Review article

Diet and haemostasis: time for nutrition science to get more involved

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Abnormal haemostasis, and specifically a pre-thrombotic state characterized by hypercoagulability, increased platelet aggregation and impaired fibrinolysis, is associated with increased atheroma and thrombosis. The recent literature clearly indicates that diet may prevent or be used to treat some abnormal haemostatic states. There are reports on effects of energy intake and expenditure, alcohol consumption, intakes of total fat, different fatty acids, fish oil, NSP and vitamins on markers of coagulation, platelet function and fibrinolysis. Some of the confusion and controversy in this field has arisen because the wrong markers of haemostasis have been measured in dietary trials. Moreover, many of the studies have lacked good dietary control. It is suggested that more sensitive, functional markers of the balance between the different facets of the haemostatic system should be measured. It is also important to test hypotheses developed from known observations and to propose mechanisms of action of the various dietary factors, based on our improved understanding of the haemostatic system.

Haemostasis: Factor VII: Cardiovascular disease

The term 'haemostasis' describes the combined processes of vascular smooth-muscle-cell contraction, platelet aggregation or plug formation, and blood (plasma) coagulation, aimed at preventing bleeding from injured smaller blood vessels. Blood coagulates or turns into a solidified mass when plasma fibrinogen is converted by thrombin (generated by the coagulation enzyme cascade) into monomers which polymerize into a fibrin network. This network entraps blood cells and aggregated platelets to form a clot. As illustrated in Fig. 1, the clot is eventually dissolved by plasmin, generated from plasminogen by tissue plasminogen activator (tPA) which is part of the fibrinolytic system. Plasminogen activator inhibitor (PAI-1) inhibits this process. The term 'thrombus' refers to an intravascular blood clot. A pre-thrombotic state (Miller, 1993) is characterized by hypercoagulability of plasma, hyperaggregability of platelets, increased viscosity of whole blood, reduced blood flow with vortices, impaired fibrinolysis and a loss of the natural anticoagulant properties of cell surfaces in contact with blood. Hypercoagulability (Miller, 1992) is defined as 'an increased reactivity of blood plasma to thrombogenic surfaces'.

There is now convincing epidemiological and clinical evidence, supported by plausible underlying molecular mechanisms, that the pre-thrombotic state is an important predictor of cardiovascular disease. Known risk factors are increased plasma fibrinogen and factor VII coagulant activity (factor VII_c), increased platelet aggregability, as well as impaired fibrinolysis because of decreased tPA and increased PAI-1. This knowledge has led to a

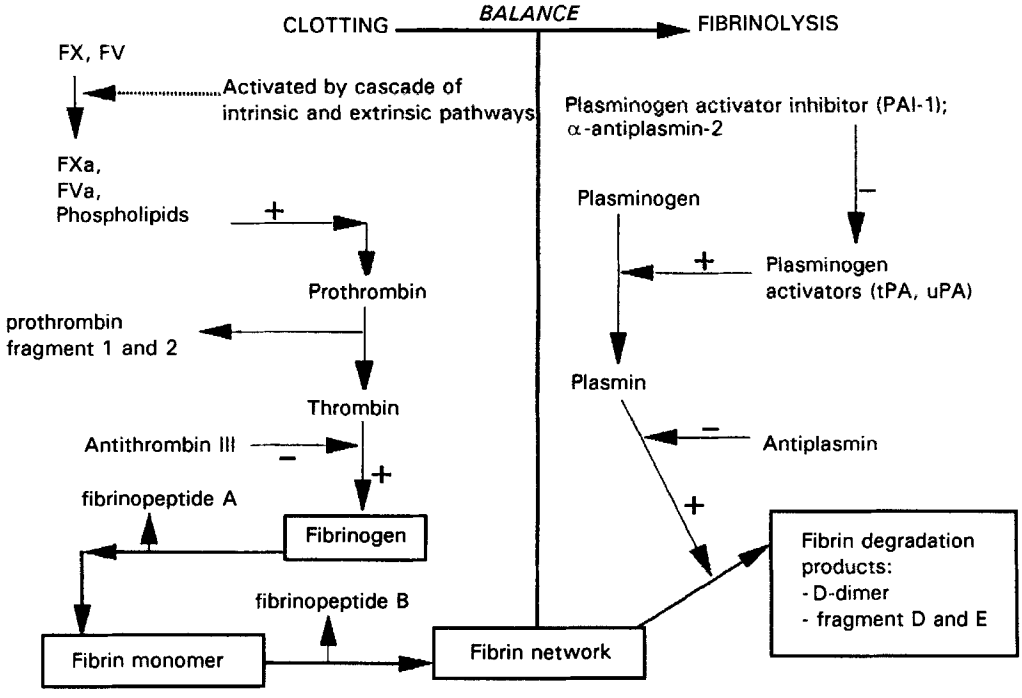

Fig 1. The relationship between formation (clotting) and dissolution (fibrinolysis) of fibrin networks. For clarity, not all activation, inhibition and feedback pathways are shown. FX, factor X; FV, factor V; FXa, factor Xa; FVa, factor Va; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator.

growing perception that dietary factors or patterns which are associated with an increased risk of cardiovascular disease (Marckmann, 1995; Simon *et al.* 1995) or which protect against these diseases (Anderson, 1995) may operate through effects on haemostatic function. For example, the positive correlation between dietary intake of saturated fatty acids and negative association of the *n*-3 polyunsaturated fatty acids with CHD still remain after adjustment for effects on blood lipid levels (Simon *et al.* 1995).

Despite agreement that diet is strongly associated with risk of cardiovascular disease, the effects of dietary patterns, specific foods or nutrients on haemostasis, and especially on the many facets of the pre-thrombotic state are not well understood. The purpose of the present contribution is to review briefly what is known about dietary effects on haemostasis, and to provide possible explanations for exising controversies in recent literature. Further research needed to make recommendations to the public for preventing cardiovascular disease through dietary interventions on the haemostatic system, will be suggested.

ENERGY: INTAKE AND EXPENDITURE

Effects of obesity

Obesity or increased BMI (> 30 kg/m^2) is associated with increased plasma concentrations of fibrinogen (Vorster *et al.* 1989; Iso *et al.* 1993*b*), increased PAI-1 (Iso *et al.* 1993*a*; Urano *et al.* 1993), impaired fibrinolytic capacity (Cepelak *et al.* 1991) and increased

plasma viscosity (Fanari *et al.* 1993). These observations were made in both men and women, from Caucasian (Iso *et al.* 1993*a*), Japanese (Iso *et al.* 1993*a*), and African (Venter *et al.* 1992) populations. The distribution of body fat may be an important determinant of fibrinogen concentration. Krobot *et al.* (1992), examining 4940 subjects in the second multinational monitoring of trends and determinants in cardiovascular disease (MONICA) trial, found a positive relationship between waist : hip ratio and fibrinogen in men and women.

