E, Ramirez J, Ortiz J, Orús J, Roqué M, Heras M, Roig E. Correlation between mast cell density and myocardial fibrosis in congestive heart failure patients. *Transpl. Proc.* 2007 Sep;39(7):2347-2349.

[124] Higuchi H, Hara M, Yamamoto K, Miyamoto T, Kinoshita M, Yamada T, Uchiyama K, Matsumori A. Mast cells play a critical role in the pathogenesis of viral myocarditis. *Circ.* 2008;118:363-372.

[125] Hara M, Ono K, Sasayama S, Matsumori A. Chapter 17: The key role of mast cells in the evolution to congestive heart failure. In: Matsumori A, ed., *Cardiomyopathies and Heart Failure: Biomolecular, Infectious and Immune Mechanisms*. Kluwer Academic Publishers, Norwell, Massachusetts, 2003, pp. 213-228.

[126] Baron TH, Koehler RE, Rodgers WH, Fallon MB, Ferguson SM. Mast cell cholangiopathy: another cause of sclerosing cholangitis. *Gastroenterol.* 1995 Nov; 109(5):1677-1681.

[127] Steer ML, Waxman I, Freedman S. Chronic pancreatitis. *New Engl. J. Med.* 1995 Jun 1, 332(22):1482-1490.

[128] Stevens T, Conwell DL, Zuccaro G. Pathogenesis of chronic pancreatitis: an evidence-based review of past theories and recent developments. *Am. J. Gastoenterol.* 2004;99: 2256-2270.

[129] Hoogerwerf WA, Gondesen K, Xiao S-Y, Winston JH, Willis WD, Pasricha PJ. The role of mast cells in the pathogenesis of pain in chronic pancreatitis. *BMC Gastroenterol.* 2005, 5:8, doi:10.1186/1471-230X-5-8.

[130] Narayanan MN, Yin JAL, Azzawi S, Warnes TW, Turck WPG. Portal hypertension and ascites in systemic mastocytosis. *Postgrad. Med. J.* 1989;65:394-396.

[131] Bonnet P, Smadja C, Szekely A-M, Delage Y, Calmus Y, Poupon R, Franco D. Intractable ascites in systemic mastocytosis treated by portal diversion. *Digest Dis. Sci.* 1987;32(2):209-213.

[132] Sant GR, Kempuraj D, Marchand JE, Theoharides TC. The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. *Urol.* 2007;69(suppl 4A):34-40.

[133] Graziottin A, Giovannini N, Bertolasi L, Bottanelli M. Vulvar vestibulitis: pathophysiology and management. *Curr. Sexual Health Reports* 2004;1:151-156.

[134] Graziottin A. Chapter 25: Sexual pain disorders: dyspareunia and vaginismus. In: Porst H, Buvat J (Eds.), ISSM (International Society of Sexual Medicine) Standard Committee Book, Standard practice in Sexual Medicine, Blackwell, Oxford, UK, 2006, p. 342-350.

[135] Bornstein J, Goldschmid N, Sabo E. Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. *Gyn. Obstetr. Invest.* 2004, 58(3):171-178.

[136] Holdsworth SR, Summers SA. Role of mast cells in progressive renal diseases. *J. Am. Soc. Nephrol.* 2008 Dec;19(12):2254-2261.

[137] Krishna A, Beesley K, Terranova PF. Histamines, mast cells, and ovarian function. *J. Endocrinol.* 1989 Mar 1;120:363-371.

[138] D'Cruz OJ, Uckun FM. Targeting mast cells in endometriosis with Janus kinase 3 inhibitor, JANEX-1. *Amer. J. Reprod. Endocrinol.* 2007 Aug;58(2):75-97.

[139] Anaf V, Chapron C, El Nakadi I, De Moor V, Simonart T, Noël J-C. Pain, mast cells, and nerves in peritoneal, ovarian, and deep infiltrating endometriosis. *Fertil. Steril.* 2006 Nov;86(5):1336-1343.

[140] Kempuraj D, Papadopoulou N, Stanford EJ, Christodoulou S, Madhappan B, Sant GR, Solage K, Adams T, Theoharides TC. Increased numbers of activated mast cells in endometriosis lesions positive for corticotropin-releasing hormone and urocortin. *Am. J. Reprod. Immunol.* 2004;52:267-275.

[141] Frungieri MB, Gonzalez-Calvar SI, Matzkin ME, Mayerhofer A, Calandra RS. Sources and functions of prostaglandins in the testis: evidence for their relevance in male (in)fertility. *Anim. Reprod.* 2007 Jul-Dec; 4(3-4):63-69.

[142] Hibi H, Kato K, Mitsui K, Taki T, Yamada Y, Honda N, Fukatsu H, Yamamoto M. Treatment of oligoasthenozoospermia with tranilast, a mast cell blocker, after long-term administration. *Systems Biol. Reproductive Med.* 2002;48(6):451-459.

[143] Chiappetta N, Gruber B. The Role of Mast Cells in Osteoporosis. *Semin. Arthritis Rheumatism* 2006 Aug;36(1):32-36.

[144] Rafii M, Firooznia H, Golimbu C, Balthazar E. Pathologic fracture in systemic mastocytosis: radiographic spectrum and review of the literature. *Curr. Orthop. Pract.* 1983 Nov;180:260-267.

[145] de Gennes C, Kuntz D, de Vernejoul MC. Bone mastocytosis: a report of nine cases with a bone histomorphometric study. *Clin. Orthop. Relat. Res.* 1992 Jun;(279):281-91.

[146] Delling G, Ritzel H, Werner M. Histological characteristics and prevalence of secondary osteoporosis in systemic mastocytosis: a retrospective analysis of 158 cases. *Pathologe* 2001 Mar;22(2):132-140.

[147] Marshall A, Kavanagh RT, Crisp AJ. The effect of pamidronate on lumbar spine bone density and pain in osteoporosis secondary to systemic mastocytosis. *Brit. J. Rheumatol.* 1997;36:393-396.

[148] Szweda JA, Abraham JP, Fine G, Nixon RK, Rupe CE. Systemic mast cell disease: a review and report of three cases. *Am. J. Med.* 1962 Feb;32(2):227-239.

[149] Dempster DW, Lambing CL, Kostenuik PJ, Grauer A. Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: a review of preclinical and clinical data. *Clin. Therapeut.* 2012 Mar;34(3):521-536.

[150] Freemont AJ, Jeziorska M, Hoyland JA, Rooney P, Kumar S. Mast cells in the pathogenesis of chronic back pain: a hypothesis. *J. Pathol.* 2002;197:281-285.

[151] Huygen FJPM, Ramdhani N, van Toorenenbergen A, Klein J, Zijlstra FJ. Mast cells are involved in inflammatory reactions during Complex Regional Pain Syndrome type 1. *Immunol. Letters* 2004 Feb;91(2-3):147-154.

[152] Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J. Pediatr.* 1999 Oct, 135(4):494-499.

