Long-Term Dicumarol Therapy to Prevent Recurrent Coronary Artery Thrombosis

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Seventy-eight patients were given long-term dicumarol therapy after one or more attacks of myocardial infarction to see whether recurrent attacks could be warded off. Encouraging results ensued over periods up to five years. Protocols of 12 fatal cases are given, only 4 of whom had recurrent acute coronary thrombosis. Hemorrhagic complications met with are analyzed. Ambulatory treatment is shown to be feasible if patients are painstakingly followed.

Following an attack of acute coronary thrombosis and/or myocardial infarction certain patients were selected to continue the use of dicumarol for the "long term" in the hope of preventing recurrent attacks. The premonitory signs of an acute attack are often absent and when present are frequently misinterpreted except in retrospect, and as no method of selecting the critical time to administer anticoagulants as a preventive measure is known, dicumarol must be used continuously in any attempt to forestall recurrent coronary thrombosis. The fear that coronary artery intimal hemorrhage induced by dicumarol might play a significant part in the pathogenesis of recurrent coronary thrombosis in patients taking dicumarol continuously has been allayed by the failure to discover any significant incidence of coronary subintimal hemorrhage at autopsy in individuals treated with anticoagulants, both in the study of 90 autopsy subjects by the American Heart Association "Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction," and in careful histologic studies* of 22 necropsy subjects, derived from 248 private patients with cardiovascular lesions of all types treated with dicumarol by one of us (E. S. N.).

Method

The Quick one-stage method of prothrombin determination was used, with a commercial rabbit-

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* Dr. Philip Rezek of the Department of Pathology, Jackson Memorial Hospital, Miami, made the pathologic studies. Numerous sections of coronary arteries were studied, but examination of complete serial sections was too monumental a task to be undertaken.

brain thromboplastin (Difco) being employed; in many of the patients the Link-Shapiro modification with the use of a commercial rabbit-lung thromboplastin (Maltine), served as a "double-check" to insure technical adequacy. We doubt that estimating prothrombin activity by the two-stage method of Warner, Brinkhaus, and Smith will prove to be a safer guide in dosage. The question of the optimal depression of prothrombin activity is not settled. Brambel and co-workers have had excellent clinical results in 3,304 postoperative patients with depression of prothrombin activity to only 40 to 50 per cent, with virtually no serious hemorrhage. Our own observations, and the experience of others,* suggests, however, that thrombo-embolization is more likely to occur if the prothrombin activity exceeds 30 per cent of normal than if it is in the 10 to 30 per cent bracket. It is less confusing to compute dosage with reference to the prothrombin time in seconds rather than percentage of prothrombin activity. Shapiro and Weiner* state: "It seems to us that to follow adequately the prothrombin response to 'dicumarol,' the clinician should know the normal range of the thromboplastin used and the therapeutic range he wishes to establish in terms of time. With this knowledge the calculation of percentage is superfluous; without it the percentage figure is misleading." For practical purposes we advocate using sufficient dicumarol to maintain the prothrombin time at two to two and one-half times the normal, which in our laboratory permits a range of twenty-four to thirty-eight seconds (the average normal prothrombin time with the technique used being 13.5 ± 1.5 seconds). Comparison with serial dilution curves shows that the range of twenty-four to thirty-eight seconds is equivalent to 30 to 10 per cent prothrombin activity.

After the first three weeks, prothrombin tests were made at four-day intervals, and this was gradually extended to seven-day and even ten- to fourteen-day intervals after several months in some patients. Only reasonably intelligent patients were selected and all were well informed concerning the purpose of treatment with dicumarol and the risk if directions were not followed. Urinalysis was performed at least once a month and liver function studies were made approximately every six months.
Clinical description of 78 patients given dicumarol prophylactically for periods ranging from three to sixty-two months follows: Forty-four patients received dicumarol for three to twelve months, twenty-three for twelve to twenty-four months, 8 patients for twenty-four to thirty-six months, 2 for thirty-six to forty-eight months, and one for sixty-two months. There were 12 patients under 50 years of age, 34 between 50 and 60 years, and 32 between 60 and 75 years. Thirty-three patients had experienced more than one attack of coronary thrombosis. Seventeen patients were not placed on the regimen until some time after their acute attack, when, because of increasing angina or acute coronary insufficiency, dicumarol therapy was started. Five cases included in this study were the subject of a preliminary report by Nichol and Fassett; 6 of these, 2 fatal cases are described and the clinical sequel of 3 patients still living is given.

