THROMBOTIC THROMBOCYTOPENIC PURPURA

REPORT OF A CASE

BY

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[WITH SPECIAL PLATE]

In 1924 Moschowitz reported the case of a patient who died following a brief illness characterized by fever, haemolytic anaemia, a bleeding tendency, and terminal neurological signs. Histological examination revealed widespread hyaline thromboses in the capillaries and terminal arterioles. Baehr *et al.* (1936) described further cases and suggested that the thrombi were composed of masses of agglutinated platelets. The ensuing platelet deficiency was held responsible for the haemorrhagic tendency. This theory remains unproved, but no convincing alternative has been proposed. Thrombotic thrombocytopenic purpura is the most widely accepted name for the condition, and originates from Baehr's concept. Changes in the walls of the vessels underlying the thromboses are presumed to predispose to their formation (Gore and Friedman, 1948). Symmers (1952) has added an extensive review to the limited British literature on the subject. His two cases brought the published total to 38, the majority of them American. Not all have been well substantiated. Since then further cases have been described by Gendel *et al.* (1952), Barondess (1952), Cooper *et al.* (1952), and Blackman *et al.* (1952).

The following case, which is typical clinically, is reported because of the special histological features.

Case Report

The patient, a hospital matron aged 46, had an allergic rash in 1947. Thereafter she remained perfectly well until the onset at the end of December, 1951, of tiredness, loss of appetite, frontal headache, and continuous uterine bleeding. On January 12, 1952, she noticed that she was jaundiced, with dark urine and normally coloured stools. She was nauseated and vomited frequently. She denied exposure to drugs or to cases of hepatitis.

On admission to hospital on January 17 she was pale and jaundiced. Her temperature was 98° F. (36.7° C.), pulse 110, and respirations 16. There were scattered petechial haemorrhages in the skin of the upper part of the trunk and both arms, and in both conjunctival sacs. The fundi were

clear. Hiss's test was negative. The liver, spleen, and lymph nodes were not enlarged. The apex beat was not displaced. A harsh localized systolic murmur was heard at the apex. The blood pressure was 160/100. The lungs and nervous system appeared normal.

Investigations.—The serial blood counts, E.S.R.s, absolute indices, and results of the flocculation tests are given in the accompanying Table. Bleeding time, 10 minutes; clotting time (capillary method), 6 minutes; clot retraction was deficient; prothrombin content, 100%; red-cell fragility, normal; direct Coombs test, negative; blood culture, sterile; agglutination reactions, negative; cold agglutinins, 1 in 4. Sternal marrow, reactive normoblastic hyperplasia. Urine: bile present; urobilin not present in excess; albumin, 0.1 g. per litre. Microscopically there were red cells and epithelial casts. Culture was sterile.

On the evening of January 17 her temperature was 100° F. (37.8° C.) and she complained of nausea and abdominal discomfort. Thereafter she ran an irregular pyrexia up to 105° F. (40.6° C.). Treatment was by repeated transfusions of whole blood. After each transfusion she appeared to be better for about twenty-four hours. Subsequently abdominal pain, nausea, vomiting, and headache recurred, fresh crops of petechiae appeared, and there was transient increase in the depth of jaundice. Apart from these fluctuations the jaundice steadily diminished, but it did not entirely disappear.

On January 22 she complained of numbness and weakness, affecting the lower half of the face and left arm. She showed a left facial weakness of upper motor neurone type with flaccidity, loss of power, and reduced tendon jerks in the left arm. The legs were normal, and both plantar responses were flexor. Re-examination on the following morning showed that these signs had entirely disappeared. Similar brief transient episodes involving the left face and arm occurred on February 4, 5, and 18; in the second and third of these her speech was slurred.

Thereafter she became increasingly weak, breathless, and confused. Altered blood appeared in the vomitus. A left hemiplegia developed on February 26, which did not fluctuate. She became comatose and died on February 28.

Permission for post-mortem examination was restricted to the abdominal organs. The body was that of a well-nourished middle-aged female, who was jaundiced and anaemic. Crops of purpura were present in the skin but not in the peritoneum. Macroscopically the abdominal organs appeared normal.

