analgesia a 3-cm. incision was made in the lower part of the scar and 3–4 oz. (85–114 ml.) of clot was removed; but this made little difference to the contour of the abdomen, and it was felt that most of the bleeding was interstitial and generalized, as it so often is in haemophilia. A fuller vaginal examination was done, a large offensive-smelling clot was removed, and a swab was taken for bacterial culture. The impression of a large haematoma in the pelvis was confirmed.

On July 14, following the examination of the previous day, there was little vaginal bleeding, but her haemoglobin level had fallen from 13.3 g. per 100 ml. on July 10 to 7.1 g. per 100 ml. It should be mentioned here that it was never possible to measure the rate of bleeding either from the vaginal loss, which was mainly of days-old clot, or by palpation of the lower abdomen, in which the size of the haematoma fluctuated from day to day. The pulse and the patient's own well-being proved the most useful guides to therapy.

She was given 1 litre of fresh plasma and 1 litre of fresh blood, and from this time on frequent similar transfusions were given. Large clots were passed with almost unchanging frequency (about four clots a day) per vaginam, and the haemoglobin level was maintained at an average of 10 g. per 100 ml., falling as low as 5.9 g. on July 20, and rising to 13.5 g. on August 6. The presence of vaginal clots caused her great discomfort and removal always gave relief. A culture of *E. coli* was obtained from clot and urine. The organism was insensitive to penicillin V, which she had been taking, but sensitive to chlortetracycline, which was started on July 15. She became afebrile, but her temperature rose again on July 26, when the chlortetracycline was stopped. From then on sulphadimidine and penicillin V were given and she remained afebrile up to the time of discharge. Her general condition improved with the control of infection, and from July 15 there was a steady reduction in the apparent size of the pelvic mass, as judged by abdominal palpation, and micturition returned to normal in spite of continued bleeding.

During her treatment in Oxford she was given 13½ litres of fresh plasma, 9 litres of fresh blood, and 5 litres of stored blood. On average the A.H.G. level was raised to 45% by the transfusion of 1 litre of fresh plasma.

On July 29 she had a minor rigor after plasma transfusion, and this recurred on July 30 after plasma. There were fortunately no further similar reactions. On July 31 she woke up to find the eyelashes of all four lids had fallen out on to the sheet in the night. There were no signs of local inflammatory change, and we have not been able to explain this. Fortunately, new growth soon started again.

On August 6 the amount of clot passed seemed to be less and it again had a foul smell. We were inclined to take the pessimistic view at this stage, and assumed that she must be forming an infected pelvic haemorrhagic "cyst." To our surprise and satisfaction she improved from then on. Transfusions and clots became less frequent and smaller, and her haemoglobin slowly rose. The abdominal wound was completely healed.

On August 11, six weeks and three days after operation, the bleeding finally stopped, and from then she improved rapidly and finally left hospital in good health one month later, her only complaint being of some urgency of micturition. Her abdomen was quite normal on palpation.

Discussion

In the absence of any clear indication of haemostatic defect, excessive bleeding in a female is particularly disconcerting. There is the natural tendency to attempt to control the bleeding by methods known to be effective in haemostatically normal people. In this patient the defect was haematologically so slight that it was unlikely to be detected in any but a specialist laboratory, and the patient's ignorance about her own family prevented any specific search for haemophilia.

Had the diagnosis been clear from the onset the general management of the case would undoubtedly have been different. Haemophilic bleeding cannot be controlled without restoring a normal clotting mechanism. Had the true problem been appreciated, the first curettage would have been preceded by a big transfusion of fresh plasma. Thereafter the local bleeding site would have been left alone to heal and bleeding treated by transfusion of fresh plasma and whole blood. Any extension of the bleeding area by operation can only increase bleeding in a haemostatically abnormal patient.