RESULTS

In 9 patients therapy was discontinued after three to twenty-three months—in 2 because of change in residence, in 4 because of lack of cooperation or difficulty in obtaining prothrombin determinations, and in 3 because of hemorrhagic complications (see below). Twelve patients, or 15.3 per cent of the group, died while under treatment—in 4 death was due to recurrent attacks of coronary thrombosis; in 6 it was ascribed to either acute coronary insufficiency, congestive heart failure, or “cessation of cardiac activity” (probably ventricular fibrillation or ventricular standstill). Cerebral hemorrhage was the cause of death in 2 patients. Autopsies were performed in 8 cases, revealing fresh coronary thrombosis or infarction in 3. No mural thrombi or other complicating thrombo-embolic manifestations were found.

Analysis of Deaths

Case 1.—The patient, J. P., aged 52 years, a hypertensive, had three attacks of coronary thrombosis in seventeen months and was incapacitated because of coronary insufficiency for the ensuing year. Dicumarol was then given for twenty-one months with clinical improvement. The patient died in fourth attack on July 1, 1946, preceding which he probably reduced dicumarol to ineffective dosage. Autopsy showed old coronary thrombi, aneurysm of left ventricle, recent posterior wall infarction.

Case 2.—The patient, H. S., aged 65 years, was a feeble man with auriculovenous and intraventricular block complicated occasionally by ventricular tachycardia. He began dicumarol therapy after his third attack of coronary thrombosis. Death occurred on Aug. 8, 1947, from a “stroke” after eight months of dicumarol treatment when prothrombin time was twenty-nine seconds (19 per cent PA*). Autopsy revealed a ruptured lenticulostriate artery with massive cerebral hemorrhage, myocardial scarring, old coronary thrombi, and left ventricular hypertrophy. Dicumarol probably did not initiate the apoplexy but made the hemorrhage more massive.

Case 3.—The patient, J. L., aged 53 years, had acute coronary thrombosis, but dicumarol therapy was discontinued on the tenth day because of hematuria due to hemorrhagic urethritis from an indwelling catheter, requiring transfusion. Femoral phlebothrombosis and pulmonary embolism occurred; he lived fifteen months. There was no improvement when dicumarol was given prophylactically for three weeks later, following which dicumarolization was successfully used for five months until May 12, 1947, when death occurred one hour after the patient experienced acute subternal pain. Prothrombin time seven days prior to death was twenty-seven seconds (20 per cent PA). Autopsy showed old myocardial infarction and a red thrombus (?) in the posterior descending coronary branch and left pleural adhesions. Death was attributed to acute coronary thrombosis, although microscopic studies failed to confirm thrombus formation.

Case 4.—The patient, F. B., aged 65 years, developed his second coronary thrombosis in April 1946, at which time dicumarol therapy was started. Intraventricular block and congestive heart failure were present. In December 1946, gross hematuria appeared when prothrombin time was twenty-eight seconds (19 per cent PA), and bleeding from hemorroids occurred in October 1947. Two months later when the prothrombin time was twenty-seven seconds (20 per cent PA) he developed more acute congestive heart failure with nodal tachycardia, but no electrocardiographic evidence of fresh myocardial infarction followed. Abdominal tenderness and distention developed. Right thoracentesis yielded 700 c.c. of straw-colored fluid one week prior to death, which occurred after twenty-one months of dicumarol therapy, when the prothrombin time was thirty seconds (15 per cent PA). Autopsy showed cardiac hypertrophy, left ventricular aneurysm, and the coronary arteries occluded at many points, but no fresh infarction was found. Right hemithorax, bilateral bronchiectasis, bronchopneumonia, and hypertensive arterial changes in the kidneys were found. The liver showed passive congestion and a lymphangiomata containing pin-point areas of hemorrhage. Several unexplained minute perforations of the cecum gave rise to a fibrinous peritonitis.