Histological Examination and Comment (Dr. Lloyd)

Evidence of haemolytic process was to be found in the spleen, which was congested and had large quantities of haemosiderin in the histiocytes of the pulp. Oddly enough a similar iron reaction was only very slight in the bone marrow. This marrow showed unusually active haematopoiesis, due to the haemolytic anaemia, and groups of haemocyto blasts also occurred in the hepatic sinusoids.

The principal thrombotic changes to be found in the smaller vessels were seen in the cortex of the kidney. Most of the vessels with thrombosis were venules (Plate, Fig. 1).

Haematological Data Other Than as Stated in Text

	Haemoglobin %	R.B.C. $\times 10^6$ per c.mm.	Colour Index	Reticulocytes %	Mean Corpuscular Diameter	Packed Cell Volume	W.B.C. per c.mm.	Neutrophils %	Eosinophils %	Lymphocytes %	Monocytes %	Platelets per c.mm.	E.S.R.	Direct van den Bergh Reaction	Serum Bilirubin (Mg./100 ml.)	Colloidal Gold Test	Thymol Turbidity (units)
18/1/52 ..	50	2.9	0.9		7.2	24	6,300	68	3	25	4	40,000	40	Immediate +	7.5		
24/1/52 ..	71	3.95	0.9		7.2		7,000	73	2	15	10	70,000					
30/1/52 ..	44	3.1	0.7			20	7,700	71	1	10	18	60,000	68	Delayed +	1.25	++	2
6/2/52 ..	60	3.45	0.8	12.2		28	8,000	68	2	21	9	50,000	65	Delayed +	1.5		
14/2/52 ..	50	2.34	1.1	17.2		20	7,700	75	4	19	2	100,000	67	Delayed +	0.8	++++	8
20/2/52 ..	55																

No nucleated red cells or abnormal white cells were ever noted in the peripheral blood. Blood transfusions, each of 2 pints (1,140 ml.), were given on the following dates: 22/1/52, 31/1/52, 4/2/52, 9/2/52, 19/2/52, 21/2/52.

between 35 and 140 μ in diameter, but a few thrombi were seen in interlobular arterioles. The glomerular arterioles were rarely affected, but a few were found in which the thrombus extended into the glomerular hilum; it was not possible to say whether it was the afferent or efferent arteriole that was affected. In consequence of this relative immunity of arterioles the glomeruli were nearly all normal.

A remarkable degree of atrophy was present, however, in the tubules, with ischaemic fibrosis (Fig. 2). As the ischaemia was due to venous rather than to arterial obstruction, the pattern was entirely different from that seen in arteriosclerosis, and the ischaemic areas were scattered irregularly over the cortex.

Most of the thrombi showed signs of organization, and invasion by spindle cells, with formation of reticulin fibrils in the more recent, while the older showed collagenous scarring. Similar thrombi were to be seen in the arterioles and venules of the hepatic portal systems.

These microscopical findings are fairly typical of this disease. The two unusual features in this case are the thrombosis of venules rather than arterioles and the ischaemic fibrosis of the renal cortex. Symmers (1952) says that it is exceptional to find thrombi in venules, and that some authors claim that the supposed venules are dilated arterioles which have been misidentified. That cannot be so in the present case, as only a few of the thrombosed vessels are so far dilated as to make their identity doubtful. The relative paucity of ischaemic lesions is usually explained by the incomplete occlusion of many affected vessels. In this case, also, many vessels only seem to have been partially occluded by thrombus, but the ischaemic fibrosis is obvious. The haphazard distribution of the ischaemic areas is additional evidence that it is not mainly arterioles that have been obstructed.

Discussion

The correct diagnosis was not made during life, owing to lack of knowledge of the syndrome. There can be little difficulty otherwise in recognizing the fully developed case, with its four cardinal clinical features of haemolytic anaemia, thrombocytopenic purpura, fever, and terminal neurological signs.

