

usually drained with an indwelling urethral catheter for 5 days. When, however, the patient has had a large residual urine for many years it is of course impossible for the bladder to recover tone in this short time. In long-standing cases, therefore, the catheter has often had to be replaced and left for varying periods, and afterwards the residual urine has often had to be checked daily until the bladder muscle eventually recovered. Occasionally in the male sex where there is gross secondary atony with a very large residual urine which does not diminish after long-continued drainage it may be necessary to carry out a partial cystectomy to reduce bladder capacity and increase intravesical pressure and sensitivity. I have not yet seen such a case in a woman, but such therapy might occasionally be required.

One patient suffering from a carcinoma of the bladder neck had to be treated surgically.

In two cases results have been poor. One was an old lady of 78 in whom I caused a vesicovaginal fistula; this was repaired by operation. She made satisfactory progress but died eventually from ascending urinary infection. The second case illustrates the difficulties that may be encountered:

Mrs. C, aged 62. Previous history of failed colporrhaphy for stress incontinence. Admitted to hospital in uræmia—very thin and emaciated. Blood-urea 83 mg. per 100 ml. Intravenous urography showed considerable dilatation of both pelvis and ureters. Urine contained numerous white blood-cells with a moderate growth of *Escherichia coli* on culture. With catheter drainage, condition improved remarkably. Investigations showed large residual urine and obstruction at the bladder neck. Transurethral resection relieved obstruction and abolished residual urine. Normal control of micturition except she still had stress incontinence. Gynæcological opinion sought and further colporrhaphy performed. After this she developed total incontinence of urine!

Some time later, in an attempt to cure the incontinence, I carried out a urethral-sling operation without success. Eventually, because she was in such a miserable state, an ileal conduit had to be made. With this, her general condition improved and the conduit was satisfactory. She still, however, was a very poor soul and complained of vaginal discharge. After long-continued gynæcological treatment, this did not clear up, and eventually it was found that the discharge was really coming from her infected bladder. As this did not clear up after prolonged continuous irrigation through a two-way indwelling catheter, the bladder finally had to be removed. It was just an abscess cavity. After this the patient's condition improved and she was discharged home.

Later she had the misfortune to fall and break her femur. After many months in hospital she was discharged home in fair condition, only to contract bronchopneumonia, from which she died.

### Summary

Bladder-neck obstruction in the female is a very real condition, just as definite as prostatic obstruction in the male. It can cause many types of urinary symptoms and may lead to severe renal dysfunction. A well-performed transurethral resection not only relieves symptoms but restores the urinary tract to a healthy state.

I should like to record my indebtedness to Dr. G. W. Ollerenshaw and the members of the department of medical illustration at the Manchester Royal Infirmary for their help in the preparation of the illustrations; also to Dr. J. W. Huffman and the American Medical Association for allowing me to reproduce fig. 2.

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## ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM A CONTROLLED TRIAL

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THE use of an anticoagulant drug in treating venous thrombosis was first reported by Murray et al. (1937) and Crafoord (1937), who administered heparin, and soon there were claims that the number of deaths from pulmonary embolism was thereby reduced.

Bauer (1946) cited 71 cases of pulmonary embolism treated with intravenous heparin with no deaths. Because of the high cost of heparin and the disadvantage of repeated intravenous injections, longer-acting anticoagulant drugs of the coumarin type came into more widespread use. Allen et al. (1947) reported 329 cases of pulmonary embolism treated with heparin and dicoumarol with only 1 death. Bauer (1959) has reported 627 cases of venous thrombosis, treated with heparin alone, with only 5 deaths from pulmonary embolism. Of the 45 other patients who had already had one pulmonary embolism 2 died.

In a retrospective survey covering thirteen years, Barker et al. (1940) found evidence of venous thrombosis or pulmonary embolism in 0.96% of 172,888 postoperative cases untreated with anticoagulants; more than half of their patients with pulmonary embolism died. In other series the mortality in cases of pulmonary embolism has been high: de Takats and Jesser (1940) and Short (1952) reported a mortality of 87% and 23% respectively.

