based on the necropsy, the microscopical preparation, and the radiograph. The task has given me many hours of happy toil. I hope that I have in a small way discharged the obligation of Dr. George Oliver to "encourage the application of physiological knowledge to the prevention and cure of disease."

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CLINICAL OBSERVATIONS ON VENO-OCCLUSIVE DISEASE OF THE LIVER IN JAMAICAN ADULTS

BY

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Veno-occlusive disease of the liver (V.O.D.) is a term given on histological grounds to a form of liver disease occurring frequently in Jamaican children and occasionally in adults (Bras *et al.*, 1954a, 1954b). The clinical features in children have been fully described by Rhodes (1954) and Jelliffe *et al.* (1954). Sometimes two or more members of the same family are affected. The disease is divided into three often ill-defined and overlapping stages. The acute stage is characterized by the sudden development of abdominal pain, hepatomegaly, often gross, and usually considerable ascites. Vomiting is common. Slight splenomegaly and ankle oedema sometimes occur. Children between the ages of 18 months and 3 years are primarily affected. Rhodes (1954) drew attention to the fact that the condition is often precipitated by other illnesses such as whooping-cough, respiratory infections, etc. Repeated paracenteses may be required in the acute stage; but subsidence of the hepatomegaly and ascites may occur with remarkable rapidity, sometimes disappearing completely in seven to fourteen days. The majority of patients appear to recover completely; but some die in the acute stage of liver failure (Bras *et al.*, 1954a, 1954b). The acute stage may pass, often imperceptibly, into the subacute stage of the disease; or it may be subacute apparently from the onset (Jelliffe *et al.*, 1954).

The subacute stage is characterized by a firm persistent hepatomegaly, and sometimes recurring ascites. It is often symptom-free, with the patient maintaining apparently normal health, and it is discovered only on routine examination or on examination for an unassociated complaint. The spleen is usually enlarged at this stage. Jaundice is rare in any stage of the disease except terminally. It would appear that complete resolution may occur even in the subacute stage of the condition. Alternatively, this stage may pass into the chronic stage of the disease. Acute episodes may occur in both the subacute and chronic stages.

The clinical features in the chronic stage are similar to those of any other form of cirrhosis, and often indistinguishable from them. It would appear, however, to progress more rapidly than cirrhosis from other causes. Death in this stage is often due to haematemesis from ruptured oesophageal varices. Hepatic failure and cholaemia are also frequent causes of death.

Theories of aetiology of this syndrome have been discussed in previous papers (Bras *et al.*, 1954a, 1954b; Rhodes, 1954). While it is possible that there is no uniform aetiology, there are certain common factors that appear to underlie this syndrome in Jamaica. All the cases seen here occur in the poorer economic groups, and, although the clinical stigmata of malnutrition are often minimal or absent, malnutrition or subnutrition, as judged from available dietary histories, forms the unvarying background to this disease (Rhodes, 1954).

Liver Function Tests of Cases Reported in Text

	Case 1				Case 2	Case 3		Case 4	
	No Symptoms	Onset of Illness	Height of Illness	Recovery	On Admission	First Admission	Second Admission	Onset of Illness	Two Days Before Death
Bilirubin (direct) (mg./100 ml.)	0.1	1.06	2.6	1.2	—	2.7	2.3	0.9	6.4
" (indirect) (mg./100 ml.)	0.5	2.0	4.0	2.4	—	6.0	6.4	1.1	9.8
Thymol turbidity (units)	2.8	1.6	2.1	2.9	3.1	7.7	6.4	2.1	5.1
Thymol flocculation	+	Neg.	+++	+	++	++++	++++	+	++
Gamma-globulin (Kunkel) units	10.8	13.2	18.2	16.8	32.1	40.0	42.4	16.1	25.0
Cephalin cholesterol flocculation	+	++	++++	+	+++	++++	+++	++	++++
Total protein (g./100 ml.)	8.5	5.8	5.6	7.7	6.5	8.4	7.5	6.0	6.3
Albumin	4.3	2.9	2.5	4.2	2.0	2.3	2.7	2.7	2.6
Globulin	4.2	2.9	3.1	3.5	4.5	6.1	4.8	3.3	3.7
Cholinesterase (Michel) (units)	0.61	0.36	0.13	0.75	0.10	0.15	0.08	0.26	0.10

This economic group habitually drinks a variety of "bush teas," which are infusions of various herbs, seeds, and roots, either medicinally or for food. Asprey and Thornton (1954) have classified and listed nearly 200 plants so used. It is conceivable that many of these may be misused, with toxic results, particularly in malnourished individuals.

