

A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone

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Summary It has long been recognized that the symptom complex of fibromyalgia can be seen with hypothyroidism. Hypothyroidism may be categorized, like diabetes, into type I (hormone deficient) and type II (hormone resistant). Most cases of fibromyalgia fall into the latter category. The syndrome is reversible with treatment, and is usually of late onset. It is likely more often acquired than due to mutated receptors. Now that there is evidence to support the hypothesis that fibromyalgia may be due to thyroid hormone resistance, four major questions appear addressable. First, can a simple biomarker be found to help diagnose it? Second, what other syndromes similar to Fibromyalgia may share a thyroid-resistant nature? Third, in non-genetic cases, how is resistance acquired? Fourth, what other methods of treatment become available through this new understanding?

Preliminary evidence suggests that serum hyaluronic acid is a simple, inexpensive, sensitive, and specific test that identifies fibromyalgia. Overlapping symptom complexes suggest that chronic fatigue syndrome, Gulf war syndrome, premenstrual syndrome, post traumatic stress disorder, breast implant silicone sensitivity syndrome, bipolar affective disorder, systemic candidiasis, myofascial pain syndrome, and idiopathic environmental intolerance are similar enough to fibromyalgia to merit investigation for possible thyroid resistance. Acquired resistance may be due most often to a recently recognized chronic consumptive coagulopathy, which itself may be most often associated with chronic infections with mycoplasmas and related microbes or parasites. Other precipitants of thyroid resistance may use this or other paths as well. In addition to experimentally proven treatment with supraphysiologic doses of thyroid hormone, the thyroid-resistant disorders might be treatable with anti-hypercoagulant, anti-infective, insulin-sensitizing, and hyaluronolytic strategies.

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INTRODUCTION

Fibromyalgia (FMS) and chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome (CFIDS), are syndromes whose overlapping symptoms have been extensively discussed. Other clinical entities that have extensive symptom overlap with

these two syndromes include Gulf war syndrome/illness (GWI/GWS), premenstrual syndrome (PMS), post traumatic stress disorder (PTSD), breast implant silicone sensitivity syndrome (BISSS), bipolar affective disorder (BAD), systemic candidiasis (SC), myofascial pain syndrome (MPS), and idiopathic environmental intolerance (IEI). IEI includes and replaces the three obsolete terms multiple chemical sensitivity syndrome (MCS), electromagnetic field sensitivity (EMS), and seismic flu syndrome (SFS). We will furnish a rationale for eliminating all the above nomenclature and replacing the names of these syndromes with the unifying term chronic metabolic debilitation syndrome (CMDS).

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CMDS would thereby be characterized as a debilitating condition associated with widespread musculoskeletal pain, immune dysfunction, neurotransmitter dysfunction, joint stiffness, fatigue, gastrointestinal and urinary distress, cognitive dysfunction and other neurological symptoms. Critical to the understanding of (indeed, the very definitions of) these symptoms is that none of the previously designated syndromes has a pathognomonic set of findings. FMS comes the closest to having a strict definition, with its 1990 ACR criteria (1) enabling the clinician to make the diagnosis as a rule-in, rather than rule-out diagnosis of exclusion. However, the 1990 criteria are estimated to have only 90% sensitivity and specificity. Each of these other syndromes has an even poorer definition, and they all have extensive symptom overlap with each other. The clinician who works extensively in this area may be forgiven for ultimately regarding all of these patients as belonging to a continuum of a singular clinical entity, with findings drawn almost at random from the constellation of possibilities described for each component syndrome. Currently, the net prevalence of this disorder is at least 2% of the population, (2) (the agreed prevalence of FMS) involving at least seven million Americans. At least 90% of diagnosed cases are women. The majority are white and between the ages of 25 and 45.

Evidence exists that most cases of FMS are associated with difficulties in thyroid production (3,4) or utilization (5–8). Previous authors have documented the similar appearance of FMS and hypothyroidism (9–18). Finally, authors working outside the field of FMS have hypothesized for decades the likely existence of a common syndrome of peripheral thyroid hormone resistance (19–21) and have even reported an incontrovertible case (22). Those cases of FMS that are related to low production can be easily identified by thyroid stimulating hormone (TSH) screening and treated appropriately. Such patients respond readily to treatment, and no labels such as FMS become attached to such patients. Therefore, the vast majority of patients who have an unrecognized hypothyroid problem, and who on that basis are labeled as having FMS, have disorders of thyroid utilization. On the basis of symptom overlap, we hypothesize that the other syndromes named above share this etiologic characteristic. We contend that within any of these syndromes, those individual patients that are resistant to thyroid hormone can be easily identified and treated. The majority of patients formerly in any of these groups, according to our hypotheses, can therefore be redesignated to have ‘type II hypothyroidism.’

