Personal Experiences with Anticoagulants for Coronary Atherosclerosis

By E. Sterling Nichol, M.D.

Clinical reports about Dicumarol in 1941 by Meyer, Bingham, and Pohle (Madison), Butt, Allen, and Bollman (Rochester) aroused my interest, which was further whetted in October 1941, by Wright and Prandoni’s lecture at the New York Academy of Medicine. These authors discussed the use of Dicumarol in venous thrombosis, pulmonary embolism, rheumatic heart disease, and peripheral arteriopathies. During 1942 at various times I talked about the possibility of utilizing Dicumarol in acute coronary thrombosis with myocardial infarction with Nelson Barker, Wilbur Duryee, Irving Wright, and others. Considerable doubt was expressed as to the likely results, but it was agreed that a clinical trial would be worthwhile. About this time, Clarence de la Chappelle noted an incidence of 12 per cent thromboembolism following acute infarction and stated, “Some day it may be demonstrated that mural thrombi will be prevented by the use of an anticoagulant such as heparin or dicumarin.” In June 1943, after hundreds of patients with thromboembolism had been treated with Dicumarol, various workers, I gave Dicumarol to my first patient with acute coronary thrombosis. After this initial venture, I continued to use Dicumarol routinely in acute myocardial infarction. No data on the use of Dicumarol in acute coronary thrombosis were available, but Barker had told me of its trial in a few cases, and after my study began, Wright and Duryee informed me that they had successfully used Dicumarol in 9 cases of coronary thrombosis. During 1944, casual references to the use of Dicumarol in acute coronary thrombosis appeared in papers describing its general use, Lam listing 3 cases, Evans 1 case, Gefter et al. 1 fatality, Townshend and Homingman 3 cases, and LeFevre mentioned 7 cases in 1945.

In October 1944 I reported the results of Dicumarol therapy in 30 patients with “acute coronary thrombosis” at a meeting of the Miami Heart Association (I keep these lantern slides for sentimental reasons). I was naive enough to believe, since the patients did well, the discussion would arouse interest in what seemed a truly constructive advance in the treatment of acute myocardial infarction, but instead of approbation, asides were audible anecdotally: “slip” showing! In spite of the prevailing opinion that such therapy was meddling and dangerous, within another year I compiled the data obtained in 50 acute attacks, but this manuscript was returned with a frank note that it lacked scientific basis by the Journal of the American Medical Association. In my “President’s Address,” American Therapeutic Society, November 11, 1945, I related the results of my study. My closing remarks were, “Dicumarol is not the ideal therapy for coronary artery thrombosis, but it is a step forward. Two patients had each experienced three episodes of coronary thrombosis within two years, so were given Dicumarol continuously for 1 year as a protective measure, watching the prothrombin time at intervals. It may be more than coincidence they have not experienced a fourth attack. I look forward with confidence to the development of more easily controlled drugs to prevent intravascular thrombosis—or is this a fond dream of a middle-aging physician desirous of eluding the onslaught of time?” My data were buried in the Society Transactions and overlooked by other workers. The report was published* in full in January 1946. Because of similar studies by Wright, Peters, et al., the American Heart Association sponsored in 1946 an investigation of the values of anticoagulants in myocardial infarction. A debt of gratitude is owed to Irving Wright, Charles Marple, and Dorothy Beek for their hard work in correlating the data furnished

*My former associate, Dr. Samuel Page, co-author.
by 16 investigators. Parker and Barker reported good results in acute coronary thrombosis soon, and a flood of similar papers appeared. In 1949 editorials appeared in several leading medical journals anent the use of anticoagulants in acute myocardial infarction. From June 1943 to June 1953 my associates and I treated 207 patients suffering acute myocardial infarction with anticoagulants. The over-all mortality rate was 14.3 per cent. (A 6 week interval was considered as the acute stage instead of the 4 week interval used by some authors.)

Twenty-two autopsies (71 per cent) were obtained. Rupture of the ventricle was found in only 3 cases (1.3 per cent), which suggested that the size of the infarcted area was limited in extent by energetic anticoagulant therapy. In contrast, Waldron found 15 per cent of 71 cases treated with anticoagulants developed myocardial rupture and 4.9 per cent of 241 patients not treated with anticoagulants. mural thrombi were found in only 2 cases. We rarely encountered "pericarditis episteneocardica" in patients who were fully heparinized early.

Armand Quick's 1-stage method of prothrombin determination soon became established as a guide in adjusting the Dicumarol dosage. In 1943 Miami was not overflowing with competent laboratory technicians so it devolved on me to learn the pitfalls of prothrombin tests to make sure that technicians performed such tests accurately. During this early period I admitted a woman with an acute attack to a hospital where the laboratory declined to set up a prothrombin method on the grounds it would seldom be used! Harrowing experiences with prothrombin tests done in outlying towns led to not a few acrimonious remarks about Dicumarol therapy, but eventually all hospitals and private laboratories in the area instituted the needed coagulation methods.