Effects of reduced energy intake and weight loss

Little is known about the effects of weight loss on haemostasis, and there is some controversy regarding effects on fibrinogen. Poggi *et al.* (1994) found that a very-low-energy diet (VLCD) followed for 3 months by fifty-two subjects with BMI > 30 kg/m^2, significantly reduced packed cell volume, blood viscosity, erythrocyte aggregation, globulin levels and leukocyte count. Albumin levels increased but no effect on fibrinogen concentration was seen. Slabber *et al.* (1992) found that a similar VLCD followed for 7 d by nine obese subjects, increased fibrinogen non-significantly from 4·22 (SD 0·66) to 4·64 (SD 1·06) g/l, but significantly reduced factor VII_c. Fanari *et al.* (1993) showed a reduction in erythrocyte aggregation index with reduced energy intake. Although these authors demonstrated a reduction of fibrinogen, whole-blood viscosity of their subjects did not change on the reducing diet. A low-energy diet improved the fibrinolytic profile of 50 % of patients with deep-vein thrombosis (Cepelak *et al.* 1991). The conflicting effects of reduced energy intake and weight loss on fibrinogen may be explained by effects on free fatty acids (FFA). Vorster *et al.* (1989) showed that during an 8-week period of diet-induced weight loss, fibrinogen levels fluctuated in a similar manner to that of circulating FFA. During periods of rapid weight loss, fibrinogen and FFA rose, and both decreased during periods of slower weight loss. It is known that FFA stimulate hepatic fibrinogen production and that increased FFA levels are associated with increased fibrinogen (Pilgeram & Pickart, 1968).

Effects of activity level and exercise

Comparison of inactive with more active or very active subjects in different studies has shown that active women have significantly lower PAI-1 and tPA antigen levels (Stevenson *et al.* 1995) and active men have lower fibrinogen and factor X levels (Rankinen *et al.* 1994). Stevenson *et al.* (1995) could not find differences in fibrinogen levels related to activity in women, but Vanninen *et al.* (1994) showed a linear inverse correlation between fibrinogen and O_2 uptake (VO_2) of patients with non-insulin-dependent diabetes mellitus. Increased exercise in healthy subjects or sedentary diabetic subjects led to a decrease in fibrinogen concentration of the diabetics accompanied by improvement in glycaemic control (Vanninen *et al.* 1994) and an improvement in fibrinolytic profiles of the healthy subjects (Boman *et al.* 1994). These changes were thought to be related to improvements in insulin sensitivity during exercise. The mechanism by which insulin sensitivity may influence haemostasis is not clear. We have hypothesized that it could be mediated through effects on FFA (Venter *et al.* 1990).

Thus, high energy intake and inactivity, leading to obesity, are associated with increased coagulation factors and decreased fibrinolytic capacities in the majority of studies. More importantly decreases in energy intake, weight loss, and increased exercise, are associated with improvement in many haemostatic variables.

ALCOHOL

Alcohol is not strictly regarded as a nutrient. However, it does provide energy, and alcoholic beverages form an important part of the diet and social life of many people. Moreover, moderate alcohol consumption is known to be protective against heart disease (Doll *et al.* 1994). Epidemiological surveys have indicated that alcohol intake is positively associated with increased tPA levels in men and women (Iso *et al.* 1993*a*; Ridker *et al.* 1994) but also with raised PAI-1 levels in men (Iso *et al.* 1993*a*). In a 3-month intervention study, Struck *et al.* (1994) showed that both red and white wine have antithrombotic effects by reducing thrombin-initiated platelet aggregation. Renaud *et al.* (1992) examined the relationship between alcohol intake and platelet aggregation in the Caerphilly prospective heart disease study. They found an increased sensitivity of platelets to thrombin stimulation, but a decreased aggregation response to ADP and collagen stimulation with increased alcohol consumption. Based on these results, Renaud & De Logeril (1992) hypothesized that the high alcohol (wine) intakes in France may be responsible for the low CHD mortality (despite high saturated fat intakes and HDL levels comparable with other populations) because of these effects of alcohol on platelet aggregation.

Many studies have shown an inverse relationship between alcohol intake and fibrinogen level. Meade *et al.* (1979) showed that drinkers had 5–7 % lower fibrinogen concentrations and increased fibrinolytic activity, compared with non-drinkers. Krobot *et al.* (1992) described a U-shaped relationship between alcohol intake and fibrinogen, suggesting that maximal beneficial effects on fibrinogen will be seen at moderate levels of alcohol consumption. This is supported by the results of Lippi *et al.* (1992) who indicated that fibrinogen concentrations of alcoholics, with or without liver damage, were raised, possibly as an acute-phase response.

The acute, postprandial effects of alcohol taken with meals have also been examined. Veenstra *et al.* (1990) found that 30 g alcohol as port and red wine taken with an evening meal tended to increase platelet aggregation and PAI-1 activity, while decreasing tPA activity. Similar results were reported by Hendriks *et al.* (1994) when 40 g alcohol as beer, spirits or wine was taken with a meal. However, both groups found that these adverse effects were temporary and that fasting haemostatic profiles on the following morning were consistent with a decrease in CHD risk.

The mechanisms through which the effects of alcohol are mediated are not clear. Basista *et al.* (1994) thought that the fact that ethanal (acetaldehyde), a metabolic product of alcohol, reacts with proteins and alters their function, could explain the prolonged clotting times they observed *in vitro* when clotting proteins were incubated with ethanal. They concluded that ethanal may be responsible for some of the deranged coagulation seen in alcoholics. Spertini *et al.* (1992) also demonstrated that ethanal forms adducts with human platelets which may interfere with platelet activation and aggregation.

The protective effect of moderate alcohol consumption on CHD may therefore be mediated in part through effects on haemostasis. A possibility that deserves to be examined is that acetate, the major metabolic product of alcohol, could, through its lowering of FFA (Crouse *et al.* 1978) influence fibrinogen synthesis, secretion or function, and therefore be responsible for some of the effects of alcohol. Veldman (1996) recently showed that acetate influenced fibrin network formation in *in vitro* as well as *in vivo* circumstances.

DIETARY FATS AND OILS

Because total fat and different fatty acids have such profound effects on serum lipoproteins and risk of cardiovascular disease, the relationship of total fat and different fatty acid

intakes with haemostatic variables has received relatively more attention than that of other nutrients. Several types of long-term or short-term studies in healthy subjects, hyperlipidaemic or diabetic patients, some with conflicting results, have been reported.

Effects of total fat

There is general agreement that a high fat intake is associated with increased factor VII_c (Miller, 1992; Bladbjerg *et al.* 1994; Vaisanen *et al.* 1995) and that low intakes correlate with low factor VII_c (Vaisanen *et al.* 1995). There is also evidence that increasing fat intake impairs fibrinolytic activity (Ho *et al.* 1995). These authors found that twenty-eight Chinese volunteers who increased their fat intake to 50% of total energy for 3 d, showed smaller rises in tPA after the venous occlusion test. However, Ferlito & Di Mauro (1990) could not show any adverse effect of an oral fat load (1 g butter/kg body weight) on postprandial haemostatic variables associated with the pre-thrombotic state such as tPA, D-dimer and β-thromboglobulin. Freese & Mutanen (1995) confirmed increases in factor VII_c after fat intake. Habitual high fat intakes are also related to other coagulation factors. Rankinen *et al.* (1994) demonstrated positive correlations between fat intake and factor X, PAI-1 and tPA. However, there is little evidence that total fat intake influences fibrinogen levels. The fatty acid profile of the diet may be a more important determinant of fibrinogen level. Comparing two groups of Africans, Vorster *et al.* (1987) found higher fibrinogen values in the group who had a higher fat intake; but this group also had higher cholesterol and animal protein and lower fibre intakes. Other variables known to influence fibrinogen concentration such as BMI, smoking habit and activity levels, were similar in the two groups.

