An allergic or sensitization basis has been suggested for thrombotic microangiopathy, so the fact of local treatment with propamidine cream and zinc and castor oil ointment is recorded, although this may well be irrelevant.

The correct diagnosis had been suggested on the clinical features and the combination of an acute haemolytic anaemia with thrombocytopenic purpura. Owing to the patient's sudden death 12 hours after admission no information was gained concerning the value of treatment in this disease. Symmers (1952) gives a full discussion of various measures that have been tried. These include penicillin (no effect), sulphonamides (useless or possibly harmful), aureomycin (no effect), and streptomycin (doubtful, probably no effect). As there is no evidence that the condition is infective in origin further trial of this line of treatment is unlikely to be of value. Anticoagulants have not been tried owing to the marked haemorrhagic tendency already present. Blood transfusion had given either transient or no benefit owing to rapid haemolysis of the transfused cells. Platelet transfusion might lessen the thrombocytopenia, but there would appear to be a risk of increasing the thrombotic element. Replacement transfusion might be worth considering in conjunction with other measures, of which treatment with A.C.T.H. or cortisone seems to be the most promising. A.C.T.H. has been tried hitherto in only one case (Meacham *et al.*, 1951), in which it may have been beneficial; the dosage given was small owing to the fear of ischaemic complications. Symmers points out that this objection may be unfounded. The place of splenectomy is doubtful, but it may be of value, perhaps as a long-term measure, if the patient could be tided over the most acute phase by other means.

Summary

A case of thrombotic microangiopathy is reported, only the sixth to be recorded in this country.

The salient features of the condition are fever, acute haemolytic anaemia, thrombocytopenia with purpura or other haemorrhagic manifestations, and fluctuating neurological signs.

The aetiology is unknown, but the morbid histology is characteristic—a widespread patchy thrombosis of minute blood vessels.

All cases so far recorded have been fatal, but earlier diagnosis would afford at least a hope of successful treatment; the condition may not be so rare as the extreme paucity of reports would suggest, and it should be considered in any case of febrile jaundice with haemorrhagic features.

Extensive reference has been made to a comprehensive paper on the subject which is readily accessible (Symmers, 1952).

We wish to thank Dr. J. C. Heather for permission to publish and Professor W. St. C. Symmers for confirming the histological diagnosis. Dr. T. Baird kindly supplied details about the patient before his admission to hospital.

REFERENCES

Meacham, G. C., *et al.* (1951). *Blood*, **6**, 706.
Symmers, W. St C. (1952). *British Medical Journal*, **2**, 897.
—— and Barrowcliff, D. F. (1951). *J. Path. Bact.*, **63**, 552.

At the annual general meeting of the Medical Sickness Finance Corporation Ltd., held on April 27, it was reported that, during 1953, 1,153 agreements were entered into for a total of £417,777. This was an increase on the previous year's business, and the corporation continues to expand. Although the largest demand was for motor-cars, agreements were also completed for caravans, motor cycles, electrocardiographs, *x*-ray apparatus, surgery furniture, and other medical equipment. The Corporation is a subsidiary of Medical Sickness Annuity and Life Assurance Society Limited, and Sir CECIL WAKELEY, P.R.C.S., is chairman.

MALIGNANT DISEASE ASSOCIATED WITH VASCULAR PHENOMENA

BY

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Trousseau (1877) drew attention to recurring phlebitis as the first sign of obscure visceral carcinoma. He pointed out that it may be diagnostic in certain cases, and that it may occur with cancer affecting any internal organ. To the present date 60 cases of thrombophlebitis migrans associated with carcinoma have been reported.

Wright (1952) mentions that he has seen 20 such cases, but does not report them in detail. He observes that the diagnosis of malignancy must be suspected (*a*) whenever thrombophlebitis persists, or is migratory, in spite of adequate anticoagulant therapy in adults over 30, and with increasing suspicion in the older age groups; and (*b*) when there is unexplained bleeding with prothrombin times in the therapeutic (not excessive) range. Gross *et al.* (1951) reviewed the literature of reported cases up to 1951. Of these cases, 10 were associated with carcinoma of the stomach, 32 with carcinoma of the pancreas (head, body, and tail), 9 with lung cancer, 2 with gall-bladder cancer, 1 with carcinoma of pancreas or stomach, and 2 were undetermined. A further four cases associated with carcinoma of the lung have been reported by Fisher *et al.* (1951).

Raynaud's phenomenon associated with malignant disease is rare, and only three cases are reported in the literature (Pasteur and Price Jones, 1901; Hamilton, 1920; Bennett and Poulton, 1928).

The object of this paper is to report four cases of malignant disease presenting as thrombophlebitis migrans and one case presenting with Raynaud's phenomenon, and to discuss the possible relationship and pathogenesis.

