medical associations initiating the revision of the 1964 Helsinki Declaration, accepted the revised declaration in November 1975. Since then it has been considered a norm for Danish doctors engaged in biomedical research. As a consequence several independent ethical committees have to be established, and such committees represent an innovation in Danish scientific life. A preparatory group was set up, representing such different institutions and organisations as universities, the National Health Service, hospital owners, general practitioners, the pharmaceutical industry, dental and pharmaceutical high schools, scientific societies, the Medical Association, etc. The preparatory group ended its work in March this year and summarised its recommendations in a report.

Procedure

The report suggests that all types of biomedical research in Denmark should be covered by the ethical committees. The investigators will have to add a "self-declaration" to the research protocol, stating that the project has been considered in the light of Helsinki Declaration II (stage 1). The protocol then has to be referred to a regional scientific-ethical committee (stage 2). Such committees will have to cover one or two counties (250 000-500 000 inhabitants) and include all research activities in the area. Scientists and citizen representatives will share the six (or 7) seats on an equal basis. If the investigator relies on his self-declaration, and thus does not ask for evaluation, the committee may still evaluate the protocol on its own initiative, but the investigator is free to start the project im-

mediately, and to continue it if no committee comments have appeared within one month. If the investigator asks for evaluation or if evaluation is statutory—for instance, when informed consent is considered inappropriate—the committee again has to consider the protocol within one month. It is suggested that membership should be honorary and the members bound by secrecy. The lay members are to be elected by the county councils and the scientific members by the scientists of the region.

A central scientific ethical committee (third stage), covering all Denmark, is planned to comprise 10 to 12 members, again with an equal number of lay and scientific members. The central committee will receive appeals from the regional committees or scientists, counsel regional committees or individual scientists, survey the field of scientific ethics, and serve ministries, courts, etc.

In the near future all groups affected (already represented in the preparatory work) will start negotiations to implement the suggestions of the report. The first committee should be elected before the end of this year.

The alternative to a committee system, as outlined, would certainly be legislation, with the risk of seriously hampering even ethically acceptable biomedical research, and probably not increasing the protection of the individual. The end result might easily be a loss to present and future patients if pathophysiological and clinical science were considerably restricted.

We in Denmark believe that a flexible committee system is a better way than restrictive legislation of obtaining a balance between the need to protect the people on whom research is performed and the need to make scientific advances that will benefit society, including patients.

Today's Treatment

Diseases of the urinary system

Treatment of blood disorders in renal disease and renal failure

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The outstanding haematological complication presented by patients with renal disease and renal failure is moderate to severe anaemia. Less common problems are abnormal haemostasis and erythrocytosis.

Anaemia in renal disease

The anaemias of renal disease are largely resistant to treatment. An understanding of the pathophysiology of the anaemia in the context of the patient's disease is essential for effective and safe management.

ACUTE RENAL FAILURE

A rapidly progressive anaemia occurs during the oliguric phase of acute renal failure. Usually by the second to third week of the illness the packed cell volume falls to 0.2-0.3. This volume is maintained regardless of the period of oliguria.

The normocytic normochromic anaemia is due to a combination of haemodilution, shortened red cell lifespan, and bone marrow depression.

In most patients blood transfusion is dangerous and unnecessary. The danger lies in the expansion of an already overloaded extracellular space, which may result in cardiac failure. Blood transfusion is unnecessary as oxygen delivery to the tissues is invariably adequate unless heart failure supervenes. In a normal man the oxygen-carrying capacity of the blood is 200 ml/l—(that is, a haemoglobin concentration of 150 g/l $\times$ 1.36 ml of oxygen per gram haemoglobin). Assuming a cardiac output of 5 l/min the oxygen available to the tissues is 1000 ml/min. The basal tissue oxygen need is 250 ml/min. Even a 50% reduction in red cell mass will leave adequate oxygen available for the tissue needs of a patient lying in bed.

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Only occasionally will the cardiac output fall sufficiently to jeopardise oxygen delivery.

Bleeding may be troublesome in some surgical or post-traumatic patients. Blood transfusion may then be indicated but should be restricted to small volumes of packed red cells.