It can, therefore, be expected that lowering fat intake should improve haemostatic profiles. Lopez-Segura (1996) showed that a low-fat diet, rich in monounsaturated fatty acids, decreased PAI-1 level, accompanied by parallel decreases in plasma insulin. Sundell *et al.* (1991) also demonstrated reductions in PAI-1 when fat intake was lowered. However, Marckmann *et al.* (1992) found that a reduction of fat intake from 39 to 31% of total energy by healthy subjects, had no effect on coagulation or fibrinolytic profiles. This reduction also did not influence blood lipid levels, suggesting that only substantial reductions will have beneficial effects.

Total fat intake may theoretically influence haemostasis indirectly through effects on blood lipoproteins. Serum or plasma triacylglycerol concentration is positively associated with factor VII_c (Miller, 1993), bleeding times (Mundal *et al.* 1994) and with tPA and PAI-1 concentrations (Iso *et al.* 1993*a*). Factor VII_c also correlates with apolipoprotein B levels (Vaisanen *et al.* 1995). HDL are negatively associated with fibrinogen (Iso *et al.* 1993*b*) while lipoprotein (a) showed a positive association with fibrinogen in a large cross-sectional study involving 4125 subjects aged 25–55 years (Howard *et al.* 1994). Miller (1993) is of the opinion that hyperlipidaemia leads to a sustained activation of the extrinsic pathway, resulting in an increased generation of thrombin (and possibly of other zymogens) which will stimulate the hepatic production of the vitamin K-dependent clotting factors.

In addition to increased levels of factor VII being an accepted risk factor for CHD, the relationship between fat intake, hyperlipidaemia and haemostasis may also be important at an acute, clinical level. Altomare *et al.* (1993) have shown that the infusion of a lipid emulsion used as a standard component of parenteral nutrition, significantly reduced tPA and had no effect on PAI-1 release after 10 min of venous occlusion. This haemostatic profile is associated with an increased thrombotic risk.

Effects of different types of fatty acids

In an earlier review on dietary factors involved in cardiovascular disease, Ulbricht & Southgate (1991) suggested that the atherogenic or hyperlipidaemic saturated fatty acids are lauric (12:0) myristic (14:0) and palmitic (16:0) acids, while the thrombogenic fatty acids are myristic, palmitic and stearic (18:0) acids. The long-chain unsaturated *n*-6 (linoleic) and *n*-3 fatty acids from fish oils are thought to be anti-atherogenic and anti-thrombogenic.

The effects of individual fatty acids will be influenced by which fats they replace in the diet. Incubation of citrated plasma with micellar stearate activates the contact system of coagulation (factors XII and IX to XIIa and IXa), with resultant increases in factor VII_c (Mitropoulos *et al.* 1994). These authors believe that dietary fat induces changes in activation of factor VII through effects on plasma free-stearic-acid concentration. However, in an *in vivo* study, Tholstrup *et al.* (1994) showed that a diet rich in stearic acid, when compared with diets rich in palmitic acid and myristic plus lauric acid lowered not only serum lipoproteins (12–26 %) but also factor VII_c by 13 %. Mustad *et al.* (1993) also compared a diet rich in stearic acid with one rich in myristic plus lauric acids and could not demonstrate any effects on prostacyclin and thromboxane production, the two prostaglandins involved in platelet function.

Not only do different experiments with the same fatty acid show different effects, but effects of a particular fatty acid or diet on different coagulation variables may also differ. Bladbjerg *et al.* (1995) showed that a diet rich in stearic acid compared with one rich in myristic plus lauric acids significantly decreased factor VII_c and other vitamin K-dependent proteins, but increased fibrinogen. Cigolini *et al.* (1994) however, found no relationship between plasma fibrinogen and fatty acid profiles of adipose tissue. The latter should reflect dietary intakes. In a comparison of diets containing monounsaturated fatty acids with those containing polyunsaturated fatty acids in hyperlipidaemic patients, Gustafsson *et al.* (1992) could not demonstrate any effects on fibrinogen, despite significant reductions of 12 and 15 % in total cholesterol concentration. In non-insulin-dependent diabetic patients, a similar study demonstrated that the diet containing monounsaturated fatty acids lowered Von Willebrand factor but had no effect on fibrinogen, fibronectin or α-2-macroglobulin (Thomsen *et al.* 1995).

These different effects of a particular diet or fatty acid on haemostatic variables were also described by Freese & Mutanen (1995). They showed that collagen-induced platelet aggregation was decreased 5 h after fat intake while factor VII_c was increased. In another study Mutanen *et al.* (1995) found that platelets from subjects on a high-saturated-fat diet were less sensitive to aggregating agents than those from subjects on an unsaturated-fat diet.

The relationship of intakes of fish, fish oils, eicosapentaenoic acid and docosahexaenoic acid with haemostatic variables have been studied in more detail, but again with some conflicting results. Their inhibitory effects on platelet aggregation with resultant prolonged bleeding times through effects on prostaglandin metabolism are well known (Dyerberg, 1986; Hansen *et al.* 1993). But fish intake also affects clotting factors and fibrinolytic enzymes. High intakes are associated with lower plasma levels of fibrinogen, factor VIII and Von Willebrand factor (Iso *et al.* 1993*b*; Shahar *et al.* 1993). However, studies which examined the effect of supplementation of diets with fish oil on plasma fibrinogen, gave conflicting results. Some studies showed a lowering of fibrinogen (Høstmark *et al.* 1988; Radack *et al.* 1989), others found no effect (Haglund *et al.* 1990; Brown & Roberts, 1991) while some even demonstrated increases (Haines *et al.* 1986; Schmidt *et al.* 1992). Haglund *et al.* (1991) showed that fish oil lowered fibrinogen levels

only when it contained 1·1 α-tocopherol equivalents (1·5 IU) vitamin E per g fish oil but not when it contained 0·2 α-tocopherol equivalents (0·3 IU)/g. Oosthuizen *et al.* (1994) showed that a vitamin E-rich fish oil lowered plasma fibrinogen level in women who had relatively high initial values (from 3·23 (SD 0·96) to 2·64 (SD 0·55) g/l) but not in men who had low baseline values (2·03 (SD 0·62) g/l). The latter study also reported decreases in factors V_c, VII_c and X_c in the women during intakes of fish oil.

The increases in fibrinogen seen with fish-oil supplementation in some studies, especially in diabetic patients (Haines *et al.* 1986; Silvis *et al.* 1990), question the 'safety' of these supplements. In several studies it was also reported that increases in PAI-1 occurred, despite decreases in triacylglycerol levels with fish-oil supplementation, both in diabetic (Boberg *et al.* 1992) and healthy subjects (Fumeron *et al.* 1991; Oosthuizen *et al.* 1994). In addition, Herrmann *et al.* (1995) reported decreases in tPA with a supplement of 12 g fish oil in CHD patients.

