is simple and easily available. Two observers using the method can make duplicate estimations of the percentage oxygen saturation on 15 specimens of blood in one hour.

A comparison between results obtained by spectrophotometric analysis and by standard manometric blood-gas analysis is reported in detail.

We have much pleasure in making grateful acknowledgment to Dr. M. W. A. Gatman, of the Department of Medicine, the Royal Hospital, Sheffield, from whose work almost the whole of this technique stems, and particularly for his invaluable help and advice during the early part of this work. We would also like to thank Mr. P. D. Oldham (M.R.C.), for advice in statistical analysis, and Professor W. Melville Arnott for his helpful encouragement. Grateful acknowledgment is made of valuable financial assistance from the Research Endowment Fund of the United Birmingham Hospitals and from Messrs. Imperial Chemical Industries Limited.

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THROMBOPHLEBITIS MIGRANS AND CARCINOMA OF BODY AND TAIL OF PANCREAS

BY

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The association between thrombophlebitis migrans and carcinoma has long been known. In 1877 Trousseau gave an excellent clinical description of the recurrent painful venous thromboses affecting the arms and legs which he regarded as an important sign of carcinoma. A remarkable feature has been the frequency with which thrombophlebitis migrans is associated with carcinoma of the pancreas, particularly of the body and tail. Thoenes (1932) noted this association in three cases, and further examples were recorded by Umlauf (1933), Thomson (1938), Kenney (1943), and Jennings and Russell (1948). Sproul (1938) made a careful analysis of 4,258 consecutive necropsies and found multiple venous thromboses in 5 out of 16 cases of carcinoma of the body or tail of the pancreas and in only 3 out of 31 cases of carcinoma of the head of that organ. In addition 2 out of 81 patients with carcinoma of the lung and 2 out of 147 with carcinoma of the stomach also had multiple venous thromboses. Sproul demonstrated that in these cases there was no invasion of the veins by neoplasm nor direct compression by tumour.

By 1949 Edwards was able to analyse 29 cases of thrombophlebitis migrans associated with carcinoma—

23 from the literature and 6 of his own. The site of the primary growth was in the pancreas in 16, the stomach in 4, the lung in 4, the gall-bladder in 2, and undetermined in 3. A further 8 cases were added to the literature by Smith and Albright (1952), who studied the necropsy records of 37 cases of carcinoma of the body and tail of the pancreas. The degree of preponderance of carcinoma of the body or tail of the pancreas compared with carcinoma in other sites cannot be determined from the figures available, because many workers have selected carcinoma of the pancreas for their reports. Only in Sproul's analysis has the relative infrequency of carcinoma of the body or tail of the pancreas, when compared, for instance, with carcinoma of the lung or stomach, been taken into account. The relatively frequent association of thrombophlebitis migrans with carcinoma of the body or tail of the pancreas thus becomes all the more significant.

We wish to report two further cases, drawing attention to the occurrence of arterial thrombi as well as venous thrombi and to the presence of thrombotic vegetations on the heart valves. One of our cases had a carcinoma of the tail of the pancreas, and in the other the primary growth was not found, but from the distribution of the secondary deposits it was probably also in the pancreas.

Case 1

A man aged 43 was admitted to the Manchester Royal Infirmary in December, 1951, with a six-months history of increasing weakness and recurrent attacks of thrombosis of the superficial veins of both legs and left arm. A course of anticoagulants had failed to prevent further attacks. More recently he had begun to lose weight, and shortly before admission he had some right-sided lower abdominal pain and vomiting.

On examination the patient was obviously seriously ill, with a normal temperature and a blood pressure of 170/100 mm. Hg. Thrombosed veins could be felt in both legs and the left arm. There was a persistent heavy albuminuria (10–20 g./litre). During his stay in hospital he developed a right femoral venous thrombosis and had two attacks of left-sided pleural pain. Four weeks after admission he suddenly developed a right hemiplegia and aphasia. He died three weeks later.

A blood count showed: red cells, 4,830,000 per c.mm.; haemoglobin, 14.2 g. per 100 ml.; white cells, 24,100 per c.mm., with 82% polymorphs. Microscopy and culture of the urine revealed some red cells, pus cells, cellular and granular casts, and a light growth of a coliform organism. Blood urea was 42 mg. per 100 ml., thymol turbidity 1.6 units per 100 ml., alkaline phosphatase (King-Armstrong) 28 units per 100 ml., serum albumin 3 g. per 100 ml., and serum globulin 2.9 g. per 100 ml. The blood sedimentation rate (Wintrobe) was 36 mm. in one hour. Sternal marrow examination showed slight myeloid hyperplasia with some increase of plasma cells. Intravenous and retrograde pyelograms showed no abnormality. X-ray examination of the lungs, skull, and pelvis was normal.

