

## Betydelsen av icke-diskocytiska erythrocyter i patogenesen av ME/CFS

Erythrocyter (röda blodkroppar) skall vara diskformade för att de skall passera kapillärerna (de finaste blodkärlen) lätt. L.O. Simpson från Nya Zeeland har mätt erythrocyter med elektronmikroskop hos ME-drabbade och har funnit att de har ökad andel icke-diskformade erythrocyter. Han har även funnit att cirka 50% av ME-patienterna får minskad andel deformerade erythrocyter av

vitamin B<sub>12</sub> (kobalamin) och att det är dessa patienter som känner att de mår bättre av B<sub>12</sub>.

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Extraktet är från kapitel 65, *The Role of Nondiscocytic Erythrocytes in the Pathogenesis of ME / CFS*, av L. O. Simpson, PhD.

### On the pathogenesis of ME / CFS. \*

*\*Note that in this paper CFS is used in the general sense and does not refer to the condition identified by prescribed criteria.<sup>7</sup>*

It is proposed that when any of the nondiscocytes shown in the Figure increased beyond some unknown threshold value which will be related to mean capillary diameter, they will impair microcirculatory blood flow.

Their main effect will be to reduce capillary perfusion rate to the extent that an autoregulated vasodilation occurs to restore the flow rate to normal. The resulting rise in intracapillary pressure will enhance transudation and such a mechanism could explain the "endogenous haemoconcentration" which was observed during emotional stress.<sup>16</sup> The slower the rate of capillary blood flow the greater the rate of proximal oxygen extraction and the lower the distal oxygen tension. In stimulated muscle (where small capillaries are common) reduced oxygen availability may lead to lactic acid formation and excessive intracellular acidosis has been demonstrated by magnetic resonance imaging.<sup>18</sup> However to explain their observations the authors opted for "excessive glycolytic activity" rather than "inadequate oxidative metabolism".

Lactic acid at physiological concentrations has been shown by an in vitro technique to reduce blood filterability.<sup>19</sup> Therefore lactic acid release will exacerbate any pre-existing problems of capillary blood flow and in the smallest capillaries stasis may develop as a prelude to focal ischaemic necrosis. While focal necrosis in muscles has been reported in subjects with the post-viral syndrome,<sup>20</sup> it seems possible that in similar conditions focal necrosis might develop in any tissue. Focal necrotic lesions arising in this manner could be associated with the high intensity signals seen by magnetic resonance imaging (MRI) in the white matter of individuals who met the criteria for CFS.<sup>21</sup>

Such signals indicate localised increases in water content and show that the blood brain barrier has been opened focally allowing enhanced transudation. It is suggested that vasoactive substances diffusing from small necrotic lesions could stimulate temporary endothelial cell contraction and breach the blood brain barrier. The MRI white matter signals would persist only until macrophages had removed necrotic tissue, i.e. the source of the vasoactive substances.

It is unlikely to be chance alone which is responsible for the occurrence of high intensity white matter signals in conditions which have been found to have increased proportions of nondiscocytic erythrocytes, namely multiple sclerosis, systemic lupus erythematosus, sickle cell anaemia and in the elderly. In two of these conditions (multiple sclerosis and the elderly) it has been shown also that cerebral blood flow was less than in controls.<sup>22</sup>

Considerable research into the antibody profiles and lymphocyte populations in subjects with the symptoms of ME/CFS have shown some unusual patterns. However the reported observations provide no obvious link with symptoms which would help to explain their pathogenesis although it is possible that antibodies may in some way influence red cell shape. A healthy subject responded to one of two viral infections with a temporary increase in cup cells (Table 2). In contrast, subjects with ME/CFS have raised percentages of cup forms which persist for considerable periods. While this could be due to the persistence of the stimulating virus it may also indicate an impaired ability to restore discocyte shape. The best evidence which suggests that cup-transformed erythrocytes are important in the development of symptoms comes from observations on the blood of individuals before and after an injection of vitamin B<sub>12</sub>. Subjects whose well being improved after the vitamin injection were found to have reduced numbers of cup forms while there was no change in the red cell population of those who felt no better.

Table 3 shows the details of the red cell shape analyses of pre- and post-B<sub>12</sub> injection samples from a subject who felt better and from another whose condition was unchanged. So far 14 pairs of pre- and post-B<sub>12</sub> blood samples have been studied and it seems that the vitamin-induced changes occur in only 50%. This result is much different from the results of Ellis and Nasser<sup>23</sup> who used much larger injections of B<sub>12</sub> to alleviate chronic tiredness. Their data showed that tiredness was not simply a consequence of vitamin deficiency and the manner in which the B<sub>12</sub> improved well being was unexplained. However the fact that only 50% of subjects benefited from B<sub>12</sub> may provide means of subdividing subjects with chronic tiredness and obtaining more homogeneous panels for future study. Because of the number of potentially confounding variables a better understanding of the pathogenesis of chronic tiredness will emerge only from the study of well defined panels.

**Table 3**

	<b>Discoid Cells</b>	<b>Cells with surface changes</b>	<b>Cup forms</b>	<b>Cells with altered margins</b>
Female 1				
Pre B <sub>12</sub>	39.0%	27.9%	32.6%	0.5%
Post B <sub>12</sub> (24 hrs)	66.2%	15.2%	13.0%	5.6%
Female 2				
Pre B <sub>12</sub>	39.4%	24.0%	36.6%	0.0%
Post B <sub>12</sub> (24 hrs)	43.6%	23.5%	32.9%	0.0%
Post B <sub>12</sub> (72 hrs)	37.6%	24.0%	38.4%	0.0%

Red cell shape analysis results from blood samples obtained before and after an injection of vitamin B<sub>12</sub>. Female 1 experienced a marked improvement in wellbeing which was accompanied by a reduction in cup forms. Female 2 obtained no benefit from the B<sub>12</sub> injection and there was no change in the red cell population.

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