Comment.—The hemothorax, which presumably was derived from the trauma of thoracentesis a week prior to death during dicumarol therapy, was a

* PA = prothrombin activity.
† This patient lived fifteen months after the preliminary report.*
contributing but not a major cause of death. Congestive heart failure and peritonitis were the major causes of death. The unusual lymphangioma of the liver was an incidental finding, and although pin-point hemorrhages were found therein, this could hardly be completely attributed to dicumarol as it is rather characteristic of this type of tumor.

**Case 5.**—The patient, R. E., aged 72 years, a hypertensive with previous myocardial infarction, received dicumarol therapy, in spite of chronic nephritis, because of coronary insufficiency, cerebral arteriosclerosis, congestive heart failure, and phlebothrombosis of the left leg veins. On Jan. 26, 1948, after two months of dicumarol therapy, he lost his power of speech and had clonic convulsions. Prothrombin time was thirty-six seconds (12 per cent PA) and after 300 mg. vitamin K were given intravenously during the next thirty-six hours it dropped to twenty-two seconds (35 per cent PA) without further change in spite of 160 mg. vitamin K given during the next twenty-four hours. The spinal fluid was normal. Convulsions recurred and death ensued on the fourth day. At autopsy the heart weighed 800 grams and showed marked fibrosis, and old occlusion of the left coronary artery. The cerebral vessels were markedly sclerotic with a few scattered pin-point hemorrhages in the internal capsule and pons. Bronchopneumonia, hepatic congestion, and renal hypertensive arterial changes were noted. The pancreas was fibrotic and was the seat of a small hemorrhage.

**Comment.**—The relationship of the pancreatic apoplexy to the terminal clinical state is difficult to evaluate, and it is questionable whether dicumarol induced it. The petechial hemorrhages in the internal capsule and pons, considered to be the cause of death, were possibly due to dicumarol.

**Case 6.**—The patient, M. S., aged 60 years, a hypertensive, was continued on dicumarol therapy following his third coronary thrombosis and was moderately active in spite of congestive failure. His anginal pain lessened, but after five months, on Sept. 22, 1948, he died suddenly. The prothrombin time nine days earlier was twenty-six seconds (20 per cent PA) and he had continued his weekly dicumarol dosage of 425 milligrams. Autopsy disclosed petechiae, coronary sclerosis, old myocardial infarction, left ventricular aneurysm, mottled subendocardial hemorrhages on the posterior aspect of the septum, but no fresh coronary occlusion or myocardial infarction. Microscopic sections of the mottled areas of the septum disclosed the same degree of hemorrhage that is often found following fatal acute coronary insufficiency which presumably was the cause of death.

**Case 7.**—The patient, L. H., aged 55 years, had an acute anterior myocardial infarction on Oct. 7, 1946, when dicumarol therapy was started, his requirement being 150 mg. daily. Prothrombin activity was 29 per cent two days before recurrent fatal coronary thrombosis on March 16, 1947. Autopsy disclosed coronary sclerosis, old thrombosis of left anterior descending and right coronary arteries, and recent thrombosis of the circumflex artery.

**Case 8.**—The patient, A. H., aged 65 years, had decompensated hypertensive heart disease and coronary insufficiency. He received 50 mg. of dicumarol daily for eight months. He died suddenly on Oct. 19, 1948, without a recent prothrombin determination. Autopsy was restricted to the heart which showed no fresh coronary thrombosis, only a severe grade of coronary sclerosis and myocardial fibrosis.

**Case 9.**—The patient, J. R., aged 62 years, was started on dicumarol therapy after an acute posterior myocardial infarction on Jan. 29, 1947, his requirement being 50 mg. daily. Prothrombin activity was 15 per cent six days before a recurrence of coronary thrombosis. Three weeks later he died suddenly after taking dicumarol for three months. No autopsy was performed. Presumably death was due to functional cessation of cardiac activity.

