THE EFFECTIVENESS OF ANTICOAGULANT THERAPY AS OBSERVED IN 303 CASES[1]

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INTRODUCTION

Anticoagulants have been administered with careful clinical and laboratory supervision to 303 cases on the various services at the University of Michigan Hospital. Treated were 133 cases of peripheral venous thrombosis; 35 cases of pulmonary embolism and infarction; and 21 cases of myocardial infarction, to which 10 cases have recently been added. Dicumarol was administered prophylactically in 74 postoperative cases and for miscellaneous purposes in 40 cases. One hundred and seventy-three of these patients were women, 100 were men; in several instances more than one course of treatment was required. Both ward and private patients were treated. Dicumarol alone was depended upon for an anticoagulant effect in 190 instances and preliminary heparinization was employed in 113.

Emphasis will be two-fold in this report.

(1) Although the use of dicumarol is always accompanied by a calculated risk, under controlled conditions the response of prothrombin activity to dicumarol is reasonably predictable and orderly.

(2) The effectiveness of the anticoagulants has been reasonably established, but it must be emphasized that they are not infallible. The collected data representative of world-wide clinical experience have demonstrated the beneficial effects of heparin and dicumarol in reducing the morbidity and mortality associated with thrombo-embolism. These data are usually presented in statistical form and fail, therefore, to emphasize that in the face of intelligent use of the drugs, subsequent thrombo-embolism does sometimes occur.

METHODS

Heparinization

Indications for an immediate anticoagulant effect by preliminary heparinization included major pulmonary or myocardial infarctions and thrombosis of the deep veins with or without progression or embolization. Heparin was continued until the prothrombin concentration had been substantially reduced by dicumarol (preferably to 30 per cent or below). It was given either by continuous infusion (100–200 mgm. in 1000 cc. of 5% glucose) or at intervals directly into the vein (50–100 mgm. at 4 to 6 hour intervals). The intermittent treatment, although more expensive and difficult to carry out over a prolonged period, appears preferable for critically ill patients in whom a continuous 36 to 48 hour infusion may be seriously fatiguing. To some extent heparin requirements are related to body weight. In half of the cases, dosage of heparin was controlled by the Lee and White clotting test (by which values up to 11 minutes are normal).

Although we have no proof that control of a thromboembolic process is necessarily favored when heparin dosage is regulated by clotting tests, their performance is recommended at least once daily as a safeguard against excessive prolongation of the clotting time. An adequate heparin effect has been obtained, in our opinion, when the pretreatment clotting time has been doubled. No fatalities were associated with the use of heparin; it did, however, cause one mild foreign protein reaction, two cases of hematuria, and one case of major wound hemorrhage. We have had limited experience with the preparations of heparin designed for subcutaneous or intramuscular use.

Testing for prothrombin

The Quick procedure, employing whole plasma, was used to test prothrombin activity, then expressed in per cent of normal concentration. Although commercial sources are now proving satisfactory, the thromboplastin employed in this study was prepared from rabbit brains after Quick's directions. Prothrombin dilution curves, from which prothrombin concentrations were interpolated, were constructed for each batch of thromboplastin. The prothrombin time of normal whole plasma varied from 12 to 16 seconds; in general, prothrombin concentrations of 30%, 20% and 10% corresponded, respectively, to 24, 30, and 45 seconds of "prothrombin time."

Accurate daily measurement of prothrombin activity is essential for safe and effective administration of dicumarol. In our experience the unmodified Quick test is reliable for this purpose. During the initiation of and recovery from dicumarol therapy, with prothrombin concentrations in the range of 100 to 30%, daily technical variations greater than 10% occurred in from 10 to 6% of the cases; in the crucial therapeutic range of 30 to 10%, important technical variations occurred in less than 5%. Simultaneous determinations of the prothrombin time of plasma diluted by saline to 12.5% (Link-Shapiro technique in part) were made in about half of these cases. This was discontinued because it added little information to the standard Quick procedure.

Dicumarol

Definition of the therapeutic prothrombin range is largely arbitrary. The Mayo Clinic group (1) reported "few instances of bleeding and almost no instances of thrombosis occurred" when the concentration was kept between 10 and 30% of normal. The therapeutic range advocated by Wright, et al (2) approximates a concentration of 10 to 20%.*

In this study, 300 mgm. of dicumarol was the initial dose (zero day), with the dosage thereafter dependent upon the daily prothrombin level. The ideal range of effective therapy was considered to be between 10 to 30% of normal. In general, from 100 to 200 mgm. were given as a single dose each day the

* Recently, Brambel, et al, (9) have recommended more conservative depression of prothrombin activity (40 to 50% of normal) as satisfactory in prophylaxis against thromboembolism following surgical procedures.

prothrombin concentration was 20% or above.[2] Effective levels were maintained until the patients became ambulatory, following which prothrombin activity was usually allowed to revert to normal spontaneously.

<center>PROTHROMBIN ACTIVITY</center>

<center>*Dicumarol sensitivity*</center>

Sensitivity to dicumarol was definitely influenced by major liver and kidney insufficiency, severe disturbances of the acid-base equilibrium and circulatory failure. Bleeding induced by dicumarol was severe in one patient with a lesion of the intestinal tract and a fatality occurred following its use in one patient with severe hypertension and a past history of cerebral-vascular accidents. We have not recently employed anticoagulants in patients with subacute bacterial endocarditis. Under these circumstances, if their use is warranted, heparin and dicumarol should be administered cautiously.
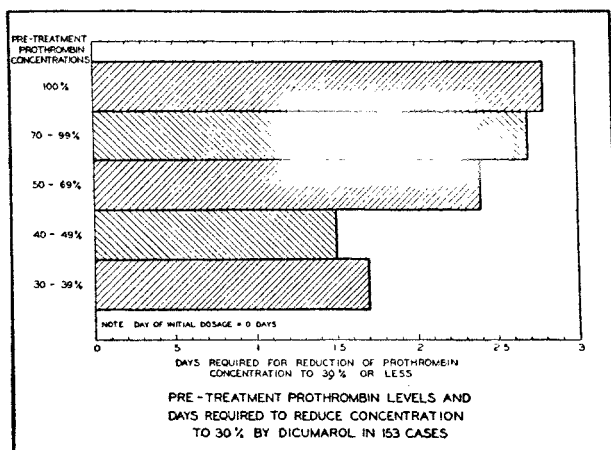

<center>Fig. 1</center>

Low pretreatment prothrombin levels generally indicated dicumarol sensitivity. Patients with prothrombin levels below 50% were brought to an effective concentration (30%) in about 1.7 days; whereas for those in the normal range (70 to 100%) the time was 2.8 days, and for a group with moderate hypoprothrombinemia (50 to 70%) it was nearly the same (2.4 days) (fig. 1). Pretreatment prothrombin levels were within the normal range in half the cases regardless of the presence or absence of thrombo-embolism. Significant hypoprothrombinemia (less than 50% concentration), found in 5% of the cases, was observed in 5 patients in the prophylactic group, 6 with venous thromboses, 3 with pulmonary emboli and infarction, and 1 with acute myocardial infarction. In only 2 of these patients did dicumarol reduce the prothrombin to less than

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[2] This guide to dosage correlates closely with that advocated by Wright (2) which is based on prolongation of prothrombin time in seconds.

10% of normal, and bleeding occurred in only one case. This emphasizes that although thrombo-embolic episodes may occur at low prothrombin levels, anticoagulant drugs may be employed with caution.

