use of hypothermia is justified in these cases, since it may reduce the metabolic needs of damaged nervous tissue.

As has been recorded, cardiac arrest developed in this patient within two minutes of the injection of neostigmine. The neostigmine had been given following intravenous atropine. In recent years some controversy has developed regarding which of these two drugs is the more responsible for cardiac arrest. Bain and Broadbent (1949) thought atropine partly responsible. They noted that subcutaneous injections of atropine first slowed the heart rate, tachycardia occurring only 15 to 20 minutes later. Pooler (1957) also blamed atropine. It has been shown by Johnstone (1951) that hyperventilation with CO₂ produced electrocardiographic irregularities, and Pooler noticed that intravenous atropine during CO₂ retention produced a wildly irregular pulse.

In our patient intravenous atropine produced no detectable irregularity of the pulse: tachycardia was produced, not bradycardia, and intravenous atropine produced no detectable irregularities of the pulse when given during anaesthesia after muscle relaxants in over 40 other patients.

These observations suggest to us that neostigmine was the most likely cause of cardiac arrest in the present case. This finding is in keeping with the views of many other workers as recorded by Pooler (1957). It emphasizes the need for the utmost vigilance immediately after the administration of neostigmine. The neurological sequelae in this case suggest that some valuable time may have been lost before the alarm was given.

Unfortunately, neostigmine is administered at the end of the operation, when an anaesthetist is often forced to busy himself with the many tasks involved in terminating one anaesthetic and preparing for the next. Some visual or audible method of monitoring the patient's pulse might be of great service both in the operating theatre and in the recovery-room, saving valuable seconds between the cessation of the pulse and the application of adequate cardiac massage.

Only by such methods can delay in recognition be prevented, and this factor may well contribute to the continuing high mortality of cardiac arrest in spite of more adequate surgical management.

Summary

A case of recovery from neurological damage following cardiac arrest is described.

Neostigmine was given two minutes before arrest of the heart, and was thought in this case to be the most responsible agent.

The need for some mechanical device to monitor the pulse during operation is emphasized, so that treatment could be initiated in the shortest possible time following stoppage of the heart.

We thank Professor C. F. W. Illingworth, in whose wards this patient was treated, for guidance in the preparation of this paper, and Dr. M. W. Paterson, of the eye department, Western Infirmary, for superintending the ophthalmological investigations carried out on this patient.

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The *Transactions and Report of the Liverpool Medical Institution for the year 1957* contains the inaugural address by Dr. MARGARET E. THOMAS, the first lady president of the Institution, who took for her subject "The Artist's Contribution to Medicine." Also included are abstracts of papers read at ordinary meetings.

HAEMORRHAGE DURING PHENINDIONE THERAPY

BY

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Anticoagulants have an accepted place in the immediate treatment of thrombotic diseases. Their value in the prophylaxis of thrombosis has yet to be established. The risk of haemorrhage, and possibly death as a consequence, is a hazard to which increasing numbers of patients are exposed as the use of these drugs and the duration of treatment extend.

Reports of the incidence of haemorrhage attributed to anticoagulant therapy relate mainly to the more extensively used coumarin group of drugs. The frequency of this complication has varied, but it would appear that experience has not succeeded in reducing the risk of haemorrhage during long-term anticoagulant therapy. The incidence of haemorrhage in patients treated with anticoagulants over a period of five years was 36% in Nichol and Borg's (1950) series and 42% in the series of Keyes *et al.* (1956); Peyman (1957), over a period of one year, found a haemorrhagic incidence of 23%. Similarly with short-term anticoagulant therapy, the frequency of haemorrhage has not decreased: Olwin (1949) reported an incidence of 15%, Gilchrist and Tulloch (1954) 11%, and Peyman (1957) 16%.

It is possible that significant haemorrhage during anticoagulant therapy may be forecast by using a simple chemical tests ("occultest") to detect microscopic haematuria (Peyman, 1956). Should significant bleeding occur with anticoagulant therapy, it is essential that adequate means should be available to overcome this complication. Toohey (1953) has discussed the indications for oral and intravenous vitamin K₁ in combating haemorrhage induced by anticoagulants. This paper is concerned with the treatment of haemorrhage and factors which may have influenced the onset of bleeding in a series of patients receiving phenindione ("dindevan").

Method

Patients were treated with twice-daily doses of phenindione, and prothrombin estimations were done each day by Quick's one-stage method, using brain extract as a source of thromboplastin. Phenindione dosage was assessed from the previous response of the patient to the drug, so that the prothrombin time was kept within the desired therapeutic range between two and three times the control prothrombin time. The duration of phenindione treatment varied between individual patients from 3 to 12 weeks, the majority receiving this therapy for a period of three to four weeks. A total of 92 patients were treated with phenindione: myocardial infarction 69, venous thrombosis 3, pulmonary embolism 15, others 5. Six deaths occurred during the period of observation; in one case death was attributed to phenindione. Four died in left ventricular failure and one from mesenteric embolus one week after stopping phenindione.

Major haemorrhage occurred in seven patients (7.6%) (see Table), one of whom died as a direct result of this complication. Minor haemorrhage—for example, microscopic haematuria (Peyman, 1956)—was not sought.

Treatment of Haemorrhage

The immediate danger of haemorrhage is determined by the presence of shock. This will occur with a sudden large haemorrhage. In a patient who is receiving anticoagulant therapy for a myocardial infarction the adverse circulatory effects associated with shock will cause further myocardial damage. Fatalities may be avoided if shock can be overcome before irreversible changes occur in the myocardium. Early blood transfusion is of paramount importance in this respect. Transfusion will correct the circulatory defects and prevent further myocardial damage, and, by increasing the prothrombin concentration, will diminish the likelihood of further haemorrhage.

