Although our experiments were all carried out with gallamine and succinylcholine, there is every reason to expect that the action of curare and pancuronium would be similarly potentiated by diazepam and that decamethonium would be antagonized.

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Prophylactic Anticoagulant Therapy against Pulmonary Emboli in Acute Paraplegia

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Summary: Prophylactic anticoagulant therapy within a few days of admitting a patient with a spinal injury appears to offer advantages in preventing pulmonary emboli. It was not found to hinder the patient's management.

INTRODUCTION

There is still a considerable morbidity and mortality in the first six weeks after spinal injuries despite the advances made since the setting up of specialized centres. A major cause of death is pulmonary embolism. Walsh and Tribe (1965) found that of 500 cases of traumatic spinal injury admitted within 14 days at Stoke Mandeville Hospital 15 died of pulmonary emboli. Cheshire (1968) in a comparable group of 325 admissions had 14 acute respiratory deaths and two from pulmonary emboli. The most recent figures are those of Watson (1968), who found that among 413 similar admissions over a 10-year period there were seven deaths from pulmonary emboli and a further 15 patients were diagnosed clinically as having this condition, though they recovered.

An analysis of the mortality in tetraplegia (Silver and Gibbon, 1968) made us more concerned with the respiratory care and the initial management of patients with new lesions and we instituted an intensive regimen of treatment, which included tracheostomy and positive-pressure ventilation on patients with cervical injuries whose vital capacity was less than 400 ml. and on those who seemed in danger of developing respiratory failure. We still found, however, that there was an appreciable mortality and morbidity from pulmonary emboli, despite the use of anticoagulant therapy when a deep vein thrombosis was suspected on the development of a swollen leg. After the death of a tetraplegic patient with a C3 lesion who had been successfully tided over four weeks on a respirator,

routine prophylactic anticoagulant therapy was instituted in all patients with new traumatic lesions admitted to the centre.

Sevitt (1959), reviewing the use of prophylactic anticoagulant therapy to prevent pulmonary emboli occurring after trauma, regarded spinal injury as a contraindication to early prophylactic therapy because of the danger of a small amount of additional bleeding that may take place into the cord, but he also stated that there may well be a place for delayed prophylaxis when the initial danger of haemorrhage has passed. Meinecke (1965) admitted to carrying out such treatment in spinal injury patients but found that he could not control the levels adequately; he thought that a minimum of three months' treatment was necessary. Watson (1968) did not consider that prophylactic anticoagulants were indicated in view of the small incidence of pulmonary emboli in his series.

PRESENT SERIES

We report our experience in the management of this complication from 1 January 1966 to 10 October 1969. During the first two-and-a-quarter years anticoagulants were administered only on accepted medical principles when a patient developed a clinical deep venous thrombosis or a pulmonary embolus. During the latter 18 months prophylactic anticoagulants were given.

Clinical details of the patients are given in Table I. The small number of female patients is probably because they do not dive, drive, or drink as recklessly as men. The high incidence of cervical injuries is partly due to the better understanding of their initial management and their early transfer to spinal centres.

REGIMEN OF TREATMENT

Admission and General Care.—No patients were admitted direct to the centre following their spinal injury. They were always admitted to a receiving hospital and transferred here after a delay of from 12 hours to 12 weeks, mostly within four days. On admission the spine and chest were radiographed,

TABLE I.—*Clinical Details of Patients*

	Total	Male	Female	Average Age	Age Range	Level			Cause				
						Cervical	Thoracic	Lumbar	Road Traffic Accident	Fall	Dive	Blow	Miscellaneous
1/1/66—3/3/68	42	32	10	39	12—77	23	16	3	20	17	2	3	—
3/3/68—10/10/69	35	31	4	35	15—65	26	7	2	16	9	3	6	1
Total	77	63	14	37	12—77	49	23	5	36	26	5	9	1

the haemoglobin, white blood count, and blood urea were estimated, and the urine was cultured. Their neurological and general condition was assessed to determine whether any further operative or medical treatment was required. Then followed the routine treatment at this centre, and they were turned two-hourly either manually or on a turning bed. Urinary bladders were drained either by intermittent catheterization or, where that was contraindicated, by continuous drainage by a polyethylene catheter of the Gibbon type. Physiotherapy began immediately on admission and consisted of passive movements to the lower limbs, but this was discontinued when there was swelling of the lower limbs. In the case of tetraplegic and thoracic lesions postural drainage and percussion were given to the chest, with a broad-spectrum antibiotic cover. When the fracture of the spine was stable the patient was mobilized, usually after about 12 weeks.

Anticoagulants.—On admission to the centre a period of 24 hours was allowed to elapse before beginning anticoagulant therapy; this enabled us to evaluate the patient's general condition and to find out if there were any contraindications to anticoagulant therapy. Immediately on the patient's admission blood was taken for prothrombin estimation and blood grouping. Phenindione (Dindevan) was used in all cases, since at the start of the trial this was the drug with which we were most familiar. The dose of phenindione varied from 25 to 100 mg. daily and was controlled by the prothrombin activity as measured by thrombotest reagent, which was performed initially twice weekly. In no patient did we use heparin to achieve anticoagulation. The prothrombin activity was kept between 7 and 40%, 20% being regarded as a satisfactory level. The duration of treatment varied from 4 to 20 weeks, average 11 weeks. Discontinuation of treatment depended on the patient's mobility and whether there was any evidence of deep venous thrombosis. Treatment was not modified in any way by the introduction of this regimen. The use of broad-spectrum antibiotic therapy initially for their chest treatment did not seem to interfere with our control of anticoagulant therapy.