Time required to obtain effective ranges of prothrombin

The time required (2.8 days) to reduce prothrombin to the therapeutic range in those cases with normal pretreatment levels generally proved to be about the same regardless of indications for treatment. Curiously, those (without known

TABLE I

Anticoagulant therapy

Range and duration of effective* prothrombin concentration

	EFFECTIVE RANGE	DAYS
	%	
Prophylactic group	15.6–21.9	6.5
Venous thrombosis	14.1–27.4	10.1
Pulmonary embolism	14.5–28.0	9.5
Myocardial infarction	12.7–27.4	16.0
Miscellaneous	16.9–27.0	8.9
Average	14.8–26.3	10.2

* 30% or less.

TABLE II

Dicumarol dosage in anticoagulant therapy

	EFFECTIVE*	1ST WEEK	TOTAL
	mg.	mg.	mg.
Prophylactic group	620	818	947
Venous thrombosis	668	1110	1216
Pulmonary embolism	593	848	1512
Myocardial infarction	590	904	2130
Miscellaneous	659	912	1160
Average	626	918	1391

* Required to reduce prothrombin concentration to 30% or less

thrombo-embolism) to whom prophylactic dicumarol was administered, required a longer time (3.5 days) to reach effective levels. They also recovered more quickly from the effects of dicumarol (4.6 days).

Range of prothrombin concentration

An effective range of prothrombin, 15 to 26%, was maintained for about 10.2 days (Table I) and the average case was tested for prothrombin 16.6 days. The average patient required 600 mgs. of dicumarol to effect a concentration of 30%; the average dose administered in the first week was 900 mgm.; 1400 mgm. was

the average total dose (Table II). These figures were not essentially altered by preliminary heparinization, nor were they consistently related to age, weight or state of nutrition. In the average case, prothrombin had returned to the normal range 6 days after the last dose of dicumarol.

Considerable unpredictable variation was observed in dosage requirements. In a group of 111 with normal pretreatment prothrombin levels, approximately 10% were reduced to 30% concentration within 24 hours by a single 300 mgm. dose of dicumarol, 37% required 48 hours and 500 mgm. of dicumarol. By way of contrast, one stalwart youth with a traumatic axillary vein thrombosis required 2400 mgm. of dicumarol over a 7 day period before the prothrombin was reduced to 30%, and in 6 other cases the effective dosage varied from 1100 to 1800 mgm. In 15 cases prothrombin concentrations were never reduced to effective levels due to reluctance to push the dosage. Variation in response to dicumarol occasionally was related to improvement or decline in the general condition of the patient.

In a few cases (9) dicumarol induced nausea, sometimes accompanied by vomiting, cramps and diarrhea, which in one case necessitated termination of treatment. In several instances low prothrombin levels were accompanied by ease of fatigue, listlessness and malaise which disappeared when the prothrombin rose again.

Escapes of prothrombin activity above the therapeutic range

Temporary and accidental elevation ("escape") of prothrombin above the therapeutic range occurred at some time in 35% of the cases and persisted an average of 1.7 days. It is questionable whether, in most cases, this could have been prevented by more adroit manipulation of daily dosages. The frequency of these aberrations was least in the group to whom dicumarol was given prophylactically; they appeared to occur most commonly in patients with myocardial infarctions. To correct these lapses, an average of about 300 mgm. of dicumarol was required.

The clinical significance of escapes above the effective range is difficult to evaluate in a study of this size. In 5 cases, progression of a thrombotic process occurred 12 to 96 hours after the prothrombin concentration rose above 30% but none of these patients sustained pulmonary emboli. Although 3 patients with myocardial infarctions died coincident with such lapses, postmortem examination in two failed to prove that death would otherwise not have occurred. Two patients with repeated pulmonary embolic episodes sustained major infarctions after elevation of prothrombin to allow surgical ligations. One of these terminated fatally but an autopsy was not permitted. In a third patient with pulmonary emboli and a fourth with a myocardial infarction, clinical evidence of peripheral venous thromboses first became apparent coincident with rise of the prothrombin above the effective range.

Incidence of decline in prothrombin levels to less than 10%

Temporary depletion of prothrombin to less than 10% concentration occurred in 22% of the cases, after an average 847 mgm. of dicumarol, and persisted for

an average of 1.5 days. On several occasions hypoprothrombinemia of this magnitude occurred two or three times during the same course of therapy. In the majority of cases this excessive dicumarol effect was unavoidable and unpredictable. The fact that only 12% of these cases were associated with bleeding emphasizes that fall of prothrombin to less than 10% concentration need not be cause for immediate concern. If spontaneous correction has not occurred within 24 hours, vitamin K should be administered; a single intravenous injection (72 mgm. of menadione bisulfite) being usually sufficient. In two cases where low levels were allowed to persist, an unusually large amount of vitamin K

TABLE III

Bleeding in anticoagulant therapy (303 cases)

	INCIDENCE		DAY OF ONSET	PREVIOUS DICUMAROL
	Cases	%		
				mgm.
Prophylactic group	12	16.2	6.6	758
Venous thrombosis	12	9.0	9.3	945
Pulmonary embolism	3	8.6	10.6	933
Myocardial infarction	1	4.8	14.0	1050
Miscellaneous	6	15.0	21.0	1925
Total	34			
Average		11.2		1102

TABLE IV

Bleeding in anticoagulant therapy (303 cases)

Heparin caused major wound hemorrhage in 1 case (employed in 113 cases)
Dicumarol induced bleeding in 11.2% of the cases
    It was minor in 71%
    It was major in 29%
    One case of fatal cerebral hemorrhage
Prothrombin concentration at which bleeding occurred
    It was less than 20% in two-thirds of the cases
    It was less than 10% in one-fifth of the cases
Bleeding ceased at an average prothrombin concentration of 37% in 26 cases
Bleeding persisted an average of 2.7 days

over a period of several days was required to restore prothrombin activity. One of these patients had severe alkalosis and the other severe acidosis.

BLEEDING

Dicumarol induced bleeding in 11.2% of all cases. Susceptibility to bleeding was not correlated with patient's age, nutritional state, or pretreatment prothrombin level. On the average, hemorrhage occurred on the 12th day, about 2.3 days after the last dose of dicumarol, and following a cumulative dosage of 1100 mgm. (Tables III and IV). Hemorrhage sufficiently severe to require re-

hospitalization in 2 cases emphasizes the wisdom of restoring prothrombin to 50% or above prior to discharge from the hospital. In the prophylactic cases, the majority of whom had had major pelvic operations, hemorrhage was most common (16%) and most severe; 6 out of the 10 cases of major bleeding occurred in this group.

Two-thirds of the cases of hemorrhage occurred at prothrombin concentration of less than 20% and one-fifth were in the range below 10%. A prothrombin concentration of 30% was the upper limit at which bleeding first appeared. Bleeding persisted on an average 2.7 days, while it appeared to cease at an average concentration of 37% (26 cases). In a few patients return to the prothrombin level at which bleeding had initially occurred was not, curiously enough, again accompanied by bleeding. The severity of bleeding was not necessarily related to the degree of hypoprothrombinemia which had been induced.

Bleeding was classified as minor (gross hematuria, wound bleeding and epistaxis) in 71% of the cases; it was major to massive (vaginal, gastrointestinal and hematuria) in 29%. The incidence of microscopic hematuria is unknown. In three cases hematuria was accompanied by costovertebral angle pain and discomfort similar to renal colic. Gross hematuria persisted in ten patients an average of 3.5 days.

Although most cases of bleeding occurred spontaneously, occasionally there was associated trauma. Ecchymoses and hematomas were common. In two cases, petechiae appeared in areas covered by compression bandages but they were unassociated with known trauma in a third patient. Hemarthrosis occurred in two ambulatory patients and necessitated hospitalization. In one patient massive hematuria followed urethral dilatation at a time when the prothrombin concentration was about 15% of normal; without the support of huge doses of vitamin K and 1000 cc. of blood, this patient would surely have exsanguinated. In a second case a nasal biopsy, performed when the prothrombin concentration was 14%, was followed by moderate epistaxis. In a third case, joint manipulation at a prothrombin concentration of 22% produced severe local bleeding in the soft tissues about the joints. These instances emphasize that elective manipulations or surgical procedures in disregard of therapeutic prothrombin levels may produce external or internal hemorrhage. Decision was made to perform emergency surgical procedures (an appendectomy and a urethrotomy) in two patients at a time when their prothrombin levels were well below 20%. Blood loss was less than expected, due to the preoperative and postoperative administration of large amounts of vitamin K and blood.

