Besides genetic defects and vitamin deficiencies, there are many other causes of hyperhomocysteinaemia. Life-style, diseases, physiological, age-related changes, and drugs can, directly or indirectly, disturb the Hcy metabolism.

Connections between lifestyle and other factors increasing tHcy concentrations and complications attributable to a disturbed Hcy metabolism have not yet been given focus. However, many interesting observations support a connection. Several lifestyle factors may influence the tHcy levels (Nygård et al. 1995, 1997a, and 1998). The most important are smoking and a high consumption of alcohol, but the consumption of coffee can also have a significant influence. Even psychological stress has recently been shown to increase homocysteine levels (Stoney 1999).

**Lifestyle factors**

**Smoking**

In the large Norwegian Hordaland study, smoking produced a shift in the distribution of tHcy towards higher values. The number of cigarettes smoked a day was one of the strongest determinants of tHcy levels (Nygård et al. 1995). In women, the increase was about 1% per cigarette smoked a day, in men about 0.5%. Smoking also affects the redox status, as it almost doubles the fraction of reduced Hcy (Bergmark et al. 1997). This might increase the damaging effects and constitute an additional risk factor in smokers due to the reactivity of the sulphydryl portion of the free reduced form.

The mechanisms by which smoking increases the tHcy levels may be manifold. There is some experimental evidence that methylation reactions can be directly influenced by nicotine (Godin and Crooks 1986). Another mechanism could be an enzyme induction in the liver by polycyclic...
Why do homocysteine levels increase?

Aromatic hydrocarbons and increased catabolism of folate has been found in smokers (Nakazava et al. 1983). Low levels of both folate and vitamin B₆ and B₁₂ in smokers are observed in several studies (Witter et al. 1982, Vermaak et al. 1990, Piyathilake et al. 1994, Mansoor et al. 1997).

A possible interaction between nitrous compounds from the smoke and methionine synthase (MS) is suggested in one study (Bergman et al. 1997). It is unnecessary to point out that smoking is associated with vascular disease and other complications that can be related to Hcy.

**High alcohol intake**

Whereas a moderate consumption of alcohol seems to be associated with lower tHcy levels (Vollset et al. 1997), a chronic, high consumption results in increased levels (Hultberg et al. 1993a, Cravo et al. 1996). The background could be multifactorial.

High alcohol consumption is often associated with gastrointestinal disturbances, which may result in decreased absorption of vitamins, thus contributing to elevated tHcy levels. RBC levels of folate and serum concentrations of vitamin B₆ have been found to be significantly lower in alcoholics than in controls in two studies (Cravo et al. 1996 and 1997). Serum tHcy was about twice as high as that in controls, fig 6. Serum levels of vitamin B₁₂ were higher, however, in the alcoholics in these studies, an observation also made in other studies. It has been proposed that alcoholic liver damage results in liver cell depletion of the vitamin and increased blood concentrations of vitamin B₁₂-binding proteins (Baker et al. 1998).

Alcohol has also been reported to inhibit methionine synthase (MS) in several animal models (Barak et al. 1993, Sherif et al. 1993, Halsted et al. 1996). This effect may be mediated by acetaldehyde. An in vitro study has shown that acetaldehyde, a degradation product of ethanol, but not ethanol itself, inhibits this enzyme (Kenyon et al. 1998). Decreased MS activity has also been demonstrated in several animal models of alcoholic liver disease (Lu 1998. Review).

An impaired methylation rate may be responsible for liver cell damage and thus alcohol related liver disease.

Patients with cirrhosis often have hypermethioninaemia that can be attributed to a 50-60% decrease in hepatic methionine adenosyltransferase (MAT) activity.

Ethanol-induced cholestasis in rats has been shown to be counteracted by S-adenosylmethionine (SAM) (Alvaro et al. 1995). Recently 1 200 mg of SAM given orally for two years to patients with alcoholic liver cirrhosis in a placebo-controlled study, indicated that longterm treatment with SAM may improve survival and delay liver transplantation (Mato et al. 1999).