CHRONIC RENAL FAILURE

The severity of the anaemia is related to the degree of renal impairment. The underlying causes of the anaemia are complex.

In a normal patient erythropoiesis in the bone marrow needs adequate amounts of protein, vitamin B₁₂, folic acid, iron, and normal haem synthesis. The cells are released into the circulation, where they survive for about 120 days. The total number of cells produced is sufficient to maintain a red cell mass at a fairly constant concentration. This concentration is adequate to sustain tissue oxygenation appropriate to the needs of the individual. The regulating link between tissue oxygenation and the committed red cell precursors in the bone marrow is erythropoietin.

The role of the kidney in producing renal erythropoietic factor, which acts with a plasma factor to produce erythropoietin, is central in explaining the anaemia of renal failure. It is commonly assumed that progressive loss of renal tissue results in reduced concentrations of plasma erythropoietin. Inappropriately low levels of erythropoietin have certainly been reported in both acute and chronic renal failure. Nevertheless, the insensitivity of the various assay techniques at low erythropoietin concentrations makes interpretation difficult. Recently the presence of a serum factor in chronic renal failure has been described. This factor inhibits erythropoietin-stimulated erythropoiesis. The inhibitor, which is not related to guanidosuccinic acid or other retention products, may play a considerable part in the genesis of anaemia in renal disease.

The accumulation of guanidosuccinic acid and related compounds in chronic renal failure directly suppresses erythropoiesis. These substances also impair the function of the red cell membrane and the red cell oxidation-reduction systems. This produces a shortening of the red cell lifespan.

The anaemia in its uncomplicated form is unresponsive to treatment. Usually, the haemoglobin concentration remains between 8 and 11 g/dl for a variable period while the patient is managed by dietary protein restriction. As further destruction of renal tissue occurs the plasma creatinine concentration rises and eventually the red cell mass is further reduced. At this point the patient is usually admitted to a haemodialysis programme.

Blood transfusion should be avoided unless specifically indicated because the sudden rise in packed cell volume can often have a disastrous effect on renal plasma flow, which in turn can further reduce the glomerular filtration rate. This causes further retention of nitrogenous products.

The major indication for blood transfusion is gastrointestinal haemorrhage, which is usually due to slow leakage from ulcers, but sudden haematemesis or melaena may occur. Replacement should be with whole blood. Rarely, small volumes of concentrated cells may be needed to raise the packed cell volume if lack of oxygen-carrying capacity is judged to be an important factor in the onset of cardiac failure, or if the symptoms of anaemia become intolerable.

Iron deficiency due to inadequate diet or other blood loss, such as menorrhagia, may occur and should be promptly diagnosed. Treatment with oral iron is usually adequate, but the response is less rapid than in normal subjects.

ANAEMIA OF MAINTENANCE HAEMODIALYSIS

Blood concentrations of waste products may be reduced by peritoneal dialysis or haemodialysis. This should result in an

improvement in erythropoiesis. Ferrokinetic studies in some patients have shown an immediate increase in iron turnover by the marrow after a single dialysis.

The observed haematological response to dialysis is, however, variable. Some patients show a fall in haemoglobin concentration with a subsequently small but appreciable rise over many months. In others the initial haemoglobin concentrations are maintained and may even increase. The factors influencing the size of the red cell mass are complex. Patients who retain their kidneys tend to do better than those who are anephric. The determining factors must be a balance of residual erythropoietin production, the level of inhibitors, and the effectiveness of dialysis. Ten years ago most dialysis patients had haemoglobin concentrations of 5-7 g/dl; today 7-9 g/dl is the norm. This is probably related to improvement in dialysis technique and equipment.

The chronic anaemia of dialysis may often be complicated by iron or folic acid deficiency. Loss of iron may occur in several ways, the most consistent of which is loss into the dialyser. A loss of 15 ml of blood at each dialysis will result in an iron deficit of 400-500 mg a year. Collection of specimens for routine patient monitoring is an important source of blood loss. Each 20 ml of blood removed from a dialysis patient will contain about 5 mg of iron. This is two to three times the average daily gastrointestinal iron absorption.

Iron deficiency is best detected by serum ferritin estimation or by bone marrow aspiration. Most patients will need 2 g of intravenous iron dextran each year, but a few will need larger doses.

