What is homocysteine?

Homocysteine was originally identified in 1962 in the urine of mentally retarded children (Gerritsen et al. 1962, Carson and Neill 1962). A couple of years later the genetic defect of cystathionine β-synthase (CBS), causing homocystinuria and very high plasma levels of total homocysteine (tHcy), was identified (Mudd et al. 1964). These patients were found to have frequent thrombo-embolic events. More than 50% of the patients had cardiovascular events and 25% died before the age of 30 (Gibson et al. 1964, Schimke et al. 1965).

In 1969 McCully described the vascular pathology in these patients, including smooth muscle proliferation, progressive arterial stenosis, and haemostatic changes. Severe defects in other enzymes, methionine synthase (MS) and methylenetetrahydrofolate reductase (MTHFR), were later discovered; these also caused homocystinuria and vascular pathology, as well as mental disturbances (Mudd et al. 1972, Rosenblatt et al. 1990, Rozen 1996).

Epidemiological studies in the general population have later demonstrated an association between moderately elevated levels of tHcy in the circulation, and not only vascular diseases but also pregnancy complications, neural tube defects, other congenital malformations, various neuro-psychiatric disorders and cognitive impairment in the elderly. These studies are outlined on pages 47-68. Two recent prospective case-control studies also show that overall mortality is correlated to tHcy levels, independent of the classical risk factors. (Hoogeveen et al. 1998, Bostom et al. 1999).

Homocysteine is a sulphur-containing amino acid that is closely related to methionine and cysteine. There is no DNA-coding for this amino acid, and it is not present in naturally occurring proteins. All homocysteine found in organisms is formed in the metabolism of the essential amino acid methionine, in the methylation cycle, page 14. This is the only known source of homocysteine.
Reduced homocysteine has a highly reactive free thiol group, which is susceptible to auto-oxidation at physiological pH, thereby forming disulphide bonds between two molecules or mixed disulphides with other thiols.

In plasma only about 1% of homocysteine normally exists in the free reduced form. About 70% is bound to albumin. The rest forms low molecular weight disulphides, predominantly with cysteine. The sum of all the forms is termed total homocysteine. Homocysteine is sometimes written homocyst(e)ine, since this term more clearly designates all the molecular species that are measured.

The abbreviations Hcy for homocysteine and tHcy for total homocysteine are used in the following, where tHcy generally refers to plasma or serum levels.

The assays generally measure the tHcy in plasma or serum, sometimes in the CSF, rarely in urine. Analysis of the different fractions of tHcy is complicated and only used for research purposes.

During the last ten years, several assays for measuring homocysteine in plasma, serum, and CSF have been developed. A further step forward is the recent introduction of enzyme immunoassays, which will allow determination of homocysteine in most routine laboratories.

Three enzymes are directly involved in the Hcy metabolism: methionine synthase (MS), betaine homocysteine methyltransferase (BHMT), and cystathionine β-synthase (CBS). Vitamin B₆, B₁₂, and folate are cofactors to these enzymes. The metabolism of Hcy is described on pages 14-19 and illustrated in fig 1, page 15. If this metabolism is disturbed, because of some enzymatic defect or intracellular deficiency of some cofactor to the mentioned enzymes, Hcy accumulates in the cell and is then exported to the circulation where levels rise.

Hcy is mainly eliminated by renal catabolism. Only about 1% of the Hcy filtered by the glomeruli is normally found in the urine (Guttormsen et al. 1997). The rest is reabsorbed and metabolized. Thus, the kidneys are Hcy-metabolizing rather than Hcy-excreting (Bostom et al. 1995a, van Guldener 1998, Refsum 1998a).

The plasma levels of tHcy in the circulation found in the general population vary with age and sex, as shown in table 6, page 75.

Plasma tHcy increases throughout life in both sexes. Before puberty, children of both sexes have low and similar levels (about 5 μmol/L). During puberty, levels markedly increase, more in boys than in girls. At the same time, tHcy values start to show a skew distribution in populations. Throughout life, the mean tHcy increases by 3-5 μmol/L. At the age of 40-42, there is a difference of about 2 μmol/L between men and women, with mean values of about 11 and 9 μmol/L, respectively (Nygård et al. 1995).