We hypothesize that a small number of patients in the above syndromes will be confirmed not to be either thyroid deficient or thyroid resistant. Should that be confirmed, these residual patients with non-thyroidal

CMDS would have in effect a new ‘diagnosis of exclusion.’ A unifying pathophysiologic hypothesis would then be needed that could explain why these patients, even in their diversity, have so much in common. Even after elimination of cases of thyroid resistance (about 90% of the total) from this group, the prevalence of the ‘new’ diagnosis of exclusion would be approximately 0.2%, or about 700 000 cases. Even after removal of thyroid-related cases, this would still be a common disorder.

PATHOPHYSIOLOGIC MECHANISMS

Thyroid hormone regulation of gene transcription

Perhaps the earliest modern attempt to ascribe an etiology to CMDS was that of Ord, who in 1877 described thyroid gland sclerosis among autopsy findings and hypothesized that this disorder was due to thyroid insufficiency. Hertoghe, in 1899, reported successful treatment of the syndrome with thyroid gland extracts, and before the era of serum thyroid hormone testing, this treatment became widespread, popularized particularly by Barnes (5). Modern work along this line has been dominated by Lowe, who made three specific critical contributions. First, he hypothesized mutated thyroid receptors as a source of thyroid resistance (23). Second, he documented in FMS an extraordinarily high (53%) prevalence of abnormal thyrotropin releasing hormone (TRH) stimulation tests. Third, using supraphysiologic dosing with thyroid hormone, (triiodothyronine, T3), he executed the first two blinded randomized controlled clinical trials that succeeded in showing substantial benefit for FMS for any kind of treatment. Lowe’s hypothesis of thyroid resistance grew out of efforts to reconcile the clinical disparity between the strikingly hypothyroid appearance of these patients with their normal serum thyroid hormone levels. Thus Lowe brought the thinking of Ord, Hertoghe, Barnes, and Albright forward to the turn of this century.

An appropriate nomenclature for this phenomenon is needed. Diabetes mellitus serves as an example of rational nomenclature, where insulin deficiency is said to be type I diabetes, and insulin resistance is said to be type II diabetes. Following that pattern, most cases of CMDS with a thyroid component would involve type II hypothyroidism, with only a few involving type I, thyroid-hormone-deficient hypothyroidism. This nomenclature is preferable to the inscrutable terminology of pseudohypoparathyroidism and pseudopseudohypoparathyroidism to express the analogous situation with parathyroid hormone resistance.

Further significant work in this area was advanced by Yaron, who found extremely elevated serum levels of

hyaluronic acid (HA) in FMS (24). This study has been replicated (25). This is important because HA is under the direct stimulatory control of fibronectin, whose transcription and expression is in turn inhibited by thyroid hormone. Lack of thyroid hormone effect leads to failed inhibition of fibronectin transcription, resulting in high levels of HA. High levels of HA have already been documented in all other known examples of lack of thyroid hormone effect. It is a recent biomarker of choice in research work involving investigation of intracellular thyroid hormone function (26–29). HA may be a reliable T3 treatment biomarker in FMS, and may be a common diagnostic and treatment biomarker in the other component syndromes of CMDS. Further, HA could be the test that distinguishes type II hypothyroidism from non-thyroidal CMDS.

Nothing in the above, with the exception of the suggestion that there may be genetic factors with thyroid receptors, speculates on why patients with CMDS should be thyroid-resistant. Among other things, we will propose a plausible mechanism, with special reference to the relationships between chronic infection, initiation of the coagulation cascade, the appearance of the euthyroid sick syndrome (ESS), and subsequent interference with capillary circulation by HA-mediated excessive thickness of the glycocalyx.