CRITERIA FOR DIAGNOSIS

Pulmonary Embolus.—The diagnosis of pulmonary embolism posed considerable problems, and repeated chest x-ray films, E.C.G.s, enzyme studies, and serum bilirubin estimations were carried out to establish or refute the clinical diagnosis in suspected cases. The signs and symptoms of pulmonary embolism in normal people present great difficulty (Browse *et al.*, 1969). In patients with high neurological lesions where there is loss of sensation over the chest the diagnosis was even more difficult. Diagnosis was based on (a) necropsy; (b) a history of pleuritic pain of sudden onset lasting more than 12 hours, with the exclusion by clinical examination, E.C.G., and x-ray films of chest infection and myocardial ischaemia; and (c) in some cases supporting evidence gained from haemoptysis and enzyme studies.

Deep Vein Thrombosis.—We considered a consistent difference of an inch (2.5 cm.) in the leg measurements to be evidence of deep venous thrombosis. Because of the impairment or total loss of sensation in our patients subjective accounts of a painful throbbing leg could not be elicited. Owing to the vasomotor disturbances in the cervical lesions (most cases) temperature changes in the limbs are extremely difficult to interpret. Before the institution of prophylactic anticoagulant therapy on 3 March 1968 we did not measure the legs routinely, and cases may have been overlooked. After that date daily leg measurements were made by the physiotherapy staff throughout the period of treatment, the sites of measurement being 9 in. (23 cm.) above and 5 in. (12.5 cm.) below the tibial tuberosity.

RESULTS

Pulmonary Embolus

Before the introduction of prophylactic anticoagulant therapy 42 patients were admitted. Six had pulmonary emboli—two were fatal, two were severely shocked as a result of massive emboli and nearly died, and two were not shocked. The emboli occurred from 11 to 42 days after injury; no patient was on anticoagulants at the time of the embolus, and only three of the patients (neither of the fatal cases) had swollen legs at that time. From 3 March 1968 to 10 October 1969 35 patients were admitted, of whom 28 were given prophylactic anticoagulants. No patient developed a pulmonary embolus and there was only one death in the acute stage during this period. This patient had severe injuries in addition to a traumatic tetraplegia, and at necropsy there was no evidence of a pulmonary embolus.

Deep Vein Thrombosis

From 1 January 1966 to 3 March 1968 six patients were observed to have swollen legs, due presumably to deep vein thrombosis 11 to 57 days after injury (Table II). As, however, we were not routinely measuring the legs, and in some cases our attention was drawn to the condition of the legs only when the patients developed a pulmonary embolus, the incidence was almost certainly much higher and little reliance should be placed on these figures.

TABLE II.—Incidence of Pulmonary Emboli and Deep Venous Thrombosis Before and During the Institution of Prophylactic Anticoagulants

	No. of Patients	Pulmonary Embolus	Deep Vein Thrombosis
Before anticoagulant therapy (1/1/66—3/3/68)	42	6	6
During anticoagulant therapy (3/3/68—10/10/69)	35	—	9

After the institution of anticoagulant therapy leg measurements were conducted daily, minimal swelling, if persistent, being thought to be indicative of deep venous thrombosis. Nine patients were observed to have swollen legs between 3 March 1968 and 10 October 1969—3 to 84 days after injury. Six of these were admitted with leg swelling or developed it before anticoagulants had been instituted or were considered to be effective; one patient was anticoagulated 32 days after injury. Two patients developed the swelling on mobilization while still on anticoagulant therapy at 12 weeks. Since Sevitt and Gallagher (1961) have shown that 19% of 26 patients who died within four days of injury and 47% of 19 patients who died four to seven days after injury had deep venous thrombosis, these patients too may have developed their deep venous thrombosis before the institution of anticoagulant therapy.

We often see swelling of the lower limbs in tetraplegic patients when they are sat up, but the observation that the swelling did not go down on decubitus makes us favour deep venous thrombosis as the diagnosis. This swelling, however, may be postural owing to loss of the muscle pump; on the other hand, it may be due to deep venous thrombosis that has developed at the time of injury (Sevitt, 1959) and is observed only when the patient sits out of bed with his legs dependent. Without venography (which is justifiable) it is difficult to be dogmatic.

DISCUSSION

Of the 35 patients admitted after 3 March 1968 28 received anticoagulants and in seven therapy was not given. Four of these seven were excluded from the series because they were

admitted more than eight weeks after injury and the danger period was considered to be passed; one suffered multiple trauma (head injury plus compound fractures of three limbs); one had such a transient and subjective neurological disturbance that it was thought that the dangers of therapy outweighed the advantages; and one who had a severe head injury with a pulsating exophthalmos together with a C3 fracture and amputation of one limb died after a week before therapy could be instituted. We used phenindione as we had most experience with this drug and did not think it necessary to begin anticoagulants rapidly by using heparin.