[153] Kanjwal K, Saeed B, Karabin B, Kanjwal Y, Grubb BP. Comparative clinical profile of postural orthostatic tachycardia patients with and without joint hypermobility syndrome. *Indian Pacing Electrophysiol. J.* 2010;10(4):173-178.

[154] Bohora S. Joint hypermobility syndrome and dysautonomia: expanding spectrum of disease presentation and manifestation. *Indian Pacing Electrophysiol. J.* 2010;10(4): 158-161.

[155] Lim AYN, Ostor AJK, Love S, Crisp AJ. Systemic mastocytosis: a rare cause of osteoporosis and its response to bisphosphonate treatment. *Ann. Rheum. Dis.* 2005;64: 965-966.

[156] Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterol.* 2004;126:693-702.

[157] Worobec AS, Metcalfe DD. Mastocytosis: current treatment concepts. *Int. Arch. Allergy Immunol.* 2002, 127(2):153-155.

[158] Álvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Esteban-López MI, Vega A, Mateo MB, de Durana MDAD, de la Hoz B, del Pozo Gil MD, Caballero T, Rosado A, Matas IS, Teodósio C, Jara-Acevedo M, Mollejo M, García-Montero A, Orfao A, Escribano L. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J. Allergy Clin. Immunol.* 2010 Jun, 125(6):1269-1278.e2.

[159] Chacko T, Ledford D. Peri-anesthetic anaphylaxis. *Immunol. Allergy Clin. North Am.* 2007 May, 27(2):213-230.

[160] Blunk JA, Schmelz M, Susanne Z, Skov P, Likar R, Koppert W. Opioid-induced mast cell activation and vascular responses is not mediated by μ-opioid receptors: an in vivo microdialysis study in human skin. *Anesthesia Analgesia* 2004 Feb, 98(2):364-370.

[161] Raffa RB. Antihistamines as analgesics. *J. Clin. Pharmacy Therapeut.* 2001 Apr, 26(2):81-85.

[162] Galeotti N, Ghelardini C, Bartolini A. *Neurosci.* 2002 Feb 22, 109(4):811-818.

[163] Karimi M, Zekavat OR, Sharifzadeh S, Mosavizadeh K. Clinical response of patients with sickle cell anemia to cromolyn sodium nasal spray. *Am. J. Hematol.* 2006;81: 809-816.

[164] Nyirjesy P, Sobl JD, Weitz MV, Leaman DJ, Small MJ, Gelone SP. Cromolyn cream for recalcitrant idiopathic vulvar vestibulitis: results of a placebo controlled study. *Sex Transm. Infect.* 2001, 77:53-57.

[165] Nakajima K, Obata H, Ito N, Goto F, Saito S. The nociceptive mechanism of 5-hydroxytryptamine released into the peripheral tissue in acute inflammatory pain in rats. *Eur. J. Pain* 2009 May, 13(5):441-447.

[166] Metcalfe DD. Mast cells and mastocytosis. *Blood* 2008 Aug 15;112(4):946-956.

[167] Metcalfe DD, Baram D, Mekori YA. Mast cells. *Physiol. Rev.* 1997 Oct;77(4): 1033-1079.

[168] Wager-Smith K, Markou A. Depression: a repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition? *Neurosci. Biobehav. Rev.* 2011 Jan;35(3):742-764.

[169] Debnath M, Doyle KM, Langan C, McDonald C, Leonard B, Cannon DM. Recent advances in psychoneuroimmunology: inflammation in psychiatric disorders. *Translational Neurosci.* 2011;2(2):121-137.

[170] Khansari PS, Sperlagh B. Inflammation in neurological and psychiatric diseases. *Inflammopharmacol.* 2012, in press, doi:10.1007/s10787-012-0124-x.

[171] Smith JH, Butterfield JH, Cutrer FM. Primary headache syndromes in systemic mastocytosis. *Cephalalgia* 2011 Nov;31(15):1522-1531.

[172] Levy D, Burstein R, Kainz V, Jakubowski M, Strassman AM. Mast cell degranulation activates a pain pathway underlying migraine headache. *Pain* 2007 Jul;130(1-2): 166-176.

[173] Secor VH, Secor WE, Gutekunst C-A, Brown MA. Mast cells are essential for early onset and severe disease in a murine model of multiple sclerosis. *J. Exper. Med.* 2000 Mar 6;191(5):813-822.

[174] Rozniecki JJ, Hauser SL, Stein M, Lincoln R, Theoharides TC. Elevated mast cell tryptase in cerebrospinal fluid of multiple sclerosis patients. *Ann. Neurol.* 1995 Jan;37(1):63-66.

[175] Graves MC, Fiala M, Dinglasa LAV, Liu NQ, Sayre J, Chiappell F, van Kooten C, Vinters HV. Inflammation in amyotrophic lateral sclerosis spinal cord and brain is mediated by activated macrophages, mast cells and T cells. *Amyotrophic Lateral Sclerosis* 2004;5(4):213-219.

[176] Mohri I, Taniike M, Taniguchi H, Kanekiyo T, Aritake K, Inui T, Fukumoto N, Eguchi N, Kushi A, Sasai H, Kanaoka Y, Ozono K, Narumiya S, Suzuki K, Urade Y. Prostaglandin D_2-mediated microglia/astrocyte interaction enhances astrogliosis and demyelination in *twitcher*. *J. Neurosci.* 2006 Apr 19;26(16):4383-4393.

[177] Hedlund E, Isacson O. ALS model glia can mediate toxicity to motor neurons derived from human embryonic stem cells. *Cell Stem Cell* 2008 Dec 4;3(6):575-576.

[178] Urade Y, Hayaishi O. Prostaglandin D_2 and sleep regulation. *Biochim. Biophys. Acta* 1999 Jan 4;1436(3):606-615.

[179] Hayaishi O. Molecular mechanisms of sleep-wake regulation: roles of prostaglandins D2 and E2. *FASEB J.* 1991 Aug;5:2575-2581.

[180] Scammell T, Gerashchenko D, Urade Y, Onoe H, Saper C, Hayaishi O. Activation of ventrolateral preoptic neurons by the somnogen prostaglandin D_2. *Proc. Natl. Acad. Sci.* 1998 Jun; 95:7754-7759.

[181] Roberts II JL, Sweetman BJ, Lewis RA, Austen KF, Oates JA. Increased production of prostaglandin D$_2$ in patients with systemic mastocytosis. *New Engl. J. Med.* 1980;303: 1400-1404.

[182] Yang H-Y, Sun C-C, Wu Y-C, Wang J-D. Stress, insomnia, and chronic idiopathic urticaria – a case-control study. *J. Formos Med. Assoc.* 2005;104:254-263.

[183] Butterfield JH, Marcoux JP, Weiler D, Harner SG. Mast cell pharyngitis as a cause of supraglottic edema. *Eur. Arch. Oto-rhino-laryngol.* 1988;245(2):88-91.

[184] Craig TJ, Sherkat A, Safaee S. Congestion and sleep impairment in allergic rhinitis. *Curr. Allergy Asthma Rep.* 2010;10:113-121.