From these studies one might conclude that although fish oil may inhibit platelet aggregability and lower some coagulation factors, it may also impair fibrinolytic potential by lowering tPA and raising PAI-1 in some circumstances. Marckmann (1995) also is of the opinion that the anti-fibrinolytic effect of the fish-oil fatty acids might counteract their anti-thrombotic influence on platelet function.

DIETARY CARBOHYDRATES

Diets high in carbohydrate (CHO) including fibre (NSP) are usually low in fat and relatively higher in plant than animal protein. Studies looking at the effect of CHO on haemostasis should therefore control for amounts and types of fat and protein. Because soluble and insoluble NSP have different physiological effects on gastrointestinal function and lipid metabolism, it can furthermore be expected that effects of different types of NSP on haemostasis will also differ.

Some of the first observations that diets high in 'fibre' may protect against thrombosis were made by British physicians who reported that incidences of post-operative deep-vein thrombosis could be lowered by feeding patients with high-fibre diets (Frohn, 1976; Latto, 1976). Fehily *et al.* (1982) then provided epidemiological evidence that high cereal-fibre intakes correlated negatively with plasma fibrinogen. However, in a follow-up study, Fehily *et al.* (1986) could not demonstrate decreases in fibrinogen when healthy subjects increased their cereal-fibre intake.

Simpson *et al.* (1982) also could not demonstrate a change in fibrinogen level with an increase in NSP intake by diabetic patients. But they found that coagulant activities of factors VII and X decreased on the higher fibre intake in non-insulin-dependent diabetic patients, and factor VIII antigen decreased in patients with insulin-dependent diabetes.

If fibre intake influences plasma fibrinogen level, it is probably due to the soluble NSP components. Koepp & Hegewisch (1981) found that supplementing the diet of ten diabetic children with 0·45 g guar gum/kg for 4 weeks reduced fibrinogen level in seven of the children from a mean of 3·13 to 2·63 g/l. Another soluble NSP, konjac-glucomannan, significantly lowered plasma fibrinogen in an obese baboon model (Venter *et al.* 1990) and the obese Zucker rat (Venter *et al.* 1991). Soluble NSP do not seem to affect platelet function. Challen *et al.* (1983) found no effects on platelet aggregation, platelet fatty acid composition, bleeding times or dilute blood-clot lysis time in healthy volunteers who were given 36 g pectin daily for 3 weeks.

Low fibre intakes are also associated with impaired fibrinolysis and this situation may be rectified by increasing fibre intake. Sundell & Ranby (1993) found that oat husk fibre,

and Landin *et al.* (1992) that guar gum, significantly reduced PAI-1 levels. Marckmann *et al.* (1993) also showed that a low-fat, high-fibre diet followed for 8 months by healthy volunteers improved fibrinolytic potential by increasing tPA activity. This study did not show changes in fibrinogen or PAI-1. Mehrabian *et al.* (1990) demonstrated, however, that a 'high-complex-CHO, low-fat' diet followed for 3 weeks significantly reduced plasminogen, tPA and PAI-1 levels, while fibrinogen level tended to decrease ($P = 0{\cdot}07$). It is however, difficult to dissect effects of fibre from those of fat in these studies.

In the past, much has been learned about the effects of NSP by analysing diets and disease risk profiles of vegetarians. Haines *et al.* (1980) showed that concentrations of factors VII and II were lower in vegetarians, while the only haemostatic difference between Chinese Buddhist vegetarians and omnivores that Pan *et al.* (1993) could find was increased levels of anti-thrombin III in the vegetarians.

These studies show that high-fibre diets have beneficial effects on coagulation and fibrinolysis. The effects of starch, resistant starch and other carbohydrates such as the oligosaccharides have not been examined.

VITAMINS

Very few studies have reported effects of vitamins on coagulation. Kruger *et al.* (1994) observed in healthy elderly women that those who took micronutrient supplements and who had significantly higher levels of serum vitamin A, retinol binding protein, pyridoxal and pyridoxal phosphate, also had significantly lower plasma fibrinogen levels. Eliasson *et al.* (1995) found in the Swedish MONICA study that high plasma retinol levels were associated with lower plasma fibrinogen but also with low tPA levels and therefore with impaired fibrinolytic activity. Haglund *et al.* (1991) showed, as already mentioned, that fish oil had a fibrinogen lowering effect only when it contained high levels of vitamin E.

Kiserud *et al.* (1995) supported these observations in their studies on the effects of various fatty acids, alone or in combination with vitamin E on fibrinogen secretion by human hepatoma (HepG2) cells. These authors showed that polyunsaturated fatty acids increased fibrinogen release by HepG2 cells. Vitamin E alone decreased the amount of fibrinogen in the medium in a dose-dependent manner. When vitamin E was added to the polyunsaturated fatty acids, fibrinogen in the cell medium was lowered. The monounsaturated oleic acid, and the saturated palmitic acid, decreased fibrinogen secretion, both alone and in combination with vitamin E. The authors hypothesized that vitamin E may have these effects by preventing oxidation of the polyunsaturated fatty acids.

SPECIFIC FOODS

There is some evidence that specific foods or substances in foods such as the flavonoids or polyphenols may influence haemostasis. Strongly flavoured foods such as onions (Menon *et al.* 1968), chillies (Glatzel & Rüberg-Schweer, 1965), spices (Glatzel & Rüberg-Schweer, 1967), capsicum (Visudhiphan *et al.* 1982) or green tea (Ali & Afzal, 1987) may increase fibrinolytic activity. However, Vorster *et al.* (1996) found no evidence that fibrinogen, tPA or PAI-1 levels were influenced by tea drinking. Vorster *et al.* (1992) also reported that an increased egg intake from two to seven and fourteen per week in young healthy men over a period of 5 months, did not influence coagulation or fibrinolytic (plasminogen) profiles.

COMMENT

Despite all the reported controversies, it is clear that many dietary factors influence different variables of haemostasis. But it is also clear that we do not know enough about the relationship between diet and haemostasis and particularly the mechanisms involved to give detailed and specific advice to patients or the public, other than that the 'prudent', low-fat, high-CHO, high-NSP diet known to protect against development of chronic diseases of lifestyle, will probably have beneficial effects, as indicated by numerous epidemiological surveys.

There are many possible reasons for the existing conflicting findings. They include differences in study design, choice of subjects or patients and their baseline values, total dietary composition, and duration of studies. A major reason is that the most important variables have not been measured in dietary studies. Normal haemostasis is a result of a complex regulatory process involving the interaction of zymogens, activators, inhibitors and activated enzymes in plasma with blood cells, and the secretions of the endothelial lining of blood vessels. To measure the balance amongst these molecules and their actions, appropriate markers of hypercoagulability, inhibition of coagulation, fibrin formation and deposition, activation of fibrinolysis and fibrinolytic products should be measured. These should include *inter alia*, prothrombin fragment $1+2$, fibrinopeptide A, thrombin–antithrombin III complexes, fibrin monomer, active PAI-1 antigen, tPA–PAI-1 complex, plasminogen, α-2-plasmin inhibitor, plasmin-α-2 plasmin inhibitor complex and D-dimer, as well as fibrinogen and factor VII_c (Kario & Matsuo, 1993; Tripodi *et al.* 1993; Hansson *et al.* 1994). Measurement of these variables will give more information on the processes of fibrin formation and dissolution.