It may be wondered why the patient's bleeding was so persistent and rapid even after her haemostatic mechanism was virtually controlled by transfusion. When first seen at the Radcliffe Infirmary she was bleeding from an inaccessible secondarily infected site. In such a wound the vessels are not normally contractile and, unless local pressure can occlude the blood flow temporarily, normal coagulation cannot arrest the bleeding. In such adverse circumstances it is necessary to have great patience and to recollect that haemophilic bleeding is usually finally arrested by healing.

Summary

A female patient, apparently suffering from mild haemophilia, was admitted to hospital with severe post-operative bleeding. Her progress and treatment in hospital are described. A study of her near relatives was made.

We thank Professor L. J. Witts for permission to publish the case; Mr. J. W. Nankivell for referring the case; and Drs. O. Gunnery, E. R. Jones, and N. M. Parkes for help in obtaining samples of blood from relatives. We also thank the Oxford Regional Blood Transfusion Service, whose very helpful co-operation was largely responsible for the patient's recovery. Miss Ruth Anderson carried out the laboratory tests on which the diagnosis was based. Dr. R. G. Macfarlane and Professor L. J. Witts kindly read the manuscript.

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VENO-OCCLUSIVE DISEASE OF LIVER IN AFRICAN CHILDREN

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All the publications on veno-occlusive disease of the liver have originated from Jamaica, where it is reported as occurring predominantly in children (Jelliffe *et al.*, 1954a, 1954b; Bras *et al.*, 1954) and more rarely in adults (Stuart and Bras, 1955). The authors who observed this condition in Jamaica had never seen it while working in equatorial Africa, in Indonesia, or in the temperate zones (Jelliffe *et al.*, 1954b). However, cases of this nature are said to have occurred in Egypt (F.A.O.-W.H.O.-Macy Foundation, 1955, p. 76).

In 1953 Hill *et al.* described a hepatic syndrome in Jamaican children clinically identical with veno-occlusive disease of the liver. They termed this syndrome serous hepatosis on the basis of certain histological observations. However, on reviewing their cases subsequently they found that these showed the histological picture of veno-occlusive disease of the liver (Addendum to Jelliffe *et al.*, 1954b; Bras and Hill, 1956).

Veno-occlusive disease of the liver occurs most commonly in children between the ages of 1½ and 3 years,

although adults, older children, and even younger infants may be affected. Bras believes that he has seen lesions of this nature in the newborn (F.A.O.-W.H.O.-Macy Foundation, 1955, p. 70). Clinically the condition has been divided into three overlapping phases (Jelliffe *et al.*, 1954b). The acute phase starts suddenly with hepatic enlargement, which is usually associated with ascites. This phase may be of short duration and complete recovery may occur; on the other hand, the disease may progress over a variable period to the subacute phase. A small proportion of the patients die in the acute phase of liver failure or intercurrent infection. During the subacute phase there is persistent firm hepatomegaly, which is often asymptomatic, but recurrent attacks of ascites may occur. It is doubtful whether any of the subacute cases recover completely, although they may improve clinically with subsidence of ascites and disappearance of hepatomegaly. Most of these cases progress to the chronic phase of liver failure and cirrhosis. Splenomegaly may occur in the chronic phase, but is an uncommon feature in the acute and subacute phases. Jaundice is unusual except terminally. Liver-function tests show progressive liver damage as the disease progresses. Serum protein levels are low, with a relatively high globulin level.

The histology of the liver in veno-occlusive disease has been thoroughly investigated by means of serial liver biopsies (Jelliffe *et al.*, 1954b; Bras *et al.*, 1954). The feature common to all phases is an occlusive process involving the smaller branches of the hepatic venous tree. This occlusion is either partial or complete, and is due to endophlebitis causing concentric intimal padding of the vessel wall. In the early phase the intima is greatly swollen by oedema, but later connective tissue is laid down. Thromboses are rare. The occlusion of the veins gives rise to intense centrilobular congestion with widening of the sinusoids, which may then rupture and coalesce to form blood "lagoons." The pressure of the blood lagoons produces necrosis of the surrounding liver cells. Finally, there is replacement fibrosis which distorts the liver architecture and progresses to centrilobular cirrhosis.