The diagnosis of pulmonary embolism is rarely proved before death. The diagnosis in life rests on a combination of symptoms and signs in the chest and legs and changes in the radiogram and electrocardiogram; and in the less severe cases the diagnosis is more uncertain. For this reason it is unsatisfactory to compare results in series reported by different workers.

There are other objections to this type of comparison. Sudden death is common in pulmonary embolism, and untreated series include patients who died before any effective treatment could have been given. In other cases the diagnosis, unsuspected in life, is made only at necropsy. Cases of these two types will not figure in any treated series.

The risk of hæmorrhage has made many physicians and surgeons unwilling to use anticoagulants routinely in the treatment of pulmonary embolism on existing evidence. There is some further support for scepticism of the protection afforded by anticoagulants in a report by Marks et al. (1954). They reported favourably on the value of anticoagulants in cases of venous thrombosis but found that it did not reduce the incidence of fatal pulmonary emboli. Once pulmonary embolism has occurred it may appear to be too late for anticoagulants to be effective.

Our object has been to measure the effect of anticoagulants in patients who have had one pulmonary embolism, both on the course of the first embolism and on the risk of further attacks. It seemed essential to use the method of observing concurrent series of patients, deciding by chance whether they received anticoagulants or not.

### Material and Methods

#### Selection of Patients

Medical and surgical colleagues were asked to notify us at the first indication that pulmonary embolism might have occurred in any of their patients. Full clinical examination was

carried out without delay and a portable chest radiograph and electrocardiogram were taken. The clinical features on which the diagnosis was based reflected the presence of acute right-sided heart-failure or of pulmonary infarction or both. Right-sided heart-failure usually declared itself with faintness, central chest pain, a fall in blood-pressure, and a rise in jugular venous pressure together with changes in the electrocardiogram. When pulmonary infarction occurred the common findings were pleuritic pain, hæmoptysis, fever, pleural friction, loss of resonance at the lung base, and rales; in these patients it was usual to find changes in the bedside chest radiograph. Tenderness or swelling of the calf or any other signs of thrombophlebitis strengthened the diagnosis, but some of the patients had no abnormal signs in the legs. The clinical features, electrocardiograms, and radiographs of these patients will be fully described in a separate report.

When pulmonary embolism was diagnosed, the suitability of the patient for anticoagulant treatment was considered. The only contraindications to anticoagulants were: (a) a recent operation, and (b) a history suggestive of recent peptic ulceration. If pulmonary embolism had occurred within a week of an operation the surgeon in charge of the case was asked if anticoagulants could be used. Anticoagulants were seldom withheld except after such operations as mastectomy or prostatectomy where a large raw area had been left. If it was considered that the risk of hæmorrhage was too great the patient was excluded from the series. The fact that a patient was thought to have had more than one episode of pulmonary embolism did not exclude him. The time that elapsed between the first symptom and inclusion in the trial varied from a few minutes to as long as twelve days. It was within twenty-four hours in 41 out of 73 cases.

Envelopes were prepared containing an equal number of cards marked "anticoagulant" or "no anticoagulant", and when a patient was admitted to the trial a card was drawn.

#### Treatment

All patients were confined to bed for ten days. There were a few whose condition did not allow them to begin to walk on the tenth day. The remainder were encouraged to walk increasing distances and then return to bed; sitting in a chair was forbidden. Where there were signs of venous thrombosis in the

TABLE I—ANTICOAGULANT DOSAGE SCHEME

Actual prothrombin-time (sec.) Control prothrombin-time (sec.)	Dosage for next 24 hr.*
4-6	$\frac{1}{8}$ of total dose previous day
4-3	$\frac{3}{4}$ " " " " "
3-2	Whole " " " " "
2- $1\frac{1}{2}$	$1\frac{1}{4}$ times " " " " "
Under $1\frac{1}{2}$	$1\frac{1}{2}$ times " " " " "

\* Divided into two roughly equal doses, given night and morning.

leg the foot of the bed was elevated and a cradle used to prevent pressure from bedclothes. Some patients in both groups were given oxygen therapy for severe breathlessness or cyanosis, pressor drugs (L-noradrenaline and mephentermine sulphate) for severe hypotension, and digitalis for atrial fibrillation or paroxysmal tachycardia. Antibiotics were not usually given for pulmonary infarction.