Fatal bleeding

Dicumarol probably caused fatal bleeding in one case in this series.

This patient, a 43 year old woman, was known to have essential hypertension of 17 years duration. Eight months before admission she had experienced transient numbness of the right side of the face followed, one month later, by sudden but transient paralysis of the right arm. Loss of vision in the right eye occurred the day before admission. On examination the blood pressure was 240/150. No abnormalities were mentioned in the neurological examination. The funduscopic picture was that of hypertensive retinopathy in addition to a

recent occlusion of the right superior retinal artery. Renal function as measured by urea clearance was moderately impaired. In view of the retinal artery occlusion, anticoagulant therapy, employing preliminary heparinization, was initiated on the 4th hospital day; the pretreatment prothrombin concentration was 100%. It was not until the 9th day of treatment, after a total of 1800 mgm. of dicumarol, that the prothrombin concentration was reduced to 30% concentration; an additional 150 mgm. of dicumarol was administered on the 9th and 10th days. During this time the patient was up, without particular complaints. The prothrombin concentration on the 11th day was 23%; the 12th day it was 14%; by the 13th day (last determination) at 9:30 A.M. it had dropped to less than 10% of normal (control 13.0 seconds; patient 55.9 seconds) for which reason one dose (72 mgm.) of prophylactic menadione bisulfite was given at 10:00 A.M. About 2:30 P.M. there was the onset of frontal headache, dizziness and vomiting; the blood pressure was 278/170. By 4:30 P.M. she had become drowsy and unable to move the left arm and leg; positive Hoffman and Babinski signs were present on the left; the left pupil was irregular and constricted. Thereafter, the patient became unconscious and incontinent; death occurred 24 hours later. Although a postmorten examination was not permitted, more than coincidental relationship was attached to the precipitous fall in prothrombin concentration and the onset of the fatal cerebral hemorrhage.

A second fatal case, occurring under similar circumstances, but since completion of this study, must also be described.

Within the year prior to hospitalization, this 79 year old woman probably sustained a cerebral thrombosis. A similar episode had occurred 8 years earlier and hypertension, varying from 230/130 to 190/110, had existed for several years. At the time of admission, one week subsequent to a fracture of the left femoral neck, she was confused, disoriented and frequently uncooperative. Following an open reduction of the fracture and fixation by nailing, prophylactic dicumarol was initiated. The pretreatment prothrombin level was 68% of normal; the NPN was somewhat elevated (41 mgm.%). By the second day of treatment, after 500 mgm. of dicumarol, the concentration had been reduced to 19%; therapeutic ranges, varying from 11 to 35%, were maintained thereafter for a total of 21 days by small doses of dicumarol. Her general condition improved somewhat in this period and she was up every day in a wheel chair. The diagnosis of organic brain disease on an arteriosclerotic basis was confirmed by a consultant from the Department of Neurology who emphasized the likelihood of a recurrent cerebral thrombosis. After consideration of the potential hazards, it was decided to continue anticoagulant therapy. On the 21st day of treatment the prothrombin concentration was 18.5%, 100 mgm. of dicumarol were given. By 9:00 A.M. the next day, the concentration had fallen to less than 10% (normal 13 seconds, patient's 51.4 seconds); six hours later she was discovered slumped over the arm of her chair, unable to move her left leg and arm. Shortly thereafter, she became comatose, respirations became irregular and soon ceased. Although permission for postmortem examination could not be obtained, death was assumed to be the result of a cerebral-vascular accident associated with the abrupt fall in prothrombin concentration.

The outcome of these two cases stresses the hazard of administering dicumarol to patients with severe hypertension and a past history of cerebral vascular accidents.

VITAMIN K

Cromer and Barker (3) reported that in 38 cases of dicumarol-induced hypoprothrombinemia, the prothrombin time was returned to safe limits within 18 hours after the intravenous administration (usually a single dose) of 62 mgm. of menadione bisulfite. They state that "a rapid decrease of the excessively elevated prothrombin time ... was the usual type of striking response and occurred in 81.1% (35) of the cases." No response occurred in two patients and it was minimal in a third.

In our study, repeated doses of vitamin K were found to be necessary to reverse the effect of dicumarol adequately (Table V). In 37 cases, the injection of 72 mgm. of menadione bisulfite resulted in an average rise of only 20% in prothrombin concentration at the end of 12 to 18 hours; in 5 cases response was negligible to absent. Since hemorrhage generally occurred at a prothrombin concentration under 20%, and did not cease until it reached about 37%, it should be stressed that large and frequent doses of vitamin K (72 mgm. at 4 hour intervals, 3 or 4 times in a 24 hour period) must be employed to counteract the effect of dicumarol, especially in the presence of bleeding. In 21 cases an average of 185 mgm. of menadione bisulfite was administered before minor bleeding ceased and in 9 cases with major bleeding an average of 272 mgm. was required. No cases failed to respond to vitamin K when this dosage program was followed. In the majority, the effect of vitamin K appeared to have been sustained. These large doses have not produced known toxic effect nor have they been observed to reinduce thrombosis. Blood transfusions were used freely to supplement vitamin K.

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TABLE V

Vitamin K

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Twelve to 18 hours after the injection of 72 milligrams of Vitamin K* (37 cases)
  There was an average rise of 20% in prothrombin concentration
  In 5 cases the response was negligible
About 185 milligrams* (2½ ampules) were administered in 21 cases before minor bleeding
  ceased; 272 milligrams (3.7 ampules) were administered in 9 cases with major bleeding

* "Hykinone" (72 milligram ampule).

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CLINICAL EFFECTIVENESS OF ANTICOAGULANTS

Prophylactic use

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Dicumarol without preliminary heparinization was employed to forestall thrombo-embolism in 50 cases following major gynecological operations, in 12 cases after general surgical procedures, after fractures in 5 cases, and following childbirth in 7 patients. Usually the initial dose of dicumarol was given on the second or third postoperative day. Effective prothrombin levels were maintained about 7 days. Sixty-three of these patients were women and 9 were men. The incidence of obesity and neoplasms was high; approximately 25%, furthermore, had experienced previous episodes of intravascular clotting.

Among these patients thrombo-embolism was not unusual (9%) when the prothrombin concentration was above the therapeutic level of 30%. In 5 cases unmistakable evidence of postoperative peripheral venous thrombosis appeared between the initial dose and the attainment of this level. In two other cases peripheral venous thromboses appeared when prothrombin activity was reversed to normal. One of these patients sustained a major pulmonary infarction.

By way of contrast, we had only one case (1.4%) in which peripheral venous thrombosis became evident after an effective prothrombin concentration, in this instance 18%, had been obtained. Since completion of this study, a second case

of thrombo-embolism has occurred in the face of technically effective prophylactic dicumarol. The details are pertinent because they illustrate that sometimes the calculated effect of dicumarol will not be complete protection against a strong tendency to thrombo-embolism.