Macroscopic examination in the early phase of the disease shows that the liver is smoothly swollen and turgid with blood, but that later it becomes finely granular, with the development of a collateral circulation and varix formation. This condition differs from the classical Chiari's syndrome (Thompson, 1947) by the total absence of thromboses in the major hepatic veins.

Three cases of veno-occlusive disease of the liver in African children at this hospital are described.

Case 1

A female African child aged 14 months was admitted to hospital on March 15, 1955. The history was of swelling of the legs and abdomen for one month and rapid respiration for four days. She had been breast-fed until 4 months of age and since then had been fed on maize porridge, small quantities of skimmed milk, and vegetables. She had never been taken to a witch-doctor or given herbs of any type. She had had no previous illnesses. One older sibling and her mother and father were quite well.

On admission the child was very dyspnoeic and oedematous, with marked abdominal distension. There was a mild degree of pallor but no jaundice. Her state of nutrition was poor; she had sparse fine hair and depigmented skin. The heart was not enlarged and there were no murmurs. Jugular venous pressure was not raised. Crepitations were heard at the bases of both lungs. The edge of the liver was

palpable three fingerbreadths below the costal margin in the mid-clavicular line and there was much free fluid in the abdomen. There were dilated veins around the umbilicus.

On chemical and microscopical examination the urine showed no abnormalities. A blood count showed: haemoglobin, 9.5 g. per 100 ml.; leucocytes 15,200 per c.mm. (33% neutrophils, 61% lymphocytes, 5% monocytes, 1% eosinophils). The Wassermann reaction was negative. Liver-function tests showed: thymol turbidity, 5.5 units; thymol flocculation, + + + +; colloidal red, + + + +; Takata-Ara, + + +; alkaline phosphatase, 18.2 units; prothrombin index, 92%. The total serum protein level was 3.5 g. per 100 ml. (globulin 2 g., albumin 1.5 g.).

Mantoux tests (1/1000 and 1/100) were negative. X-ray examination of the chest showed consolidation of the right lower lobe and collapse of the left lower lobe and a lamellar effusion in the right pleural cavity. The heart was not enlarged, and on fluoroscopy was shown to be pulsating normally. Barium swallow examination revealed no oesophageal varices. The electrocardiogram was normal.

Paracentesis abdominis was done on several occasions, yielding considerable quantities of straw-coloured fluid. The fluid had a total protein content of 1.5 g. per 100 ml. and a specific gravity of 1008. Culture of the fluid did not reveal *Mycobacterium tuberculosis*.

Biopsy of liver and peritoneum and a portal venogram were done through a small abdominal incision (Mr. L. Stein). The peritoneum was healthy and the liver appeared swollen and plum-coloured, and on microscopical examination

FIG. 1.—Case 1. Showing areas of centrilobular congestion of the liver (low power).

FIG. 2.—Case 1. Showing endophlebitis of a central vein of the liver with centrilobular congestion and a blood lagoon (high power).

revealed marked centrilobular congestion. The portal venogram suggested obstruction to the intrahepatic blood flow.

During her stay in hospital the patient's condition steadily deteriorated. Ascitic fluid re-formed at frequent intervals, causing distress. Paracentesis abdominis produced only brief relief, and four weeks after admission the patient died of bronchopneumonia.

Necropsy Findings (Dr. R. V. Dando).—The right pleural cavity contained a small amount of straw-coloured fluid. The lungs showed the features of bilateral bronchopneumonia. A branch of the right pulmonary artery was occluded by ante-mortem thrombus. Microscopical examination of this vessel showed no abnormality of the wall. The heart and pericardium were normal. The liver was smooth and intensely congested. Neither the hepatic veins nor the inferior vena cava contained ante-mortem thrombi. Microscopical examination of the liver showed well-marked centrilobular congestion with atrophy of liver cords and merging of adjacent sinusoids. Many of the sublobular and centrilobular veins showed acute oedematous intimal thickening with almost complete occlusion of the lumina. There were no ante-mortem thrombi in these vessels. Pathologist's comment: The histological features are those of veno-occlusive disease of the liver. Death was due to veno-occlusive disease of the liver and bronchopneumonia.