Case 1

A man aged 35 was admitted to hospital on September 2, 1951, with a history of vague malaise for seven months. Five weeks previously he had developed a thrombosis of the superficial veins of the left arm. Twelve days before admission thrombophlebitis in the left leg developed, associated with haemoptysis five days later. During the course of his illness until his death further episodes of haemoptysis occurred, the radiological appearances being compatible with pulmonary infarcts. At various times thrombophlebitis occurred in the left leg, right leg, superficial abdominal veins, dorsum of the right hand, and left external jugular vein.

Three months after admission a right-sided pleural effusion developed. Malignant cells were identified in the pleural fluid, indicative of a bronchogenic carcinoma. The liver became enlarged and nodular, and he died on January 2, 1952.

Anticoagulant therapy with ethyl biscoumacetate ("tromexan," 4-hydroxycoumarin) was maintained during his whole illness until December 22. The maintenance dose varied between 300 and 450 mg. daily, the prothrombin concentration being kept at 10 to 25%, with occasional escapes. In spite of this, thrombotic episodes occurred even with a prothrombin concentration of 10%.

Case 2

This patient, a man aged 46, was admitted to hospital on March 8, 1952. One month previously thrombophlebitis

occurred in the left leg. Sudden pain in the left side of the chest with dyspnoea and coughing of blood-stained sputum occurred on the day of admission.

During the course of his illness until his death on December 14 thrombophlebitis migrans occurred in both arms, superficial and deep veins of both legs, superficial veins on the abdominal wall, the corpus cavernosum, and finally the inferior vena cava. There were also recurrent episodes of pain in the chest, dyspnoea, and haemoptysis, and radiographs at these times showed lesions in the left mid-zone, left upper zone, left base, and right base respectively, all of which appeared to be compatible with pulmonary infarcts. Terminally, gross radiological changes occurred in the chest, particularly elevation of the left diaphragm due to involvement of the left phrenic nerve by neoplasm. Extensive investigations, including bronchoscopy on two occasions, failed to reveal a primary neoplasm.

A thrombophlebitic lesion on the abdominal wall did not resolve as the other lesions had, and gradually increased in size. This was removed for biopsy on September 9, and showed a secondary deposit from an adenocarcinoma. Vein biopsy had been done previously: on April 17 biopsy showed a simple venous thrombus, the vein wall being normal. A further biopsy on May 10 showed blood clot in the lumen of the vein. There was an intramural cellular reaction containing some cells of unidentified origin, ? malignant cells.

Treatment with ethyl biscoumacetate was begun on admission. The dose varied between 300 and 1,500 mg. daily to maintain a prothrombin concentration of 10 to 25%. The anticoagulant was changed to phenylindanedione ("dindevan") on August 2, and was continued until November. While the patient was on anticoagulants, rectal haemorrhage occurred at the same time as a thrombotic episode.

Post-mortem Examination (December 15).—The lungs contained a few hard nodules with reddish centres which were healing infarcts. In the right stem bronchus was a primary bronchogenic carcinoma. Secondary deposits were present in the mediastinum, the left suprarenal gland, and the liver. The other organs were normal. Numerous sections of veins did not reveal any malignant cells in the lumen or the wall of the veins; neither were malignant cells seen in the pulmonary infarcts.

Case 3

This patient, a man aged 43, was admitted to hospital on December 10, 1953. Four months previously thrombophlebitis occurred in the left leg. This was followed in a few weeks by a similar episode in the right leg. Later, a troublesome cough and haemoptysis developed, and thrombophlebitis occurred in the right arm. At the time of admission his condition was poor. Thrombophlebitis was present in the right arm and both legs; these were new lesions. A radiograph of the chest showed congestion at the right base.

Bronchoscopy on December 14 revealed a bronchogenic carcinoma partly occluding the bronchus. Biopsy confirmed the diagnosis. His condition deteriorated rapidly, with the development of secondary deposits in the liver, and he died on January 7, 1954. Permission for a post-mortem examination was refused.

Case 4

A man aged 63 was admitted to hospital on April 9, 1953, complaining of abdominal pain, loss of weight, and recent onset of jaundice. He had been perfectly well until December 5, 1952, when he developed pain in his right thigh due to thrombophlebitis. This resolved in the ensuing weeks, but was followed by a similar episode in the left leg. The thrombophlebitis in the left leg resolved in three weeks. A further thrombotic episode occurred in the right leg, associated with a chill, a stabbing pain in the chest, and a cough. This cleared up quickly. There were no further thrombotic episodes. In February, 1953, he developed umbilical pain, constant in character and associated with paroxysms of more severe pain. During the next six weeks his condition deteriorated, with progressive loss of weight and weakness. Jaundice developed two weeks before admission to hospital.