This 59 year old male had an impressive past history of thrombo-embolism. In 1925, subsequent to a cholecystectomy and appendectomy, he had suffered two separate pulmonary infarctions. In 1929, following confinement to bed because of a fractured wrist, the third pulmonary embolism occurred. In January, 1948, he sustained a comminuted right acetabular fracture for which, at another hospital, he spent 7 to 8 weeks in Russells' traction, during the course of which thrombophlebitis of the right calf and leg developed, complicated by pulmonary emboli. Convalescence on anticoagulant therapy (heparin and dicumarol) thereafter had been uneventful. Progressive pain in the right hip led to his admission to the University Hospital for a right vitalium cup arthroplasty. To spare him further thrombo-embolism, dicumarol was started on the first postoperative day, supplemented by intermittent intravenous heparinization. By the third day of treatment, the prothrombin concentration had been reduced to 26% of normal, and was maintained thereafter in the therapeutic range. On the 7th day, at a concentration of 20%, he complained of persistent pain in the right popliteal space associated, 3 days later, with pain and tenderness in the right calf. Considerable apprehension on the part of the patient made difficult the evaluation of chest pain, in the absence of significant alteration in the temperature or pulse curve and a negative chest x-ray. Because of the definite evidence of a venous thrombosis, however, 150 mgm. of intravenous heparin was administered via continuous intravenous infusion over a period of 24 hours; dicumarol was continued with eventual complete subsidence of all signs of peripheral venous thrombosis. Therapeutic dosages of dicumarol were continued thereafter for over 50 days, convalescence being essentially uneventful.

The indications for the routine use of prophylactic dicumarol after major operations are not clearly defined. On the basis of this study, its apparent protective advantage after pelvic operations, must be weighed against the increased incidence of bleeding which it induced (16%) and which was often major in extent (6 out of 10 cases). The cost of a course of prophylactic dicumarol was equivalent to about one or one and one-half days of extra hospitalization.

We are, however, convinced of the value of providing, when possible, the protection of prophylactic anticoagulant therapy to any patient who has a past history of thrombo-embolism and who faces prolonged bed rest or an operative procedure. This protection may be desirable, too, for patients who are immobilized by organic heart disease and congestive failure, fractures of a lower extremity, or injuries to the spine since, in this study, they commonly experienced thrombo-embolism. Although difficult to administer, such treatment carried out over a prolonged period may offer hope to those patients with rheumatic heart disease, auricular fibrillation and recurrent systemic emboli.

PERIPHERAL VENOUS THROMBOSIS

One hundred and thirty-three cases of acute peripheral venous thrombosis (phlebothrombosis or thrombophlebitis) were treated with anticoagulant therapy. Sixty-two of these patients were women, 48 were men, and 21% had past histories of thrombo-embolism. At the time of treatment the pathologic conditions associated with the development of thromboses included congestive failure,

myocardial infarctions, pulmonary emboli, pelvic neoplasms, etc. (47 cases); postoperative cases (50); complicating fractures, the majority of which were of the hip and in elderly individuals (20 cases); postpartum (9 cases); subsequent to fracture dislocations of the spine with transverse myelitis (5 cases); in association with a ruptured nucleus pulposus (5 cases, 4 of which followed laminectomies

Surgical ligations were performed infrequently in this group. Anticoagulant therapy was successfully employed to supplement previous surgical ligation in 4 patients. Combined treatment was employed in 12 other cases because of the recurrence of pulmonary infarctions or progression of the thrombotic process following or in spite of anticoagulants (3 cases) or venous ligations (9 cases), including 2 inferior vena cava ligations.

Heparin was used with dicumarol in 66 cases; dicumarol was used alone in 67 (Table VI). An average of 10.2 days of effective prothrombin concentrations were obtained. Reduction of prothrombin to the therapeutic range was generally accompanied by gratifying subjective and objective signs of improvement, i.e.,

TABLE VI

Effectiveness of anticoagulant therapy in peripheral venous thrombosis

	CASES TREATED	DAY OF ATTAINING EFFECTIVE PROTHROMBIN LEVEL	IMPROVEMENT*		SUBSIDENCE,† DAY OF
			Day of	Proth. Conc.	
				%	
Heparin and Dicumarol........	66	1.8	2.8	29.4	6.8
Dicumarol alone..............	67	2.5	3.5	24.0	7.5

* Symptomatic and objective evidence.
† Objective evidence.

relief of pain and aching, fall in temperature and pulse curves, and subsidence of tenderness and swelling. In 16 cases, however, improvement was not evident until the concentration was pushed below 20% and sometimes to less than 10%. In 7 cases actual progression of the thrombosis continued until these low levels were obtained. Symptomatic relief was obtained more quickly when heparin was used (2.8 days) than when dicumarol was employed alone (3.5 days). The thrombotic process, moreover, appeared to subside more quickly with the addition of heparin (6.8 days) than with dicumarol alone (7.5).

Coincident with anticoagulant therapy satisfactory resolution of the thrombotic process was observed in 96% (128) of the cases. The response in 5 cases could not be evaluated. After conclusion of treatment and reversal of prothrombin levels to normal, the thrombus recurred in 9% (12 cases) within 14 days to 4 months, necessitating a second and even third course of treatment. In all but three instances the recurrence was observed in the extremity previously involved. Post-treatment complications still present more than 6 months after treatment, appear to have been less frequent and less severe than in a group of similar size treated by surgical ligations (4).

One patient in this group sustained a minor pulmonary embolism despite effective prothrombin concentrations, in this instance 20%. It is of interest to review the clinical course of these patients while the prothrombin levels were above the therapeutic range. In 7 cases, none of which had received preliminary heparinization, the thrombotic process first became apparent before a level of 30% had been reached. Fourteen patients being treated for venous thromboses improved despite concentrations above 30%; 6 of these received heparin as well as dicumarol. By way of contrast, the thrombi progressed in 9 other cases (6 with heparin) before the 30% level was attained; 2 of these patients had pulmonary emboli during this critical period. Temporary and unintentional escape of prothrombin above the therapeutic range, which occurred in 35% of these cases, was accompanied in only 5 by unmistakable evidence of an exacerbation of the thrombotic process within 12 to 96 hours. All responded to more effective anticoagulant therapy and pulmonary emboli did not occur.

The majority of these thromboses occurred during hospitalization and were, therefore, relatively recent in onset. Dicumarol has been administered over a period of months to 3 patients in whom the thrombotic process and its sequelae were of several months' duration. Their response has been encouraging, as evidenced by varying degrees of subsidence of disabling discomfort and swelling.

PULMONARY EMBOLISM AND INFARCTION

Thirty-five instances of pulmonary embolism and infarction, occurring in 33 patients (19 men, 14 women; average age 53 years) were treated in this study. Preliminary heparinization was employed in 18. Effective levels of prothrombin, obtained an average of 2.5 days after the initial dose of dicumarol, were maintained about 9.5 days. Anticoagulants were not observed to increase the incidence or severity of hemoptysis. One patient, while on active treatment, developed a pulmonary abscess, and cavitation has occurred in a second case not included in this study.

In 20 of these instances pulmonary emboli followed surgical procedures; the remaining 15 cases are classified as "medical". Two-fifths (15) of the entire group had organic heart disease and 11 were in congestive failure. Thirteen, by the time of admission, had sustained at least one pulmonary infarction and in half of the cases there was x-ray evidence of involvement of two or more lobes of the lungs. Peripheral venous thromboses were present at some time in 20. Interestingly enough, in 4 patients clinical evidence of peripheral thrombosis only became manifest *after* pulmonary emboli had occurred.

In one-half of the postoperative group, anticoagulant therapy was instituted within 48 hours of the occurrence of the accident; in the remainder, treatment was delayed from 3 to 9 days. Relationship of mortality to delay in starting treatment is not evident, inasmuch as there was but one fatality (5%). By way of contrast, in the "medical" group, embolism with pulmonary infarction had occurred at least a week prior to admission in 12 patients and institution of anticoagulant therapy was further delayed in this group an average of 5 days. Despite effective reduction of prothrombin concentration, 5 of 15 patients (33%)

in this group died as a result, in part at least, of multiple pulmonary emboli and extensive areas of infarction. It is quite possible that the mortality in this group would have been reduced by more prompt use of anticoagulant therapy.