Measurement of fibrinogen concentration alone will only give limited information. Nieuwenhuizen (1994) mentions that the term 'fibrinogen' covers a large, heterogeneous family of closely related molecules whose functional properties may differ. Measurement of polymerization of fibrin monomers, as reflected in fibrin network structure and properties (Nair & Dhall, 1991) will give information on plasma factors which affect clot formation, the thrombogenicity of the clot (Collet *et al.* 1993) as well as its potential to influence the conversion of plasminogen to plasmin by tPA and therefore to be digested (Carr & Alving, 1995).

It could also be worthwhile to measure the macromolecular protein complex described by Lipinski *et al.* (1995). Macromolecular protein complex is known to form complexes with fibrin in the clot, increasing its mass and making it resistant to fibrinolysis. It therefore increases risk of thrombosis. There is no information on the effects of diet on macromolecular protein complex level.

The determinants of the different haemostatic factors or markers in different population groups, should be studied in more detail. Jerling *et al.* (1994) found that a group of rural Venda men had lower PAI-1 but higher fibrinogen levels than a matched control group of white men, indicating that the determinants of fibrinogen and PAI-1 may differ or that there are ethnic (genetic) differences in these variables. It is also not known to what extent compensatory increases or decreases in haemostatic variables are possible in an attempt to maintain balance between and within the coagulation and fibrinolytic systems.

In conclusion, there may be several different hypercoagulable states (Miller, 1993) depending on which variables are abnormal. We need to know much more about the effects of specific foods and nutrients, as well as the total diet on a broader range of sensitive markers of the total haemostatic system, before these different conditions can be prevented or treated by diet. With a better understanding of the complexities of the haemostatic

system, and with our existing knowledge of effects of specific dietary substances, we believe it is possible to develop working hypotheses that could be tested in controlled dietary trials. The challenge is there: it is now time for nutritional scientists to accept it! The reward will be improved dietary prevention and treatment of many chronic diseases of lifestyle in which abnormal haemostasis plays a role.

REFERENCES

Ali, M. & Afzal, M. (1987). A potent inhibitor of thrombin stimulated platelet thromboxane formation from unprocessed tea. *Prostaglandins, Leukotrienes and Medicine* **27**, 9–13.

Altomare, D. F., Semeraro, N. & Colucci, M. (1993). Reduction of the plasma levels of tissue plasminogen activator after infusion of a lipid emulsion in humans. *Journal of Parenteral and Enteral Nutrition* **17**, 274–276.

Anderson, J. W. (1995). Dietary fibre, complex carbohydrate and coronary artery disease. *Canadian Journal of Cardiology* **11**, Suppl. G, 55G–62G.

Basista, M. H., Joseph, A., Smolen, S., Koterba, A. & Brecher, A. S. (1994). Acetaldehyde alters coagulation protein function. *Digestive Diseases and Sciences* **39**, 2421–2425.

Bladbjerg, E. M., Marckmann, P., Sandstrom, B. & Jespersen, J. (1994). Non-fasting factor VII coagulant activity (F VII:C) increased by high-fat diet. *Thrombosis and Haemostasis* **71**, 755–758.

Bladbjerg, E. M., Tholstrup, T., Marckmann, P., Sandstrom, B. & Jespersen, J. (1995). Dietary changes in fasting levels of factor VII coagulant activity (F VII:C) are accompanied by changes in factor VII protein and other vitamin K-dependent proteins. *Thrombosis and Haemostasis* **73**, 239–242.

Boberg, M., Pollare, T., Siegbahn, A. & Vessby, B. (1992). Supplementation with *n*-3 fatty acids reduces triglycerides but increases PAI-1 in non-insulin dependent diabetes mellitus. *European Journal of Clinical Investigation* **22**, 645–650.

Boman, K., Hellsten, G., Bruce, A., Hallmans, G. & Nilsson, T. K. (1994). Endurance physical activity, diet and fibrinolysis. *Atherosclerosis* **106**, 65–74.

Brown, A. J. & Roberts, D. C. (1991). Fish and fish oil intake: effect on haematological variables related to cardiovascular disease. *Thrombosis Research* **64**, 169–178.

Carr, M. E. & Alving, B. M. (1995). Effect of fibrin structure on plasmin-mediated dissolution of plasma clots. *Blood Coagulation and Fibrinolysis* **6**, 567–573.

Cepelak, V., Dvorak, J., Vit, L., Cepelakova, H. & Beranek, V. (1991). Disorders of fibrinolysis and thrombophilic states, risk factors and possibilities of dietary effects. *Vnitrni Lekarstvi* **37**, 13–20.

Challen, A. D., Branch, W. J. & Cummings, J. H. (1983). The effect of pectin and wheat bran on platelet function and haemostasis in man. *Human Nutrition: Clinical Nutrition* **37C**, 209–217.

Cigolini, M., Targher, G., de Sandre, G., Muggeo, M. & Seidell, J. C. (1994). Plasma fibrinogen in relation to serum insulin, smoking habits and adipose tissue fatty acids in healthy men. *European Journal of Clinical Investigation* **24**, 126–130.

Collett, J. P., Soria, J., Mirshahi, M., Hirsch, M., Dagonnet, F. B., Caen, J. & Soria, C. (1993). Dusart syndrome: a new concept of the relationship between fibrin clot architecture and fibrin clot degradability: hypofibrinolysis related to an abnormal clot structure. *Blood* **82**, 2462–2469.

Crouse, J. R., Gerson, C. D., De Carli, L. M. & Lieber, C. S. (1978). Role of acetate in reduction of plasma free fatty acids produced by ethanol in man. *Journal of Lipid Research* **9**, 509–512.

Doll, R., Peto, R., Hall, E. I., Wheatley, K. & Gray, R. (1994). Mortality in relation to consumption of alcohol: 13 years' observation on male British doctors. *British Medical Journal* **309**, 911–918.

Dyerberg, J. (1986). Linolenate-derived polyunsaturated fatty acids and prevention of atherosclerosis. *Nutrition Reviews* **44**, 125–134.

Eliasson, M., Asplund, K., Evrin, P. E., Huhtasaari, F. & Johansson, I. (1995). Plasma fibrinogen, fibrinolysis and (pro) vitamins; is there a connection? *Fibrinolysis* **9**, 87–92.

Fanari, P., Semazzi, R., Nasrawi, F., Ticozzelli, P., Gragni, G., Agosti, R. & Longhini, E. (1993). Haemorheological changes in obese adolescents after short-term diet. *International Journal of Obesity and Related Metabolic Disorders* **17**, 487–494.