At the time of admission he was cachectic and jaundiced. The liver was a little enlarged. Palpable glands in the left side of the neck, consistent with malignant deposits, were noted. It was considered that this patient had secondary carcinomatosis. His condition deteriorated, and he died on April 27.

Post-mortem Examination (April 28).—The main findings were a mass of secondary carcinoma in the tracheobronchial angle. The liver was somewhat enlarged and was bile-stained. There were no secondary deposits in the liver. In the head of the pancreas was a large mass obstructing the common bile duct. Secondary deposits were present in the glands at the root of the mesentery. The other organs were normal. The histological appearance of the carcinoma of the head of the pancreas was that of an anaplastic carcinoma.

Case 5

A bank cashier aged 54 was admitted to hospital on November 23, 1951, complaining that his fingers had become blue and painful. The onset had been quite sudden, occurring three weeks previously, when the patient was out in the country engaged in sport. Pain and throbbing had become persistent and more severe in the ensuing weeks.

On admission the only abnormal findings were that both hands were cold and blue from the mid-palms to the finger-tips, with commencing gangrene of all the finger-tips on both hands. Radiographs of the cervical spine and chest were normal. The blood count was normal, and no haemagglutinins were detected. The Wassermann and Kahn reactions were negative. An electrocardiograph was within normal limits.

Treatment with tolazoline hydrochloride ("priscol") produced a definite warming of the hands with return to normal colour, except for the fingers, which remained white and the tips blue.

A cervical sympathectomy (Mr. E. W. Grahame) was performed on the right side on December 6. Although Horner's syndrome was produced there was no improvement in the fingers. The small gangrenous areas separated satisfactorily and the patient was discharged from hospital on December 23. He was readmitted on March 10, 1952, complaining of loss of appetite and nausea. Raynaud's phenomenon had not improved. A barium meal examination showed a small hypertonic stomach with an atrophic mucosa and rapid emptying. No ulcer or filling defect was noted. His general condition was unchanged and he was discharged on March 28. One month later he was again admitted. There had been persistent vomiting and marked loss of weight. He was now cachectic. A large craggy mass was palpable in the upper abdomen, which was thought to be an inoperable carcinoma of the stomach. He died one week later.

Post-mortem Examination.—On May 8 necropsy showed extensive carcinomatous deposits in the abdominal cavity arising from a primary carcinoma of the stomach. The other organs were normal. A portion of the thumb was taken for histological examination. This showed no evidence of arteriosclerosis or endarteritis.

Discussion

Sproul (1938) investigated the frequency of multiple venous thrombosis associated with carcinoma of the body or tail of the pancreas. In only a small number of this post-mortem series were malignant cells identified in the vein wall. She suggested that an increase in pancreatic secretion might increase the quantity of prothrombin in the blood, and this, with the tumour cells in the blood stream, might initiate the formation of thrombi.

Kenney (1943), Edwards (1947), and Gross *et al.* (1951) all implicated an altered clotting mechanism, due to various factors, as responsible for thrombophlebitis migrans in this syndrome.

It has been suggested that estimation of the coagulation power of the blood may be an aid in the diagnosis of cancer (Bock and Ransche, 1926). The results, however, are contradictory (Van Allen, 1927; Perlmann and Rodin, 1927). The reports of these authors were prior to the use of anticoagulant therapy. The failure of anticoagulant therapy to control these thrombotic episodes even with dangerously low prothrombin concentration indicates that altered blood coagulation is not an adequate explanation.

Raynaud's phenomenon associated with malignant disease is rare. Bennett and Poulton (1928) suggested that in their case it was due to a malignant gland invading the right inferior cervical ganglion. Raynaud's phenomenon, however, was bilateral. In Case 5 no secondary deposits were found above the diaphragm.

Coman (1953) discussing blood-borne tumour metastases, points out that direct dissemination of cancer cells depends mainly on their entrance into the vascular channels, and that the size of the emboli vary from single cancer cells to fairly large clumps. It is also known that cancer cells have amoeboid properties and can invade tissues, including the walls of the veins.

It is suggested, therefore, that both thrombophlebitis migrans and Raynaud's phenomenon, when associated with malignant disease, are due to emboli of malignant cells. The size of the emboli determines the site in which they settle: in the lungs, causing pulmonary infarcts; in the digital arteries, resulting in Raynaud's phenomenon; or in the peripheral veins, causing thrombophlebitis. In most cases the emboli are small, and the formation of a thrombus around the malignant cells results in the death of these cells. This is the commoner event. Occasionally, this does not occur, and a metastatic deposit can then be observed to develop.