In spite of technically effective anticoagulant therapy, unmistakable and recurrent pulmonary embolism and infarction occurred in 8 cases covered by this study (two are discussed more fully under myocardial infarctions). Of these 8 patients, only 1 recovered. All had severe organic heart disease, with congestive failure. Intracardiac thrombi were present in 5 (demonstrated in the right heart chamber at autopsy in 4; two of whom, in addition, had thrombi in the left ventricles) while two also had peripheral venous thrombi. The leg veins were undoubtedly the source of emboli in the remaining cases in whom autopsy, in two, revealed no intracardiac thrombi. Three of these cases experienced systemic arterial emboli. We have recently seen three other patients, who eventually recovered, in whom recurrent pulmonary infarctions arose from peripheral thrombi despite therapeutic prothrombin levels. These cases are important because they illustrate, again, that anticoagulant drugs may not always be immediately or completely protective against progression of a thrombus or embolization and infarction. We stress, too, that they must be used, under certain circumstances, in conjunction with surgical ligations. One case in particular demonstrates that thrombo-embolism may sometimes pursue a chaotic course, taxing the effectiveness of anticoagulants and surgical procedures:

This patient, a 39 year old woman, developed a thrombosis of the deep veins of the left thigh and leg 16 days following a chordotomy. Despite the previous administration of 500 mgm. of intramuscular heparin and 200 mgm. of dicumarol, she sustained a pulmonary embolism on the second day of anticoagulant therapy at a time when the prothrombin concentration was 57%. With the administration of an additional 500 mg. of heparin via continuous infusion, over the succeeding 36 hours, she was considerably improved. By the 5th day of treatment, appreciable resolution of the thrombotic process in the left thigh and leg appeared evident. On the 10th day, however, when the prothrombin concentration was 20%, very definite exacerbation of the thrombosis became evident. Three days later the inferior vena cava was ligated, after the prothrombin level had been reversed to 40% by the use of vitamin K. Anticoagulants were not resumed postoperatively. Within 48 hours, definite clinical evidence was present of a thrombosis in the deep veins of the *right* thigh and leg. The prothrombin at this time was 100% of normal. Large doses of dicumarol were reinstituted, following which convalescence was uneventful.

A recent study (4) made in this institution indicates that the incidence of postoperative pulmonary embolism, over an eight year period, has been sharply reduced from 47 to 12 cases per year. In contrast, the incidence of pulmonary infarction in "cardiac" cases in this same period has remained essentially unchanged (9 to 11 cases per year). The prognosis is considerably less favorable for these patients despite the use of anticoagulant therapy and venous ligations.

MYOCARDIAL INFARCTIONS

Thirty-one cases of myocardial infarction occurring in 20 men and 11 women are included in this study. Their average age was 57, with variation from 34 to 71 years. The standard regimens of treatment were employed as indicated. All

were given dicumarol and 19 also received heparin. No attempt was made to select patients on the basis of severity or mildness of systemic reaction to the infarction or of a past history of a similar episode. None had previously been treated with anticoagulants. In only three patients was the interval less than 12 hours between the onset of the myocardial infarction and the institution of anticoagulant therapy. Treatment was instituted in 9 other cases within 24 to 48 hours of the accident, and in the remaining 19, this period of time varied from $2\frac{1}{2}$ to 14 days. The average period of hospitalization was 31 days, and 5 fatalities occurred after an average of 16 days of hospital care.

In the average case 439 mgm. of heparin were administered during a 33 hour period. Nine patients received heparin via continuous intravenous infusion, while in the remainder it was given intermittently into the veins. Attempt was made to prolong clotting times approximately 70 to 100% of pretreatment levels, but the success with which this was accomplished was not uniform. Prompt relief of chest pain was not necessarily guaranteed by the use of heparin.

Effective levels of prothrombin concentration, obtained about 2.5 days after the initial dose of dicumarol, were maintained an average of 17 days. In all cases a concentration of 30% was achieved for at least 3 days and in 2 patients death occurred after 3 and 4 days of technically effective levels of prothrombin. Hematuria occurred in 4 patients and epistaxis was severe and frequent in a fifth case. In the 3 cases coming to autopsy, no evidence of bleeding into the infarcted areas was observed.

In 22 cases the diagnosis on admission was myocardial infarction, the accident occurring to one patient in the Medical Out Patient Clinic. Five sustained infarctions while hospitalized and at bed rest, and in a 6th case, the infarction occurred 16 hours following a bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathectomy for essential hypertension. In the three remaining patients, admitted because of angina pectoris, development of characteristic electrocardiographic changes was delayed from 4 to 15 days.

Eighteen of these patients had hypertension, varying from 6 months to 12 years in duration. Twenty-one (including 7 out of 11 women) had experienced angina pectoris varying in duration from 5 years to less than 2 weeks, while angina and hypertension were concomitant in 14. One patient had luetic aortitis and another had treated lues without known cardiac involvement. A third had thyrotoxic and arteriosclerotic heart disease with auricular fibrillation. One patient with pernicious anemia of 13 years duration, had had paroxysmal auricular fibrillation for 10 years. Eleven in the group were overweight, five had diabetes mellitus and one patient had far advanced silico-tuberculosis.

Prior to institution of anticoagulant therapy the incidence of known recent thrombo-embolism was 16%. Two patients had sustained pulmonary infarction, while embolization to peripheral arteries had occurred in two other cases and a fifth patient had experienced a cerebral-vascular accident 24 hours prior to the myocardial infarction. In addition 4 patients, in a period of time varying from 5 months to 9 years before admission, had experienced cerebral-vascular accidents.

Three patients had sustained 4 definite previous episodes of myocardial infarction, from which uneventful convalescence had occurred in the University Hospital. In 2 additional cases, healed infarctions were demonstrated at autopsy, while in 4 other cases, two of whom died without postmortem examination, unrecognized infarction may also have occurred.

The electrocardiograms were interpreted as suggestive or unequivocally diagnostic in 28 cases. The changes were not diagnostic in one case and inconclusive in two (left bundle branch block). Localization of the infarction was as follows: 8 were anterior, 3 were antero-lateral, 5 were primarily antero-septal, 8 were posterior, 2 postero-lateral, and localization was not designated in 2 reports. The infarcted areas were described as "extensive" in 5 and "minor" in a 6th case. Duration was thought to be "fresh" in 4, "recent" in 20, "fairly recent" in 1, and no comment as to duration was made in 3.

Electrocardiographic description of the infarction was not necessarily correlated with the clinical findings. Fourteen (45%) were in definite shock as evidenced by fall in blood pressure, cyanosis, dyspnea, rapid pulse, etc. These symptoms varied from moderate to very severe. Of the 18 known to have had hypertension in the past, only 12 had definite elevation of the blood pressure upon admission. In 21 the white blood cell count was above 10,000, varying in three from 16,500 to 27,000. Sedimentation rates, obtained in 14, were elevated in 11 instances. Significant temperature elevations occurred in 21. Four, at some time, had a pericardial friction rub, while abnormalities of the cardiac rhythm occurred at some time in 5. Nine were either in heart failure on admission or experienced it sometime in the course of treatment, four of these eventually succumbed.

Non-thrombo-embolic deaths

In the entire group of patients with myocardial infarction there were 5 deaths, a mortality rate of 16%, and in 3 instances sudden death is believed to have resulted from a non-thrombo-embolic mechanism. One patient died suddenly 4 days after infarction on the 4th day of effective anticoagulant therapy (heparin and dicumarol) when the prothrombin concentration was less than 10%. Sudden death occurred in a second 13 days after the infarction and on the 13th day of anticoagulant therapy (heparin and dicumarol) with a prothrombin concentration of 25%. Although postmortem examinations were not permitted in these two cases, and fatal massive thrombo-embolism may have occurred, death is believed to have probably been on the basis of acute heart failure, myocardial rupture, or ventricular fibrillation.