Excessive hyaluronic acid synthesis

HA has long been recognized to have important function in cartilage and in the extracellular matrix. Recent work has indicated that it is also a dominant functional constituent of the vascular endothelial glycocalyx (30–32). This glycocalyx has been likened to a 'pile carpet' extending from the endothelial cell surface into the lumen. While its existence has been known for years, newer in vivo techniques of observation have led to a better appreciation of its extent and of its importance. Among other things, this glycocalyx significantly reduces the effective lumen diameter of capillaries. It also forms a two-way barrier to diffusion of certain (especially large and especially negatively charged) molecules, and shields from expression a number of surface antigens and receptors. With regard to the latter function, injury to the glycocalyx exposes a variety of normally-latent antigens and receptors and initiates a number of reactions associated with endothelial injury. The glycocalyx barrier consists largely of a matted meshwork of cross-linked HA. HA appears to be continuously synthesized on the interior surface of the plasma membrane and extruded through the membrane into the glycocalyx. Therefore, the thickness, and therefore the permeability, of the glycocalyx is to a large extent influenced by the balance of the rates of HA synthesis and removal.

The rate of synthesis of HA is, as has been noted earlier, largely under the inhibitory control of T3. Decreased T3 effect leads to a faster rate of synthesis of HA. From this we hypothesize a thicker, less permeable glycocalyx, and a smaller effective capillary lumen diameter. If this is the case, poor cellular nutrition/respiration would likely result, and indeed biomarkers of such poor respiration have been demonstrated, such as elevations in lactate. Furthermore, we hypothesize that excessive thickness of glycocalyx is a contributing factor to the polyhormonal resistance seen in FMS, as ordinarily-exposed cell surface receptors become submerged and concealed.

The rate of removal of HA may have a two-fold mechanism. First, circulating hyaluronidase digests the HA matrix, freeing various-molecular-weight polymers. These polymers are removed to lymph nodes and to liver sinusoids for digestion to low molecular weight products including lactate and acetate. Second, circulating white blood cells, themselves about the size of the capillary lumen, may 'shear' or 'scrub' the surface of the glycocalyx, fracturing off bits of the HA matrix as they pass.

While definite experimental evidence shows that increases in HA production are likely in FMS, no evidence has been sought concerning changes in rates of removal. Known disorders of HA removal, such as disease of the hepatic sinusoids, result in relatively modest increases in serum HA that are far smaller than the increases seen with FMS. Consequently, the increases seen in serum HA in FMS are likely predominantly from increased production and less so from decreased removal.

We hypothesize that treatment with hyaluronidase will be effective in reducing excessive glycocalyx and in relieving the symptoms of FMS. Results of a blinded, N-of-1 case are supportive (33).

Chronic infection, especially with mycoplasmas and rickettsias

According to Nicolson (34–41), over 100 000 veterans of the Persian Gulf War in 1991 have been found to have GWS, not including immediate family members. Although a US Senate committee study was incomplete, investigators found after surveying approximately 1200 GWI families that 77% of spouses and a majority of children born after the war had the signs and symptoms of GWS. This by itself suggests an infectious etiology. Nicolson has also found chronic active infection by plausible organisms, mycoplasmas (42) and others, in approximately half of those surveyed. Because of reliance on DNA probes and other hyper-specific technologies, his methodology eliminates the false positives of other methods but will underestimate the true numbers of patients with chronic infection. Successful treatment

with anti-biotic regimens directed against these pathogens has been described.

Jadin has described a micro-agglutination method that identifies *Rickettsia* and related genera (*erlichia*, *orientia*, *coxiella*, *chlamydia*) with a much higher prevalence than controls in patients in South Africa and Australia. Antibiotic regimens directed at this finding have also been shown to be effective in relieving the symptoms of CMDS (43).

While this area of research has far-reaching implications, it has not been very well tied in with the thyroid hypothesis, and accounts for just over half of patients surveyed. We will tie this work to the lineage of Ord, Hertoghe, Barnes, Lowe, and Yaron, principally by considering the link between infection and initiation of the coagulation cascade.

Chronic consumptive coagulopathy (CCC)

The severe, acute version of disseminated intravascular coagulation (DIC) is a familiar killer in the context of the Intensive Care Unit (44,45). Generally precipitated by tissue necrosis, foreign body, missed abortion, amniotic fluid embolism, or overwhelming sepsis (usually with gram-negative organisms), this clinical entity has a mortality rate of about 80%. In all such cases the only hope for successful treatment is to identify the underlying cause and to eliminate it, after which the coagulopathy tends to take care of itself.