Most workers at first transposed the results of the prothrombin time to a hyperbolic serial dilution curve and expressed results in "percentage of prothrombin activity" rather than in "seconds of prothrombin time." Study of the pitfalls in computing "percentage" of prothrombin activity convinced me that maintaining the prothrombin time between 2 and 2½ times the normal would provide a satisfactory range of hypoprothrombinemia, and I urged an early Anticoagulant Panel of the American Heart Association to report prothrombin tests in "seconds" instead of "percentage." Shepard Shapiro stated in 1951, "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." Some laboratories here and abroad computed a "percentage of prothrombin" or "clotting index" by a linear ratio of the normal prothrombin time compared to the patient's prothrombin time, which led to gross errors in adjusting Dicumarol therapy. The Link-Shapiro modification of Quick's method, comparison of the prothrombin time of a 12.5 per cent plasma dilution with that of whole plasma, has some advantages. Although the 2-stage prothrombin method is often advocated, in our hands it has not been of superior value in regulating anticoagulant dosage. In 1945, Hurn, Barker, and Magath pointed out that the nature of the thromboplastin used has great bearing on the validity of the prothrombin tests, and marked discrepancies arising from various thromboplastins employed were emphasized by Bramble. Knowledge about the vagaries of prothrombin tests has not become widely disseminated. Our laboratory ran thousands of tests between 1945 and 1955 using 2 different sources for thromboplastin (rabbit lung and brain) and the conflicting results with "pathologic" plasma were often so striking that repeated studies sometimes uncovered a hidden source of error, but more often the variation was due to the difference in the source of thromboplastins. Recently variable results obtained using different thromboplastins were carefully analyzed in an excellent exposé by Verstraete, Clark, and Wright.

When Moloney in 1948 showed the effect of Dicumarol on the clotting time in silicone-
treated tubes, I meticulously prepared such tubes, only to find that clotting was often delayed several hours, so I abandoned this procedure as impractical.

**Heparin**

Jay McLean, studying the blood clotting effect of cephalin, incidentally discovered the anticoagulant heparin in 1916; hence the finding of this natural anticoagulant as well as Dicumarol may properly be termed "serendipitous." McLean's recent obituary in the Journal of the American Medical Association made no mention of heparin, one part of which will prevent the clotting of 100,000 times its weight of blood! In 1936 heparin was purified sufficiently by Charles and Scott to permit its clinical trial in thromboembolism. On the basis of animal experimentation, Best suggested in 1940 that heparin might prove effective in the treatment of acute coronary thrombosis, but it was seldom utilized during the next few years. Only after McLean's talk in 1945 I began to use it, and have relied on it more and more during the initial 7 to 10 days of the acute episode.

Helen Glueck and co-workers in Cincinnati reported on the combined use of heparin and Dicumarol in myocardial infarction in 1948. About the same time Loew reported on the use of heparin* alone during the acute and healing stage of myocardial infarction. In 1949 I treated 24 patients with acute coronary thrombosis for 4 to 6 weeks with delayed action heparin† with good results except for occasional painful hematomas, but I failed to report my experience. Since the description by Stats and Newhof in 1947 of the advantages of concentrated heparin, I have used this preparation, preferably in concentration of 200 mg. per ml. The dosage ranges from 50 to 75 mg. every 6 hours, given subcutaneously not intramuscularly, in the areolar tissue along the iliac crest. Heparin tolerance tests and heparin-retarded coagulation times as indicators of the need for heparin therapy proved unreliable. I found no occasion to use hyaluronidase with depot injections to minimize pain as suggested by Tuchman and Moolten. In spite of the fact that heparin induced bleeding sometimes, protamine sulfate was required to control bleeding in only 1 patient. The prolongation of the prothrombin time by heparin as first shown in 1946 by Long and Barker was sometimes a source of dosage error when changing from heparin to other anticoagulants, until we became more alert.

**Long-Term Therapy in Coronary Disease**

In February 1944 I began long-term anticoagulant therapy to forestall recurrent myocardial infarction, and made a preliminary report* before the Southern Medical Association in November 1946. Although Wright and Foley had begun continuous treatment in rheumatic heart disease with embolic episodes, no trial of long-term anticoagulant therapy to prevent myocardial infarction had been essayed. The first patient treated merits some description.