Previous reports on this syndrome in Jamaica have been concerned mainly with its effects in children (Bras *et al.*, 1954a, 1954b; Jelliffe *et al.*, 1954; Hill *et al.*, 1953). The present paper deals with the clinical features and pathological findings in four cases of V.O.D. in Jamaican adults. In Case 1 we were able to get a detailed history of an increased number of bush teas taken immediately before the onset of illness.

The histology has been studied from serial liver biopsy specimens obtained by the Vim-Silverman needle, using the modified technique described by Hoffbauer (1947), and from post-mortem material. Liver-function tests on all cases are summarized in the Table.

Case 1

A 33-year-old Jamaican man was first seen on December 31, 1953, complaining of having had cough and occasional blood-stained sputum for the previous four months. There was some loss of appetite, but no weight loss or any other relevant symptoms. He had been x-rayed at the local chest clinic and told that he had pulmonary tuberculosis. Domiciliary treatment was started; and he had been in bed for two months before attending here. He had always taken a variety of "bush teas," and at the onset of his illness he added a number of others for their supposed medicinal value. These included donkey weed (*Stylosanthes hamata*), dandelion seeds (*Cassia ligustrina*), Cerasee (*Momordica charantia*), Jack-in-the-bush (*Eupatorium odoratum*), Nicker (*Caesalpinia bonducella*), and simple bible (*Aloe vulgaris*). There were no other relevant points in his previous history, and nothing significant in his family history.

On examination he was found to be a man of good physique, 6 ft. 2 in. (188 cm.) in height, and well proportioned. Physical findings at the time were completely negative except for a few persistent moist rales at the right lung base. His liver and spleen were not enlarged and there was no ascites. His haemoglobin was 15 g. per 100 ml., erythrocyte sedimentation rate 3 mm. in the first hour (Wintrobe), and repeated sputum examinations were negative for tubercle bacilli. A chest x-ray examination showed no signs of pulmonary tuberculosis; but there was increased shadowing of the right base, with localized emphysema and pleural thickening. The lesser fissure was depressed and the appearances suggested partial collapse of the right middle lobe. Liver-function tests were within normal limits (see Table). He was kept under close observation as an out-patient for the next ten weeks, during which time his condition remained unchanged.

On March 3, 1954, nine weeks after his first visit and one week after his last out-patient visit, he attended complaining

of severe abdominal pain and distension, and anorexia. His symptoms had started two days before, and he had vomited twice. He had also noticed a marked reduction in his urinary output. His weight had increased from 88.5 to 93 kg. in one week.

He was afebrile, but obviously ill and in acute discomfort. There was no anaemia, jaundice, or oedema. The chest signs were unchanged, and the cardiovascular and central nervous system examinations were again normal. There was now a tense ascites, and the liver was enlarged about 10 cm. below the costal margin (Fig. 1) and very tender. The spleen could not be palpated. He was admitted to hospital with a diagnosis of acute veno-occlusive disease of the liver.

Investigations.—Liver-function tests on admission showed impairment (see Table). Other laboratory investigations, including haematological examination and tests for sickling, serological tests for syphilis, and blood electrolytes, were normal. A chest x-ray film showed no change from the previous one.

Treatment and Progress

He was immediately put on a high-protein diet (150 g. a day), intramuscular injections of mersalyl, 2 ml. on alternate days, and restricted fluid and salt intake. The liver continued to increase in size until in two weeks it was palpable 14 cm. below the costal margin, and repeated paracenteses were required. Polyacrylic-carboxylic acid resin ("resodex"), 15 g. three times daily by mouth, was then added to the treatment schedule without any effect on the accumulation of ascitic fluid. Severe abdominal pain, and nausea with occasional vomiting, continued. There was

FIG. 1.—Photograph of Case 1, showing changes in size of liver.

FIG. 2.—Case 1. Clinical and laboratory features.

further deterioration in liver-function tests. A liver biopsy at this stage showed the changes of acute V.O.D.

After six weeks the ascitic fluid ceased to accumulate and the patient became clinically clear of ascites in ten days. The hepatomegaly disappeared in 21 days. This was paralleled by symptomatic improvement and improvement in tests of liver function (Fig. 2). He was discharged well ten weeks after admission, and readmitted three weeks later for a second liver biopsy.

Sputum culture for tubercle was positive just before his discharge from hospital; and on this account he was given 200 mg. of isoniazid daily by mouth and 1 g. of streptomycin twice weekly by intramuscular injection as an out-patient. This did not appear to have any relationship to his liver disease. When last seen in October, 1954, five months after discharge from hospital, he was well and free of symptoms except for slight occasional abdominal discomfort. His liver-function tests have remained normal and there has been no recurrence of ascites or hepatomegaly.