[185] Lipton JM, Clark WG. Neurotransmitters in temperature control. *Annu. Rev. Physiol.* 1986;48:613-623.

[186] Uda R, Horiguchi S, Ito S, Hyodo M, Hayaishi O. Nociceptive effects induced by intrathecal administration of prostaglandin D2, E2, or F2α to conscious mice. *Brain Res.* 1990 Feb 26;510(1):26-32.

[187] Theoharides TC. Panic disorder, interstitial cystitis, and mast cells. *J. Clin. Psychopharmacol.* 2004 Aug;24(4):361-364.

[188] Gupta MA, Gupta AK. Chronic idiopathic urticaria and post-traumatic stress disorder (PTSD): an under-recognized comorbidity. *Clinics Dermatol.* 2012 May-Jun;30(3): 351-354.

[189] Theoharides TC, Doyle R, Francis K, Conti P, Kalogeromitros D. Novel therapeutic targets for autism. *Trends Pharmacol. Sci.* 2008;29:375-382.

[190] Theoharides TC. Autism spectrum disorders and mastocytosis. *Int. J. Immunopathol. Pharmacol.* 2009, 22(4):859-865.

[191] Marshall P. Attention deficit disorder and allergy: a neurochemical model of the relation between the illnesses. *Psychol. Bull.* 1989, 106(3):434-446.

[192] Chinellato I, Piazza M, Sandri M, Peroni DG, Cardinale F, Piacentini GL, Boner AL. Serum vitamin D levels and exercise-induced bronchoconstriction in children with asthma. *Eur. Resp. J.* 2011 Jun 1;37(6):1366-1370.

[193] Siebler T, Robson H, Bromley M, Stevens DA, Shalet SM, Williams GR. Thyroid status affects number and localization of thyroid hormone receptor expressing mast cells in bone marrow. *Bone* 2002 Jan;30(1):259-266.

[194] Heymann WR. Chronic urticaria and angioedema associated with thyroid autoimmunity: review and therapeutic implications. *J. Am. Acad. Dermatol.* 1999 Feb; 40(2):229-232.

[195] Tsuchiya S, Tachida Y, Segi-Nishida E, Okuno Y, Tamba S, Tsujimoto G, Tanaka S, Sugimoto Y. Characterization of gene expression profiles for different types of mast cells pooled from mouse stomach subregions by an RNA amplification method. *BMC Genomics* 2009;10:35, doi:10.1186/1471-2164-10-35.

[196] Brissot P, Guyader D, Loréal O, Lainé F, Guillygomarc'h A, Moirand R, Deugnier Y. Clinical aspects of hemochromatosis. *Transfus. Sci.* 2000;23:193-200.

[197] Theoharides TC, Sismanopoulos N, Delivanis D-A, Zhang B, Hatziagelaki EE, Kalogeromitros D. Mast cells squeeze the heart and stretch the gird: their role in atherosclerosis and obesity. *Trends Pharmacol. Sci.* 2011 Sep;32(9):534-542.

[198] Shi MA, Shi G-P. Different roles of mast cells in obesity and diabetes: lessons from experimental animals and humans. *Frontiers Immunol.* 2012 Jan;3:article 7, pp. 1-12, doi:10.3389/fimmu.2012.00007.

[199] Zhang J, Shi GP. Mast cells and metabolic syndrome. *Biochim. Biophys. Acta* 2012 Jan, 1822(1):14-20.

[200] Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature* 1998 Jan 1;391(6662):79-82.

[201] Yong LCJ. The mast cell: origin, morphology, distribution, and function. *Exp. Toxic. Pathol.* 1997;49:409-424.

[202] Sur R, Cavender D, Malaviya R. Different approaches to study mast cell functions. *Int. Immunopharmacol.* 2007 May;7(5):555-567.

[203] Butterfield JH, Li C-Y. Bone marrow biopsies for the diagnosis of systemic mastocytosis: is one biopsy sufficient? *Am. J. Clin. Pathol.* 2004;121:264-267.

[204] Pardanani A. Systemic mastocytosis in adults: 2011 update on diagnosis, risk stratification, and management. *Am. J. Hematol.* 2011;86:363-371.

[205] Sánchez-Muñoz L, Alvarez-Twose I, García-Montero AC, Teodósio C, Jara-Acevedo M, Pedreira CE, Matito A, Morgado JMT, Sánchez ML, Mollejo M, Gonzalez-de-Olano D, Orfao A, Escribano L. Evaluation of the WHO criteria for the classification of patients with mastocytosis. *Modern Pathol.* 2011;24:1157-1168.

[206] Sánchez-Muñoz L, Teodósio C, Morgado JM, Escribano L. Immunophenotypic characterization of bone marrow mast cells in mastocytosis and other mast cell disorders. *Methods Cell Biol.* 2011;103:333-359.

[207] Amon U, Hartmann K, Horny H-P, Nowak A. Mastocytosis -- an update. *JDDG J. Germ. Soc. Dermatol.* 2010 Sep;8(9):695-712.

[208] Homann J, Kolck UW, Ehnes A, Frieling T, Raithel M, Molderings GJ. Systemic mastocytosis -- definition of an internal disease. *Med. Klin. (Munich)* 2010 Aug; 105(8):544-553.

[209] Horny HP, Metcalfe DD, Bennett JM, Bain BJ, Akin C, Escribano L, Valent P. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, et al., eds., *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues*. 4th ed. Lyon: International Agency for Research on Cancer; 2008. p. 54-63.

[210] Afrin LB. Mast cell activation syndrome masquerading as agranulocytosis. *Military Med.* 2012 Jan;177(1):113-117.

[211] Steensma DP, Dewald GW, Lasho TL, Powell HL, McClure RF, Levine RL, Gilliland DG, Tefferi A. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both "atypical" myeloproliferative disorders and myelodysplastic syndromes. *Blood 2005* Aug 15;106(4):1207-1209.

[212] Sotlar K, Bache A, Stellmacher F, Bültmann B, Valent P, Horny H-P. Systemic mastocytosis associated with chronic idiopathic myelofibrosis: a distinct subtype of systemic mastocytosis-associated clonal hematological nonmast cell lineage disorder carrying the activating point mutations KIT^{D816V} and $JAK2^{V617F}$. *J. Mol. Diagn.* 2008 Jan;10(1):58-66.

[213] Olofsson K, Mattsson C, Hammarström M-L, Hellström S. Structure of the human uvula. *Acta Otolaryngol.* 1999;119:712-717.

[214] Kobune M, Miyanishi K, Takada K, Kawano Y, Nagashima H, Kikuchi S, Murase K, Iyama S, Sato T, Sato Y, Takimoto R, Kato J. Establishment of a simple test for iron absorption from the gastrointestinal tract. *Int. J. Hematol.* 2011;93:715-719.

[215] Carmel R, Weiner JM, Johnson CS. Iron deficiency occurs frequently in patients with pernicious anemia. *JAMA* 1987 Feb 27;257(8):1081-1083.

[216] Hershko C, Ronson A, Souroujon M, Maschler Z, Heyd J, Patz J. Variable hematological presentation of autoimmune gastritis: age-related progression from iron deficiency to cobalamin depletion. *Blood* 2006 Feb;107:1673-1679.

