

# HOMOCYSTEINE METABOLISM: FROM BASIC SCIENCE TO CLINICAL MEDICINE

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# 21. IS METHIONINASE USEFUL FOR THE PREVENTION OF HYPERHOMOCYSTEINEMIA-ASSOCIATED CARDIOVASCULAR DISEASE?

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## Summary

In 1969, McCully concluded that homocysteine is a causative agent in arteriosclerosis [1]. A recently concluded study of 1,041 people from the Framingham Heart Study found that elevated plasma homocysteine leads to an increased risk of arteriosclerosis [2]. Other studies [2] have linked even moderate hyperhomocysteinemia to peripheral vascular, cerebrovascular, and coronary heart disease. Although vitamin B<sub>12</sub>, vitamin B<sub>6</sub>, and folate therapy have been suggested to lower hyperhomocysteinemia, acute medical intervention may be indicated for a large fraction of individuals at risk for this disease.

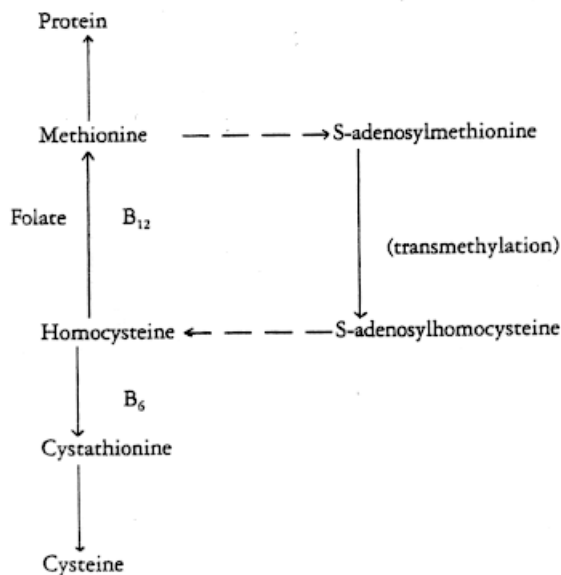


FIGURE 21-1. Methionine-homocysteine metabolic cycle.

We propose the enzyme methioninase as a potential therapeutic for acute intervention to immediately lower homocysteine levels. Methioninase has been recently isolated in pure form [3] and cloned [6] from *Pseudomonas putida* and is now in Phase I clinical trials for the treatment of cancer [7,8]. Methioninase lowers circulating methionine levels in mice and humans from 30–100  $\mu\text{M}$  to less than 1  $\mu\text{M}$  and homocysteine levels in mice and humans to under 1  $\mu\text{M}$  with no apparent toxic side effects and well below cardiovascular toxicity levels [7,8].

## Introduction

Methionine-homocysteine metabolism is basically cyclic (fig. 21-1) [5]. The vitamins B<sub>12</sub>, B<sub>6</sub>, and folate influence the “left-hand” part of this cycle and will be helpful in the maintenance of normal homocysteine levels in some individuals if the appropriate enzymes are present in sufficient amounts. However, as can be seen, the “right-hand” side of the cycle is independent of these vitamins. In the “right-hand” side of the cycle, methionine can lead to excess homocysteine levels via elevated transmethylation reactions [5].

For individuals with abnormalities in the “right-hand” side of the cycle, as well as the individuals with insufficient enzymes on the “left-hand” side of the cycle, maintenance use as well as acute use of methioninase may be necessary to maintain normal levels of homocysteine. Methioninase will lower both the methionine level, which is a precursor of homocysteine, and will also lower the homocysteine level directly. Polyethylene glycol-conjugated recombinant methioninase (PEG-r METase) is now available for Chronic in vivo use [9].

Clinical trials to test the hypothesis of the use of methioninase to lower homocysteine levels for pre-

vention of cardiovascular disease should start as soon as possible.

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