**Case 10.**—The patient, J. W., aged 58 years, a hypertensive, was started on dicumarol therapy on Aug. 28, 1946, because of persistent pain following myocardial infarction. He improved but six months later developed microscopic hematuria and purpura when the prothrombin time was sixty seconds (6 per cent PA). Vitamin K was given intravenously and dicumarol omitted for one week, when he developed acute coronary insufficiency with subendocardial infarction during a period of normal prothrombin activity. Heparin and dicumarol therapy produced rapid improvement. In October 1947, he developed a transitory "cerebral vascular crisis" which recurred three months later. General muscular cramps developed in the spring of 1948. On Aug. 1, 1948, while taking his customary dicumarol dose of 900 mg. weekly, with the prothrombin time at twenty-three seconds (25 per cent PA), he developed somnolence and weakness and a few days later was unable to talk coherently for some days. On Dec. 22, 1948, when the prothrombin time was seventeen seconds (50 per cent PA), he became disoriented and could not move without aid, and had tremors and ankle clonus. Rigidity of the extremities and coma appeared before he expired on Dec. 30, 1948. No autopsy was performed.

**Comment.**—As this patient had been partaking of Westsai liberally, in retrospect we believe lithium poisoning contributed to his death, although cerebral vascular disease was marked.

**Case 11.**—B. S., aged 60 years, had coronary thrombosis in 1943 followed by left ventricular hypertrophy, congestive failure, and angina pectoris. On Nov. 8, 1947, dicumarol therapy was started because of premonitory signs of myocardial infarction. The patient improved and had only occasional anginal pain until he died suddenly after five months of dicumarol therapy. The prothrombin time four days prior to death was twenty-three seconds (25 per cent PA). No autopsy was performed.

**Comment.**—The degree of congestive heart failure
at death was not marked so presumably death resulted from cessation of cardiac activity.

Case 12.—The patient, A. P., aged 65 years, a hypertensive, gave a history of cerebrovascular accident seven years previously. Dicumarol was started, because of angina pectoris and left ventricle failure, on Aug. 18, 1948, one month after he developed acute coronary thrombosis. His anginal pain subsided but mild left ventricle failure persisted. He died suddenly after approximately three months of dicumarol therapy. The prothrombin time five days before death was twenty-one seconds (38 per cent PA). No autopsy was performed. Death was attributed to functional cessation of cardiac activity.

In seven of eight autopsied patients who had used dicumarol for two to twenty-three months, no toxic changes were found in the liver or kidneys attributable to dicumarol except for the possibility that the microscopic hemorrhage in the hepatic hemangioma in patient 4 might have been due to the dicumarol, although this is unlikely. No evidence of liver or renal injury after one or more years of dicumarol therapy has developed in the living patients.

Clinical Sequel of Living Patients

In the 57 patients remaining on dicumarol, anginal pain has been minimal or absent in nearly all, in spite of their being moderately active in business or home. The willingness of patients to adhere to the regimen faithfully reflects substantial subjective improvement hardly fully attributable to the psychotherapeutic effect of taking dicumarol. Four of the living patients have experienced episodes of acute coronary insufficiency with possible sub-endocardial infarction followed by recovery without thrombo-embolic complications. The clinical features of one exceptional case, occurring in an elderly woman who developed a third recurrent acute myocardial infarction while dicumarol was in force, follow:

Patient Mrs. J. R., aged 63 years, had survived an attack of myocardial infarction thirteen years previous to development of premonitory signs of coronary thrombosis on Sept. 2, 1948. She was given heparin and dicumarol but continued to have cardiac pain with occasional nausea and vomiting. When the prothrombin time was forty-six seconds (9 per cent PA), fifteen days after cessation of severe pain, the electrocardiogram showed evidence of anterior wall infarction. Complete relief of her pain, much of which was provoked by the gastrointestinal tract, was not obtained. By the sixth week she was able to be slightly ambulant. The prothrombin time was maintained between twenty and thirty-five seconds (40 to 10 per cent PA). On Jan. 19, 1949, she had severe substernal pain when the prothrombin time was thirty seconds (18 per cent PA). The electrocardiogram showed changes indicative of acute anterolateral myocardial infarction. Congestive heart failure and various ectopic rhythms appeared, and heart failure persists four months later, but the patient is able to be ambulant at home with only mild anginal pain.