Necropsy

Naked-eye Examination.—The body was that of an emaciated man. *Venous system:* There were thrombi of varying ages in all the large and small veins of the right leg. The inferior vena cava was occluded by a thrombus to just below the entrance of the renal veins, but the latter were normal. *Heart:* On the lines of closure of the aortic cusps there were friable vegetations, the largest 1 cm. long, resembling those seen in subacute bacterial endocarditis. The underlying valve and the other valves appeared to be healthy. *Liver* (weight 1,570 g.): This contained many secondary carcinomatous deposits 2 to 15 mm. in diameter.

*In receipt of a scholarship from the Medical Research Council.

Lungs: Carcinomatous tissue was found in an apical plaque and round some of the bronchi of the lower lobes. The distribution was more suggestive of secondary spread than of primary carcinoma of the bronchus, which was carefully looked for by cutting the lungs into thin slices after fixation. There were also many infarcts and bronchopneumonia. **Brain:** The left middle cerebral artery was distended and occluded by a plug of thrombus at its first bifurcation. On section there was infarction of the white matter and cortex in the left parietal region and also in both frontal lobes. The kidneys and spleen each contained many large, old, and recent infarcts. The pancreas was congested. **Other organs** were within normal limits.

Histological Examination.—Carcinomatous deposits were found in the following sites: liver, lungs, tracheo-bronchial and aortic lymph nodes, and hilum of the spleen. The carcinoma was anaplastic with a hint of glandular differentiation. There was some mucin secretion. **Venous system:** The large veins mentioned above and many small ones in nearly every organ examined contained thrombi at various stages of organization. There were no metastases in or near the affected veins. A few of the sections examined showed some round-cell infiltration of the adventitia and cuffing of the vasa vasorum and small veins near by; but this reaction was no more than might be found near any thrombosed vessel. **Heart:** The vegetations were composed of eosinophilic fibrinous material covered by endothelium. They showed only a slight degree of organization, and the cellular reaction in the underlying valve was minimal. Gram's stain failed to show any organisms. The myocardium contained many minute infarcts. A few of the myocardial veins were thrombosed. **Arterial system:** Thrombi were seen in the following arteries: pulmonary, many cerebral pial, splenic, renal, pancreatic, and prostatic. **Lungs:** Numerous infarcts and thrombosed arteries and veins were present. Carcinomatous infiltration was found in the perivascular and peribronchial lymphatics and in an old apical scar. **Brain:** This contained many infarcts, probably about three weeks old. Many of the pial arteries but none of the intracerebral arteries or veins contained thrombi. **Kidneys and spleen:** Some of the infarcts were recent, but others were completely healed. **Pancreas:** Autolysed. There was patchy fibrosis, and a number of arteries and veins were thrombosed. **Other organs:** Prostate and adrenal glands contained many thrombosed veins. Pituitary gland contained a small chromophobe adenoma.

No primary carcinoma was found. Unfortunately the pancreas was sectioned in only three or four places, and a small tumour may have escaped detection. The distribution of the secondary deposits, especially the infiltration at the hilum of the spleen, suggests an origin in the tail of the pancreas.

Case 2

A woman aged 56 was first admitted to the Manchester Royal Infirmary in November, 1950, with a six-months history of weakness. Clinical examination was negative apart from a moderate anaemia (haemoglobin, 9.5 g. per 100 ml.; colour index, 0.71), which responded only slightly to iron therapy. She was readmitted in December, 1951. Six months previously she had had an attack of "pleurisy" followed by thrombosis of the superficial veins of the left leg associated with oedema, which gradually resolved in three months. One week before admission she developed phlebitis of the left forearm followed by severe abdominal pain and a rigor.

On admission the temperature was 100.4° F. (38° C.) and the patient was ill. Apart from anaemia, old thrombosed veins in the left arm, and slight albuminuria, no abnormality was found. During the next three months she developed phlebitis of the right leg and left arm in spite of a course of anticoagulants. She also had several episodes of abdominal and pleural pain accompanied by pyrexia and attacks of severe frontal headache. In February, 1952, a tender hepatic enlargement was noted and she had obviously lost

weight. There were further attacks of phlebitis in both legs and increasing epigastric pain and vomiting. She gradually became more drowsy, and died in March, 1952.