Patient J.R.T., aged 54 years, had an attack of posterior wall myocardial infarction in January 1943. Six months later, he had a severe anterior infarction and was treated with Dicumarol for 6 weeks. In February 1944, he developed a third attack. Dicumarol therapy was instituted again and this time was continued to see if additional attacks could be warded off. In December 1945, gross hematuria with renal colic appeared, but never recurring. In November 1946, hematemesis and tarry stools developed due to a bleeding peptic ulcer. Dicumarol was omitted for 5 weeks, then resumed because of worsening anginal pain. Attacks of bronchitis recurred frequently and pulmonary emphysema developed in 1918. The Dicumarol requirement was remarkably constant (700 to 800 mg. weekly) until a summer holiday in 1948 in Nova Scotia when he imbibed ale instead of milk, a dietary change which reduced his Dicumarol requirement to 600 mg. weekly. He continued business activities up to 6 months before his death, when he gradually developed intractable congestive heart failure, azotemia, and anemia. As inanition increased, his Dicumarol requirement dropped to 500 mg. per week. He was comatose for 3 days before death. Continuous Dicumarol therapy had been followed for 90 months, except

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†Depo-hepin, Upjohn Company.

*My associate, David Passett, was co-author.
for 5 weeks during the bleeding ulcer episode. Autopsy showed no fresh coronary thrombus or infarction, old posterior wall infarction, calcified left ventricular aneurysm, nephrosclerosis, purulent bronchiolitis and emphysema, and healed gastric ulcer.

It would be an understatement to say it was an uphill battle, promoting the concept that permanent ambulatory anticoagulant therapy was feasible and worthwhile. In spite of the askant mien of my colleagues, I took heart in reading again a statement first made by E. V. Allen in 1945, "It is timely to consider that blood may normally clot in blood vessels too well to serve the interest of the health of man—some time in the future there may be no valid reason why the coagulability of the blood in man may not be maintained indefinitely and safely at a level which will not permit intravascular thrombosis." In 1949 Foley and Wright reported their results in 19 patients on long-term therapy, 5 of whom were "coronary" patients. Yet Bean in the same year stated that the use of anticoagulants in ambulatory patients as a prophylactic measure was out of the question! In 1950, Borg and I reported on 78 patients treated continuously to prevent recurrent myocardial infarction. Subsequent reports by Hellem, Keyes and co-workers, Suzman and co-workers, Owren, Coogan, and Davis, Tulloch and Wright, Manchester, and more recently Bjerkelund and Owren, indicated benefit from permanent anticoagulant therapy. A cooperative study comprising 1,091 cases treated by 10 physicians* for a total of 24,454 months, compiled by me in 1954, but only published recently, confirms the value of long-term anticoagulants in reducing the incidence of recurrent myocardial infarction and in lengthening the span of life after 1 or more attacks.

**IMPESSING MYOCARDIAL INFARCTION**

During long-term anticoagulant therapy to prevent myocardial infarction, it appeared likely that some episodes of worsening anginal pain might well have ended in full-blown myocardial infarction had anticoagulants not been in force. This observation led me in 1946 to use anticoagulants in patients presumed to be showing premonitory signs of myocardial infarction, a condition which at the outset is indistinguishable from the clinical syndrome of acute coronary insufficiency since the eventual diagnosis is made only in retrospect after a number of days have elapsed. Results in 41 patients in this category constituted my "Address of Chairman," Section of Medicine, Southern Medical Association, November 1949, published in July 1950, and was the first paper on this topic in the world literature. Paul Wood had described the use of anticoagulants in 10 cases of "angina at rest" at the December 1948 meeting of the Medical Society of London. In April 1954 I reported results obtained in 150 additional cases at the American College of Physicians. My associates and I during the past 11 years have treated 313 private patients presenting premonitory signs of myocardial infarction, heparin being used for 1 week before instituting oral anticoagulants. Relief of pain was often strikingly coincident with full heparinization. Only 20 of the 313 patients (6.3 per cent) developed frank myocardial infarction, 5 of whom died within 30 days. Of the remaining 293 cases not developing frank infarction, none died within 60 days while using anticoagulants. Twenty-seven patients abandoned anticoagulants before the expiration of 60 days, of whom 16 (60 per cent) developed frank infarction during the ensuing 60 days. (Unpublished data except for an abstract in the program of the 1957 American Heart Association Clinical Sessions) Similar observations have been reported since 1952 by Maynard, Thompson, Engelberg, Lenègre, and Beaumont, and in the past year by VanderVeer, Anderson, and Waaler.