[217] Oldenburg B, Koningsberger JC, Van Berge Henegouwen GP, Van Asbeck BS, Mark JJM. Iron and inflammatory bowel disease. *Aliment Pharmacol. Therapeut.* 2001 Apr;15(4):429-438.

[218] Annibale B, Capurso G, Chistolini A, D'Ambra G, DiGiulio E, Monarca B, DelleFave G. Gastrointestinal causes of refractory iron deficiency anemia in patients without gastrointestinal symptoms. *Am. J. Med.* 2001 Oct;111(6):439-445.

[219] Weiss G, Gasche C. Pathogenesis and treatment of anemia in inflammatory bowel disease. *Haematologica* 2010 Feb 1;95(2):175-178.

[220] Azzolina A, Bongiovanni A, Lampiasi N. Substance P induces TNF-α and IL-6 production through NFκB in peritoneal mast cells. *Biochim. Biophys. Acta Mol. Cell Res.* 2003 Dec;1643(1-3):75-83.

[221] McColl KE. Effect of proton pump inhibitors on vitamins and iron. *Am. J. Gastroenterol.* 2009 Mar;104 Suppl 2:S5-S9.

[222] Hutchinson C, Geissler CA, Powell JJ, Bomford A. Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary hemochromatosis. *Gut* 2007 Sep;56(9):1291-1295.

[223] Miret S, Simpson RJ, McKie AT. Physiology and molecular biology of dietary iron absorption. *Annu. Rev. Nutr.* 2003;23:283-301.

[224] Nations SP, Boyer PJ, Love LA, Murritt MF, Butz JA, Wolfe GI, Hynan LS, Reisch J, Trivedi JR. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. *Neurology* 2008;71:639–43.

[225] Afrin LB. Fatal copper deficiency from excessive use of zinc-based denture adhesive. *Am. J. Med. Sci.* 2010 Aug;340(2):164-168.

[226] Horton L, Coburn RJ, England JM, Himsworth RL. The haematology of hypothyroidism. *QJM* 1976;45(1):101-123.

[227] Fritsche-Polanz R, Jordan J-H, Feix A, Sperr WR, Sunder-Plassmann G, Valent P, Födinger M. Mutation analysis of *C-KIT* in patients with myelodysplastic syndromes without mastocytosis and cases of systemic mastocytosis. *Brit. J. Haematol.* 2001 May; 113(2):357-364.

[228] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RHWM, de Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid antibody syndrome (APS). *J. Thromb. Haemost.* 2006;4:295-306.

[229] Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, Baudo F, Berrettini M, Testa S, D'Angelo A, Tognoni G, Barbui T. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J. Thromb. Haemost.* 2005;3:848-853.

[230] Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, Laskin C, Fortin P, Anderson D, Kearon C, Clarke A, Geerts W, Forgie M, Green D, Costantini L,

Yacura Y, Wilson S, Gent M, Kovacs MJ. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N. Engl. J. Med.* 2003 Sep 18;349:1133-1138.

[231] Rosove MH, Brewer PM. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann. Intern. Med.* 1992 Aug 15;117:303-308.

[232] Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. *N. Engl. J. Med.* 1995 Apr 13;332:993-997.

[233] Trabucchi E, Radaelli E, Marazzi M, Foschi D, Musazzi M, Veronesi AM, Montorsi W. The role of mast cells in wound healing. *Int. J. Tissue React.* 1988;10:367-372.

[234] Galinsky DS, Nechushtan H. Mast cells and cancer – no longer just basic science. *Crit. Rev. Oncol. Hematol.* 2008 Nov;68(2):115-30.

[235] Ryan JJ, Fernando JF. Mast Cell Modulation of the Immune Response. *Curr. Allergy Asthma Reports* 2009;9:353-359.

[236] Maltby S, Khazaie K, McNagny KM. Mast cells in tumor growth: angiogenesis, tissue remodeling and immune-modulation. *Biochim. Biophys. Acta* 2009 Aug;1796(1):19-26.

[237] Van Merriënboer JJG, Sweller J. Cognitive load theory in health professional education: design principles and strategies. *Med. Educ.* 2010;44:85-93.

[238] Xue G, Dong Q, Chen C, Lu Z, Mumford JA, Poldrack RA. Greater neural pattern similarity across repetitions is associated with better memory. *Science* 2010 Oct 1;330(6000):97-101.

[239] Fiscella K, Epstein RM. So much to do, so little time: care for the socially disadvantaged and the 15-minute visit. *Arch. Intern. Med.* 2008 Sep 22;168(17): 1843-1852.

[240] Østbye T, Yarnall KSH, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care? *Ann. Fam. Med.* 2005 May 1;3(3):209-214.

[241] Tai-Seale M, McGuire TG, Zhang W. Time allocation in primary care office visits. *Health Serv. Res.* 2007 Oct;42(5):1871-1894.

[242] Colwill JM, Cultice JM, Kruse RL. Will generalist physician supply meet demands of an increasing and aging population? *Health Aff.* 2008 May;27(3):w232-w241.

[243] Grosso L, Iobst W, Lipner R, Jacobs C. American Board of Internal Medicine's workforce data: residents, fellows, and practicing physicians. American Board of Internal Medicine 2010, available at https://www.aamc.org/download/122832/data/grosso.pdf.pdf, accessed May 10, 2012.

[244] Schwartz LB, Bradford TR. Regulation of tryptase from human lung mast cells by heparin: stabilization of the active tetramer. *J. Biol. Chem.* 1986 Jun 5;261(16): 7372-7379.

[245] Fajardo I, Pejler G. Human mast cell β-tryptase is a gelatinase. *J. Immunol.* 2003;171:1493-1499.

[246] Goldstein SM, Wintroub BU. Chapter 12: Mast cell proteases. In: Kaliner MA, Metcalfe DD, eds., *The Mast Cell in Health and Disease*. Marcel Dekker, New York, 1993, pp. 343-380.

[247] Prasad P, Yanagihara AA, Small-Howard AL, Turner H, Stokes AJ. Secretogranin III directs secretory vesicle biogenesis in mast cells in a manner dependent upon interaction with chromogranin A. *J. Immunol.* 2008;181:5024-5034.

[248] Takiyyuddin MA, Cervenka JH, Hsiao RJ, Barbosa JA, Parmer RJ, O'Connor DT. *Hypertension* 1990;15:237-246.

[249] Pregun I, Herszényi L, Juhász M, Miheller P, Hritz I, Patócs A, Rácz K, Tulassay Z. Effect of proton-pump inhibitor therapy on serum chromogranin A level. *Digestion* 2011;84:22-28.

[250] Sanduleanu S, Stridsberg M, Jonkers D, Hameeteman W, Biemond I, Lundqvist G, Lamers C, Strockbrügger RW. Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. *Aliment Pharmacol. Ther.* 1999;13:145-153.

[251] Fossmark R, Jianu CS, Martinsen TC, Qvigstad G, Syversen U, Waldum HL. *Scand. J. Gastroenterol.* 2008;43:20-24.