Those who were to have anticoagulants were treated with heparin and nicoumalone ('Sinthrome'). Heparin was given by intravenous injection 10,000 units every six hours for six doses, without laboratory control. Nicoumalone was begun concurrently and the prothrombin-time estimated by the one-stage Quick test on the third day. Nicoumalone was usually given in the following doses: 16 mg. followed at twelve-hourly intervals by 8, 8, and 4 mg. The dose was then regulated to maintain the prothrombin-time at between two and three times control time. Table I shows the dosage used.

It was never necessary to give an injection of protamine sulphate to counteract the effect of heparin. Vitamin K<sub>1</sub> was administered—probably unnecessarily—to 3 patients who had minor hæmorrhages. Anticoagulants were given for fourteen days except to those who bled and 1 other patient who was thought to have developed drug sensitivity. 5 patients received

a longer course of anticoagulants for periods up to twenty-eight days because they were unable to get up from bed on the tenth day.

#### Findings

The first patient was admitted to the trial in March, 1957. By April, 1958, 35 patients had been included, and at this stage it became necessary to review the further conduct of the trial. Of 19 patients who had not received anticoagulants 5 had died of pulmonary embolism. Of 16 who had received anticoagulants none had died of pulmonary embolism, and 1 had died of suppurative pneumonia with hæmorrhage from a duodenal ulcer as a con-

TABLE II—RESULTS IN FIRST 35 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	16	0	0	1

tributory factor. In addition 5 others in the untreated group had non-fatal recurrences of pulmonary embolism. In the treated group there was no recurrence.

#### First Stage of Trial (35 cases)

An analysis of the results (table II) showed that the difference in deaths in the two groups from pulmonary embolism was unlikely to be due to chance:  $P=0.036$  (1 in 28). When deaths from pulmonary embolism and non-fatal recurrences were taken together the result was convincing:  $P=0.0005$  (1 in 1987).

In view of this situation it was felt that the trial could not be continued in its original form. The low mortality in the treated series, however, needed confirmation. Accordingly the trial was continued with the same criteria for inclusion, but thereafter all patients were to receive anticoagulant treatment. By July, 1959, a total of 54 patients had been treated with anticoagulants and the trial was stopped.

#### Complete Series (73 cases)

To test the significance of the results (table III) the following comparisons were made:

*Deaths from pulmonary embolism.*—Untreated cases 5 out of 19, treated cases 0 out of 54:  $P=0.0007$  or 1 in 1292.

*Deaths from pulmonary embolism added to non-fatal recurrences.*—Untreated cases 10 out of 19, treated cases 1 out of 54:  $P=0.000014$  or 1 in 704,225.

*Deaths from all causes.*—Untreated group 5 out of 19, treated group 2 out of 54:  $P=0.011$  or 1 in 90.

#### Deaths

The 5 deaths in the untreated group were all due to pulmonary embolism.

**Case 1.**—A woman of 56 with carcinoma of the breast and pelvic metastases. Massive pulmonary embolism occurred four days after admission to hospital and was followed by steadily increasing signs of infarction of both lungs. The patient became increasingly dyspnoeic and produced terminally large quantities of very offensive sputum. She died twenty-one days after the first symptom of embolism, and necropsy showed massive pulmonary infarction with cavitation. There were large, organising clots in both main pulmonary arteries but no very recent thrombi.

TABLE III—RESULTS IN COMPLETE SERIES OF 73 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated ..	19	5	5	0
Treated ..	54	0	1	2



**Case 2.**—A man of 56 who five days after a second laparotomy for intestinal obstruction developed very severe constricting central chest pain and signs of right-sided heart-failure. The presence of extensive thrombophlebitis of the leg and the recurrence of slight hæmoptysis pointed to the diagnosis. He survived for forty-eight hours, after massive pulmonary embolism. In addition to the thrombophlebitis of the leg, large clots were found in the hepatic veins that were thought to be the result of pylephlebitis.