The third case, a 63 year old woman, had tertiary lues, luetic aortitis and diabetes mellitus. Two days after admission for uncontrolled diabetes, she sustained an anterior myocardial infarction. A pericardial friction rub was present, the heart was somewhat enlarged, and she was in mild congestive failure. Dicumarol was instituted 4 days after the infarction. The prothrombin concentration was reduced to an effective level by the 6th post-infarction day, and thereafter it varied from 10 to 33%. During this time the patient appeared to be doing well. On the 9th post-infarction day, sudden death occurred at a prothrombin concentration of 33%. At autopsy the infarcted area, which measured 3 centi-

meters in breadth, was found to extend through the wall from the apex to the junction of the upper and middle third of the left ventricle. A fragile, recently organized and organizing mural thrombus adhered to the apical portion of the softened area. Focal acute fibrinous epicarditis was present and there was evidence of old healed myocardial infarctions and luetic aortitis. The lungs revealed acute passive congestion. Other than for the presence of organizing thrombi in the bladder, renal, mesoovarium and paravaginal veins, evidence of thrombo-embolism was missing. It seems likely in this case that the formation of the mural thrombus preceded anticoagulant therapy and that thrombo-embolism was not an important factor in the mechanism of death.

Thrombo-embolic deaths

The role of thrombo-embolism as an important mechanism in the cause of death is not too definite in the fourth case, although it cannot be excluded.

This patient, a 60 year old woman, experienced severe chest pain associated with dyspnea and orthopnea two days before admission. She was in shock when first seen, but congestive failure was not evident, nor were there signs of peripheral vein thromboses. A pericardial friction rub was heard. The electrocardiographic findings were suggestive of a recent anterior myocardial infarction. Anticoagulants (heparin and dicumarol) were begun immediately and effective prothrombin concentrations were maintained for 31 days. During this period her clinical course was characterized by persistent severe chest pain and recurring cardiac failure which required almost constant maintenance in an oxygen tent. The day before death, 37 days after the infarction, at which time the prothrombin concentration was about 40%, the left foot became cold, cyanotic and pulseless. At autopsy the left ventricle appeared somewhat dilated, and obliterative epicarditis was present. There was a recent anterior myocardial infarction of the left ventricle and multiple focal areas of healed older infarctions. The endocardium was smooth and glistening. No evidence of a mural thrombus was found. The lungs showed acute exacerbation of a chronic passive congestion, organized thrombi or emboli were observed in pulmonary arterial branches and terminal acute purulent lobular pneumonia was present. Death in this case is attributed to cardiac failure, terminal pneumonia, and pulmonary emboli. Abnormalities were not detected in the iliac arteries and veins, although the prosector was not permitted to examine the blood vessels below the pelvis. The terminal vascular occlusion is assumed to have been on the basis of arterial thrombosis or embolism.

In the fifth and last case, uncontrolled thrombo-embolism was undoubtedly the cause of death.

This patient, a 42 year old man, was admitted to the hospital in congestive failure 9 days after sustaining an extensive anterior myocardial infarction. Clinical evidence of peripheral vein thromboses was lacking. On the second hospital day, despite administration of 200 mg. of heparin in the preceding 24 hours, pulmonary infarction occurred. An effective prothrombin concentration, obtained by the third hospital day, was maintained 10 days. On the 9th day, and persisting for the last two days of life, the prothrombin concentration "escaped" to a level of 50 to 57%. During this period the patient's course was progressively downhill, being characterized by severe chest pain and dyspnea requiring maintenance in an oxygen tent. The sputum was always grossly bloody. Death occurred 25 days after the myocardial infarction. At necropsy, an extensive apical and anteroseptal myocardial infarction was demonstrated in addition to older areas of infarction. Fibrinous pericarditis was present. Organizing mural thrombus was present in both ventricles and a recanalizing thrombus was present in the anterior descending coronary artery. Multiple old and recent hemorrhagic pulmonary infarctions were present with organizing emboli in the pulmonary artery. It seems likely that the mural thrombi were present before admission to the hospital. Heparin

and dicumarol failed to prevent recurrent and eventually fatal pulmonary emboli and infarctions.

Non-fatal thrombo-embolism

Four thrombo-embolic episodes were experienced despite anticoagulant therapy, by three patients (10%) who subsequently recovered.

One of these, a 60 year old woman, probably sustained a myocardial infarction 3 days before admission; the electrocardiographic signs were obscured by the presence of left bundle branch block. When first seen she was in shock and congestive failure, and pulmonary infarction had already occurred. Clinical evidence of peripheral venous thrombi was lacking. On the 5th hospital day dicumarol therapy was instituted. Satisfactory reduction of the prothrombin concentration prolonged over a period of 37 days did not prevent the recurrence of major pulmonary emboli. Recurrent congestive failure was a prominent feature of her illness. Her recovery, although prolonged over a course of 78 hospital days, was eventually satisfactory.

The second patient was a 48 year old male who had sustained a myocardial infarction for which he was treated at another hospital; anticoaglants were not employed. Twenty-four hours after the development of multiple arterial emboli to both lower extremities he was admitted to the University Hospital, 22 days after the initial infarction and about a week after its extension. The admission electrocardiogram indicated the presence of a recent and extensive anterolateral infarction which likely involved the interventricular septum. Ischemic gangrene of the left foot was present. At about 7:30 P.M. on the third hospital day, while straining on the bed pan, this patient sustained a cerebral embolism, despite the administration in the preceding 48 hours of 700 mgm. of heparin (the clotting time one hour after the accident was 2 minutes although previously it had varied from 7 to 22 minutes) and 600 mgm. of dicumarol. The prothrombin concentration 10 hours prior to the cerebral embolism was 50% and on the succeeding day it was 21%. Further thrombo-embolic complications did not occur; bilateral supracondylar amputations were, however, eventually required.

A third patient to whom dicumarol alone was administered for a posterior myocardial infarction of 4 days duration, had definite clinical evidence of extension of the infarction on the second day of anticoagulant therapy when the prothrombin concentration was 34%. The electrocardiogram at this time remained unchanged. Subsequently, while at effective prothrombin levels, she experienced continued episodes of chest pain, of several hours duration, accompanied by electrocardiographic evidence of extension of the infarction. On the 32d day of her convalescence, with sudden lapse of her prothrombin concentration from 19 to 37%, there was evidence of a minor but definite peripheral venous thrombosis, the symptoms and signs of which regressed with heparin and further dicumarolization.

In this group of patients, there was temporary "escape" of the prothrombin concentration above the therapeutic range on 32 different occasions. Coincident with the rise of prothrombin levels, peripheral vascular thrombosis or embolsim occurred in two. Three patients with such lapses eventually succumbed, but postmortem examination in 2 failed to prove that death would not have otherwise occurred.

The principal objectives to be attained by the use of anticoagulant therapy in myocardial infarctions include (5) the prevention of:

1. An extension of the coronary thrombosis or the occurrence of a second infarction,

2. The formation or extension of intracardiac mural thrombi,

3. Peripheral and pelvis vein thromboses with secondary pulmonary embolism,

4. Thromboses in peripheral and cerebral arteries.

The recently reported cooperative study sponsored by the American Heart Association (2) substantiates the value of heparin and dicumarol in preventing these complications. In that study 432 patients received anticoagulants; 368, receiving only conventional therapy, constituted the "control group". Twenty-four per cent of the control patients died as contrasted to a mortality of 15% in the treated patients. In 25% of the control series at least one or more thrombo-embolic complications developed, but in the patients treated with anticoagulants this incidence was only 11%. Although our series is much too small for comparison, it is of interest that the mortality rate (16%) and the incidence of thrombo-embolism (10%), among those patients who survived, are comparable.