**NOTES ON THE RISK OF HEMORRHAGE**

Clinical bleeding due to anticoagulants was first described by Prandoni and Wright in 1941, and by the year 1948, 28 deaths were recorded in the world literature ascribed to the use of anticoagulants, at which point I

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obtained by questionnaire further data from 136 clinicians who reported that significant hemorrhage occurred in 2 per cent of 15,500 patients with 35 deaths not previously reported. My paper on “Risk of Hemorrhage” appeared in February 1950 and was later summarized as a guest editorial in the J.A.M.A.

One instance of hemopericardium without myocardial rupture due to anticoagulant therapy in acute myocardial infarction was included, but the first case report dealing with this complication was made by Hammarsten in 1949 and was further emphasized by Goldstein and Wolff in 1951. Three deaths resulted primarily from performing lumbar sympathetic blocks when anticoagulant effect was in force, although hemorrhage was found elsewhere in these cases. The concomitant use of heparin and spinal anesthesia in 1 case, causing transverse hemorrhagic myelitis, and the performance of dorsolumbar sympathectomy without omission of anticoagulants in another, accounted for 2 deaths, both deaths exemplifying poor clinical judgment rather than faulty anticoagulation measures. Most instances of major bleeding were associated with pathologic lesions. The first case of vaginal bleeding in my experience occurred in an elderly woman being treated for coronary thrombosis who proved to have an early carcinoma of the cervix. Sometimes melena induced by anticoagulants led to the discovery of an occult lesion in the gastrointestinal tract.

An extraordinary hemorrhagic death* was that of a 53 year old man on long-term therapy to prevent recurrent infarction, who developed a peritonsillar abscess complicated by edema and hemorrhage into the cervical structures and larynx which produced fatal respiratory obstruction while he was en route to a hospital by ambulance. (Death might well have been prevented by earlier hospitalization.)

Although hematuria was the most common type of bleeding encountered, in no instance was it fatal or followed by added renal impairment. Ureteral colic from clots may follow the free use of vitamin K-1 in hematuria as first noted by me in 1945. One death due to hemorrhage from dissecting aortic aneurysm mistakenly treated as pulmonary infarction was reported by Evans in 1944 and I recorded 2 examples, one wrongly diagnosed as myocardial infarction, the other as saddle embolus. The incidence of fatal hemorrhage in the cooperative long-term study was 0.5 per cent in 1091 patients treated for an average of 22.4 months. Permanent use of anticoagulants is naturally associated with a greater risk of bleeding than when anticoagulants are used for a few weeks only.

In 1950 a patient to whom I had administered long-term Dicumarol therapy to prevent myocardial infarction for 6 months became psychotic and attempted suicide by slashing his wrists, so anticoagulants were stopped. He died a few years later with a recurrent infarction. A suicidal attempt by the self-administration of sodium warfarin was recorded in 1952 by Holmes and Love.

In March 1954 I wrote:

Most hemorrhagic episodes developed because of hypoprothrombinemia, but in some instances in patients using Cumopyran the prothrombin time was found well within the accepted safe therapeutic range, but the Lee-White coagulation time was abnormally prolonged, suggesting that in long-range anticoagulant therapy other coagulation factors may be upset.

In 1957 Herbert Sise and co-workers showed that phenylindanedione produces a deficiency of proconvertin factor (factor VII) and plasma thromboplastin component (PTC), thus accounting for some clinical hemorrhagic episodes in the absence of marked prothrombin deficiency. Currently an intensive study of these effects is going on in the Miami Heart Institute Anticoagulant Laboratory under the direction of Paul Boyles in patients on long-term therapy.

**Side Effects of Anticoagulants**

Alopecia as a toxic manifestation of dicumarin anticoagulants seems more prevalent in Europe than in this country, and I have encountered only 2 examples, but alopecia induced by heparin is somewhat more frequent.

*Related by Dr. R. V. Edwards.
Lack of toxic effects on the liver due to Dicumarol were reported by Meitus and Wasserman in 1953. Liver function studies and autopsy data from our patients on permanent therapy with oral anticoagulants revealed no hepatic injury.

One untoward effect of oral anticoagulants is the production of fatigue, malaise, or even anorexia in some patients. Skin eruptions, occasionally scarletiform, may occur. Febrile reactions are not common but one of my patients, whom I attempted to treat continuously, developed a fever in 1950 proven to be due to Dicumarol, and in the next year, during a trial of Tromexan, fever recurred and did not abate till the drug was stopped, but she was able to tolerate Hedulin. The same patient developed moderate alopecia. A colleague, Dr. Sidney Davidson, in West Palm Beach, had the reverse experience with a patient manifesting febrile reaction proved to be due to Hedulin but Dicumarol was well borne.

Heparin intravenously may induce shock-like reactions in “sensitive” subjects, as happened in one of my patients, and a few instances have followed its use intramuscularly. Local reactions at the site of injection of heparin are usually not of consequence.
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