Folic acid is only loosely bound to its plasma transport proteins and is easily dialysed. Megaloblastic anaemia is prevented by taking 5 mg of folic acid by mouth each day.

The compensatory mechanisms that sustain tissue oxygenation in severe anaemia are worth noting. The red cells of most dialysis patients contain increased concentrations of 2, 3-diphosphoglyceric acid (2, 3-DPG). These concentrations of 2, 3-DPG will increase the oxygen released from haemoglobin by 15-25%. Reduction of mixed venous oxygen tension also occurs. Both of these factors tend to minimise the increase in cardiac output necessary to compensate for the anaemia. This is partly why, despite a persistent anaemia, 80% of patients on dialysis can return to full-time work. It is against this background that potentially harmful therapeutic efforts at correcting the anaemia should be considered.

Anabolic steroids have been used to stimulate erythropoiesis. The most widely used preparations are testosterone, oxymetholone, and nandrolone decanoate. The results of androgen treatment in patients on maintenance haemodialysis are conflicting. Many studies show an increase in packed cell volume or red cell mass during the three months after starting treatment. The increase in red cell mass is achieved by stimulating erythropoietin production and increasing erythropoietic responsiveness to erythropoietin. Other factors must be considered in evaluating the clinical usefulness of these drugs. Androgens produce a reduction in plasma volume and an increase in red cell 2, 3-DPG. Both of these mechanisms are found in other conditions as a response to hypoxia. An increase in red cell mass is of little advantage if it is accompanied by a concomitant increase in tissue oxygen consumption due to the anabolic effect of androgens.

In view of the other complications of androgen treatment, such as impaired liver function, more detailed trials are necessary before androgen treatment can be recommended without reservation.

Cobalt chloride also stimulates erythropoiesis but should not be used because of its toxicity.

The evidence on the value of amino-acid supplements in the diet is conflicting. If the dietary protein intake is more than 60 g a day it is unlikely that oral amino-acids will be of value.

The only indications for blood transfusion are symptomatic anaemia and haemorrhage. Apart from suppressing erythro-

poiesis, repeated transfusion can have several disadvantages. The most obvious is post-transfusion hepatitis. Despite screening blood donors for hepatitis B surface antigen (HBsAg), the incidence of post-transfusion hepatitis has been reduced by only 30-50%. The cases of hepatitis that do occur are probably caused by giving blood from undetected HBsAg carriers, but hepatitis C and cytomegalovirus infections may occur.

The stimulation of white cell antibodies is more complex. The presence of these antibodies is generally held to jeopardise future transplantation. If no antibodies develop multiple transfusion appears to improve allograft survival. Immune enhancement has been suggested as a possible mechanism, but this is still open to speculation.

Some dialysis units try to minimise the risks of infection and immunological complications by giving frozen red cells that are repeatedly washed during preparation. These are not generally available.

ANAEMIA AND KIDNEY INFECTIONS

Chronic pyelonephritis and tuberculosis of the kidney may be accompanied by mild to moderate anaemia. This occurs in the absence of detectable renal impairment. In common with the anaemias due to other chronic disorders the haemoglobin concentration lies between 8 and 11 g/dl. The reduction in red cell mass is due to a shortened red cell life span caused by an extracorporeal defect. The concentration of erythropoietin is inappropriately low for the degree of anaemia, but inhibitors of erythropoietin-stimulated erythropoiesis are not present.

The haemoglobin concentration returns to normal after adequate treatment of the infection.

A few patients with continued chronic infection progress to renal failure. Their haemoglobin concentration is often lower than would be expected for the degree of renal impairment.

Haemostasis in renal disease

ABNORMAL PLATELET FUNCTION

Purpura, epistaxis, and gastrointestinal haemorrhage were once common in renal failure. Recently bleeding has become increasingly rare. This is probably due to better medical care, earlier dialysis, and the avoidance of aspirin. The major cause of the haemorrhage is abnormal platelet function, which is associated with low levels of platelet factor 3 and abnormal platelet aggregation. These defects are reversible by dialysis.