Case 2

A female African child aged 5 months was admitted to hospital on August 8, 1955. The history was one of abdominal swelling for 10 days. She had been breast-fed since birth, and this had been supplemented with three daily feeds of porridge, milk, and water for the month before admission. No herbs or witch-doctors' medicine had been given. Pregnancy and delivery had been normal and there was no history of previous illnesses. Mother, father, and three siblings were all well.

Examination on admission revealed a small child with gross oedema of the body, particularly affecting the abdomen and lower limbs. There was no pallor or jaundice or any obvious signs of malnutrition. The heart and lungs were normal. The liver edge was palpable at the umbilicus and the spleen was just palpable at the costal margin. There was much free fluid in the abdomen.

Chemical and microscopical examination of the urine showed no abnormalities. A blood count revealed: haemoglobin, 11.6 g. per 100 ml.; leucocytes, 9,800 per c.mm. (32% neutrophils, 67% lymphocytes, 1% monocytes). The Wassermann reaction was negative. Blood urea was 22 mg. per 100 ml. Liver-function tests showed: thymol turbidity, 2 units; thymol flocculation, ++++; colloidal red, ++; Takata-Ara, negative; prothrombin index, 75%. The total serum protein level was 4.2 g. per 100 ml. (globulin 2.4 g., albumin 1.8 g.).

Mantoux tests (1/1000 and 1/100) were negative. X-ray examination showed normal heart and lungs, and no evidence in bones of congenital syphilis. Intravenous pyelography showed normal renal excretion and normal renal calices. Barium swallow examination revealed no oesophageal varices.

Paracentesis abdominis on several occasions yielded considerable quantities of straw-coloured fluid. The specific gravity of the fluid was 1007 and the protein content was 0.9 g. per 100 ml. Neither *M. tuberculosis* nor any other organism could be cultured from the fluid.

Laparotomy was performed through a small abdominal incision (Mr. L. Stein). The liver was found to be congested and very swollen. The peritoneum was healthy. A portal venogram showed marked delay in the blood flow through the liver. The hepatic artery was ligated in the hope of relieving the hepatic congestion. Microscopical examination of a biopsy specimen of the liver showed marked centrilobular congestion.

During the child's stay in hospital her abdomen became distended with fluid, necessitating repeated paracentesis.

Blood and plasma transfusions were given. Five weeks after admission she became febrile and dyspnoeic, and was found to have bilateral bronchopneumonia. In spite of antibiotics she died four days later.

Necropsy Findings (Dr. R. V. Dando).—Both lungs showed numerous atelectatic areas and the features of a well-marked bronchopneumonia. The pulmonary arteries, the heart, and the pericardium were normal. The cardiac end of the oesophagus contained numerous small varices. The liver was greatly enlarged and mottled owing to congestion. The inferior vena cava and hepatic veins contained no thrombi. The spleen was congested and slightly enlarged. Microscopical examination of the liver showed diffuse centrilobular congestion and marked dilatation of the sinusoids. In many of the sections the centrilobular and sublobular veins showed striking oedematous thickening of the intima with almost complete occlusion of the lumina of these veins. Pathologist's comment: The histological features are those of veno-occlusive disease of the liver.

Case 3

A female African child aged 1 year was admitted to hospital on March 2, 1956. The history was of swelling of the legs and abdomen for four months. She had been fully breast-fed for three months, and on admission was still being breast-fed as well as receiving maize porridge, vegetables, and small quantities of meat. There was no history of medicines or herbs having been given. She had had no previous illnesses, and her mother, father, and two siblings were quite well.