Histology

The first biopsy showed the classical picture of acute V.O.D. with intimal thickening of the hepatic vein branches, associated with severe congestion and sinusoidal dilatation (Bras *et al.*, 1954a, 1954b). The hepatic cells in the centrilobular areas were compressed owing to the widening of the sinusoids, otherwise the liver lobules showed normal cells. The second biopsy, three months later, showed nothing worthy of remark in the sinusoids. There was only slight residual intimal thickening in some of the hepatic veins. There was no discernible increase in reticulin.

Comment

A case of acute V.O.D. with clinical and histological recovery. We were fortunate in being able to observe this patient in the out-patient department for nine weeks before the onset of his illness. Two interesting features are (1) the onset soon after the addition of a number of "bush teas" to his diet, and (2) the rapid and unexplained subsidence of ascites and hepatomegaly after the sixth week of illness (Fig. 1).

Case 2

An 18-year-old Jamaican girl was admitted to hospital in October, 1952, with a twelve-days history of abdominal distension with severe pain, anorexia, and vomiting. There was nothing significant in her own or her family history. She had been in the habit of taking "bush teas" frequently. Her diet had always been predominantly carbohydrate with very little protein.

On examination she was found to be underweight (41 kg.) and obviously undernourished, with an angular stomatitis, cheilosis, and glossitis, and loss of normal skin texture and elasticity. There was no jaundice or pyrexia. The liver was tender, firm, irregular, and enlarged as far as the umbilicus. All investigations were negative except the liver-function tests, which showed gross impairment (see Table).

Treatment was started as in Case 1. The response was extremely slow, repeated paracenteses being required over a period of five months. Accumulation of ascitic fluid then gradually decreased, and she was discharged clinically much improved and free of ascites seven months after admission. There was, however, little improvement in her liver-function tests and a firm irregular hepatomegaly persisted. She was followed up in the out-patient department for two months after discharge, during which time there was no clinical deterioration. She died suddenly at home three weeks after her last out-patient visit, following a massive haematemesis. A post-mortem examination was not made.

Histology

Serial liver biopsies were performed on this patient while in hospital. The first biopsy one week after admission again showed sinusoidal widening surrounding partly or completely occluded hepatic veins. There was also a condensa-

tion and an increase in reticulin fibres in the centrilobular areas. The second biopsy, four weeks later, showed very little difference except that the fibrosis had increased appreciably. The liver cells showed regenerative phenomena such as mitoses. The third biopsy, four months after the first, gave essentially the same picture, but the non-portal fibrosis had progressed markedly.

Comment

Chronic V.O.D. often presents for the first time as suddenly as the acute stage of the disease; and these acute exacerbations may recur at varying intervals throughout the course of the illness. The absence of any history of the preceding acute or subacute stage is to be noted. By serial liver biopsies it was possible to observe progression of the fibrosis in spite of apparent clinical improvement.

Case 3

A 45-year-old Jamaican was admitted to hospital in September, 1953, with a history of loss of appetite, loss of weight, and listlessness for two months. Three days before admission his anorexia became worse, and he developed central abdominal pain and vomited after each meal.

On examination he was thin and wasted, his conjunctivae were injected, and he was jaundiced. There was generalized abdominal tenderness, but no ascites. His liver and spleen were not enlarged, and he was afebrile. All investigations, including chest x-ray examination, haematological examination, and serological tests for syphilis, were normal except the liver-function tests, which revealed marked impairment (see Table).

A diagnosis of infectious hepatitis was made; liver biopsy was not performed. Response to treatment was rapid, and on discharge in 18 days the patient had a normal appetite and the jaundice had almost cleared.

He was followed up in the out-patient department and seemed to be progressing favourably for three months, when he attended again complaining of severe abdominal pain and distension, nausea and vomiting, deepening jaundice, and reduction in urinary flow. On examination his jaundice was seen to have deepened considerably since his last visit one month previously. There was also a tense ascites with marked abdominal tenderness, and a very firm liver could now be palpated one fingerbreadth below the costal margin. Liver-function tests again showed marked abnormalities. A diagnosis of post-necrotic scarring following severe infectious hepatitis was made because of his previous history. His condition deteriorated rapidly in spite of

FIG. 3.—Case 3. Area of scarring in the liver. There is a branch of the hepatic vein with subintimal thickening and narrowing of the lumen. Mallory-trichrome stain. ($\times 70$.)

vigorous treatment. The jaundice increased, repeated haematemeses occurred, and he died five days after his second admission, in hepatic coma.