On the other hand, a non-lethal chronic consumptive coagulopathy that differs from DIC is seen in CMDS. Early data suggest that over half of these patients may have at least two of the following: elevated fibrinogen, elevated thrombin/antithrombin complexes, elevated fibrin fragments I and II, elevated soluble fibrin monomer, or hyperactivated platelet aggregation (46). Anecdotal reports and a pilot trial claim improvements in patient status after the use of standard mini-dose heparin and low-dose coumadin.

Of the various precipitants of DIC, particular attention is drawn to gram-negative sepsis and to pathologies of parturition. With regard to CMDS, a very large number of cases have well-documented onset either in a post-infectious or post-partum time-frame. Is this because there is increased susceptibility to activation of the coagulation cascade at those times? We hypothesize exactly that.

Toxins

We have seen cases of sudden-onset CMDS temporally associated with acute exposure to toxins of two types. These are the organic solvents and the acetyl-cholinesterase inhibitors. Common clinical settings for such exposures include industrial exposures and general

anesthetic agents. Direct causal relationships are difficult to assess, due to the usual swift course of elimination of these toxins from the patient. In such cases pathophysiological positive feedback loops may possibly persist long after elimination of the toxic trigger. We have not seen cases that are clearly associated with heavy metal poisoning, but suspect that these may occur. In the absence of evidence of a persistent toxin, a clinical history of sudden onset after acute exposure raises the possibility that a toxic factor is at work. We will propose a connection with the above-mentioned factors.

Trauma

FMS has long been appreciated to exacerbate following cervical flexion-extension injury, childbirth, general anesthetic, and overwhelming psychological trauma, most prominently including rape. Because general anesthetics are often associated with repair of major mechanical trauma, the respective role of each may be difficult to clarify.

Multiple hormone resistance

It has been mentioned previously that thickened glyco-calyx from excessive HA production could lead to multiple hormonal resistances. Anecdotally, type II diabetes mellitus seems overly prevalent in the FMS population. In addition, two syndromes of polyhormonal resistance have been previously described, and both seem over-represented among FMS patients. These are polycystic ovary syndrome (PCOS) and pseudopseudohypoparathyroidism (PPHP). These respectively primarily involve multiple resistances to gonadal and calcium metabolic hormones, but both may involve other hormonal systems as well. PCOS, for example, prominently involves insulin resistance. Recently it has been strikingly shown that treatment of the insulin resistance with metformin, inositol, or thiazolidinediones most often leads to resumption of ovulation, implying lysis of the gonadal hormone resistance. While this may be a direct action of these antidiabetic drugs, it is also possible that relief of one hormonal resistance cascades into relief of others. Anecdotally we have noted that in FMS patients who also are diabetic, treatment of either the diabetes or the FMS leads to improvement in both glycemic control and FMS symptoms. Therefore, we surmise that hormone resistances demonstrate a tendency toward cascading and producing a 'domino effect' of other resistances.

Biomarkers

In addition to the potentially clinically useful HA, there are many other biomarkers for FMS (47–52), and al-

though none of these others is presently clinically useful, taken together they represent fertile ground for discovering other aspects of the molecular basis of CMDS.

SYNTHESIS OF A NEW, MORE INCLUSIVE HYPOTHESIS

The most straightforward, and probably the most common, example of the interactions that occur among the above pathophysiologic mechanisms is the following five-step sequence:

1. infection by an indolent infectious agent, followed by
2. the initiation and maintenance of a chronic coagulopathy, followed by
3. perpetual stimulation of thyroid resistance, followed by
4. numerous hypometabolic manifestations including interference with capillary diffusion, followed by
5. development of multiple hormonal resistances.

However, many other possible combinations are possible. While it appears that CCC and type II hypothyroidism are high-prevalence final common pathways for producing symptoms, it is by no means certain that they must be present. In fact, early data suggest that about 7% of these patients show no evidence of abnormal thyroid hormone production or utilization. Nor is it apparently mandatory that the triggering event for coagulopathy be infectious. It may be that toxic and traumatic factors act directly on the patient to produce symptoms, or they may trigger CCC and/or type II hypothyroidism.

In the simplest, most common construct, symptoms could be due to the infectious agent itself, to the coagulopathy, or to the resulting type II hypothyroid state. The links in this proposed sequence are all plausible.