FIBRIN DEPOSITION IN RENAL DISEASE

Inappropriate formation of fibrin may occur in renal disease owing to a breakdown in the normal mechanisms that maintain blood in the fluid state. Normally fibrin is constantly formed in the body and is removed by the balancing fibrinolytic system. In some cases the release of procoagulant material (red cell or tissue thromboplastin), vascular endothelial damage, or abnormalities of blood flow may accelerate the coagulation process. The fibrinolytic system cannot cope with the amount of fibrin formed, and thrombosis may ensue. This process may be localised in the kidney or may be generalised, causing depletion of the coagulation factors and platelets. The generalised condition, disseminated intravascular coagulation (DIC), may be accompanied by a bleeding diathesis. In addition, when red cells are forced through the meshwork of fibrin they become fragmented. This may result in a microangiopathic haemolytic anaemia.

LOCAL FIBRIN DEPOSITION IN THE KIDNEY

Local fibrin deposition in the kidney occurs in the glomerular

crescents found in rapidly progressive glomerulonephritis, in the glomerular capillaries in haemolytic-uraemic syndrome allograft rejection, and in some patients with acute renal failure. Fibrin is also found in the arteriolar walls in malignant hypertension. In each of these conditions, especially rapidly progressive glomerulonephritis, the deposition of fibrin is thought to be an important factor in the development of the renal lesion.

The haematological findings include red cell fragmentation and raised urinary fibrin degradation products. The plasma concentrations of fibrinogen and the other coagulation factors are usually normal. The serum concentration of fibrin degradation products may be raised, and the platelet count commonly lies between 50 and $100 \times 10^9/l$ (5000 and 100 000/mm³).

Rapidly progressive glomerulonephritis is regarded as an immune complex disease. The immunosuppressive drug azathioprine is commonly used, but the recent use of plasmapheresis to reduce the concentration of circulating immune complexes may offer a better approach. Dipyridamole, an inhibitor of platelet aggregation, and heparin have been used to reduce the degree of fibrin deposition; when combined with azathioprine the incidence of side effects, especially haemorrhage, is high.

Similarly in allograft rejection the usual approach to treatment is immunosuppression, bolus injections of methylprednisolone sodium succinate (Solu-Medrone), and anticoagulation with heparin or warfarin.

The major therapeutic effort in these conditions has therefore been to minimise the extent of the observed renal lesions. The concept of anticoagulation is logical but still remains to be tested by adequately controlled studies. In summary, there is no good evidence that anticoagulation or inhibition of platelet function are of any value when there is local fibrin in the kidney.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

The commonest condition in which renal failure and DIC occurs is in the "shocked" patient in the intensive care ward. DIC may occur in the haemolytic-uraemic syndrome, when the distinction between that condition and thrombotic thrombocytopenic purpura becomes blurred. Toxaemia of pregnancy may be complicated by DIC.

The haematological features of DIC include red cell fragmentation, low platelet levels, and depletion of the coagulation factors, especially fibrinogen, factor V, and factor VIII. There may be generalised clinical bleeding. Treatment consists of removing or modifying the cause, correcting the deficiencies, and giving anticoagulant treatment.

The role of replacement treatment and heparin is still controversial. Giving heparin at a dose level of 5000-10 000 units/6 hours often results in severe haemorrhage. On the other hand, there are risks that fibrinogen may cause thromboembolic complications if the underlying cause of the DIC is still active. In practice replacement treatment has few observable side effects.

Non-bleeding patients with DIC but without dangerously low levels of platelets and coagulation factors should be closely monitored. Repeated coagulation tests will indicate the general trend of the disease after treatment of the primary condition.

If the patient is bleeding adequate replacement treatment should be given. Ideally specific component treatment is indicated, but it must be remembered that there are delays due to crossmatching, thawing frozen products, or reconstituting freeze-dried products. In patients with appreciable renal impairment an additional problem is fluid overload. Once the hypovolaemia has been corrected the volume of fluid given becomes critical.

Initially fresh frozen plasma should be given, followed by whole-blood transfusion. The blood chosen should be the most recently donated to provide the maximum oxygen-carrying capacity, adequate levels of coagulation factors, and some

platelets. The blood in most hospital transfusion departments is usually at least two to three days old. Arrangements should be made to obtain freshly drawn blood (less than six hours old) from the regional transfusion centre; alternatively, donors from a local or national panel should be bled.

