

Information from Rich Van Konynenburg, Ph.D. ([richvank@aol.com](mailto:richvank@aol.com))

**It's been about two and a half years since I proposed** the Glutathione Depletion-Methylation Cycle Block hypothesis for the pathogenesis of CFS, and a simplified **treatment approach based on it**. About six months ago, I presented a poster paper proposing that Lyme disease is a route of entry into CFS for people who are genomically predisposed to developing a partial methylation cycle block, based on the observed depletion of glutathione by *Borrelia burgdorferi*.

During the past two and a half years, I estimate that at least several hundred and probably now over a thousand PWCs have tried this treatment. There are several physicians who have added methylation cycle treatment to their protocols. Dr. Neil Nathan and I also carried out and reported on an open-label clinical study of the simplified treatment approach on patients in his practice in Missouri.

There have also been a large number (I don't know how many, but I have probably personally seen a couple of hundred) methylation pathways panels run by Vitamin Diagnostics in New Jersey and the European Laboratory of Nutrients in the Netherlands. For people who have CFS, nearly all have shown a partial methylation cycle block and/or glutathione depletion, most showing both.

**The treatment used by itself seems to help about two-thirds of those who try it.** When it is combined with other treatments, it has brought what appears to be complete recovery to at least a few people, who have been able to return to full-time work. Some of the other treatments have been treatments for Lyme disease, mold illness, or toxic metals overload.

**Based on all of this experience, I continue to believe that this model does describe the pathogenesis of CFS for many and perhaps most PWCs.**

With regard to viruses or other pathogens, I believe that they are responsible for the onset of CFS in some cases, especially in the cluster or epidemic cases, such as the one at Incline Village. These cases fit within the GD-MCB model, except that the genomic predisposition aspect does not seem to be as important, or is not involved at all. But the rest is likely the same, i.e. that the viral infection depletes glutathione and brings on a partial block in the methylation cycle. I think the explanation for this is that the virus in the cluster cases has been particularly virulent, at least until it mutated and became less so, ending the local epidemic.

**So as far as the pathogenesis model is concerned, I think it is correct and that it is able to explain essentially all the features of CFS.** The model allows for a variety of routes into this pathogenesis, i.e. a variety of etiological factors. These include the whole variety of stressors--physical, chemical, biological and psychological/emotional.

The stressors involved in the onset of each case can be different from those involved in other cases, but they all channel into causing oxidative stress and a partial methylation cycle block.

In most cases the oxidative stress is accompanied by a depletion of glutathione, but in a minority of cases, there is a genetic polymorphism in the glutathione peroxidase enzyme. In those cases, glutathione does not drop, but the effect is the same, because it cannot be used effectively to counter the oxidative stress without a functional glutathione peroxidase.

**There's still an issue in the model that is unsolved, and that is how the partial methylation cycle block interacts with glutathione synthesis to deplete glutathione.** We know that it does, in both autism and CFS, because when the methylation cycle block is lifted, glutathione comes back up automatically. But the details of this interaction are still undefined from a theoretical biochemical standpoint.

**Note that the issue of whether the methylation cycle block is at the root of the pathogenesis is a separate issue from what is the best way to treat it.**

There may be, and likely are, better ways to treat it than the simplified treatment approach. I proposed that as a simple and relatively inexpensive, and thus accessible treatment for PWCs, and at the same time a way to test the model for pathogenesis. I would say that it has been successful in testing the model, and the model has survived the test. I think we still have more to learn about treatment, though the simplified treatment approach has made a significant contribution, and for some PWCS, has been the last thing they needed to get well.

I don't know if you have been following the "demonstration project" for treating M.E. patients that is going on in Ohio, USA, at present, which is updated on the forum called "A New Day," part of Cort Johnson's forums. The approach to treatment being used there involves IV nutrition, homeopathic neural therapy, acupuncture, proliferative therapy, and laser therapy. This is quite an innovative approach to treatment, and I can't say that I understand how it works from a fundamental scientific viewpoint. It does, however, so far appear to be a promising approach, and I am following the updates?

I don't know the details of what is included in the IVs, and perhaps there is some B12 and folate involved, which would seem to be important for lifting the methylation cycle block. On the other hand, perhaps the other techniques used are able to cause the body to make more effective use of the resources of B12 and folate that it already has. In any case, I do think there is good evidence that many or most PWCs have a methylation cycle block, and to lift this block, the methionine synthase activity has to be increased, which entails greater functional use of B12 and folate. So I'm trying to understand how this treatment intersects with that need.

You asked about treatment timescale. This seems to vary, depending on a variety of factors. If the simplified treatment approach is used by itself, the experience is that improvements usually occur within a couple of months, but full recovery hasn't happened for many people over a year later, though it has for a few. Lately I've been studying some of the cases with slow improvement, and I think that the lack of enough of the cofactors or enough of the amino acids to feed the methylation cycle and associated pathways may be the reasons for the slow progress in at least some of the cases. B-complex vitamins, minerals including zinc, copper, magnesium and selenium, and amino acids including methionine, serine, and the precursors for glutathione (glycine and glutamine or glutamate) are frequently found to be low.

**Dysfunction of the gut** seems to be at the basis of the low amino acids. I think that's why the IV amino acids are an important part of the treatment in Ohio, but for many PWCs, it may be possible to take free-form amino acids in order to increase their absorption, even with gut dysbiosis going on.

Beyond this, there are other treatments that may need to be added, depending on the particular case. These include attention to food sensitivities, efforts to improve the condition and function of the gut, support for the adrenal and thyroid axes, treatment of infections, treatment for mold illness if present, and treatment of heavy metal toxicity. There are various ways of approaching these issues in treatment, and physicians differ in their methods, but I think these are the things that can be required.

**So in summary, I think** the theoretical model and the lab test are holding up well, and though there is more to be learned in treatment, lifting the methylation cycle block and thereby bringing up glutathione seem to be essential parts of the treatment.

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