Impaired Coagulation in the Bleeding of Chronic Liver Disease

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Abnormal bleeding is a relatively common occurrence in patients with liver disease (Ratnoff and Patch, 1942; Stefanini, 1951), the most common sites of bleeding being the skin, mucous membranes, uterus, oesophagus, stomach, duodenum, and rectum.

In some situations anatomical lesions are recognisable. In the uterus there is the raw area produced by menstruation (although many women with liver disease have amenorrhoea). In the gastro intestinal tract various lesions are known to be associated with liver disease: haemorrhoids in the rectum, varices in the oesophagus, gastritis of the stomach and chronic ulceration of the duodenum. Thus, patients with upper gastrointestinal haemorrhage and liver disease are by no means always bleeding from oesophageal varices, even when oesophageal varices are present (McCray et al., 1969). Factors precipitating haemorrhage from these sites in patients with liver disease are unknown, with the exception of menorrhagia and bleeding from haemorrhoids following straining at stool.

DEFECTIVE HAEMOSTASIS

The following mechanisms are involved:

Blood Flow

This is clearly important in, for example, bleeding from oesophageal varices. The flow through these vessels is very much greater than normal, and their walls are stretched, thin and under a relatively high pressure.

Primary Abnormalities of Small Blood Vessels

These may be important in some forms of bleeding in liver disease in that there is suggestive evidence of increased capillary fragility (Stefanini, 1951; Hedenberg and Korsan-Bengtsen, 1962; Kupfer et al., 1964).

Platelet Abnormalities

These are well described in liver disease and may contribute to haemorrhage. They can be divided into two groups, those representing a quantitative defect (thrombocytopenia) and those representing a qualitative defect of platelets.

Thrombocytopenia may be due to defective production or excessive loss of platelets. Defective production of platelets can be caused by marrow depression by alcohol, marrow aplasia in hepatitis or folate deficiency. Alcohol has a direct toxic effect on the bone marrow and a major intake of alcohol over a short period may be followed by transient thrombocytopenia (Cowan and Hines, 1971). Infective hepatitis also has a toxic effect on the bone marrow with aplasia and resulting thrombocytopenia (Levy *et al.*, 1965; *Lancet*, 1971). Folate deficiency reduces platelet production and is associated with chronic liver disease, particularly in the chronic alcoholic.

Excessive loss of platelets may be due to platelet agglutinins, which have been described in patients with chronic liver disease (Tullis, 1956) but the magnitude of their effect is not established. In patients with portal hypertension, platelet loss may be related to 'hypersplenism', the phenomenon by which splenomegaly of any cause may be associated with diminution in circulating erythrocytes, platelets, or leucocytes, or any combination of these, at least partly due to sequestration of these elements within the enlarged spleen. Excessive loss of platelets in liver disease may also be due to their utilisation in disseminated intravascular coagulation (DIC) for which there is evidence both in chronic and acute liver disease (Verstraete *et al.*, 1965; Hörder, 1969; Lasch, 1969; Rake *et al.*, 1970, 1971).

Qualitative defects in platelets. Impaired platelet aggregation occurs in liver disease (Thomas *et al.*, 1967) and may be due to the presence of breakdown products of fibrin in the plasma (from DIC or abnormal fibrinolysis), or to an insufficient level of factor XII (Hageman factor) which may be low in liver disease and is necessary for the normal aggregation of platelets (Jurgens, 1962). Reduced adhesiveness of platelets to foreign surfaces has also been demonstrated (Cortet *et al.*, 1964). Impaired clot retraction in the absence of thrombocytopenia, implying abnormal platelet function, and abnormal platelet morphology suggesting abnormal function, have been recognised in liver disease (Stefanini, 1951).

Plasma Clotting Factors

The levels of the various plasma clotting factors in liver disease have attracted considerable study and the subject has been reviewed by Deutsch (1965), Walls and Losowsky (1971) and Losowsky *et al.* (1973). The literature gives an impression of confusion and contradiction. A simple approach is invalid

because there are many different mechanisms for alterations in clotting factor activities.

There is considerable evidence that the liver is the site of synthesis of clotting factors (Olson *et al.*, 1966) and failure of hepatocellular function is accompanied by diminished synthesis of these factors. Vitamin K is necessary for the synthesis of certain clotting factors and its deficiency, associated particularly with the malabsorption of biliary obstruction, may lead to diminished synthesis of these factors. Synthesis of fibrinogen, factor VIII and perhaps other clotting factors probably takes place both in the liver and in the reticulo-endothelial system (Deutsch, 1965). In liver disease, an increased synthesis in extrahepatic sites may mask decreased hepatic synthesis. For example, factor VIII levels are rarely low in liver disease and plasma fibrinogen is not infrequently increased in certain diseases of the liver and biliary system. In some cases, however, increased fibrinogen levels may be due to decreased fibrinolytic activity (Jedrychowski *et al.*, 1973).

Activation of the extrinsic clotting pathway is initiated by tissue damage, and in liver disease activation may be caused by damage to liver cells.