Fehily, A. M., Burr, M. L., Butland, B. K. & Eastham, R. D. (1986). A randomized controlled trial to investigate the effect of a high fibre diet on blood pressure and plasma fibrinogen. *Journal of Epidemiology and Community Health* **40**, 334–337.

Fehily, A. M., Milbank, T. E., Yarnell, J. W. G., Hayes, T. M., Kubiki, A. J. & Eastham, R. D. (1982). Dietary determinants of lipoproteins, total cholesterol, viscosity, fibrinogen, and blood pressure. *American Journal of Clinical Nutrition* **36**, 890–896.

Ferlito, S. & Di Mauro, C. (1990). Effects of an oral fat load on some prothrombotic markers in coronary heart patients. *Panminerva Medica* **32**, 101–104.

Freese, R. & Mutanen, M. (1995). Postprandial changes in platelet function and coagulation factors after high-fat meals with different fatty acid compositions. *European Journal of Clinical Nutrition* **49**, 658–664.

Frohn, M. J. N. (1976). Left leg varicose veins and deep vein thrombosis. *Lancet* **ii**, 1019–1020.

Fumeron, F., Brigant, L., Ollivier, V., De Prost, D., Oriss, F., Darcet, P., Bard, J. M., Para, H. J., Fruchart, J. C. & Apfelbaum, M. (1991). *n*-3 Polyunsaturated fatty acids raise low-density lipoproteins, high-density lipoprotein 2, and plasminogen-activator inhibitor in healthy young men. *American Journal of Clinical Nutrition* **54**, 118–122.

Glatzel, H. & Rüberg-Schweer, M. (1965). Kreislaufregulation and Ernährung. 7. Aktivierung der Fibrinolyse durch Gewürze (chilliès) (Circulatory regulation and nutrition. 7. Activation of fibrinolysis by spices). *Kreislaufforsch* **53**, 374–384.

Glatzel, H. & Rüberg-Schweer, M. (1967). Beeinflussung von Gerinnung und Fibrinolyse durch landesübliche Gewürze (Influence of locally used spices on coagulation and fibrinolysis). *Medizinische Klinik* **62**, 1086–1088.

Gustafsson, I. B., Vessby, B. & Nydahl, M. (1992). Effects of lipid-lowering diets enriched with monounsaturated and polyunsaturated fatty acids on serum lipoprotein composition in patients with hyperlipoproteinaemia. *Atherosclerosis* **96**, 109–118.

Haglund, O., Luostarinen, R., Wallin, R., Wibell, L. & Saldeen, T. (1991). The effects of fish oil on triglycerides, cholesterol, fibrinogen and malondialdehyde in humans supplemented with vitamin E. *Lipids* **121**, 165–169.

Haglund, O., Wallin, R., Luostarinen, R. & Saldeen, T. (1990). Effects of a new fluid fish oil concentrate, ESKIMO-3, on triglycerides, cholesterol, fibrinogen and blood pressure. *Journal of Internal Medicine* **227**, 347–353.

Haines, A. P., Chakrabarti, R., Fisher, D., Meade, T. W., North, W. R. S. & Stirling, Y. (1980). Haemostatic variables in vegetarians and non-vegetarians. *Thrombosis Research* **19**, 139–148.

Haines, A. P., Sanders, T. A. B., Imeson, J. D., Mahler, R. F., Martin, J., Mistry, M., Vickers, M. & Wallace, P. G. (1986). Effects of a fish oil supplement on platelet function, haemostatic variables and albuminuria in insulin-dependent diabetics. *Thrombosis Research* **43**, 643–655.

Hansen, J. B., Olsen, J. O., Wilsgard, L., Lyngmo, V. & Svensson, B. (1993). Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. *European Journal of Clinical Nutrition* **47**, 497–507.

Hansson, P. O., Eriksson, H., Eriksson, E., Jagenburg, R., Lukes, P. & Risberg, B. (1994). Can laboratory testing improve screening strategies for deep vein thrombosis at an emergency unit? *Journal of Internal Medicine* **235**, 143–151.

Hendriks, H. F., Veenstra, J., Velthuis-te Wierik, E. J., Schaafsma, G. & Kluft, C. (1994). Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *British Medical Journal* **308**, 1003–1006.

Herrmann, W., Biermann, J. & Kostner, G. M. (1995). Comparison of effects of N-3 to N-6 fatty acids on serum level of lipoprotein (a) in patients with coronary artery disease. *American Journal of Cardiology* **76**, 459–462.

Ho, C. H., Chwang, L. C. & Hwang, B. H. (1995). The influence of high fat diet on the fibrinolytic activity. *Thrombosis Research* **77**, 201–208.

Høstmark, A. T., Bjerkedal, T., Kierulf, P., Flaten, H. & Ulshagen, K. (1988). Fish oil and plasma fibrinogen. *British Medical Journal* **297**, 180–181.

Howard, B. V., Le, N. A., Bekker, J. D., Flack, J. M., Jacobs, D. R., Lewis, C. E., Macrovina, S. M. & Perkins, L. L. (1994). Concentrations of Lp(a) in black and white young adults: relations to risk factors for cardiovascular disease. *Annals of Epidemiology* **4**, 341–350.

Iso, H., Folsom, A. R., Koike, K. A., Sato, S., Wu, K. K., Shimamoto, T., Iida, M. & Komachi, Y. (1993*a*). Antigens of tissue plasminogen activator and plasminogen activator inhibitor 1: correlates in nonsmoking Japanese and Caucasian men and women. *Thrombosis and Haemostasis* **70**, 475–480.

Iso, H., Folsom, A. R., Koike, K. A., Sato, S., Wu, K. K., Shimamoto, T., Iida, M. & Komachi, Y. (1993*b*). Plasma fibrinogen and its correlates in Japanese and US population samples. *Arteriosclerosis and Thrombosis* **13**, 783–790.

Jerling, J. C., Vorster, H. H., Oosthuizen, W., Silvis, N. & Venter, C. S. (1994). Differences in plasminogen activator inhibitor 1 activity between blacks and whites may be diet related. *Haemostasis* **24**, 364–368.

Kario, K. & Matsuo, T. (1993). Lipid-related haemostatic abnomalities in the elderly: imbalance between coagulation and fibrinolysis. *Atherosclerosis* **103**, 131–138.

Kiserud, C. E., Kierulf, P. & Hostmark, A. T. (1995). Effects of various fatty acids alone or combined with vitamin E on cell growth and fibrinogen concentration in the medium of HepG2 cells. *Thrombosis Research* **80**, 75–83.

Koepp, P. & Hegewisch, S. (1981). Effects of guar on plasma viscosity and related parameters in diabetic children. *European Journal of Paediatrics* **137**, 31–33.

Krobot, K., Hense, H. W., Cremer, P., Eberle, E. & Kewil, U. (1992). Determinants of plasma fibrinogen: relation to body weight, waist-to-hip ratio, smoking, alcohol, age, and sex. Results from the second MONICA Augsburg survey 1989-1990. *Arteriosclerosis and Thrombosis* **12**, 780–788.

Kruger, A., Vorster, H. H., Venter, C. S. & Viljoen, M. J. (1994). Increased plasma fibrinogen with age – eugeriatric or pathogeriatric phenomenon? *Cardiovascular Journal of Southern Africa* **5**, 110–116.