[252] Furuta T, Shirai N, Sugimoto M, Ohashi K, Ishizaki T. Pharmacogenomics of proton pump inhibitors. *Pharmacogenom.* 2004 Mar;5(2):181-202.

[253] Sanduleanu S, De Bruïne A, Stridsberg M, Jonkers D, Biemond I, Hameeteman W, Lundqvist G, Stockbrügger RW. Serum chromogranin A as a screening test for gastric enterochromaffin-like cell hyperplasia during acid-suppressive therapy. *Eur. J. Clin. Invest.* 2001;31:802-811.

[254] Seidel H, Molderings GJ, Oldenburg J, Meis K, Kolck UW, Homann J, Hertfelder HJ. Bleeding diathesis in patients with mast cell activation disease. *Thromb. Haemost.* 2011 Nov;106(5):987-989.

[255] Emborg J, Laursen BG, Dalgaard P. Significant histamine formation in tuna (*Thunnus albacares*) at 2°C – effect of vacuum- and modified atmosphere-package on psychro-tolerant bacteria. *Int. J. Food Microbiol.* 2005 Jun 15;101(3):263-279.

[256] Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs: comparison of plasma histamine and tryptase. *Anesthesiol.* 1991 Dec;75(6):945-949.

[257] Takeda J, Ueda E, Takahashi J, Fukushima K. Plasma *N*-methylhistamine concentration as an indicator of histamine release by intravenous *d*-tubocurarine in humans: preliminary study in five patients by radioimmunoassay kits. *Anesth. Analg.* 1995;80: 1015-1017.

[258] Lake AM, Kagey-Sobotka A, Jakubowicz T, Lichtenstein LM. Histamine release in acute anaphylactic enteropathy of the rat. *J. Immunol.* 1984 Sep;133(3):1529-1534.

[259] Laroche D, Dubois F, Gérard J-L, Lefrançois C, André B, Vergnaud M-C, Dubus L, Bricard H. Radioimmunoassay for plasma histamine: a study of false positive and false negative values. *Brit. J. Anaesth.* 1995;74:430-437.

[260] Meyers CD, Liu P, Kamanna VS, Kashyap ML. Nicotinic acid induces secretion of prostaglandin D_2 in human macrophages: an in vitro model of the niacin flush. *Atherosclerosis* 2007 Jun;192(2):253-258.

[261] Hsueh W. Prostaglandin biosynthesis in pulmonary macrophages. *Am. J. Pathol.* 1979; 97:137-148.

[262] Decker K. Biologically active products of stimulated liver macrophages (Kupffer cells). *Eur. J. Biochem.* 1990;192:245-261.

[263] Kuiper J, Zijlstra FJ, Kamps JAAM, van Berkel TJC. Identification of prostaglandin D_2 as the major eicosanoid from liver endothelial and Kupffer cells. *Biochim. Biophys. Acta Lipids Lipid Metab.* 1988 Mar 25;959(2):143-152.

[264] Maciejewski-Lenoir D, Richman JG, Hakak Y, Gaidarov I, Behan DP, Connolly DT. Langerhans cells release prostaglandin D_2 in response to nicotinic acid. *J. Invest. Derm.* 2006;126:2637-2646.

[265] Ali M, Cerskus AL, Zamecnik J, McDonald JWD. Synthesis of prostaglandin D_2 and thromboxane B_2 by human platelets. *Thromb. Res.* 1977 Oct;11(4):485-496.

[266] Tanaka K, Ogawa K, Sugamura K, Nakamura M, Takano S, Nagata K. Cutting edge: differential production of prostaglandin D_2 by human helper T cell subsets. *J. Immunol.* 2000 Mar 1;164(5):2277-2280.

[267] Gallant MA, Samadfam R, Hackett JA, Antoniou J, Parent J-L, de Brum-Fernandes AJ. Production of prostaglandin D_2 by human osteoblasts and modulation of osteoprotegerin, RANKL, and cellular migration by DP and CRTH2 receptors. *J. Bone Mineral Res.* 2005 Apr;20(4):672-681.

[268] Jowsey IR, Murdock PR, Moore GBT, Murphy GJ, Smith SA, Hayes JD. Prostaglandin D_2 synthase enzymes and PPARγ are co-expressed in mouse 3T3-L1 adipocytes and human tissues. *Prostaglandins Other Lipid Mediators* 2003 Jan;70(3-4):267-284.

[269] Bochenek G, Niżankowska E, Gielicz A, Świerczyńska M, Szczeklik A. Plasma $9α,11β$-PGF_2, a PGD_2 metabolite, as a sensitive marker of mast cell activation by allergen in bronchial asthma. *Thorax* 2004;59:459-464.

[270] Dahlén S-E, Kumlin M. Monitoring mast cell activation by prostaglandin D_2 in vivo. *Thorax* 2004;59:453–455.

[271] Morrow JD, Guzzo C, Lazarus G, Oates JA, Roberts II LJ. Improved diagnosis of mastocytosis by measurement of the major urinary metabolite of prostaglandin D_2. *J. Invest. Dermatol.* 1995;104:937-940.

[272] Suzuki F, Hayashi H, Hayaishi O. Transport of prostaglandin D_2 into brain. *Brain Res.* 1986 Oct;385(2):321-328.

[273] Maclouf J, Corvazier E, Wang ZY. Development of a radioimmunoassay for prostaglandin D2 using an antiserum against 11-methoxime prostaglandin D_2. *Prostaglandins* 1986 Jan;31(1):123-132.

[274] Schuligoi R, Schmidt R, Geisslinger G, Kollroser M, Peskar BA, Heinemann A. PGD2 metabolism in plasma: kinetics and relationship with bioactivity on DP1 and CRTH2 receptors. *Biochem. Pharmacol.* 2007 Jun 30;74(1):107-117.

[275] Haberl C, Hültner L, Flügel A, Falk M, Geuenich S, Wilmanns W, Denzlinger C. Release of prostaglandin D_2 by murine mast cells: importance of metabolite formation for antiproliferative activity. *Mediators Inflamm.* 1998;7:79-84.

[276] Zhang J, Gong Y, Yu Y. PG $F_{2α}$ receptor: a promising therapeutic target for cardiovascular disease. *Frontiers Pharmacol.* 2010 Oct 14;1,article 116:1-7, doi:10.3389/fphar.2010.00116.

[277] Liston TE, Roberts II LJ. Metabolic fate of radiolabeled prostaglandin D_2 in a normal human male volunteer. *J. Biol. Chem.* 1985 Oct 25;260(24):13172-13180.

[278] Kindblom L-G. Factor VIII-related antigen and mast cells. *Acta Pathol. Microbiol. Scand.* 1982 Jul;90A(1-6):437-439.

[279] Akiyama M, Watanabe Y, Nishikawa T. Immunohistochemical characterization of human cutaneous mast cells in urticaria pigmentosa (cutaneous mastocytosis). *Pathol. Int.* 1991 May;41(5):344-349.