A blood count showed: red cells, 4,820,000 per c.mm.; haemoglobin, 11.5 g. per 100 ml.; white cells, 13,600 per c.mm., with 81% polymorphs. Blood cultures were repeatedly negative. Thymol turbidity was 1 unit per 100 ml., alkaline phosphatase (King-Armstrong) 60 units per 100 ml., serum albumin 3.5 g. per 100 ml., serum globulin 3.2 g. per 100 ml., serum amylase 20 units per 100 ml., and serum lipase 0.6 unit per 100 ml. The electrocardiogram was normal. X-ray examination of the lungs, stomach, and pelvis was normal.

Necropsy

Naked-eye Examination.—The body was that of a thin woman. There was no jaundice. Oedema of the right ankle and left leg was present. **Pancreas:** The tail was expanded into a hard irregular tumour measuring 5 by 3 by 3 cm. and invading the surrounding tissue. The para-aortic glands contained macroscopic tumour deposits. **Venous system:** All the major superficial and deep veins of both legs down to the ankles were thrombosed, and a thrombus spread into the inferior vena cava to just below the entry of the renal veins. The left brachial and axillary veins and the splenic vein near the tumour were also thrombosed. **Heart:** Friable vegetations, about 3 mm. long, were found on each aortic cusp, and smaller ones were present on the atrial surface of the mitral valve. The valves appeared otherwise normal. At the apex of the left ventricle the muscle was infarcted and the endocardium was covered with ante-mortem thrombus. The coronary arteries appeared healthy. **Liver** (weight 2,250 g.): This was enlarged and to a great extent replaced by necrotic neoplastic deposits, the largest measuring 17 cm. in diameter. **Lungs:** Congestion and early bronchopneumonia were present. **Kidneys and spleen:** Each contained typical wedge-shaped infarcts, both recent and fibrotic. **Other organs:** There was a colloid goitre and an endometrial polyp.

Histological Examination.—The carcinoma in the tail of the pancreas was a moderately well-differentiated adenocarcinoma showing only a little mucin secretion. Metastases were found in the liver and the tracheo-bronchial and para-aortic lymph nodes. **Venous system:** Thrombi of varying ages were seen in the inferior vena cava, the large limb veins, and in the small veins of nearly every organ examined. There was no evidence of metastases in or near the affected veins. A few sections showed slight phlebitis and periphlebitis. **Heart:** The vegetations were similar to those of Case 1. The valves themselves were normal, apart from a little atheroma. The muscle underlying the mural thrombus was infarcted and minute infarcts were seen in the myocardium elsewhere. Many myocardial veins, venules, and several arteries were thrombosed. **Lungs:** There was bronchopneumonia. Thrombi were seen in both arteries and veins. **Brain:** Many superficial cortical arteries contained organized thrombi, and small infarcts were scattered throughout the grey and white matter. **Kidneys and spleen:** Multiple infarcts were present, some of which were several weeks old. **Head of pancreas:** This showed subacute pancreatitis. There were areas of fibrosis, possibly infarcts, as some of the arteries were occluded by thrombi. **Other organs:** There were many thrombosed veins in the thyroid and adrenal glands. The thyroid contained a non-toxic colloid nodule.

Lipase Content of Various Tissues in Case 2

Tissue	Lipase Content Units/g. (wet weight)	Normal Values Units/g. (wet weight)
Head of pancreas	2,800	1,110-9,000 (average 4,600)
Pancreatic tumour	45	—
Liver	57	10-460 (average 190)
Secondary deposit in liver	50	—

Enzyme analysis was carried out by Mr. H. Varley, of the Department of Clinical Pathology, Manchester Royal Infirmary. The tumour and its metastases were found to be non-functioning so far as lipase secretion was concerned (see Table). The serum amylase and lipase had been normal during life. (For full details of the method employed see Jackson *et al.*, 1952.)

Comment on Cases

The similarities and contrasts between these two cases are interesting. Both had widespread venous thrombosis affecting large and small veins throughout the body, thrombotic vegetations on the heart valves, and infarcts in the lungs, brain, kidneys, spleen, and myocardium. One had a well-differentiated adenocarcinoma of the tail of the pancreas with extensive metastases in the liver, whereas the other showed only a few small anaplastic secondary deposits, the primary growth being so small as to escape detection, though there was some presumptive evidence of a pancreatic origin.