Landin, K., Holm, G., Tengborn, L. & Smith, U. (1992). Guar gum improves insulin sensitivity, blood lipids, blood pressure and fibrinolysis in healthy men. *American Journal of Clinical Nutrition* **56**, 1061–1065.
Latto, C. (1976). Postoperative deep-vein thrombosis, pulmonary embolism, and high-fibre diet (letter). *Lancet* **ii**, 1197.
Lipinski, B., Federman, S. M. & Krolewski, A. S. (1995). Macromolecular protein complex of human plasma: interaction with fibrin and fibrinolysis. *Thrombosis Research* **78**, 461–465.
Lippi, G., Fedi, S., Grassi, M., Rose, E., Liotta, A. A., Fontanelli, A., Cellai, A. P. & Mazzanti, R. (1992). Acute phase proteins in alcoholics with or without liver injury. *Italian Journal of Gastroenterology* **24**, 383–385.
Lopez-Segura, F., Velasco, F. & Lopez-Miranda, J. (1996). Monounsaturated fatty acid-enriched diet decreases plasma plasminogen activator inhibitor type 1. *Arteriosclerosis Thrombosis Vascular Biology* **16**, 82–88.
Marckmann, P. (1995). Diet, blood coagulation and fibrinolysis. *Danish Medical Bulletin* **42**, 410–425.
Marckmann, P., Sandström, B. & Jespersen, J. (1992). Fasting blood coagulation and fibrinolysis of young adults unchanged by reduction in dietary fat content. *Arteriosclerosis and Thrombosis* **12**, 201–205.
Marckmann, P., Sandström, B. & Jespersen, J. (1993). Favorable long-term effect of a low-fat/high-fibre diet on human blood coagulation and fibrinolysis. *Arteriosclerosis and Thrombosis* **13**, 505–511.
Meade, T. W., Chakrabarti, R., Haines, A. P., North, W. R. S. & Stirling, Y. (1979). Characteristics affecting fibrinolytic activity and plasma fibrinogen concentrations. *British Medical Journal* **1**, 153–156.
Mehrabian, M., Peter, J. B., Barnard, R. J. & Lusis, A. J. (1990). Dietary regulation of fibrinolytic factors. *Atherosclerosis* **84**, 25–32.
Menon, S., Kendal, R. Y., Dewar, H. A. & Newell, D. J. (1968). Effect of onions on blood fibrinolytic activity. *British Medical Journal* **3**, 351.
Miller, G. J. (1992). Haemostasis and cardiovascular risk. The British and European experience. *Archives of Pathology and Laboratory Medicine* **116**, 1318–1321.
Miller, G. J. (1993). Hyperlipidaema and hypercoagulability. *Progress in Lipid Research* **32**, 61–69.
Mitropoulos, K. A., Miller, G. J., Martin, J. C., Reeves, B. E. & Cooper, J. (1994). Dietary fat induces changes in factor VII coagulant activity through effects on plasma free stearic acid concentration. *Arteriosclerosis and Thrombosis*, **14**, 214–222.
Mundal, H. H., Meltzer, H. M. & Aursnes, I. (1994). Bleeding times related to serum triglyceride levels in healthy young adults. *Thrombosis Research* **75**, 285–291.
Mustad, V. A., Kris-Etherton, P. M., Derr, J., Reddy, C. C. & Pearson, T. A. (1993). Comparison of the effects of diets rich in stearic acid versus myristic acid and lauric acid on platelet fatty acids and excretion of thromboxane A2 and PGI2 metabolites in healthy young men. *Metabolism* **42**, 463–469.
Mutanen, M., Krusius, T., Rasanen, L., Freese, R., Vahtera, E. & Viikari, J. S. (1995). Habitual diet, platelet function, fibrinogen and factor VII coagulant activity in young Finns. *Journal of Internal Medicine* **237**, 577–583.
Nair, C. H. & Dhall, D. P. (1991). Studies on fibrin network structure: the effect of some plasma proteins. *Thrombosis Research* **61**, 315–325.
Nieuwenhuizen, W. (1994). Biochemistry and measurement of fibrinogen. *Blood Coagulation and Fibrinolysis* **5**, Suppl. 2, 1.
Oosthuizen, W., Vorster, H. H., Jerling, J. C., Barnard, H. C., Smuts, C. M., Silvis, N., Kruger, A. & Venter, C. S. (1994). Both fish oil and olive oil lowered plasma fibrinogen in women with high baseline fibrinogen levels. *Thrombosis and Haemostasis* **72**, 557–562.
Pan, W. H., Chin, C. J., Sheu, C. T. & Lee, M. H. (1993). Hemostatic factors and blood lipids in young Buddhist vegetarians and omnivores. *American Journal of Clinical Nutrition* **58**, 354–359.
Pilgeram, L. O. & Pickart, L. R. (1968). Control of fibrinogen biosynthesis: the role of free fatty acids. *Atherosclerosis Research* **8**, 155–166.
Poggi, M., Palareti, G., Biagi, R., Legnani, C., Parenti, M., Babini, A. C., Baraldi, L. & Coccheri, S. (1994). Prolonged very low calorie diet in highly obese subjects reduced plasma viscosity and red cell aggregation but not fibrinogen. *International Journal of Obesity and Related Metabolic Disorders* **18**, 490-496.
Radack, K., Deck, C. & Huster, G. (1989). Dietary supplementation with low-dose fish oils lowers fibrinogen levels: a randomized, double-blind controlled study. *Annals of Internal Medicine* **111**, 757–758.
Rankinen, T., Rauramaa, R., Vaisanen, S., Penttila, I. M. & Uusitupa, M. (1994). Relation of habitual diet and cardiorespiratory fitness to blood coagulation and fibrinolytic factors. *Thrombosis and Haemostasis* **71**, 180–183.
Renaud, S. C., Beswick, A. D., Fehily, A. M., Sharp, S. & Elwood, P. C. (1992). Alcohol and platelet aggregation: the Caerphilly Prospective Heart Disease Study. *American Journal of Clinical Nutrition* **55**, 1012–1017.
Renaud, S. & De Lorgeril, M. (1992). Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* **339**, 1523–1526.
Ridker, P. M., Vaughan, D. E., Stampfer, M. J., Glynn, R. J. & Hennekens, C. H. (1994). Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *Journal of the American Medical Association* **272**, 929–933.

Schmidt, E. B., Lervang, H. H., Varming, K., Madsen, P. & Dyerberg, J. (1992). Long-term supplementation with *n*-3 fatty acids, 1: effect on blood lipids, haemostasis and blood pressure. *Scandinavian Journal of Clinical and Laboratory Investigation* **52**, 221–228.

Shahar, E., Folsom, A. R., Wu, K. K., Dennis, B. H., Shimakawa, T., Conlan, M. G., Davis, C. E. & Williams, O. D. (1993). Associations of fish intake and dietary *n*-3 polyunsaturated fatty acids with a hypocoagulable profile. The Atherosclerosis Risk in Communities (ARIC) Study. *Arteriosclerosis and Thrombosis* **13**, 1205–1212.