**Case 3.**—A 78-year-old woman had severe pulmonary embolism twenty-one days after an operation to reduce a Pott's fracture. She died suddenly twelve days later, and necropsy revealed large fresh clots in the main pulmonary artery.

**Case 4.**—A man of 57 who had had a cerebral thrombosis six years previously developed thrombophlebitis of the right leg. Right pleural pain and hæmoptysis led to the diagnosis of pulmonary embolism, and he was admitted to the trial. One day later sudden breathlessness, severe hypotension, and obvious electrocardiographic changes gave evidence of a second large embolism. He developed increasing signs of bilateral pulmonary infarction with foetid sputum and swinging fever. He survived for fifteen days after the second episode. At necropsy there were large clots in both pulmonary arteries and massive infarction of the lower lobes of both lungs with cavitation.

**Case 5.**—A 41-year-old man survived for fourteen days after the first symptoms of pulmonary embolism. He had been admitted to hospital for treatment of the nephrotic syndrome. Six days before his death signs of acute pulmonary oedema developed, but he recovered from this attack and improved after treatment with diuretics. He died during a major epileptic fit. Necropsy showed that his renal disease was due to primary amyloidosis. Large clots were found in the pulmonary arteries, and in the left lower lobe the pulmonary vein was filled with clot which was continuous with a mass of clot 6 cm.  $\times$  3 $\frac{1}{2}$  cm.  $\times$  3 $\frac{1}{2}$  cm. lying in the left atrium. Emboli were found saddling the bifurcation of both common carotid arteries. Pulmonary oedema had presumably been caused by the obstruction in the left atrium, and the immediate cause of death was cerebral infarction.

Of the 2 deaths in the treated series which are now to be described, the 1st was due to suppurative pneumonia complicated by hæmorrhage from a duodenal ulcer; and the 2nd was due to anuria resulting from necrosis of the renal tubules of unknown cause.

**Case 6.**—A woman of 68 years, known to have hypertension, was admitted to a mental hospital with a diagnosis of depression. Intestinal obstruction was found, and she was transferred to this hospital where a strangulated hernia was repaired. After operation she ran a very low-grade fever and on one occasion auricular fibrillation was thought to have developed. An electrocardiogram on the same day showed sinus rhythm. Six days after operation she complained of severe right pleural pain of sudden onset. Friction was to be heard; and there were dullness to percussion, and rales at the right base. She coughed blood-stained sputum which increased in amount. A portable chest X-ray showed extensive shadowing at the right base and mid-zone. Electrocardiography revealed hypertensive changes only.

No adequate history could be obtained from the patient. She was admitted to the trial, and after a card had been drawn anticoagulants were begun. Supervision of the dosage of nicoumalone was inadequate, and on the fourth day of treatment her prothrombin-time was prolonged to eight times normal. Again on the sixth day it was between five and six times normal.

Her condition deteriorated and greater quantities of purulent sputum were produced. On the ninth day of treatment melæna was noticed and anticoagulants were stopped. She died on the following day. Necropsy revealed suppurative pneumonia with abscess formation which was presumed to have followed inhalation of vomit. There was also a subacute duodenal ulcer in the base of which a small artery had been eroded. Considerable intestinal hæmorrhage had occurred. Minor pulmonary emboli were found, and there were antemortem thrombi in the calves of both legs and in the right long

saphenous vein. Suppurative pneumonia was considered to be the major cause of death, but intestinal bleeding was an important contributory factor, and this death has therefore been classified as due to treatment.