If facilities are available, probably every patient with a myocardial infarction sustained not more than 3 weeks prior to hospitalization should be provided the protection of heparin and/or dicumarol. Although the gravity of subsequent thrombo-embolism may thereby certainly be lessened, the anticoagulant drugs are not complete insurance against these complications. In this small series, the incidence of thrombo-embolism prior to employment of heparin and/or dicumarol (16%) was not greatly different from that following treatment (10%). We have described the development, in spite of technically effective treatment, of peripheral arterial and venous thromboses, the occurrence of systemic and pulmonary emboli, and the extension of a myocardial infarction. Others (6, 7) have witnessed the development of a second infarction during anticoagulant therapy.* The value of these drugs in preventing the formation of mural thrombi is hard to establish. We have gained the impression that the clinical course of a patient suffering from a myocardial infarction may be especially stormy when associated with intracardiac thrombosis.

MISCELLANEOUS GROUP

Among the miscellaneous cases treated with anticoagulants are 8 patients with multiple sclerosis, 6 with systemic arterial embolization, 8 with venous or arterial retinal occlusion, and 6 with cerebral thrombosis. Since the effectiveness of anticoagulant drugs in these fields is essentially unexplored, details of our experience with this small number of patients may be justified.

The prolonged administration of dicumarol, on an out-patient basis, appeared warranted in several cases in this group. We wish to emphasize that the difficulties of anticoagulant therapy are considerably increased under these conditions. Satisfactory control will be facilitated by initial hospitalization to determine the maintenance dose of dicumarol. This figure, once established, remains constant enough to discharge the patient with a small supply of dicumarol and

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* Since completion of this study, we, too, have observed a patient who experienced a second and fatal myocardial infarction, despite an effective prothrombin level.

carefully written instructions relative to dosage. Obviously he must also be instructed as to common manifestations of bleeding, and the importance of contacting the physician in charge should they occur. We supply him with an identification card similar to that carried by diabetics, outlining the method of administration and dosage of vitamin K. Therapy of this kind demands an intelligent and cooperative patient who lives within a reasonable distance of the clinic and laboratory. Return visits at first are usually necessary twice a week, but eventually the maintenance dosage may be so stabilized that they may be lengthened to 10 to 14 days. This program will be considerably facilitated if one physician sees all patients and assumes responsibility for their control. Needless to say, administration of dicumarol to out-patients without such control is unthinkable. We stress, too, that even under the best of circumstances the physician and the patient should be prepared for an increased incidence of bleeding. In these patients, maintenance of prothrombin levels within the therapeutic range has been associated with bleeding in almost 50% (7 out of 16 cases) and has necessitated hospitalization in 4 cases. Although the therapeutic benefits of less drastic reduction of prothrombin levels (30 to 50% concentration) are unknown, the hazard of associated bleeding would certainly be less.

Multiple sclerosis

With the above in mind, prolonged and safe administration of dicumarol is not impossible to achieve. Two patients with multiple sclerosis have taken therapeutic quantities of the drug almost continuously for about 3 years, each with apparent benefit, inasmuch as they have been free of crippling exacerbations which previously recurred at 2 to 6 month intervals. Liver and renal function tests have remained essentially unaltered. In 4 other cases treatment was of such short duration that no statement can be made as to effectiveness. In the remaining 2, dicumarol, prolonged over a period of months, was without obvious benefit. Indeed, in one case, a severe exacerbation of the disease occurred when the prothrombin was within the therapeutic range. The high percentage of bleeding in this small group (50%) which may be more apparent than real, indicates the need for caution in the employment of dicumarol under these circumstances.

Retinal thrombo-embolism

Among the treated cases of retinal thrombo-embolism are included 4 patients with arterial occlusions and 4 with venous thromboses, 6 were women, the average age was 52. In 3, in whom the duration of treatment (heparin and dicumarol) was less than 3 weeks, there was slight if any objective improvement. All had long-standing hypertension. One had a thrombosis of a central retinal vein of 5 months' duration, another an occlusion of a superior temporal artery of 18 hours' duration, and the third had an occlusion of a central retinal artery of about 48 hours' duration. In a fourth patient, with a "recent" occlusion of an inferior nasal retinal vein and essential hypertension, there was but slight objective change despite treatment prolonged over a 3 months' period. Severe epistaxis, necessitating hospitalization, terminated treatment in this case. A fatal

cerebro-vascular accident, previously discussed, occurred in this group. This patient, receiving anticoagulants because of a "recent" superior temporal retinal artery occlusion, had severe hypertension and had experienced cerebral thromboses in the past.

Anticoagulant therapy, prolonged over an average of 3 months, appears to have been of value in the remaining 3 cases. It should be emphasized that these patients did not have hypertension. One had a partial occlusion of a central retinal vein of 19 days' duration, the second a partial occlusion of the superior branch of a central retinal vein of unknown duration, and the third had an occlus on of a superior temporal artery of 3 weeks' duration. Visual acuity in these patients was not markedly altered by the pathological process. Subsequent to treatment, the appearance of the fundi reverted to normal in 2 and has markedly improved in the other. Whether this improvement would have occurred spontaneously cannot be said, but the fact remains that the funduscopic picture did not become worse.

Cerebral thrombosis

Six patients with cerebral thrombosis were treated with heparin and dicumarol. Two were women, the average age was 53, the youngest being 49. All had normal blood pressures. The diagnosis was made after consultation, in all cases, with the Department of Neurology. The duration of the thrombotic process in 3 of these patients did not exceed 24 hours. In this group, less drastic reduction of the prothrombin concentration was obtained (30 to 50%) and treatment was continued over a period of one to two weeks. Anticoagulant therapy, in one case, produced no obvious benefit and in a second patient improvement was not particularly striking. Impressive improvement in the general condition of 2 patients was accompanied by reversal, in part, of the neurological findings. Deterioration in the general condition of the 2 remaining patients resulted in prompt withdrawal of anticoagulants. We make no claims for the effectiveness of anticoagulant drugs in cerebral thrombosis. We think their use unjustified in the treatment of thrombo-embolism occurring in patients with repeated episodes of cerebral thrombosis and known hypertension.

Arterial embolic occlusion

Five patients in this series were treated for arterial occlusions of the lower extremities. Heparin and dicumarol were instituted within a 24 hour period after the accidents. Treatment in this group by and large was discouraging. Prolonged and prompt anticoagulant therapy did not prevent the need for bilateral supracondylar amputations in one patient admitted to the hospital within 24 hours subsequent to multiple arterial emboli arising from a mural thrombus, while prompt use of heparin failed to prevent the necessity of a mid-leg amputation in a diabetic patient who sustained an arterial occlusion presumably on the basis of an arterio-sclerotic plaque. The other 3 patients had rheumatic heart disease with auricular fibrillation. Treatment of one of these was inadequate in terms of duration and follow-up. A second recovered from the first episode of arterial

embolic occlusion as a result of an early embolectomy and vigorous anticoagulant therapy but succumbed within 6 months from an aortic saddle embolus. In retrospect, she was probably an ideal candidate for prophylactic dicumarol. The last patient is considered in detail to illustrate the precarious existence which may be forced upon these patients. The case serves also as a graphic example of the benefits and hazards which may be anticipated from prolonged treatment with dicumarol.