[280] Freeman JG, Ryan JJ, Shelburne CP, Bailey DP, Bouton LA, Narasimhachari N, Domen J, Siméon N, Couderc F, Stewart JK. Catecholamines in murine bone marrow derived mast cells. *J. Neuroimmunol.* 2001 Oct;119(2):231-238.

[281] Gordon JR, Galli SJ. Mast cells as a source of both preformed and immunologically inducible TNF-α/cachectin. *Nature* 1990 Jul 19;346:274-276.

[282] Echtenacher B, Männel DA, Hültner L. Critical protective role of mast cells in a model of acute septic peritonitis. *Nature* 1996 May 2;381:75-77.

[283] Kaartinen M, Penttila A, Kovanen PT. Mast cells in rupture-prone areas of human coronary atheromas produce and store TNF-α. *Circulation* 1996;94:2787-2792.

[284] Suto H, Nakae S, Kakurai M, Sedgwick JD, Tsai M, Galli SJ. Mast cell-associated TNF promotes dendritic cell migration. *J. Immunol.* 2006;176:4102-4112.

[285] Nakae S, Suto H, Kakurai M, Sedgwick JD, Tsai M, Galli SJ. Mast cells enhance T cell activation: importance of mast cell-derived TNF. *Proc. Natl. Acad. Sci. USA* 2005 May 3;102(18):6467-6472.

[286] Bradding P, Mediwake R, Feather IH, Madden J, Church MK, Holgate ST, Howarth PH. TNF α is localized to nasal mucosal mast cells and is released in acute allergic rhinitis. *Clin. Exper. Allergy* 1995 May;25(5):406-415.

[287] Walsh LJ, Trinchieri G, Waldorf HA, Whitaker D, Murphy GF. Human dermal mast cells contain and release tumor necrosis factor α, which induces endothelial leukocyte adhesion molecule 1. *Proc. Natl. Acad. Sci. USA* 1991 May;88:4220-4224.

[288] Nakae S, Ho LH, Yu M, Monteforte R, Iikura M, Suto H, Galli SJ. Mast cell-derived TNF contributes to airway hyperreactivity, inflammation, and T_H2 cytokine production in an asthma model in mice. *J. Allergy Clin. Immunol.* 2007 Jul;120(1):48-55.

[289] Raithel M, Zopf Y, Kimpel S, Naegel A, Molderings GJ, Buchwald F, Schultis HW, Kressel J, Hahn EG, Konturek. The measurement of leukotrienes in urine as diagnostic option for systemic mastocytosis. *J. Physiol. Pharmacol.* 2011;62(4):469-472.

[290] Sampson AP, Castling DP, Green CP, Price JF. Persistent increase in plasma and urinary leukotreines after acute asthma. *Arch. Dis. Childhood* 1995;73:221-225.

[291] Brightling CE, Bradding P. The re-emergence of the mast cell as a pivotal cell in asthma pathogenesis. *Curr. Allergy Asthma Reports* 2005;5:130-135.

[292] Tanaka S, Tanaka H, Abe S. High dose of inhaled fluticasone reduces high levels of urinary leukotriene E4 in the early morning in mild and moderate nocturnal asthma. *Chest* 2003 Nov;124(5):1768-1773.

[293] Leukotriene B4. Human metabolome database, version 2.5, http://www.hmdb.ca/metabolites/HMDB01085, accessed December 16, 2012.

[294] Akhavein A, Patel NR, Muniyappa PK, Glover SC. Allergic mastocytic gastroenteritis and colitis: an unexplained etiology in chronic abdominal pain and gastrointestinal dysmotility. *Gastroenterol. Res. Pract.* 2012, article ID 950582, doi:10.1155/2012/950582.

[295] Dent, J, El-Serag, HB, Wallander, MA, Johansson, S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54:710-717.

[296] Talley NJ. Functional gastrointestinal disorders as a public health problem. *Neuro-gastroenterol. Motil.* 2008;20(suppl 1):121-129.

[297] Inadomi, JM, McIntyre, L, Bernard, L, Fendrick, AM. Step-down from multiple- to single-dose proton pump inhibitors (PPIs): a prospective study of patients with

heartburn or acid regurgitation completely relieved with PPIs. *Am. J. Gastroenterol.* 2003; 98:1940-1944.

[298] Carlsson, R, Dent, J, Watts, R, et al. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. International GORD Study Group. *Eur. J. Gastroenterol. Hepatol.* 1998; 10:119-124.

[299] Crawley, JA, Schmitt, CM. How satisfied are chronic heartburn sufferers with their prescription medications? Results of the patient unmet needs study. *J. Clin. Outcomes Manag.* 2000; 7:29-34.

[300] Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. *Gut* 2009;58:295-309.

[301] Nakajima S, Krishnan B, Ota H, Segura AM, Hattori T, Graham DY, Genta RM. Mast cell involvement in gastritis with or without Helicobacter pylori infection. *Gastroenterol.* 1997 Sep;113(3):746-754.

[302] Yamamoto J, Watanabe S, Hirose M, Osada T, Ra C, Sato N. Role of mast cells as a trigger of inflammation in Helicobacter pylori infection. *J. Physiol. Pharmacol.* 1999 Mar;50(1):17-23.

[303] Bamba N, Nakajima S, Andoh A, Bamba M, Sugihara H, Bamba T, Hattori T. Stem cell factor expressed in human gastric mucosa in relation to mast cell increase in Helicobacter pylori-infected gastritis. *Digest Disease Sci.* 2002 Feb;47(2):274-282.

[304] Hall W, Buckley M, Crotty P, O'Morain CA. Gastric mucosal mast cells are increased in *Helicobacter pylori*-negative functional dyspepsia. *Clin. Gastroenterol. Hepatol.* 2003 Sep;1(5):363-369.

[305] Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N. Engl. J. Med.* 2002;346:1699-1705.

[306] Kristensen T, Broesby-Olsen S, Vestergaard H, Bindslev-Jensen C, Møller MB. Circulating *KIT*D816V mutation-positive non-mast cells in peripheral blood are characteristic of indolent systemic mastocytosis. *Eur. J. Haematol.* 2012 (in press), doi:10.1111/j.1600-0609.2012.01789.x

[307] Molderings GJ, Kolck U, Scheurlen C, Brüss M, Frieling T, Raithel M, Homann J. Systemic mast cell disease with gastrointestinal symptoms - a diagnostic questionnaire. *Dtsch. Med. Wochenschr.* 2006;131:2095-2100.

[308] Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. *Blood* 2010 Dec 23;116(26):5812-5817.

[309] Rotolo A, Familiari U, Nicoli P, Cilloni D, Saglio G, Guerrasio A. Chapter 18: Systemic mastocytosis: an intriguing disorder. In: Lawrie CH, ed., *Hematology – Science and Practice*, InTech, Rijeka, Croatia, 2012, pp. 467-486.

[310] Thomas PS, Schreck RE, Lazarus SC. Tobacco smoke releases preformed mediators from canine mast cells and modulates prostaglandin production. *Am. J. Physiol.* 1992 Jul;263(1 Pt 1):L67-72.