Both cases showed the classical features of thrombophlebitis migrans, and because of the severity of the illness and the loss of weight an underlying neoplasm was suspected. The marked albuminuria in Case 1 was thought to be due to thrombosis of the renal veins or of the inferior vena cava above them, but this was not confirmed at necropsy. The hemiplegia in Case 1 was also ascribed to venous occlusion, but was shown to be due to blockage of the middle cerebral artery by embolus.

Discussion

Radical removal of the pancreas is now possible (Brunschwig, 1945; Whipple, 1946; and others); and early diagnosis of carcinoma of that organ becomes increasingly more important. Clinically this is notoriously difficult when the neoplasm is situated in the body or tail of the pancreas (Ransom, 1935; Duff, 1939), and any sign which may attract attention to the condition is important. In a number of patients migratory thrombophlebitis is the presenting sign of the disease; indeed, Edwards (1949) found the association so striking that he advocated laparotomy in all cases of thrombophlebitis migrans if no neoplasm was discovered by the usual investigations. The main conditions which have to be excluded before such a course is taken are thromboangiitis obliterans and so-called idiopathic thrombophlebitis migrans. The migratory phlebitis of the deep and superficial limb veins with accompanying oedema, occasional visceral thrombosis, pulmonary emboli, and variable general reaction are so similar in the idiopathic thrombophlebitis and that associated with carcinoma that the two conditions cannot be distinguished until obvious signs of neoplasm have appeared.

The value of biopsy of a vascular bundle in the differential diagnosis cannot yet be established, although thromboangiitis obliterans can usually be excluded. No biopsies have been reported from cases with multiple venous thromboses and carcinoma. From post-mortem studies it seems that the slight inflammatory reaction such as was occasionally seen in our sections is very similar to that reported by Barker (1936) in the idiopathic variety. To attempt to establish the diagnosis laparotomy may have to be resorted to, but in the few cases in which this has been done metastatic spread had already taken place (Edwards, 1949).

It has repeatedly been stated that the recurring thromboses affect the venous system exclusively, with the exception of the pulmonary arteries, which may contain emboli. In both our cases there were infarcts in many organs, due to arterial occlusion. In view of the presence of friable vegetations on the heart valves, embolization seems the most likely explanation, but there was such widespread occlusion of small arteries, especially in both brains, that the possibility of local arterial thrombosis should be considered. Infarcts

have been described by various workers, but have always been ascribed to venous occlusion. The vegetations on the aortic and mitral valves appear to be another manifestation of the thrombotic tendency. Sproul (1938) reported them in four of her five cases of multiple venous thrombi with carcinoma of the body or tail of the pancreas, and they have also been described in idiopathic thrombophlebitis migrans (Hirschhorn *et al.*, 1939; Swirsky and Cassano, 1943). The vegetations were macroscopically and histologically similar to those described by Gross and Friedberg (1936) as non-bacterial thrombotic endocarditis.

The theories put forward to explain the pathogenesis of the multiple venous thromboses are not satisfactory. The subject has been reviewed by Sproul (1938) and by Kenney (1943), and little has since been added. No local causes such as neoplasm or inflammation (other than the slight cellular reaction thought to be the consequence rather than the cause of thrombosis) have been demonstrated histologically. Attention has been focused on those cases of thrombophlebitis migrans with carcinoma of the body or tail of the pancreas and the possibility of increased or abnormal enzyme secretion, which has been thought to alter the coagulability of the blood. However, no abnormality has been demonstrated in the blood-clotting mechanism, and anticoagulants have had no effect on the course of the disease. So far as we are aware, the only enzyme study actually carried out in this disease has been in our second case, in which the tumour and its metastases were inactive so far as lipase secretion was concerned. It must be remembered that any theory concerning the pathogenesis of thrombophlebitis migrans with carcinoma must explain those cases in which the primary growth arises in organs other than the pancreas.

Summary

Two cases of thrombophlebitis migrans with carcinoma are reported. In one the primary growth was in the tail of the pancreas, and in the other the site was undetermined. The association between carcinoma of the body or tail of the pancreas and thrombophlebitis migrans is emphasized.

The occurrence of non-bacterial thrombotic endocarditis in this syndrome is stressed, and attention is drawn to the fact that the clinical picture may consist of arterial embolic as well as venous thrombotic episodes.

The possibility of arterial as well as venous thromboses is considered.

The lipase content of one of the tumours and its metastases was estimated and found to be negligible.

We wish to thank Professor A. C. P. Campbell and Dr. N. Kletts for advice and constructive criticism.

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