By anticipating sudden massive haemorrhage, arrangements can be made for immediate blood transfusion. Specific inquiry should be made in all cases subjected to anticoagulant therapy regarding a past history of dyspepsia or of known peptic ulceration, since bleeding from this source is likely to be sudden and severe. It would be prudent to retain a blood sample from these patients on admission, so that, should haematemesis or melaena occur, blood can be cross-matched and transfused at the earliest opportunity. The value of early blood transfusion for massive haemorrhage is well illustrated in this series. In Case 4 an 84-year-old woman was severely shocked by the sudden gastric haemorrhage but made a striking clinical improvement after early blood transfusion. Melaena occurring in Case 6 was not associated with shock. Although phenindione therapy was stopped and intravenous vitamin K₁ given, a further haemorrhage occurred the following day. On this occasion the patient was shocked, and he died within 30 minutes. When melaena subsequently occurred in Case 7, earlier experience dictated immediate blood transfusion and the patient made a good recovery.

Death is uncommon when haemorrhage, although severe—for example, profuse haematuria—is unassociated with shock. Sudden loss of a large volume of blood into the renal tubules is unlikely, and even gross haematuria usually subsides within 48 to 72 hours of stopping anticoagulant therapy. Haematuria ceased in Cases 1 and 2 when phenindione therapy was stopped; no further measures were required. In Case 3 profuse haematuria continued unabated for three days, and it was thought advisable to give oral vitamin K₁. The quantity of blood in the urine rapidly diminished and within 24 hours macroscopic haematuria had disappeared. Severe loin pain coinciding with the onset of haematuria and continuing was considered to be an indication for intravenous vitamin K₁ in Case 5. The loin pain persisted for a further 12 hours before subsiding;

haematuria gradually decreased, and by the fourth day there was no macroscopic evidence of bleeding.

Factors Influencing the Onset of Haemorrhage

Although a pre-existing lesion determined the site of haemorrhage in six of the seven patients who bled, a potentially haemorrhagic lesion was present in 38% of the patients who did not bleed. The frequency of haematuria and gastro-intestinal bleeding in this series was, however, far greater than similar haemorrhage in patients with known lesions of the genito-urinary tract or peptic ulceration receiving other forms of hospital treatment. It is therefore unlikely that fortuitous rupture of damaged vessels was the cause of bleeding with phenindione therapy.

Five of the seven patients who bled received a daily average dosage of phenindione much higher than that required by the non-bleeders in this series. The patient who received the highest average dosage (Case 5) was the only one without a pre-existing lesion. There were, however, individual patients amongst the non-bleeders who tolerated phenindione in amounts as high as those who subsequently bled, though none so much as Case 5. Neither age nor estimated "prothrombin" activity was related to the onset of haemorrhage.

It must be concluded that localized vascular damage will not alone cause haemorrhage during phenindione therapy; by forming the weakest links in the vascular chain it could determine the site of haemorrhage. Excessive administration of phenindione might precipitate bleeding.

Summary

In a series of 92 patients treated with phenindione, major haemorrhage occurred in seven, one of whom died.

Early blood transfusion is of paramount importance when a sudden large haemorrhage occurs during phenindione therapy.

Factors which may have induced bleeding are discussed.

I thank Dr. M. M. Deane, Dr. P. M. McAllen, Dr. K. Shirley Smith, and Dr. N. S. Plummer for permission to use their patients from the West Middlesex and Charing Cross Hospitals.

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Case Histories of Patients who Bled During Phenindione Therapy

Case	Sex	Age	Diagnosis	Pre-existing Lesion	Site of Haemorrhage	Treatment	Course	Result	Average Daily Phenindione
1	M	55	Myocardial infarction	Urinary infection 12th day	Haematuria 19th day	Anticoagulants stopped	Bleeding ceased after 3 days	Discharged to convalescence	175 mg.
2	M	43	Syndrome of impending cardiac infarction	Renal calculus 15 years previously	Haematuria 26th day	"	Bleeding ceased in 24 hours	" "	160 "
3	M	49	Myocardial infarction	Urinary infection 10th day	Haematuria 21st day	Anticoagulants stopped. Oral vit. K ₁ 3rd day	Bleeding ceased after 4 days	" "	165 "
4	F	84	" "	30 years' history of dyspepsia. Proved G.U.	Haematemesis 18th day	Anticoagulants stopped. Blood transfusion within 1 hour of haemorrhage	No further bleeding	" "	100 "
5	M	62	" "	—	Haematuria 17th day	Anticoagulants stopped. Vit. K ₁ I.V. 2nd day	Bleeding ceased after 4 days	" "	260 "
6	M	62	" "	Dyspepsia for many years. Chronic D.U.	Melaena 12th day. Further profuse melaena 13th day; associated shock	Anticoagulants stopped. Vit. K ₁ I.V. at time of initial haemorrhage	Died 30 minutes after recurrence of bleeding	Necropsy: Myocardial infarction. Ruptured atheromatous artery in base of chronic D.U.	160 "
7	M	65	" "	Recurrent dyspepsia for many years. D.U.	Melaena 26th day; associated shock	Anticoagulants stopped. Immediate blood transfusion	No further bleeding	Discharged to convalescence. A subsequent barium-meal examination showed a deformed D.U. cap	100 "