**Case 7.**—A man of 52 developed superficial thrombophlebitis of the left leg for which he was given phenylbutazone. This was discontinued when an erythematous rash developed. Three weeks later superficial thrombophlebitis appeared in the right leg, followed in a further two weeks by pulmonary embolism. He was later admitted to hospital where superficial thrombophlebitis of the left long saphenous vein, tenderness of both calves, and bilateral pulmonary infarction were found. During eighteen days' treatment with phenindione the signs of pulmonary infarction and of phlebitis subsided and he was discharged home. Two weeks later he was readmitted with pleural pain and was found to have pain and swelling again in both calves and signs of bilateral pulmonary infarction. There was no fall in blood-pressure. He was admitted to the trial and treatment was begun with heparin and phenindione. That phenindione rather than nicoumalone had mistakenly been prescribed was not realised for several days, and it was then thought that the treatment should continue unchanged. In addition to phenindione, butobarbitone was also given at night. On the twelfth day of treatment a generalised erythematous rash appeared, followed by fever and diarrhoea. All drugs were withheld. Oliguria and later anuria developed, and the blood-urea rose to 560 mg. per 100 ml. He died suddenly four weeks after the appearance of the skin rash which followed the second course of phenindione. Necropsy confirmed the diagnosis of thrombophlebitis of both legs and old pulmonary infarction. Death was due to extensive renal tubular necrosis and uræmia.

The cause of the renal lesion is unknown. There was no period of hypotension. It was felt that the skin eruption could have been due to sensitivity to the phenindione or butobarbitone which he was taking.

#### *Recurrences*

In the first stage of the trial there were during the trial period (i.e., fourteen days) 5 non-fatal recurrences of embolism in the untreated group and no recurrences in the treated group. Among the 54 treated patients in the complete series there was 1 non-fatal recurrence.

#### *Subsequent Progress*

After the trial period it was not possible to keep all the patients under review. The fate of the 29 survivors of the first period of the trial is known. In 1 of the untreated group a further embolism developed eight weeks after the trial period, following a second operation on her fractured neck of femur. This was the only recurrence in a follow-up ranging from twelve to twenty-four months. 2 of the patients in the later series were readmitted to hospital with recurrence of infarction in the fourth week after completing the fourteen-day course of anticoagulant treatment.

#### *Effect of Anticoagulants on Leg Vein Thrombosis*

No attempt was made to assess the progress of the venous lesions of the legs in all patients with tenderness or swelling. In 3 patients who were being treated with anticoagulants there was obvious extension of superficial thrombophlebitis.

#### *Severity of Cases in the Two Groups*

Evidence of stress on the right side of the heart indicates that the embolism is massive (Wood 1950). In all the cases records were kept of the presence or absence of a significant fall of blood-pressure and of severe electrocardiographic changes, and these were the two criteria we have used in defining which cases were "severe" and which were not. The changes which were sought in the electrocardiogram were those described by Cutforth and Oram (1958), inversion of the T waves in leads II, AVF and V<sub>2</sub>, and the

presence of right bundle-branch block. Using these criteria there were 20 severe cases. All had a considerable fall in blood-pressure, 15 fulfilled both criteria; and in 1 other the electrocardiographic evidence of severity was dubious. The distribution of the severe cases was similar in the two groups.

*Severe cases.*—Untreated cases 6 out of 19, treated cases 14 out of 54:  $\chi^2$  (with Yates' correction) = 0.031 0.8 < P < 0.9.

#### *Lung Changes with Stress on Right Side of Heart*

Of the 20 patients with evidence of stress on the right side of the heart, some later had massive pulmonary infarction while others showed neither clinical nor X-ray evidence of this. Lung changes were more in evidence in the 6 severe cases from the untreated group. Of these 6, 2 died (cases 1 and 4) of massive pulmonary infarction with virtual dissolution of the lower zones of both lungs. Nothing like this was seen in any of the treated cases. Of the remaining 4 severe cases in the untreated group, 1 died within forty-eight hours and 2 of the other 3 had extensive pulmonary infarction but recovered. Of the 14 severe cases in the treated group, 2 recovered without clinical signs or X-ray evidence of infarction and in 2 others only a few rales and no radiographic changes developed. Thus anticoagulants appeared to diminish the extent of pulmonary infarction.

#### *Mistaken Diagnoses*

The diagnosis was proved wrong in case 6 (already described) and in 1 other patient who came to necropsy. Again suppurative pneumonia following oesophageal rupture after instrumentation was found. No anticoagulants had been given, and this patient does not therefore figure in the final analysis of the results.