The liver is the site of removal of activated clotting factors (Deykin *et al.*, 1966; Wessler *et al.*, 1967) and also of factors involved in the fibrinolytic system (Fletcher *et al.*, 1964) and this function may be impaired in liver diseases.

Increase in fibrinolysis may occur in liver disease (Das and Cash, 1969) and the lytic enzymes destroy not only formed clot but also some of the clotting factors and can thus be responsible for lowered plasma levels of clotting factors. A decrease in fibrinolysis has been demonstrated in patients with obstructive jaundice (Jedrychowski *et al.*, 1973) and may be responsible for an increase in the fibrinogen level and might lead to increased susceptibility to thrombo-embolism.

Increased utilisation of clotting factors occurs, due to DIC, and may lead to secondary deficiencies of these factors.

Inhibitors of clotting factors and of fibrinolysis occur normally in the plasma but abnormal levels, either high or low, may occur in liver diseases and may affect clotting function.

By analogy with albumin levels, it has been suggested that dilution may play a part in the low levels of some clotting factors in liver disease, because in many such patients there is considerable expansion of the plasma volume and of the entire extracellular volume.

Aberrant molecular structure of clotting factors may explain a bleeding tendency in occasional patients with liver disease: a patient with hepatoma and an abnormal fibrinogen has been described (Von Fetten *et al.*, 1969).

THE USE OF CLOTTING FACTOR MEASUREMENTS

Diagnosis

If it could be shown that low levels of clotting factors in a jaundiced patient were restricted to those dependent on vitamin K (Table 1), and that these

TABLE 1

Factor	I	II	V	VII	IX	X
Synthesised in liver	+	+	+	+	+	+
Vitamin K dependent		+		+	+	+
Measured in one-stage PT	+	(+)	+	+		+

improved after vitamin K, this would be evidence in favour of a diagnosis of obstructive jaundice. Conversely, low levels of fibrinogen and factor V, which do not depend on vitamin K (Table 1), would suggest hepatocellular disease. In practice, individual clotting factors are rarely measured and, since the prothrombin time is easy to perform and widely available, it is often used instead. The factors that influence the prothrombin time are also shown in Table 1. A standardised assessment of the response of the prothrombin time to vitamin K may be of some value in diagnosis (Deutsch, 1965). This simple interpretation is, however, frequently invalidated by the other mechanisms of alteration in clotting factor activities. When individual clotting factors have been measured, some changes have been reported to be suggestive of certain diagnoses but the literature on many points is incomplete and contradictory. There is no convincing evidence that clotting factors give better diagnostic discrimination than the more commonly used biochemical tests of liver function.

Prognosis

Measurement of clotting factors as a guide to prognosis has a limited use. It has been suggested that low levels of factor V and, perhaps more particularly, a falling level of factor V, are of bad prognostic significance (Owren, 1949; Anderson, 1967). There is little evidence that this is more accurate than the usual tests of liver function. In the case of acute hepatic necrosis, however, a prolonged prothrombin time may be one of the most useful, if not the most useful, indication of a poor prognosis (Cook and Sherlock, 1965; Ritt et al., 1969).

Bleeding might be expected to be a circumstance in which tests of clotting function would be of prognostic value. Deutsch (1965) suggested that those patients who are most likely to bleed have very severe depression of the

'prothrombin group' (factors II, VII, IX and X) and factor V, or milder defects of these factors associated with some other haemostatic defect such as thrombocytopenia, DIC, or excessive fibrinolysis. Other authors suggest that factor IX (Spector and Corn, 1967), prothrombin as measured by the one-stage assay (Mannucci, 1970a) platelet count and adhesiveness (Cortet *et al.*, 1964), or the 'P and P' test (Mannucci, 1970b) are the best indicators of the likelihood of abnormal bleeding. None of these tests, however, provides a very convincing separation between those patients who do and do not have episodes of abnormal bleeding.

Management of Bleeding
The assessment of clotting factors might be expected to be of most value in the management of bleeding where a number of forms of therapy need to be considered.

Vitamin K therapy is widely known and widely used.

Transfusion may, on occasion, be thought desirable to attempt to improve levels of plasma clotting factors but both theory and practice suggest that such therapy is not likely to be of great value. The levels of clotting factors in patients with liver disease are rarely as low as in patients with bleeding due to congenital deficiencies of individual clotting factors: there is no evidence to suggest that multiple, less severe deficiencies might have a synergistic contribution to bleeding. Furthermore, infusion of blood or blood products results in a relatively transient effect on plasma clotting factors at the expense of a rise in plasma volume (Finkbiner *et al.*, 1959; Spector *et al.*, 1966) which might tend to precipitate haemorrhage. Calculation of the amount to be infused, on a basis of the level of clotting factors required for haemostasis, is invalidated by inhibitors of coagulation or by excessive utilisation of clotting factors by DIC or by fibrinolysis. When it is necessary to replace blood after acute haemorrhage, fresh blood is preferable, but stored blood does supply appreciable amounts of factors II, VII, IX and X. The survival of factor V in stored blood is inconstant and if it is thought necessary to supply factor V, blood that is as fresh as possible should be used. If it is desired to replete clotting factors, and red cells or platelets are not required, plasma may be used. Fresh frozen plasma is preferable in order to provide the greatest concentration of clotting factors, but it may be necessary to transfuse unacceptably large volumes, in which case concentrates containing particular clotting factors would be indicated. Factor VIII concentrates, which have been widely used in the treatment of haemophilia, are not necessary in patients with liver disease since factor VIII levels are not low. Fibrinogen is relatively easily available. Unfortunately, other concentrates are not yet widely available.