Summary

Four cases of thrombophlebitis migrans associated with carcinoma are reported. In three cases the primary growth was in the lung; in the fourth it was in the head of the pancreas.

One case of Raynaud's phenomenon with carcinoma of the stomach is reported.

Attention is drawn to the fact that, when thrombophlebitis migrans is not adequately controlled by anticoagulant therapy the possibility of an underlying carcinoma must be considered.

It is suggested that the mechanism is due to emboli of malignant cells and that there is no underlying alteration in blood coagulation.

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REFERENCES

Bennett, T. Izod, and Poulton, E. P. (1928). *Amer. J. med. Sci.*, **176**, 654.
Bock, H., and Ransche, C. (1926). *Dtsch. med. Wschr.*, **52**, 2025.
Coman, D. R. (1953). *Cancer Res.*, **13**, 397.
Edwards, E. A. (1947). *Amer. Practit. Philad.*, **2**, 143.
Fisher, M. D., Hochberg, L. A., and Wilensky, M. D. (1951). *J. Amer. med. Ass.*, **147**, 1213.
Gross, F. B., Jaehning, D. G., and Coker, W. G. (1951). *N.C. med. J.*, **12**, 97.
Hamilton, W. F. (1920). *Canad. med. Ass. J.*, **10**, 670.
Kenney, W. E. (1943). *Surgery*, **14**, 600.
Pasteur, W., and Jones, C. Price (1901). *Trans. clin. Soc. Lond.*, **34**, 160.
Perlmann, I., and Rodin, A. (1927). *Zbl. Chir.*, **54**, 1995.
Sproul, E. E. (1938). *Amer. J. Cancer*, **34**, 566.
Trousseau, A. (1877). *Clinique Médicale de l'Hôtel-Dieu de Paris*, 5th ed., 3, 94. Baillière, Paris.
Van Allen, C. M. (1927). *J. exp. Med.*, **45**, 87.
Wright, Irving S. (1952). *The Pathogenesis and Treatment of Thrombosis*. Grune and Stratton, New York.

FACIAL DIPLEGIA IN THE GUILLAIN-BARRÉ SYNDROME

BY

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The Guillain–Barré syndrome, or acute infective polyneuritis, has aroused much interest in recent years. It is still a matter of discussion whether or not it is a disease *sui generis*, and recent opinion seems to favour a diverse aetiology for the syndrome. Laurans (1908) published the first adequate review of the condition, emphasizing the widespread flaccid paralysis and the facial diplegia. Guillain *et al.* (1916) did not recognize the facial diplegia as part of the syndrome, and it was not until 1936 that Guillain admitted the frequency of this form of paralysis. Holmes (1917) described cases in soldiers which were obviously of this syndrome, and Bradford *et al.* (1919) published a series which included 17 cases with involvement of the seventh nerve. Petch (1949) gives an excellent review of the subject, stating that the aetiology is unknown and the infective nature unproved. He described eight cases, in two of which bilateral facial paralysis (facial diplegia) had occurred. Bannwarth (1949) regards the condition as a parallergic process which may occur in a great variety of diseases, and Shaby (1949) also takes the same view of its multiple aetiology. Other authors hold the opinion that it is primarily an infective process of unknown, probably virus, aetiology—hence the name "infective neuronitis" used in American literature. McIntyre (1937) and de Jong (1940) indicate three groups—acute cases ending in recovery; cases running a protracted course, often with development of permanent paralysis; and cases terminating fatally, usually with bulbar paralysis.

The present report includes six cases, all females, who developed bilateral facial paralysis. Four of these were seen before paralysis of the face or body had developed, and the principal reason for reporting them is the observation, not hitherto recognized, that in the early stages the deep tendon reflexes are exaggerated. It is maintained from observation of these cases that it is possible to diagnose the condition in the pre-paralytic phase, and in three of the cases the development of facial diplegia was forecast before the onset of paralysis. Diagnostic points in the *early* stage of the disease are intense paraesthesiae, beginning in the feet, hands, and limbs, and spreading in severe cases all over the body. One patient said she felt as if she had "passed through fire." At the same time, pain is experienced in the muscles of the limbs, mainly in the proximal groups; pain in the eyes is common; and on clinical examination exaggeration of the deep reflexes is present, with no objective sensory change, and there is muscle tenderness on pressure; later the deep reflexes disappear and varying degrees of paralysis ensue. Four of these six cases had a preceding febrile illness six to thirteen days previously. A differentiating point from poliomyelitis is the widespread tenderness, which is bilateral and symmetrical, and as a rule principally affects the proximal groups of limb muscles.

Case 1

A married woman aged 36 was seen at home on July 20, 1948. Six days previously she had developed a right facial paralysis with inability to taste. Her eyes were aching, and