#### Discussion

The first conclusion drawn from this trial is that in a patient who has already had pulmonary embolism the subsequent course of the disease is affected by the regime of anticoagulant therapy we have used: the mortality of pulmonary embolism is reduced. The results show that deaths from pulmonary embolism are likely to outnumber the deaths that may be attributed to treatment.

In the *treated group* we have assumed that the 1 fatal case of renal tubular necrosis was caused by the anticoagulant drug. In the other fatal treated case other factors were important in causing death.

Of the 5 deaths in the *untreated group* only 1 followed immediately the lodging of a second embolism in the pulmonary artery (case 3). In 1 other a second embolism occurred the day after his inclusion in the trial, but the patient lived a further fifteen days (case 4). In the others, only one episode of embolism was diagnosed and the three patients lived for two, fourteen, and twenty-one days. 2 of the 5 deaths were due to very extensive pulmonary infarction with superadded infection and cavitation. In another, death was due to extension of the thrombus through the pulmonary veins to fill the left atrium. These 5 cases suggest that the idea that it is too late to use anticoagulant treatment when a pulmonary embolism has already occurred is ill founded.

There were no comparable deaths in the treated group, even in the most severe cases; and it seems reasonable therefore to conclude that even after embolism has reached the pulmonary arteries anticoagulant therapy reduces the risk of death from heart-failure or from pulmonary infarction—probably by discouraging further deposition of thrombus in the pulmonary arteries where the blood-flow is so grossly impeded. This would explain its effect in diminishing the extent of subsequent pulmonary infarction.

2 patients died very quickly after the first signs of

embolism. We have, however, been impressed by the fact that every patient in this series who received the first injection of heparin survived. This suggests that there is no longer any place for considering Trendelenburg's operation of pulmonary embolectomy. One of our patients required long-continued infusions of L-noradrenaline, and several others required repeated intravenous injections of mephentermine sulphate to maintain the blood-pressure. All subsequently recovered. No instance of chronic cor pulmonale has yet been diagnosed in these cases.

The diagnosis of pulmonary embolism can never be established with absolute certainty during life, and there is always a risk of mistakenly treating postoperative pneumonia with anticoagulants. This not only entails additional risk, but also deprives the patient of the benefit of specific treatment. Case 6 shows that the two conditions may arise in one patient at the same time.

Without close supervision of the administration of the anticoagulant, unnecessary deaths may occur, as in case 6, who had extensive intestinal hæmorrhage at a time when the prothrombin-time was unduly prolonged.

#### Summary

73 patients in whom pulmonary embolism had been diagnosed and in whom there was no contraindication to anticoagulant therapy were admitted to a clinical trial. One group were to receive treatment without anticoagulants, and the other heparin and nicoumalone ('Sinthrome'). The treatment period was fourteen days.

In the first 35 patients a card was drawn to decide whether anticoagulants should be used or not. Of the 19 untreated cases 5 died and 5 others had non-fatal recurrences of embolism. Of the 16 cases treated with anticoagulants 1 died and none had recurrences of embolism. The 1 death in the treated series was due to a combination of suppurative pneumonia and alimentary bleeding.

No further cases were admitted to the untreated series, but 38 others were taken into the treated group, making a total of 54. There was only 1 further death, and this was due to renal tubular necrosis in a patient mistakenly treated with phenindione instead of nicoumalone.

It is concluded that when a patient has had pulmonary embolism, heparin and nicoumalone reduce the risk of death from that embolism. The likelihood of recurrent embolism is also diminished.

Prof. C. Bruce Perry, Dr. J. E. Cates, Dr. D. H. Davies, Dr. J. E. G. Pearson, and Dr. J. A. Cosh suggested the form of this trial and the type of treatment that should be tested. We are indebted to them, and to all the physicians and surgeons of the United Bristol Hospitals who allowed us to include their patients.

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#### Addendum

Since this paper was completed R. H. Brooks and H. B. Calleja (*Ann. intern. Med.* 1960, 52, 706) have reported the occurrence of a nephropathy accompanying a generalised sensitivity reaction to phenylindione. Their patient developed fever, hepatitis, and a rash; and the urine contained albumin, casts, and red blood-cells. Recovery was complete.