For example, DIC is often triggered by infection. Our past experience with this phenomenon has been in the usual context of overwhelming sepsis. Organisms like mycoplasmas, however, are far better known for causing low-grade disease such as 'walking pneumonia.' We hypothesize that in this more indolent situation, the result would be a more low-grade coagulopathy, or as Berg has termed it, 'walking DIC.' Hence, the proposed link whereby chronic infection precipitates chronic coagulopathy is plausible.

In addition, the biological mediators of the physiologic response to shock are known to be capable of initiation of ESS. ESS is well known in the aftermath of surgery or trauma. The leading candidates for the initiator function include, among other things, activation of the clotting cascade. If this is so, an identifiable evolutionary advantage is conferred: in the context of shock, whether from mechanical or psychological trauma,

hemorrhage, or infection, rapid cessation of non-essential functions by the route of thyroid resistance enhances efforts to conserve and direct scarce vital resources to the most essential functions. This correlates with the clinical picture seen in CMDS of preservation of vital function with loss of most or all non-vital functions. Therefore, chronic coagulopathy could logically create an ongoing resistance to thyroid hormone.

Further, the symptoms of CMDS are essentially the same as those known to be associated with thyroid hormone deficiency, as previously noted. Finally, increased thickness of the glycocalyx has been experimentally shown to adversely affect cell membrane permeation. This could be among the mechanisms precipitating polyhormonal resistance.

Therefore, there is good plausibility for the scenario chaining indolent infection to chronic coagulopathy to thyroid resistance to the symptomatic expression of CMDS, to the development of polyhormonal resistance.

TREATMENT IMPLICATIONS

At this point there appear to be five viable, experimentally supported treatment strategies for CMDS. These are anti-infective, anti-hypercoagulant, insulin sensitizing, hyaluronolytic, and thyroid hormonal strategies. These treatments do not appear to be mutually exclusive. It may be that rational therapy should target all five strategies in certain patients.

All five of these treatment modalities may be slow in producing benefits. This raises the necessity of intensive supportive care for these patients while they are attempting to execute whatever plan may have been selected. These supports may be nutritional, or may be physical modalities including manipulation/massage, exercise, and behavior modification.

Anti-infectives

Approximately 75% of patients with CMDS have demonstrable chronic infection with PCR- or microagglutination-provable organisms. While positive tests for infection may be encouraging in the face of treatment that may need to last for a year or longer, these tests may not yet be sensitive enough for general usage. Patients with tuberculosis, for example, are motivated to continue an arduous one-year course of multiple antibiotics based on the certain knowledge that they do indeed have infection present, and it is possible to track antibiotic sensitivities when a growable pathogen is known. In the more difficult case of CMDS, PCR methodologies are expensive, hyperspecific, and non-reimbursable by third party payors. They also cannot illuminate antibiotic sensitivities. Microagglutination testing is not

available in the USA. For now, treatment choices for antibiotics, antivirals, antifungals, antiparasitics, and immune system enhancers may need to be empiric. Experience to date suggests that a cure rate of about 50% can be expected from a one-year course of treatment with four cycles of 12 weeks of azithromycin and doxycycline followed by a week of amoxicillin/clavulanate. Replacement of the azithromycin and doxycycline with ciprofloxacin appears to give similar results. This cure rate appears to be improvable, possibly with triple antibiotic or with longer courses. Jardin, for example, asserts a better cure rate and utilizes both longer courses and more antibiotics.

Anti-hypercoagulation

It is important that this variety of treatment not be confused with anticoagulation. The goal of anticoagulation is to render the clotting system less functional than normal, as manifested in prolongation of prothrombin time, partial thromboplastin time, or bleeding time. This is not the goal of therapy in FMS. In FMS, a chronic coagulopathy is present as a manifestation of a hypercoagulable state. While it is desirable to achieve a normal state of coagulation, it is not desirable to anticoagulate.

Tests of coagulopathy are expensive, but less so than with PCR for evidence of chronic infection. Some third parties reimburse this testing. Therefore, in certain cases, mini-dose anti-hypercoagulation may be on a less empiric footing. For those patients that cannot have that testing done, empiric use of mini-dose heparin at 5000 units or Lovenox at 30 mg twice a day may be acceptable, given the rapidity of symptom relief, the low cost, and the known safety of the regimen. After demonstration of efficacy in an individual case, conversion to coumadin at 1 mg per day may be attempted, though this often fails to yield the same benefit. Perhaps this means that another mechanism of action other than interference with the clotting cascade may be operative in heparin.