[311] Walter A, Walter S. Mast cell density in isolated monkey lungs on exposure to cigarette smoke. *Thorax* Sep 1982;37(9):699-702.

[312] Small-Howard A, Turner H. Exposure to tobacco-derived materials induces overproduction of secreted proteinases in mast cells. *Toxicol Applied Pharmacol* 2005 Apr 15;204(2):152-163.

[313] Mortaz E, Redegeld FA, Sarir H, Karimi K, Raats D, Nijkamp FP, Folkerts G. Cigarette smoke stimulates the production of chemokines in mast cells. *J. Leukocyte Biol.* 2008 Mar;83(3):575-580.

[314] Bidri M, Royer B, Averlant G, Bismuth G, Guillosson J-J, Arock M. Inhibition of mouse mast cell proliferation and proinflammatory mediator release by benzodiazepines. *Immunopharmacol.* 1999 Jun;43(1):75-86.

[315] Homann J, Kolck UW, Ehnes A, Frieling T, Raithel M, Molderings GJ. Die systemische Mastozytose – Standortbestimmung einer internistischen Erkrankung. *Medizinische Klinik* 2010;105(8):544-553.

[316] Meis K, Spitzlei P, von Kügelgen I, Molderings GJ. Investigation on the molecular mechanisms mediating the inhibitory effect of benzodiazepines on mast cells. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 2009;379 (Suppl. 1):R43.

[317] Xifro RA, Hoffmann K, Meis K, Spitzlei P, Molderings GJ, von Kügelgen I. Evidence for the involvement of peripheral-type benzodiazepine receptors in the inhibitory effcet of diazepam, flunitrazepam and 4-chlorodiazepam on the interleukin-8 production in human mast cells. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 2010;381(suppl 1):R40.

[318] Haenisch B, Huber M, Wilhelm T, Molderings GJ. Molecular-genetic investigations on the mechanisms mediating the inhibitory effect of benzodiazepines on mast cells. *Naunyn-Schmiedeberg's Arch. Pharamcol.* 2012;385(suppl 1):S60.

[319] Skoutakis VA. Comparison of the parenteral histamine2-receptor antagonists. *Ann. Pharmacother.* 1989 Oct 1;23(10):17-22.

[320] Rendiæ S. Drug interactions of H_2-receptor antagonists involving cytochrome P450 (CYPs) enzymes: from the laboratory to the clinic. *Croat. Med. J.* 1999 Mar;40(3): 357-367.

[321] Bourdet DL, Pritchard JB, Thakker DR. Differential substrate and inhibitory activities of ranitidine and famotidine toward human organic cation transporter 1 (hOCT1; SLC22A1), hOCT2 (SLC22A2), and hOCT3 (SLC22A3). *J. Pharmacol. Exper. Therapeut.* 2005 Dec;315(3):1288-1297.

[322] Roberts LJ, Anthony LB, Oates JA. Disorders of vasodilator hormones: carcinoid syndrome and mastocytosis. In: Wilson JD, Foster DW, Kronenberg HM, et al., eds., *Williams Textbook of Endocrinology, 9th ed.* Philadelphia: W. B. Saunders Company, 1998, p. 1718-1732.

[323] O'Sullivan S, Dahlén B, Dahlén S-E, Kumlin M. Increased urinary excretion of the prostaglandin D_2 metabolite $9\alpha,11\beta$-prostaglandin F_2 after aspirin challenge supports mast cell activation in aspirin-induced airway obstruction. *J. Allergy Clin. Immunol.* 1996 Aug;98(2):421-432.

[324] Butterfield JH, Schwenk NM, Colville DS, Kuipers BJ. Severe generalized reactions to ibuprofen: report of a case. *J. Rheumatol.* 1986 Jun;13(3);649-650.

[325] Butterfield JH, Kao PC, Klee GG, Yocum MW. Aspirin idiosyncrasy in systemic mast cell disease: a new look at mediator release during aspirin desensitization. *Mayo Clin. Proc.* 1995 May;70(5):481-487.

[326] Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *New Engl. J. Med.* 2005;352:1071-1080.

[327] Yang Y, Lu JY, Wu X, Summer S, Whoriskey J, Saris C, Reagan JD. G-protein-coupled receptor 35 is a target of the asthma drugs cromolyn disodium and nedocromil sodium. *Pharmacol.* 2010;86:1-5.

[328] Larson AJ, Symons JD, Jalili T. *Pharmaceuticals* 2010;3:237-250, doi:10.3390/ph3010237.

[329] Hayashi A, Gillen AC, Lott JR. Effects of daily oral administration of quercetin chalcone and modified citrus pectin on implanted colon-25 tumor growth in Balb-c mice. *Altern. Med. Rev.* 2000;5(6):546-552.

[330] Lamson DW, Brignall MS. Antioxidant and cancer III: quercetin. *Altern. Med. Rev.* 2000;5:196-208.

[331] Ferry DR, Smith A, Malkhandi J, Fyfe DW, deTakats PG, Anderson D, Baker J, Kerr DJ. Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for in vivo tyrosine kinase inhibition. *Clin. Cancer Res.* 1996;2:659-68.

[332] Kalogeromitros D, Makris M, Chliva C, Aggelides X, Kempuraj D, Theoharides TC. A quercetin containing supplement reduces niacin-induced flush in humans. *Int. J. Immunopathol. Pharmacol.* 2008;21(3):509-514.

[333] Molderings GJ, Raithel M, Kratz F, Azemar M, Haenisch B, Harzer S, Homann J. Omalizumab treatment of systemic mast cell activation disease: experiences from four cases. *Int. Med.* 2011;50:611-615.

[334] Bell MC, Jackson DJ. Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab. *Ann. Allergy Asthma Immunol.* 2012 May;108(5):383-384.

[335] Okayama Y, Kawakami T. Development, migration, and survival of mast cells. *Immunol. Res.* 2006;34(2):97-115.

[336] Scott MJ, Godshall CJ, Cheadle WG. Jaks, STATs, cytokines, and sepsis. *Clin. Vaccine Immunol.* 2002 Nov;9(6):1153-1159.

[337] Vega-Ruiz A, Cortes JE, Sever M, Manshouri T, Quintas-Cardama A, Luthra R, Kantarjian HM, Verstovsek S. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. *Leukemia Res.* 2009 Nov;33(11):1481-1484.

[338] Ustun C, DeRemer DL, Akin C. Tyrosine kinase inhibitors in the treatment of systemic mastocytosis. *Leukemia Res.* 2011 Sep;35(9):1143-1152.

[339] Verstovsek S, Tefferi A, Cortes J, O'Brien S, Garcia-Manero G, Pardanani A, Akin C, Faderl S, Manshouri T, Thomas D, Kantarjian H. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. *Clin. Cancer Res.* 2008 Jun 15;14:3906-3915.

[340] Laroche M, Livideanu C, Paul C, Cantagrel A. Interferon alpha and pamidronate in osteoporosis with fracture secondary to mastocytosis. *Am. J. Med.* 2011 Aug; 124(8): 776-778.