Hypofibrinogenaemia is best controlled by using freeze-dried fibrinogen. Each bottle contains 1.5-2.5 g of dried product, which is usually reconstituted in 200 ml of sterile water. If there is a problem with fluid overload the amount of water can be reduced to 100 ml.

Thrombocytopenia should be treated with platelet concentrates. In most hospitals there is a delay while platelet concentrates are being prepared or transported from the regional transfusion centre. Each unit consists of the platelets from four to five donors. Two units should be given as soon as they are available.

At this point the clinical and haematological effect of replacement treatment should be assessed. If bleeding continues heparin treatment should be tried. The dosage is started at the rate of 10 000 units every 24 hours by constant intravenous infusion or 5000 units subcutaneously every 12 hours. This may

be cautiously increased if indicated. Heparin treatment should be stopped when the platelet count reaches $100 \times 10^9/l$ ($100\,000/mm^3$).

Erythrocytosis

Carcinoma of the kidney, other renal tumours, polycystic kidneys, and a hydronephrosis may be accompanied by an increase in the red cell mass. The incidence of erythrocytosis in carcinoma of the kidney has been variously reported as 1-10%. Erythropoietin may be produced by some tumours. The increased erythropoietin concentration, however, is more likely to originate from the distorted renal tissue surrounding the various lesions. Removal of the diseased kidney results in the red cell mass returning to normal.

Renal transplantation is usually followed by a progressive rise in packed cell volume. It is not uncommon for the haemoglobin concentration to reach 17-18 g/dl or higher. Sometimes patients must be treated by venesection to avoid thromboembolic episodes.

Clinical Topics

Menstruation and control of diabetes

C H WALSH, J M MALINS

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Summary

Seventy per cent of the patients aged 45 years or under and suffering from diabetic ketoacidosis who were seen in one diabetic clinic over five years were women. The association of menstruation with ketoacidosis was assessed over two and a half years, and it was found that menstruation was associated with ketoacidosis more often than would be expected by chance ($P < 0.01$).

Two hundred women were interviewed and 76 observed that menstruation changed their diabetic control. Fifty-three found that control deteriorated and hyperglycaemia occurred, while 23 found that control improved and hypoglycaemia was a common problem.

Menstruation appears to be an important factor in influencing control of diabetes. The mechanism of the changes observed has not yet been determined, but it seems to be a subject worthy of further investigation.

Introduction

Several textbooks^{1,2} indicate that control of diabetes may be impaired around the time of menstruation. These observations

are based largely on clinical impressions and are supported by occasional case reports of severe and sometimes fatal ketoacidosis occurring at the onset of menstruation.^{3,4} They do not, however, indicate the frequency of changes in diabetic control at the time of menstruation, nor do they indicate whether changes other than hyperglycaemia and ketoacidosis occur. Clearly such information is necessary so that patients can be advised about this problem and acute metabolic disturbances minimised. We undertook a study to determine the type of changes in diabetic control that occur at menstruation and their frequency.

Patients and methods

The study was carried out in three parts.

The incidence of diabetic ketoacidosis was assessed over five years (1971-5) and related to sex and age. Diabetic ketoacidosis was defined as uncontrolled diabetes requiring intravenous fluid and electrolyte replacement, the presence of ketonuria ++ or +++, and a standard bicarbonate concentration of 17.5 mmol (mEq)/l or less.

Association between diabetic ketoacidosis and menstruation—This was determined in women who were admitted from January 1974 to June 1976. Throughout this time we took a detailed menstrual history from all except nine of the women with ketoacidosis once they had recovered from the acute metabolic disturbance. All the patients who complied with our criteria for ketoacidosis were included in this part of the study, except those in whom menstruation had stopped because of pregnancy, hysterectomy, or the menopause. Six patients whose presenting feature of diabetes was diabetic ketoacidosis were also excluded, though it is noteworthy that ketoacidosis was associated with menstruation in five of them. Diabetic ketoacidosis was considered to be associated with menstruation when menstruation was present on admission or on either of the two days before or after admission.

Questionnaire—In the third part of the study 200 consecutive women

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