Supraphysiologic thyroid hormone administration

Treatment with supraphysiologic doses of thyroid hormone, given that there is no validated biomarker presently available to guide therapy, is tedious and involves significant patient involvement to arrive at the correct dose. It may not be safe in the elderly, in those with significant cardiopulmonary disease, or in those patients unable to cooperate actively in their own dose-finding. Nevertheless, it is the single treatment most likely to produce relief of symptoms, and is the best-studied treatment so far.

The deliberate therapeutic overwhelming of hormone resistance is theoretically objectionable on several grounds. Foremost among these is the idea that while side effects may not be immediately apparent, they are bound to be present, and may be catastrophic. As an example we have the effects of hyperinsulinism, where the resistance to its effects in bringing glucose into the cell may not be mirrored in resistance of the hunger centers in the brain. In such a case, appetite is stimulated at insulin levels that are inadequate to regulate glucose metabolism. As hyperinsulinemia worsens, appetite increases, so that obesity is often the result of using large amounts of insulin in type II diabetes. This demonstrates that a diabetic's tissues are not all resistant to insulin to exactly the same degree. In exactly the same way, it may be feared that tissues not so resistant to thyroid hormone as are most, would become locally hyperthyroid even as the remainder of the body becomes less symptomatic. Of particular concern is bone metabolism, where osteoporosis is a consequence of FMS, but may also be aggravated by the treatment of FMS with supraphysiologic thyroid hormone (53–58).

RECOMMENDATIONS FOR FURTHER STUDY

This hypothesis could drive many investigations on a variety of sub-topics. These would include the previously-mentioned survey of the various 'kinds' of CMDS to see which of them are characterized by elevated serum HA. In addition, we recommend that future clinical trials of CMDS involve investigation of microbial and coagulation status sorted by both the phenotypic expression of symptom presentation, by apparent temporal associations at onset of disease, and by thyroid resistance status. Given the hyperspecificity of the currently available DNA probes for finding offending microbes, we recommend resurrection of the Rife microscope technology of 60 years ago. Rife microscopes, capable of making *in vivo* observations of cells and intracellular pathogens at up to 60 000X, may be much more sensitive for detection of microbial agents than the very specific DNA probe technology. In addition, we recommend direction of darkfield microscopic research to this problem.

If serum HA studies confirm that patients with sudden onset after toxin exposure are biochemically marked, focus should be applied to the issue of which toxins are capable of triggering CMDS, and to the issue of their pathophysiologic mechanisms.

We recommend that trials of guaifenesin should include investigation both of serum HA response and of anticoagulant effect, since its uricosuric effect is not a logical explanation for any clinical utility it may eventually be shown to have.

We recommend comparative trials of different antimicrobial regimens, at least some of which ought to include antivirals, antifungals, and antiparasitics. Given the long term of possible antibiotic treatment that may be indicated in CMDS, we believe that such treatment furnishes fertile and practical ground for studying immune-enhancing strategies. Any salutary effect of an immune-enhancing strategy would be more likely to surface in this context. Given the resistance problem associated with long-term antibiotic administration, we recommend increased attention to a related Rife technology, the frequency generator, as a treatment modality that does not depend on antibiotics.

Given the nature of the slow responses to definitive therapy, we recommend that supportive therapies be investigated to determine which are more helpful in weathering the delay between treatment onset and symptom relief.

We believe we have observed a higher than normal prevalence of peptic ulcer disease (PUD), Crohn's disease (CD), PCOS, DM, and PPHP in the CMDS population. We therefore recommend that epidemiological studies determine whether or not any of these disorders are verified to be of increased prevalence in this group.

We recommend more study of hyaluronidase as a therapeutic option, starting with transdermal preparations. Should this demonstrate efficacy, we recommend that intravenous therapy be studied.

Finally, we recommend that consideration be given to the implications of this hypothesis to cardiovascular disease, particularly with respect to atherosclerosis. This would be a fitting follow up of the work of Barnes in this area. The recent findings of (1) chronic chlamydial infection of atherosclerotic plaque; (2) the hypercoagulable state associated with acute vessel thrombosis; and (3) the accelerated atherogenesis seen with PCOS; makes it appear somehow related to CMDS.

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