Silvis, N., Vorster, H. H., Mollentze, W. F., De Jager, J. & Huisman, H. W. (1990). Metabolic and haemostatic consequences of dietary fibre and *n*-3 fatty acids in black type 2 (NIDDM) diabetic subjects: a placebo controlled study. *International Clinical Nutrition Reviews* **10**, 362–380.

Simon, J. A., Hodgkins, M. L., Browner, W. S., Neuhaus, J. M., Bernert, J. T. & Hulley, S. B. (1995). Serum fatty acids and the risk of coronary heart disease. *American Journal of Epidemiology* **142**, 469–476.

Simpson, H. C. R., Mann, J. I., Chakrabarti, R., Imeson, J. D., Stirling, Y., Tozer, M., Woolf, L. & Meade, T. W. (1982). Effect of high fibre diet on haemostatic variables in diabetes. *British Medical Journal* **284**, 1608.

Slabber, M., Barnard, H. C., Kuyl, J. M. & Badenhorst, C. J. (1992). Effect of a short-term very low calorie diet on plasma lipids, fibrinogen and factor VII in obese subjects. *Clinical Biochemistry* **25**, 334–335.

Spertini, O., Hauert, J. & Bachmann, F. (1992). Reaction of acetaldehyde with human platelets. *Thrombosis and Haemostasis* **67**, 126–130.

Stevenson,. E. T., Davy, K. P. & Seals, D. R. (1995). Hemostatic, metabolic and androgenic risk factors for coronary heart disease in physically active and less active postmenopausal women. *Arteriosclerosis Thrombosis Vascular Biology* **15**, 669–677.

Struck, M., Watkins, T., Tomeo, A., Halley, J. & Bierenbaum, M. (1994). Effect of red and white wine on serum lipids, platelet aggregation, oxidation products and antioxidants: a preliminary report. *Nutrition Research* **14**, 1811–1819.

Sundell, I. B., Dhalen, G. H. & Ranby, M. (1991). Diet-induced changes in glucose and triglycerides are associated with changes in plasminogen activator inhibitor levels. *Haemostasis* **21**, 175–180.

Sundell, I. B. & Ranby, M. (1993). Oat husk fiber decreases plasminogen activator inhibitor type 1 activity. *Haemostasis* **23**, 45–50.

Tholstrup, T., Marckmann, P., Jespersen, J. & Sandström, B. (1994). Fat high in stearic acid favorably affects blood lipids and factor VII coagulant activity in comparison with fats high in palmitic acid or high in myristic and lauric acids. *American Journal of Clinical Nutrition* **59**, 371–377.

Thomsen, C., Rasmussen, O. W., Ingerslev, J. & Hermansen, K. (1995). Plasma levels of von Willebrand factor in non-insulin-dependent diabetes mellitus are influenced by dietary monounsaturated fatty acids. *Thrombosis Research* **77**, 347–356.

Tripodi, A., Mannucci, P. M., Chantarangkul, V., Bottasso, B., Arbini, A. A., DellaBella, S. & Scorza, R. (1993). Markers of procoagulant imbalance in patients with localized melanomas and autoimmune disorders. *British Journal of Haematology* **84**, 670–674.

Ulbricht, T. L. V. & Southgate, D. A. T. (1991). Coronary heart disease: seven dietary factors. *Lancet* **338**, 985–992.

Urano, T., Kojima, Y., Takahashi, M., Serizawa, K., Sakakibara, K., Takada, Y. & Takada, A. (1993). Impaired fibrinolysis in hypertension and obesity due to high plasminogen activator inhibitor-1 level in plasma. *Japanese Journal of Physiology* **43**, 221–228.

Vaisanen, S., Rankinen, T., Penttila, I. & Rauramaa, R. (1995). Factor VII coagulant activity in relation to serum lipoproteins and dietary fat in middle-aged men. *Thrombosis and Haemostasis* **73**, 435–438.

Vanninen, E., Laitinen, J. & Uusitupa, M. (1994). Physical activity and fibrinogen concentration in newly diagnosed NIDDM. *Diabetes Care* **17**, 1031–1038.

Veenstra, J., Kluft, C., Ockhuizen, T. H., Van der Pol, H., Wedel, M. & Schaafsma, G. (1990). Effects of moderate alcohol consumption on platelet function, tissue-type plasminogen activator and plasminogen activator inhibitor. *Thrombosis and Haemostasis* **63**, 345–348.

Veldman, F. J. (1996). Possible mechanisms through which pectin influences fibrinogen concentration and fibrin network structure. PhD Thesis, Potchefstroom University for Christian Higher Education, South Africa.

Venter, C. S., Vorster, H. H., Silvis, N., Kruger, A., Mia, F. & Seftel, H. C. (1992). Determinants of plasma fibrinogen level in South African communities. In *Fibrinogen: a 'New' Cardiovascular Risk Factor*, pp. 166–171 [E. Ernst, W. Koenig, G. D. O. Lowe and T. W. Meade, editors]. Wien: Blackwell-MZV.

Venter, C. S., Vorster, H. H. & Van der Nest, D. G. (1990). Comparison between physiological effects of konjac-glucomannan and propionate in baboons fed 'western' diets. *Journal of Nutrition* **120**, 1046–1053.

Venter, C. S., Vorster, H. H., Van der Nest, D. G. & Wight, A. W. (1991). Effects of konjac-glucomannan and propionate on plasma fibrinogen and serum and liver lipids in Zucker rats. *South African Journal of Clinical Nutrition* **4**, 6–11.

Visudhiphan, S., Podsuppasit, S., Piboonnukarintr, O. & Tumliang, S. (1982). The relationship between high fibrinolytic activity and daily capsicum ingestion in Thais. *American Journal of Clinical Nutrition* **35**, 1452–1458.

Vorster, H. H., Badenhorst, C., Barnard, H. C., Walker, A. R. P., Kruger-Locke, M. M. & Van Jaarsveld, P. (1989). Effects of weight reduction on plasma fibrinogen levels and other metabolic variables in obese women. *South African Journal of Clinical Nutrition* **2**, 8–13.

Vorster, H. H., Benadé, A. J. S., Barnard, H. C., Locke, M. M., Silvis, N., Venter, C. S., Smuts, C. M., Engelbrecht, G. P. & Marais, M. P. (1992). Egg intake does not change plasma lipoprotein and coagulation profiles. *American Journal of Clinical Nutrition* **55**, 400–410.

Vorster, H., Jerling, J., Oosthuizen, W., Cummings, J., Bingham, S., Magee, L., Mulligan, A. & Runswick, S. (1996). Tea drinking and haemostasis: a randomized, placebo-controlled crossover study in free-living subjects. *Haemostasis* **26**, 58-64.

Vorster, H. H., Silvis, N., Venter, C. S., Van Ryssen, J. J., Huisman, H., Van Eeden, T. S. & Walker, A. R. P. (1987). Serum cholesterol, lipoproteins and plasma coagulation factors in South Africa blacks on a high egg but low-fat intake. *American Journal of Clinical Nutrition* **46**, 52–57.