Owing to the fact that all patients with spinal injuries are admitted to another hospital after injury, there is an unavoidable delay in starting therapy, in contradistinction to Sevvit and Gallagher (1959), who worked in a receiving hospital; they showed that up to 50% of these patients developed deep venous thrombosis within a week of injury, and we realize that we may have been instituting therapy at a later stage than was ideal.

We controlled the therapy by the thrombotest reagent, as this was in use in the laboratory. We kept the level between 7 and 40%. We realize that the upper limit is slightly higher than recommended. If the level fell below 10% we had frequent bleeds, particularly from the bladder; however, it did not interfere with treatment in any way. Fifteen patients were in fact circumcized while under treatment (normal practice to reduce urinary infection and to facilitate the wearing of a urinal), nor did we find any ascent of the spinal lesion due to bleeding into or around the cord. One patient (an asthmatic) was sensitive to both phenindione and warfarin and developed bleeding from the bladder and mouth, so the treatment was discontinued. Of greater theoretical interest is the observation

that there appears to be a greater incidence of ectopic ossification around the hips in patients on treatment (Silver, 1969), possibly owing to bleeding into the adductor muscles.

The regimen of general management has not substantially changed over the past four years, and, while we realize the pitfalls of retrospective comparisons, the fact that no patient has had pulmonary embolus since the institution of this prophylactic regimen in contrast to the previous period quoted, would indicate that this treatment is effective. The observation that four of the six patients who developed pulmonary emboli had thoracic lesions is of great interest since Walsh and Tribe (1965) and Watson (1968) observed the highest incidence in this group of patients (17.1% and 7% respectively).

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Medical Memoranda

Acute Sprue in Britain

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"Sprue" normally describes a classical clinical picture occurring within certain defined geographical regions. The following case is reported because we believe that sprue may occur in Britain and go unreported because of the difficulty of offering a satisfactory diagnosis.

CASE REPORT

A woman aged 34 developed diarrhoea, anorexia, and vomiting in April 1968. She had no history of any previous gastrointestinal disorder, and no one else in the family was affected. She lived in poor circumstances in central Birmingham and had never been abroad. She used lard for cooking, and there had been no recent change in her eating habits. Vomiting stopped after a week, but she remained weak and profoundly anorexic and diarrhoea persisted, accompanied by flatulence, distension, and central abdominal pain. After three weeks she developed a sore tongue, ulcers on the lips, and crusting of the eyelids, and had lost about 6 kg. in weight. She was treated by her family doctor with a kaolin mixture and topical gentian violet, but no antibiotics.

Examination showed a thin, depressed, apathetic woman of small stature (which was familial). There was a low-grade pyrexia. The tongue was bright red and atrophic, and ulceration of the lips, angular stomatitis, blepharitis, and pyoderma of several fingers were also present. The appearance of the mouth suggested candida infection, but this could not be confirmed. Abdominal examination was negative. The stools were profuse, pale, and unformed, and

the fat content on a poor dietary intake averaged 10 g./day. Sigmoidoscopy showed a reddened mucosa with a few white granules suggestive of candidiasis, but no other abnormality. Rectal biopsy showed nothing abnormal. Eye swabs grew *Staphylococcus aureus*, but repeated stool examinations showed no staphylococci, fungi, giardia, or other pathogens.

Investigations.—Haemoglobin 9.0 g./100 ml.; M.C.H.C. 32%; W.B.C. 6,500, normal differential; normochromic blood film with anisocytosis, macrocytosis, and nuclear hypersegmentation of polymorphs. E.S.R. 57 mm. in one hour (Westergren); serum folate 0.3 ng./ml.; vitamin B₁₂ 170 pg./ml. Blood urea, liver function tests, and electrolytes normal. Serum albumin 4.0 g. and globulin 2.1 g./100 ml., with a normal electrophoretic pattern. Urine analysis and chest x-ray picture normal. Xylose absorption test showed 8.5% excretion of a 5-g. dose in five hours. Resting gastric juice pH 6.4. Jejunal biopsy specimen showed finger-like and leaf-like villi in about equal proportions, many of the leaves being broad. Microscopy showed mild villous atrophy with irregular shortened villi, pronounced shedding of the surface epithelium, and a moderate pleomorphic infiltrate in the lamina propria.

Initial treatment consisted of bed rest, normal diet, folic acid 5 mg. by mouth three times a day, and topical neomycin to skin and eyelids. The stools became semi-formed, but were still pale, and the skin sepsis cleared. The patient felt better and slowly gained 3 kg. in weight, but her mouth and tongue were still sore. By 28 May the haemoglobin had fallen to 8.1 g./100 ml. Oral ferrous fumarate was added to the folic acid and she was allowed home. A barium series in June showed normal transit time in the small intestine and no local intestinal lesion, but there was slight coarsening of the folds and widening of the lumen of the lower jejunum (33 mm. diameter). A barium enema was negative. The patient lost weight again and anaemia increased (see Chart).