Platelet infusions have not been adequately assessed in bleeding associated with liver disease. Personal experience suggests that they are unlikely to be helpful in patients in whom no more definitive measures are available for stopping bleeding. However, it would seem reasonable to attempt platelet infusion if there is massive bleeding and severe thrombocytopenia, or as a pre-operative measure for the thrombocytopenic patient. If blood is necessary, fresh blood would retain a useful proportion of its platelets for 24 hours. Platelet-rich plasma retains its platelets for a rather longer period, as do platelet concentrates, but these require special care in preparation and storage. As a rough guide to therapy one might aim at infusing the platelets from perhaps six pints of blood initially, and aim at a platelet count of over 50,000 per mm^3.

Inhibitors of fibrinolysis would not be expected to be of general benefit in liver disease, since the commonly occurring increase in fibrinolysis is not sufficient to be of clinical importance. Inhibition of fibrinolysis in patients with cirrhosis shows no useful effect (Lewis and Doyle, 1964; Tytgat et al., 1971). But in occasional patients, after shunt surgery or liver transplantation, excessive fibrinolysis may be a major mechanism responsible for abnormal bleeding (Starzl et al., 1963; Grossi et al., 1964). In such patients inhibitors of fibrinolysis (epsilon amino caproic acid (EACA) or aminomethyl cyclohexane carboxylic acid (AMCA)) might justifiably be used, with careful laboratory control.

Heparin has been tried in patients with acute or chronic liver disease in view of evidence that DIC may occur in these conditions (Zetterqvist and Francken, 1963; Johansson, 1964; Rake et al., 1970). Apart from a possible value in improving clotting function and preventing bleeding, it was hoped that heparin might have some effect in improving overall morbidity and mortality if DIC were an intermediary mechanism responsible for some of the tissue damage. Treatment with heparin has been shown to reduce the fibrinogen turnover and increase the fibrinogen level, platelet count and factor V level in patients with cirrhosis (Verstraete et al., 1965; Hörder, 1969; Lasch, 1969; Tytgat et al., 1971) but there is no evidence of overall benefit to the patient. Features of DIC may be present in some patients with fulminant hepatic failure, and there are impressive case reports of clinical improvement and improvement in the fibrinogen turnover after carefully monitored use of heparin (Rake et al., 1971), and some of these patients survived. Some patients with fulminant hepatic failure do, however, survive whatever form of therapy is used (Trey et al., 1970) and heparin may well contribute to gastrointestinal or other bleeding. Perhaps it may ultimately prove possible to select a sub-group of patients with fulminant hepatic failure in whom DIC is a major

feature and who may benefit from therapy with heparin. There is, however, at the moment, no controlled evidence of ultimate benefit from heparin in this condition, and there may be considerable dangers in its use.

CONCLUSIONS

1. Impaired coagulation is only one of the many factors in the bleeding diathesis in patients with liver disease. Impaired coagulation probably plays only a minor part in abnormal bleeding in liver disease.

2. Measurements of clotting factors are, in general, not very useful in diagnosis or prognosis in patients with liver disease, with the exception of the prognostic value of the prothrombin time in acute hepatic necrosis.

3. Therapy directed at impaired coagulation may be of some benefit in selected patients with liver disease, but there is no controlled clinical evidence of this.

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The Grand Manner

Georgian physicians had style in their financial dealings. Huge fees were asked and received but they made courteous exceptions. 'I had rather return the fee of a gentleman with whose rank I am not perfectly acquainted than run the risk of taking it from a man who ought perhaps to be the object of my bounty', wrote Dr John Fothergill. When Nelson suggested that his doctor in Bath had charged too little, the physician said, 'Pray, Captain Nelson, allow me to follow what I consider my professional duty. Your illness, sir, was brought on by serving your King and Country, and believe me, I love both too well to be able to receive any more'. The style could be used to demand a fee. Dr Mead, much tried by a cleric who kept mentioning the treatment he had received from Dr Cheyne, wrote: 'Sir, I have never yet, in the whole course of my practice, taken or demanded the least fee from any clergyman; but, since you have been pleased, contrary to what I have met with in any other gentleman of your profession, to prescribe to me rather than follow my prescriptions, when you had committed the care of your recovery to my skill and trust, you must not take it amiss, nor will, I hope, think it unfair, if I demand ten guineas of you.'