Examination on admission revealed an undernourished child. The skin showed patchy depigmentation but no nutritional dermatosis. The hair growth was moderate. A mild degree of pallor was present but no jaundice. The lungs were healthy and no evidence of cardiac failure was found. The abdomen was distended and there were several dilated tortuous veins filling from below over the epigastrium. The liver had a firm rounded margin palpable three finger-breadths below the costal margin in the mid-clavicular line. There was a small amount of free fluid in the abdomen. The legs were mildly oedematous.

No abnormalities were found in the urine, chemically or microscopically. A blood count showed: haemoglobin 8.2 g. per 100 ml.; leucocytes, 21,400 per c.mm. (69% neutrophils, 28% lymphocytes, 1% eosinophils, 1% monocytes, 1% basophils); reticulocytes 5%. Erythrocyte sedimentation rate was 28 mm. in one hour. Red-cell fragility test was normal. Coombs and Schumm's tests were negative. No malaria parasites were seen on blood smears. Eagle's test was negative. Liver-function tests showed: thymol turbidity, 5.5 units; thymol flocculation, ++++; colloidal red, ++++; Takata-Ara, +; alkaline phosphatase, 15.5 units; prothrombin index 76%; serum bilirubin, 3.1 mg. per 100 ml. Total serum protein level was 6.1 g. per 100 ml. (globulin 3.6 g., albumin 2.5 g.).

A bone-marrow smear showed an erythroid reaction, normoblastic in type. Platelet genesis was normal. The myeloid series showed no abnormality.

Mantoux test 1/1000 strength was negative, but 1/100 strength was positive. X-ray examination of the chest revealed clear lung fields and the presence of hilar glands. The heart and pericardium were normal.

Paracentesis abdominis yielded only a very small quantity of straw-coloured fluid.

Treatment consisted of blood transfusion, streptomycin and isoniazid, and vitamin K. Three weeks after admission a liver biopsy and portal venogram were done through a small laparotomy wound (Mr. L. Stein). The liver was smooth and intensely congested, and numerous venous collaterals were seen. The venogram showed a striking hold-up of the blood flow through the liver.

About six hours after operation the patient had a severe haematemesis and died in spite of blood transfusion.

Section of the liver biopsy showed extremely severe centrilobular congestion with destruction and loss of parenchymal cells and condensation of the stroma. In one area of the section fibrous intimal thickening of a small venous channel with partial obstruction of the lumen was seen.

Necropsy Findings (Dr. J. Shapiro).—Lungs were congested and oedematous. Hilar glands were enlarged and caseous; microscopical examination of these showed tubercle follicles. Heart and pericardium were normal. Several dilated varices were found in the oesophagus. Dilated veins were seen in the wall of the stomach. Spleen and kidneys were congested. Liver was enlarged, rubbery firm, and plum-coloured. There were no thrombi in the hepatic veins. On section large quantities of dark red blood exuded from the cut surface of the liver. Microscopical examination of the liver revealed very marked congestion of the sinusoids with compression and atrophy of the parenchymal cells. The centrilobular veins showed intimal thickening with fibrosis and in many cases complete occlusion. The portal tracts showed scanty infiltration by lymphocytes and plasma cells. Pathologist's comment: The features suggest those of veno-occlusive disease of the liver.

Discussion

The three cases reported above were in all respects typical of veno-occlusive disease of the liver as originally described in Jamaica, except that our patients were all less than 18 months of age and were thus younger than the average of the Jamaican cases. Cases 1 and 2 were of the acute fulminating variety of the disease, and death was due to intercurrent infection after a relatively short illness. Case 3 corresponded to the description of the subacute phase of veno-occlusive disease of the liver with a longer history of swelling of the legs and hepatomegaly and more advanced liver disease, and finally death from haematemesis. There were marked disturbances of liver-function tests in all our cases, and serum proteins showed inverted albumin globulin ratios. Jaundice was not detectable clinically in any of the patients, but the serum bilirubin was raised in Case 3. The livers of all three patients were intensely congested, and microscopical study of necropsy specimens showed endophlebitis of the smaller venous radicles, with centrilobular congestion and associated cellular atrophy and stromal condensation in Case 3. There were no thrombi in large hepatic veins or inferior venae cavae. Case 3 had a primary tuberculous lesion in the lungs, but there was no evidence of tuberculosis in the abdomen or liver.