Necropsy Findings

The liver weighed 840 g. The capsule was irregularly thickened and the liver surface coarsely nodular. The liver edge was sharp. On cut section a pseudo-lobulation was present throughout the liver, the pseudo-lobules being up to 5 mm. in diameter. The gross aspect was not unlike that of post-necrotic scarring. The histology, however, revealed a typical picture of acute-on-chronic V.O.D. in addition to post-necrotic scarring. Fig. 3 gives the appearance of a branch of the hepatic vein. The necropsy further revealed jaundice, 1,200 ml. of straw-coloured ascitic fluid, congestive splenomegaly, a moderate degree of lung oedema, adhesive pleurisy on both sides, and arteriosclerosis.

Comment

The presentation with jaundice, and without ascites or hepatomegaly, was unlike acute V.O.D., and because no biopsy was performed that diagnosis was not considered. From the appearance at necropsy, however, it is possible that V.O.D. was present at the time of the first admission, and that infectious hepatitis then occurred on a background of the V.O.D. type of liver injury.

FIG. 4.—Case 4. Cut surface of liver. Note the remarkable mottled appearance caused by extreme centrilobular congestion.

Case 4

A 16-year-old Jamaican girl was admitted to hospital in July, 1954, with a history of abdominal swelling and pain with repeated vomiting for one week. The girl was a mongol and apparently very neglected. A detailed history could not be obtained from the relative who attended with her, but her diet was obviously

FIG. 5.—Case 4. Branch of hepatic vein. There is marked occlusion of the lumen through subintimal thickening of the wall. Mallory-trichrome stain. ($\times 180$.)

grossly deficient in protein. She was said to have been in good health up to this illness. Nothing of significance could be elicited from her own or her family history.

On examination she showed the physical and mental characteristics of mongolism. She was afebrile. There was no jaundice or anaemia. There was a tense ascites, and the liver was firm and tender and enlarged as far as the umbilicus. The spleen was not palpable. Chest x-ray examination, haematological investigations, and syphilis serology were normal. Liver-function tests gave abnormal results (see Table). Paracentesis was performed on admission with considerable relief of abdominal pain, and a liver biopsy done at the same time showed the changes of acute V.O.D.

Her condition remained unchanged for five days after treatment started. Jaundice then appeared for the first time and rapidly deepened. This was followed by the development of stomatitis, subconjunctival haemorrhages, and a generalized purpuric rash. Liver-function tests showed further impairment. Her clinical condition deteriorated rapidly, and she died in liver failure 18 days after admission.

Pathology

The liver biopsy specimen showed the typical changes of acute V.O.D. At necropsy, two weeks later, the liver weighed 1,275 g.; the cut surface showed the striking mottled appearance of acute V.O.D. (Bras *et al.*, 1954a, 1954b), and this was confirmed by histological examination (Figs. 4 and 5). There was only about 100 ml. of amber-coloured ascitic fluid in the peritoneum at the time of death.

Discussion

Diagnosis

The diagnosis is usually readily made in the acute stage from the history, the characteristic clinical picture, and the liver biopsy findings. When seen for the first time in the chronic stage the clinical picture is frequently indistinguishable from that produced by any other form of cirrhosis; and when of long standing it is often impossible to trace its evolution either clinically or histologically. We, however, suspect it (a) when there is a past history of the acute or sub-acute stage; (b) when cirrhosis occurs at an unusually early age; (c) at any age when the onset of ascites with or without hepatomegaly is unusually acute; and (d) when cirrhosis is associated with the relatively early development of oesophageal varices and haematemeses, distended abdominal veins, and other signs of intrahepatic obstruction. The latter feature we attribute to the nature of the histological lesion within the liver.

When the chronic stage presents for the first time in an acute phase, as in Case 2, the differential diagnosis from primary or secondary carcinoma of the liver may be difficult. If liver biopsy is contraindicated, peritoneoscopy is sometimes a useful method of differentiating the two conditions.

Liver-function tests are usually only moderately upset at the onset and become progressively impaired with advancement of the condition. They do not conform to any definite pattern, and are of more assistance in assessing progress and response to treatment than in arriving at a diagnosis. We find the serum albumin and cholinesterase of greatest value in this respect (Fig. 2).

Mechanisms

Previous reports on hepatic venous occlusion (Chiari, 1899; Rao, 1935; Teilum, 1949) have been based on post-mortem material in fatal cases. By serial liver biopsies, in the present series of cases, it has been possible to demonstrate the reversibility of the hepatic venous occlusion in the early stages of the disease, and how closely it relates to changes in liver-function tests and the appearance and disappearance of ascites and hepatomegaly (Case 1). Liver biopsy also shows that the enlargement of the liver is due

to vascular congestion produced by this occlusion of the hepatic venous radicles. It would appear that, if the hepatic congestion is severe and prolonged, hepatic failure with jaundice, cholaemia, and death may occur in any stage of the disease (Cases 3 and 4); if it is of short duration, complete recovery may occur (Case 1); if it is moderate and prolonged, death of liver cells and fibrosis occur with the usual mechanical results of hepatic fibrosis (Case 2).