This patient developed acute myocardial infarction while on dicumarol fifteen days after onset of premonitory signs, and four months later, while on supposedly adequate dicumarol therapy, a frank anterolateral infarction developed. Obviously dicumarolization did not forestall a recurrent attack, and her case demonstrates that the regimen even when carefully followed may fail to prevent coronary thrombosis.

Eleven patients have followed the regimen two years or longer without recurrence although six had multiple previous attacks. The clinical sequel of 3 surviving cases described in the preliminary report follows:

Patient W. A. S., a 53 year old hypertensive man, had anterior myocardial infarction in October 1945, with recurrence five months later. Dicumarol has been used ever since, a matter of three years. He has remained relatively free of anginal pain, and is able to work. His dicumarol requirement remains remarkably constant at 350 mg. weekly.

Patient W. T. M., a 57 year old bookkeeper, developed hypertension and left hemiplegia in 1939. Attacks of coronary thrombosis occurred in 1942 and 1945. On May 1, 1946, he had a third myocardial infarction so dicumarol therapy was initiated. In January 1947, when prothrombin time increased to fifty-nine seconds (6 per cent PA), he developed gross hematuria with renal colic but no evidence of renal calculus was found. Dicumarol was omitted temporarily and vitamin K was given with reduction in prothrombin time the following day to thirty-one seconds (18 per cent PA). Since then he has done well except for emotional instability, and is employed. He required 700 mg. or more dicumarol weekly for twenty-nine months, but in the past eight months his requirement has been nearer 600 mg. weekly, probably owing to an increase in his consumption of alcoholic beverages (figure 1).

Patient J. R. T., aged 54 years, had his first attack
of coronary thrombosis with posterior wall myocardial infarction in January 1943. In June 1943, he had a second severe attack with anterior infarction and was given dicumarol. In February 1944, he developed a third attack, ushered in by intractable pain. Dicumarol therapy was started again and was continued to see if additional attacks could be warded off. In December 1945, gross hematuria with renal colic appeared when the prothrombin time was thirty-six seconds (12 per cent PA) but no evidence of renal calculus was found. Gross hematuria has never recurred, but in November 1946, when the prothrombin time was thirty-five seconds (15 per cent PA), he developed hematemesis and tarry stools due to a bleeding duodenal ulcer which had been first diagnosed in 1942. The bleeding was soon controlled with vitamin K and 1000 c.c. whole blood, the prothrombin time dropping in twenty-four hours to twenty-two seconds (30 per cent PA) and in forty-eight hours to sixteen seconds (80 per cent PA). Dicumarol therapy was omitted for five weeks, but was resumed because of an increase in anginal pain, and has not been interrupted again except for dental extractions. In 1947, recurrent upper respiratory infections and bronchitis appeared and pulmonary emphysema developed with reduction in vital capacity. No left ventricular failure has developed although the heart is moderately enlarged with suggestive signs of ventricular aneurysm. The patient lost weight owing to poor appetite and unsatisfactory dentures, and the pulmonary symptoms remained troublesome but improved when he took a holiday trip to Nova Scotia last summer. His dicumarol requirement was remarkably constant (700 to 800 mg. weekly for four years) until the dietary change occurred as described under "Variable Dicumarol Requirement"; since then he has required only 550 to 600 mg. weekly. He was free of any significant anginal pain until January 1949, when after overexertion, business worries, and excessive use of tobacco, he developed moderate substernal pain not associated with additional electrocardiographic changes. His feeling of well-being deteriorated somewhat but has improved again during the past four months. The probability is strong that the use of dicumarol has forestalled additional attacks of coronary thrombosis, since the patient experienced three attacks in thirteen months prior to initiating the dicumarol regime over five years ago. (Fig. 2).