This 58 year old woman had had rheumatic heart disease since the age of 20. Embolic phenomena first occurred in February, 1948, in the form of a sudden but transient right hemiplegia. On April 3, 1948, she sustained an embolus to the left popliteal artery for which she was seen within 4 hours at the University Hospital. The dorsalis pedis and posterior tibial arterial pulsations were absent on the left and the leg was pale and cool from the knee downward. The heart was enlarged, auricular fibrillation was present, and a murmur characteristic of mitral stenosis was heard. There was x-ray evidence of a minor pulmonary embolism. After large and repeated doses of tetraethylammonium chloride, papaverine, and anticoagulants, the leg became less painful, improved considerably in color and warmth, and within a week the pulsations became palpable. In view of the probability of future embolic phenomenon, the decision was made to continue her on prophylactic dicumarol as an out-patient. Therapeutic ranges of prothrombin were maintained by doses of 50 to 100 mgm. of dicumarol approximately 4 to 5 times a week, governed by prothrombin tests done at 7 to 10 day intervals. Bleeding in the form of hematuria occurred at one time, and hematomas and ecchymoses were frequently sustained. For short periods of time, following these episodes, the prothrombin levels were allowed to revert toward normal. In general, however, effective therapy was continued without too great difficulty and with apparent benefit, inasmuch as further embolic episodes did not occur. In the eighth month of treatment she began to experience increasing discomfort in both legs, possibly the result of multiple small hemorrhages into the subcutaneous tissues. Bleeding into the left knee, accompanied by severe pain, necessitated rehospitalization on December 12, 1948, at which time the prothrombin concentration was 21%. In view of the repeated episodes of bleeding and associated discomfort, continuation of dicumarol therapy was felt to be unwarranted. It was hoped that the thrombus within the heart chambers might have become completely organized. Accordingly, within a 3 day period, the prothrombin concentration was reverted to normal by the administration of vitamin K. Ten days later there was an embolic occlusion of the left femoral artery. Once more, following the use of tetraethylammonium chloride and anticoagulants, the leg improved. At the time of completing this report, decision has been made to continue dicumarol for an indefinite period, but with less drastic reduction of prothrombin levels. How successful this venture will be is unknown. The hazard of repeated bleeding induced by dicumarol, however, appears preferable to the consequences of repeated embolic phenomenon.

SUMMARY

The response of prothrombin to the controlled administration of dicumarol is generally predictable and orderly. In the average case, 600 mgm. of dicumarol, administered over a 3 day period, reduced prothrombin concentrations to less than 30%. About 1400 mgm. were administered over a period of 10 days to maintain a therapeutic concentration varying from 15 to 26%. Normal values were observed about 6 days after the last dose of dicumarol. Anticoagulants may be employed with reasonable safety to treat thrombo-embolism occurring at low prothrombin levels although sensitivity to dicumarol is thereby increased, as it is also in certain other pathological states.

It was sometimes difficult to maintain prothrombin levels within the desired therapeutic range since concentrations of less than 10% were reached at some time in 17% of the cases. The incidence of bleeding induced by dicumarol was 11%. Hemorrhage was infrequent at prothrombin concentrations above 20% but it occurred as commonly in the range of 10 to 20% as below 10%. Performance of elective manipulative or surgical procedures in disregard of therapeutic prothrombin levels may be accompanied by severe internal or external hemorrhage. Frequent and massive doses of vitamin K, varying from 185 to 272 mgm., were required before bleeding ceased. Fatal intracranial bleeding in patients with severe hypertension and a past history of cerebral-vascular accidents has been described. Death of one patient in this series can be directly attributed to dicumarol.

"Escape" of prothrombin above the therapeutic range occurred at some time in one-third of the group, in only 9 of whom coincident thrombo-embolism occurred. During the initiation of anticoagulant therapy, at a time when the prothrombin concentration varied from 100 to 30%, thrombo-embolism took place in an additional 18 cases. The over-all incidence of intravascular clotting at nontherapeutic prothrombin levels was 8.9% and 1 death occurred from recurrent pulmonary infarctions under these circumstances. The predictable incidence of thrombo-embolism in a group of similar size not receiving anti-coagulant therapy is unknown.

In all, only 14 patients (4.6%) sustained thrombo-emboli after prothrombin activity had been reduced to therapeutic levels. Eight of these accidents were fatal. (This does not include 7 cases in which progression of a peripheral thrombus occurred at therapeutic prothrombin concentrations, inasmuch as resolution eventually took place with continuation of anticoagulants.) Clinical experience in this study substantiates the technical definition and limitation of the therapeutic prothrombin range to concentrations below 30%.

The value of prophylactic dicumarol in preventing thrombo-embolism has been reasonably established, but in our opinion indications for its routine use need to be more sharply defined (4) and its protective advantages in routine postoperative cases must be weighed against the appreciable incidence of bleeding which it induces.

Early and satisfactory response of peripheral venous thromboses was observed in 96% of the cases. This response was accelerated by supplementing dicumarol with preliminary heparinization. Restoration of prothrombin to normal was accompanied, within a period of 2 weeks to 4 months, by recurrence of the thrombotic process in 9% of all these cases.

Present day methods of prevention and treatment have significantly lowered the incidence and mortality from postoperative pulmonary embolism and infarction. Despite anticoagulants and venous ligations, the prognosis remains poor for the patient with organic heart disease, congestive failure and repeated pulmonary infarctions. Seven out of 8 patients treated under these circumstances have succumbed.

Although anticoagulants are not always completely protective against throm-

bo-embolism, the lessened frequency and gravity of these complications warrants the use of heparin and dicumarol where circumstances permit in every case of myocardial infarction.

Results, while not particularly impressive, suggest that prolonged trial of anticoagulant therapy may be worthwhile in carefully selected cases of chronic venous thrombosis, retinal thrombo-embolism, and systemic arterial occlusion, If prolonged administration of dicumarol in full therapeutic doses is on an out-patient basis, it will be associated with an appreciable increase in the incidence of bleeding.

It must be stressed repeatedly that the protection afforded by anticoagulants is not always complete. As others (8) have emphasized, failure to enlist the complementary benefits of medical and surgical methods of controlling thrombo-embolism, will occasionally lead to catastrophe. In an occasional patient the tendency to thrombo-embolism may be stronger than the effect of anticoagulants, but even so the gravity of thrombo-embolism will be lessened by their use. Despite the most intelligent of all measures of control, unfavorable results must be expected in an occasional truly desperate situation of thrombo-embolism.

CONCLUSIONS

1. The effect of dicumarol in reducing prothrombin is reasonably orderly, but absolute control cannot be anticipated since variation of prothrombin from the limits of the therapeutic range occurred in one-half of the cases in this series.

2. The increased incidence of thrombo-embolic episodes when the prothrombin concentration was above 30% is basis for our conviction that dicumarol must be used in sufficient quantities to secure and maintain concentrations below this figure.

3. Inasmuch as the hazard of bleeding is appreciable at low prothrombin levels, dicumarol cannot be administered safely without adequate daily laboratory control and hospitalization is advised for initiation of treatment. Under careful supervision, some patients may be continued on an out-patient basis but it should be recognized that the incidence of bleeding will be increased.

4. A low pretreatment prothrombin level is not in itself a reason for withholding dicumarol. To the recognized contraindications to anticoagulant therapy, we have added the patients with severe hypertension and past cerebro-vascular accidents.

5. *Large and frequently repeated* doses of vitamin K are the antidote to an excessive effect of dicumarol on prothrombin.

6. Although the anticoagulant drugs are unquestionably beneficial in reducing the frequency and gravity of thrombo-embolism, their protection is not always complete. Some cases of recurrent and fatal thrombo-embolism will be encountered in spite of technically effective anticoagulant therapy.

7. The high mortality rate among patients with organic heart disease and congestive failure from recurrent pulmonary infarctions on the basis of peripheral and/or intracardiac thrombi warrants more general use of the anticoagulant drugs in this group. Our study suggests that this treatment should be started much earlier than is currently practiced.

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