[341] Kiladjian J-J, Mesa RA, Hoffman R. The renaissance of interferon therapy for the treatment of myeloid malignancies. *Blood* 2011 May 5;117(18):4706-4715.

[342] Lim KH, Pardanani A, Butterfield JH, Li C-Y, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, imatinib mesylate or 2-chlorodeoxyadenosine. *Am. J. Hematol.* 84(12):790-794.

[343] Baur DM, von Werder A, Brockow K, Schmid RM, Weidenbach H. Severe secondary osteoporosis in a patient with systemic mastocytosis stabilized by therapy with low-

dose pegylated interferon alpha. Eur Congress Endocrinol 2008, *Endocrine Abstracts* 2008;16:P114.

[344] Saban N, Bujak M. Hydroxyurea and hydroxamic acid derivatives as antitumor drugs. *Cancer Chemother. Pharmacol.* 2009;64:213-221.

[345] Finazzi G, Barbui T. Hydroxyurea: the comparator in studies with the new anti-JAK2 inhibitors. *Hematol. Meeting Reports* 2009;3(3):108-114.

[346] Navarra P, Preziosi P. Hydroxyurea: new insights on an old drug. *Crit. Rev. Oncol/Hematol.* 1999 Feb;29(3):249-255.

[347] Ohnishi K. Oral antitumor drugs for hematological malignancies. *Gan To Kagaku Ryoho* 1999 Feb;26(3):295-300.

[348] Ware RE, Aygun B. Advances in the use of hydroxyurea. *Amer. Soc. Hematol. Education Book* 2009, pp. 62-69.

[349] Quintás-Cardama A, Jain N, Verstovsek S. Advances and controversies in the diagnosis, pathogenesis, and treatment of systemic mastocytosis. *Cancer* 2011 Dec 15;117(24):5439-5449.

[350] Nakamura R, Chakrabarti S, Akin C, Robyn J, Bahceci E, Greene A, Childs R, Dunbar CE, Metcalfe DD, Barrett AJ. A pilot study of nonmyeloablative allogeneic hematopoietic stem cell transplant for advanced systemic mastocytosis. *Bone Marrow Transpl.* 2006;37:353-358.

[351] Hennessy B, Giles F, Cortes J, O'Brien S, Ferrajoli A, Ossa G, Garcia-Manero G, Faderl S, Kantarjian H, Verstovsek S. *Am. J. Hematol.* 2004;77:209-214.

[352] Grubb BP. Postural tachycardia syndrome. *Circulation* 2008;117:2814-2817.

[353] Kanjwal Y, Kosinski D, Grubb BP. The postural orthostatic tachycardia syndrome: definitions, diagnosis, and management. *Pacing Clin. Electrophysiol.* 2003 Aug;26(8):1747-1757.

[354] Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008 Feb;63(2):226-232.

[355] Slee VM. Emergency room protocol: a handy reference guide to provide everything you need for emergency room visits as a patient with a mast cell disorder. Website of The Mastocytosis Society, 2010, available at http://www.tmsforacure.org/documents/ ER_Protocol.pdf, accessed May 12, 2012.

[356] Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment: sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. *Gastroenterol.* 2007 Oct;133(4):1342-1363.

[357] Spergel JM, Andrews T, Browne-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann. Allergy Asthma Immunol.* 2005 Oct;95(4):336-343.

[358] Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, Melin-Aldana H, Li BUK. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin. Gastroenterol. Hepatol.* 2006;4:1097-1102.

[359] Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? *Clin. Gastroenterol. Hepatol.* 2004;2:523-530.

[360] Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Rev. Immunol.* 2011 Sep;11:607-615.

[361] Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *J. Appl. Physiol.* 2005 Apr 1;98(4):1154-1162.

[362] Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. *Clinica Chim. Acta* 2010 Jun 3;411(11-12):785-793.

[363] Hansen CJ, Stevens LC, Coast JR. Exercise duration and mood state: how much is enough to feel better? *Health Psychol.* 2001;20(4):267-275.

[364] Backhouse SH, Ekkekakis P, Biddle SJ, Ekkekakis P, Foskett A, Williams C. Exercise makes people feel better but people are inactive: paradox or artifact? *J. Sport Exercise Psychol.* 2007 Aug;29(4):498-517.

[365] Ekkekakis P, Lind E. Exercise does not feel the same when you are overweight: the impact of self-selected and imposed intensity on affect and exertion. *Int. J. Obesity* 2006; 30:652-660.

[366] Maruotti N, Crivellato E, Cantatore FP, Vacca A, Ribatti D. *Clin. Rheumatol.* 2007; 26:1-4.

[367] Garza LA, Liu Y, Yang Z, Alagesan B, Lawson JA, Norberg SM, Loy DE, Zhao T, Blatt HB, Stanton DC, Carrasco L, Ahluwalia G, Fischer SM, FitzGerald GA, Cotsarelis G. Prostaglandin D2 inhibits hair growth and is elevated in bald scalp of men with androgenetic alopecia. *Sci. Transl. Med.* 2012 Mar 21;4(126):126ra34, doi: 10.1126/scitranslmed.3003122.

[368] Valent P, Bain BJ, Bennett JM, Wimazal F, Sperr WR, Mufti G, Horny H-P. Idiopathic cytopenia of undetermined significance (ICUS) and idiopathic dysplasia of uncertain significance (IDUS), and their distinction from low risk MDS. *Leukemia Res.* 2012 Jan;36(1):1-5.

[369] Halfdanarson TR, Kumar N, Li C-Y, Phyliky RL, Hogan WJ. Hematological manifestations of copper deficiency: a retrospective review. *Eur. J. Haematol.* 2008 Jun;80(6):523-531.

[370] Cardet J-C, Castells MC, Hamilton MJ. Immunology and clinical manifestations of non-clonal mast cell activation syndrome. *Curr. Allergy Asthma Rep.* 2012 ahead of print, doi:10.1007/s11882-012-0326-8.

[371] Renné T, Schmaier AH, Nickel KF, Blombäck M, Maas C. In vivo roles of factor XII. *Blood* 2012 Nov 22;120(22):4296-4303.

[372] Kushnir-Sukhov N, Brown J, Wu Y, Kirshenbaum A, Metcalfe D. Serotonin synthesis, storage and transport in human mast cells. *Clin. Immunol.* 2006;119:S53, doi:10.1016/j.clim.2006.04.048.

[373] Schulman ES, Nishi H, Jameson BA. Cultivated human lung mast cells express multiple serotonin receptors. *J. Allergy Clin. Immunol.* 2005 Feb;115(2):S187.

[374] Grosser T, Fries S, Lawson JA, Kapoor SC, Grant GR, FitzGerald GA. Drug resistance and pseudoresistance: an unintended consequence of enteric coating aspirin. *Circ.* 2012 ahead of print, doi:10.1161/CIRCULATIONAHA.112.117283.

[375] Butterfield JH. Survey of aspirin administration in systemic mastocytosis. *Prostaglandins Other Lipid Mediators* 2009;88:122-124.