The aetiology of veno-occlusive disease of the liver is unknown. All the cases seen in Jamaica occur in the poorer economic groups, and, although clinically there is no striking evidence of malnutrition, the dietary histories in these cases suggest that malnutrition or subnutrition forms the unvarying background to this disease (Stuart and Bras, 1955). However, in veno-occlusive disease of the liver there is a remarkable rarity of fatty infiltration of the liver, which is the common hepatic manifestation in malnutrition (*British Medical Journal*, 1953). In a series of 150 cases of serous hepatitis (later found to be veno-occlusive disease of the liver), only 5 had associated fatty infiltration of the liver (Hill *et al.*, 1953). It has been suggested that veno-occlusive disease of the liver is caused by bush teas which are consumed by the poorer classes in Jamaica, and that these teas, which consist of various herbs, seeds, and roots, may be especially toxic to malnourished individuals (Jelliffe *et al.*, 1954b; Stuart and Bras, 1955).

None of our patients were strikingly undernourished, although two showed some evidence of malnutrition. At this hospital we see very many severely undernourished African children, and although fatty infiltration of the liver is a very common finding on biopsy or at necropsy, veno-occlusive disease of the liver is very rare. In our experience it would appear almost certain that malnutrition alone is not the cause of the disease.

In South Africa, Selzer and Parker (1951) reported a condition identical with veno-occlusive disease of the liver. They

described 12 cases in European and coloured adults and children. No liver biopsies were done, but six of the patients died and necropsies were carried out on them. Selzer and Parker present strong evidence that the condition observed by them was caused by the consumption of bread made of inadequately winnowed wheat and contaminated with senecio, or ragwort, a common wild plant.

Although there was no evidence to suggest that our patients had taken any herbs or plant substances such as senecio, it is common for African children to be given witch-doctors' medicines, this fact usually being concealed when the child is brought to hospital.

Thus it appears that although malnutrition was very unlikely to have been the only or even the primary cause of veno-occlusive disease in our patients, we cannot exclude the possibility that toxic substances, especially witch-doctors' herbs, were important aetiologically.

Summary

1. Clinical and pathological features of veno-occlusive disease of the liver are briefly reviewed.

2. Three cases of veno-occlusive disease of the liver in African children are described. All were less than 18 months of age, the first two presenting in the acute phase of the disease and dying from intercurrent infection, and the third in a subacute phase and dying from a haematemesis.

3. Our cases are discussed in relation to those described in Jamaica, particularly with regard to aetiology.

ADDENDUM.—Recently a further case of veno-occlusive disease of the liver was diagnosed on liver biopsy in a female African child aged 2 years with hepatosplenomegaly. She had a history of abdominal distension for two months and a previous history of having been given witch-doctors' herbs on several occasions.

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The Alcoholic and the Family is introduced by these words: "This booklet is not a medical handbook, nor does it set out to cover all the many aspects of alcoholism. Its purpose is to show that, by a true understanding of his problem and his position, the family of an alcoholic may do much to help him when he wishes to recover." The booklet is issued by the Church of England Temperance Society. It discusses some of the reasons why a person may become an alcoholic and how to help him. In outlining various forms of treatment, emphasis is placed on the need for co-operation between the alcoholic himself, his family, and his medical adviser. The booklet may be obtained from the Church of England Temperance Society, 4, Palace Gate, London, W.8, price 6d. net, together with another, *Alcohol and Drug Addiction* (free), which lists hospitals, institutions, and nursing-homes where such cases are admitted.