In discussing the differential diagnosis, Symmers (1952) has stressed that thrombotic purpura must be considered wherever haemolytic anaemia and thrombocytopenic purpura are associated. Only thus can the diagnosis be made before the appearance of the essentially terminal neurological signs. Biopsy has an obvious place in diagnosis and, although the haemorrhagic tendency must limit the procedures undertaken, successes have been recorded with both skin and muscle specimens. Cooper *et al.* (1952) demonstrated the typical lesions in paraffin sections of aspirated bone marrow in both of their cases, but this is contrary to all previous experience.

In the above case the haemolytic origin of the jaundice was overlooked in the early stages. Its depth, the presence of bile in the urine and the absence of urobilin, and the positive flocculation tests suggested some form of hepatitis. Hirsch and Dameshek (1951) have stressed the frequency with which virus infections precede the onset of the acute form of thrombocytopenic purpura, and it was thought conceivable that a virus hepatitis could behave in this way. Furthermore, neurological signs are a recognized occurrence in liver failure (Walshe, 1951).

The only apparent therapeutic success is that of Meacham *et al.* (1951). In their case splenectomy was performed after an unusually early diagnosis, and was followed by a remission of three years' duration. No other patient has survived for more than ten months. Splenectomy has conspicuously failed in other cases, and the same applies to A.C.T.H., cortisone, various antibiotics, and repeated blood transfusions. Mepacrine has so far not been employed in the treatment of thrombotic thrombocytopenic purpura, but a trial of its effect seems justifiable, on empirical grounds, in view of the possible relationship between this disease and

disseminated lupus erythematosus (Editorial, 1952; Symmers, 1952; Barondess, 1952). Page (1951) has reported the value of mepacrine in the treatment of some cases of the latter disease.

Summary

A case of thrombotic thrombocytopenic purpura is reported.

The characteristic thrombotic lesions were found in the renal cortex and hepatic portal systems.

The principal vessels affected were the venules. This is in contrast to previous reports, in which the changes have been found only in capillaries and terminal arterioles, and their occurrence in venules disputed.

Ischaemic fibrosis of the renal cortex was more evident than is usual.

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GALACTOSAEMIA

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[WITH SPECIAL PLATE]

Children with galactosaemia are unable from birth to metabolize galactose normally. Galactose, derived from lactose in milk, accumulates in the blood and gives rise to enlargement of the liver, often jaundice, and commonly death in early infancy. The survivors develop cataracts, and are mentally deficient. Although this is a rare condition it is important that those who care for newborn babies should be familiar with it; with early treatment life can be saved, and a normal child may result. Diagnosis is thus more urgent than in most congenital metabolic anomalies.

The first clear account of this condition was published by Goppert (1917), although the case described by Von Reuss (1908) may also have been an example. Mason and Turner (1935) published the first American case report, and 12 others have since appeared, including papers by Townsend *et al.* (1951) and Donnell and Lann (1951) which incorporated reviews of the literature. Görtter (1951) and De Haas (1951) have given brief accounts of three affected Dutch families. The first report from Great Britain is that of Bray *et al.* (1952).

P. J. N. COX AND R. J. P. PUGH: CHRONIC GALACTOSAEMIA

FIG. 1.—Case 4. Liver at necropsy. Fatty change, necrosis, and disorganization of parenchyma.

FIG. 2.—Case 5. Liver at necropsy. Gross fatty infiltration but less necrosis and disorganization than in Case 4.

FIG. 3.—Case 6. Aged 3 weeks. Liver biopsy. Fatty change, necrosis, and early fibrosis.

FIG. 4.—Case 6. Aged 11 weeks. Liver at necropsy. Fatty infiltration persists, but necrosis and fibrosis are less obvious.

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FIG. 1.—Organizing thrombus in two larger vessels, apparently venules. (Stained blue trichrome. $\times 150$.)

FIG. 2.—A glomerulus with thrombosis of one of its arterioles and some of its capillaries. Some of the neighbouring tubules are atrophied and there is interstitial fibrosis. (H. and E. $\times 150$.)