The rapidity of appearance and disappearance of ascites in acute V.O.D. and its high protein content (usually 2 to 2.5 g.%) parallel very closely the events in acute experimental ascites in animals (Schilling *et al.*, 1952). In cirrhosis from any other cause and in the cirrhosis of chronic V.O.D. it is likely that one or more of several factors might be operative together—circulatory and hydrostatic, osmotic, inflammatory, nutritional, renal, endocrine, etc. In acute V.O.D., however, it would appear that we are dealing with the immediate mechanical effects of acute hepatic congestion produced by occlusion of the hepatic veins. The liver, as it were, becomes “stuffed” with blood through this impediment to venous drainage. The hepatomegaly and ascites so produced, in the early stages of the disease at any rate, sometimes disappear as promptly as they do in the “ascitic” dog preparation with release of vena caval constriction.

Treatment

The cause is still undetermined, and the treatment necessarily remains empirical and symptomatic. The diet of these patients is invariably deficient in proteins, although there may be an adequate calorie intake. It seems reasonable that an adequate protein intake should be sought in these patients both to improve nutrition and to slow the rate of ascites accumulation. In this connexion Kark *et al.* (1951) have postulated that severe protein depletion may directly influence capillary permeability favouring augmented ascites formation. A high-protein diet with added vitamins has been our main dietary regimen to date. Many patients show a dramatic response to these measures, bed rest, limited salt intake, and adequate attention to fluid balance. The natural history of the disease, however, is not fully known, and it would appear to be so variable and unpredictable that it is difficult to assess properly the importance of any therapeutic measures. Control studies along these lines have been started.

When accumulation of ascitic fluid is excessive repeated paracenteses may be necessary. With frequent paracenteses symptoms of hyponatraemia may develop, and the serum proteins become even more depleted. We have had little experience of the use of the various surgical procedures that have been used successfully in eliminating stubborn ascites and reducing the incidence of haematemeses. Their place, however, in selected cases of portal hypertension is well established.

Summary

The clinical features of veno-occlusive disease of the liver (V.O.D.) in Jamaica are described, with details of four cases occurring in adults.

The mechanisms of hepatomegaly and ascites formation are briefly considered. It is thought that in acute cases they are the mechanical results of hepatic congestion produced by occlusion of the hepatic venous radicles. A comparison has been drawn with the experimental ascites produced by ligation of the thoracic inferior vena cava in animals.

Treatment with a high-protein diet and fluid and salt restriction is suggested. The difficulty in assessing response to treatment is stressed.

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TREATMENT OF PARKINSONISM WITH A NEW COMPOUND (B.S. 5930)

BY

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The correct management of patients suffering from Parkinsonism in all its forms still remains one of the most difficult problems in therapeutics. Many so-called “spasmolytic” agents have been tried in this condition with variable success. Most compounds of this group have both an antihistamine and a parasympatholytic effect, and it would appear that the drugs which are most useful in the treatment of Parkinsonism are those in which the latter effect is predominant. The advent of a new compound with pronounced anti-acetylcholine activity was felt to be of considerable interest as a possible addition to the range of drugs available for the alleviation of the distressing symptoms of the Parkinson syndrome.

Pharmacology

The new compound (B.S. 5930) is β -dimethylaminoethyl-2-methylbenzhydryl hydrochloride. It belongs to a class of which the best-known example is the antihistamine agent diphenhydramine hydrochloride. This class of compound antagonizes both histamine and acetylcholine. Investigations into substitution in the benzhydryl group gave the rather unexpected result that substitution of a methyl group at the ortho (2) position produces a very much increased anti-acetylcholine effect and a very much reduced antihistamine action.

The toxicity of B.S. 5930 is about the same as that of diphenhydramine, the L.D.₅₀ in mice being approximately 200 mg./kg. subcutaneously and 25 mg./kg. intravenously.

Patients in this trial were given 150 mg. of B.S. 5930 daily, divided into three doses of 50 mg. each. In some cases the amount was increased to 250 mg. daily. If the amount was raised above 250 mg. signs of intolerance developed, including restlessness, slight blurring of vision, and nausea. Little trouble was encountered from unpleasant side-effects when the daily dose was below 250 mg. In only one instance was the daily amount