Complications

Hemorrhagic manifestations occurred in 28 patients (35.8 per cent), in thirteen (16.6 per cent) of whom hemorrhage was of major type (table 1). Hemorrhage occurred in some patients in more than one site and on more than
one occasion. It is to be expected that patients taking dicumarol for months or years should experience more episodes of hemorrhage than patients taking dicumarol for a few weeks only. The two fatal hemorrhages encountered have been described above (in Patients H. S. and R. E.). One occurred in a 63-year-old man who had three attacks of coronary artery thrombosis and died after eight months of dicumarol therapy with massive cerebral hemorrhage due to rupture of the right lenticulostriate artery. The other took place in a 72 year old hypertensive man with coronary artery disease and congestive heart failure, who, after two months of dicumarol therapy, died in coma and convulsions due to petechial hemorrhages in the internal capsule and pons.

In only 3 patients was it necessary to abandon the dicumarol regime because of hemorrhage: In one of these patients repeated hematuria associated with urologic disease occurred after five months of therapy; in another hemorrhage into the shoulder joint followed automobile injury after twenty-three months of therapy; in the third, massive, silent gastrointestinal hemorrhage occurred after thirteen months of therapy. This last patient was a Greek man with an alcoholic history. Gastrointestinal x-ray studies and liver function studies showed no abnormality when his prothrombin time reached sixty seconds (6 per cent PA), following an increase in his weekly dosage from 400 mg. to 500 mg. during a period of increased consumption of alcoholic beverages. An episode of hematuria had occurred three months previously in this patient when the prothrombin time was thirty-five seconds (15 per cent PA), yet no hematuria developed at the time of the gastrointestinal hemorrhage in spite of the prothrombin activity being only 6 per cent,

![Graph](image_url)

**Fig. 3.**—Demonstration of variable dicumarol requirement in three patients.

*Long-Term Dicumarol Regimen for Fifty-two Weeks to Prevent C.A.T.* (ADD = Average daily dose; AWD = Average weekly dose)

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<thead>
<tr>
<th></th>
<th>H. P.</th>
<th>J. S.</th>
<th>R. D.</th>
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<tr>
<td>Wh. F.</td>
<td>78 yr.</td>
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<td>Wh. 7</td>
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<td>Wgt.</td>
<td>144</td>
<td>170</td>
<td>125</td>
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<td>B. P.</td>
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*Dicumarol*

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<tr>
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<th>ADD = 30.8 mg.</th>
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<th>ADD = 172 mg.</th>
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<tr>
<td>AWD</td>
<td>222.5 mg.</td>
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which shows the unpredictability of dicumarol-induced bleeding.

Hemorrhagic episodes are not always well correlated with the prothrombin activity. Bleeding may occur in some patients when the prothrombin activity is only moderately reduced, and on other occasions in the same patient bleeding might not occur with considerably less prothrombin activity. Adequate amounts of synthetic vitamin K given intravenously controlled the bleeding and lowered the prothrombin time, except in 2 patients requiring transfusions. The risk of hemorrhage in anticoagulant therapy, and the obligation
of the clinician to make sure that the laboratory understands the technical pitfalls of prothrombin determinations, have been stressed repeatedly in the literature.

Variable Dicumarol Requirement

Although it has been known since earliest clinical use of dicumarol that the dosage required for producing effective hypoprothrombinemia is variable, it is not so well known that in long-term dicumarol therapy marked disparity in the weekly requirement of dicumarol by different patients may occur, as recently emphasized by Foley and Wright and by Olwin.6

Figure 3 illustrates this variability. Of 3 patients receiving dicumarol for fifty-two weeks, one required approximately 225 mg. per week, another 500 mg. per week, and a third 950 mg. per week, to maintain the prothrombin concentration between 30 and 10 per cent of normal (twenty-four to thirty-eight seconds). Even more important is the sudden change in a patient’s tolerance that may occur after many months of dicumarol therapy. This is shown also in figure 3 by the excessive peak of prothrombin time of fifty-five to sixty seconds which occurred once in the course of the year in each patient while on usual dosage. A more striking example of change in tolerance is Patient J. R. T., described above and illustrated in figure 2, who has taken dicumarol for sixty-two months, and whose usual weekly requirements were 700 to 800 milligrams. On returning from a summer trip in 1948 the prothrombin time had increased to fifty-five seconds (8 per cent PA) on his usual dosage instead of the customary twenty-five to forty seconds (22 to 10 per cent PA). Inquiry revealed that instead of drinking milk freely, as was his custom because of duodenal ulcer, he had been imbibing ale moderately, thereby apparently changing his tolerance for dicumarol. A similar relationship between dietary content of protein or alcoholic beverages and dicumarol requirement has been commented on by Foley and Wright.7

DISCUSSION

The continuous use of dicumarol over a period of years to prevent recurrent coronary thrombosis has been shown to be feasible and relatively safe. No conclusions as to the efficacy of the regime can be drawn from this small uncontrolled series. We believe a long-range cooperative study of a large group of cases should be undertaken in order to properly evaluate the effect of the regimen. even though the establishment of adequate controls would be admittedly difficult. Such a study would require the cooperation of many clinicians in private practice.

It must be borne in mind that sudden death may occur several days after the final prothrombin determination, and hypoprothrombinemia may have developed. If no autopsy is obtained, therefore, coronary artery subintimal hemorrhage, or hemorrhage in the myocardium or brain, may escape detection since clinical signs might not be present long enough for them to be recognized as causes of death. This consideration applies to the 4 patients described above who died and upon whom autopsies were not performed. It is, however, well recognized that sudden death occurs not infrequently in persons with coronary artery disease without the presence of demonstrable acute lesion. In either case the mechanism of the sudden cessation of cardiac activity is probably ventricular standstill or ventricular fibrillation.

The distinct reduction in anginal pain experienced by most of the dicumarolized group calls forth speculation as to the possible mechanism inducing such striking improvement. The probability of increased coronary blood flow due to lessened blood viscosity has been mentioned.8 However, if the claims of Gilbert and co-workers are borne out and dicumarol proves to have a strong dilating effect on the coronary arteries, this would readily explain the decrease in anginal pain. We have noted no significant reduction in blood pressure during long-term therapy in any patient, which throws doubt on the vasodilation action of the drug. In evaluating any reduction in anginal pain, it is of course necessary to consider the factor of psychotherapy. We are aware also that following myocardial infarction some patients seem to have less pain than prior to the acute episode for no well-established reason.
LONG-TERM DICUMAROL THERAPY

SUMMARY

Since 1944 dicumarol therapy has been continued indefinitely following an attack of acute coronary thrombosis and/or myocardial infarction in 78 patients in the hope of preventing recurrent attacks.

Twelve patients died, but of these only 4 had recurrent coronary thrombosis (8 autopsy studies). Nine patients discontinued therapy. Fifty-seven patients remaining on the regimen are active and doing well with little anginal complaint, and in 10 of these two or three years have passed without an attack, and in one noteworthy patient, who had three previous myocardial infarctions, over five years have passed since the last recurrence. Four of the living patients have experienced episodes of acute coronary insufficiency with possible sub-endocardial infarction followed by recovery without thrombo-embolic complications. One elderly patient still alive developed a recurrent myocardial infarction while dicumarolized.

Major hemorrhagic episodes occurred in thirteen patients resulting in two fatalities (only one of which could fairly be attributed to the use of dicumarol) and abandonment of the regimen in 3 other patients; the remainder resumed dicumarol treatment satisfactorily. No toxic effect on the kidneys or liver was found in 7 autopsy subjects who had received dicumarol two to twenty-three months, nor has clinical evidence of such toxicity been found in the living patients. The variability in dicumarol requirement from year to year in a few patients has been illustrated.

No conclusions are drawn from this study but actual reduction of frequency of recurrent attacks may eventually be proved. A cooperative five-year study by clinicians in private practice would reveal whether or not the long-term use of an anticoagulant justifies the trouble and risk involved.

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