Long-Term Anticoagulant Therapy

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DR. IRVING WRIGHT: The subject for the conference today is long-term anticoagulant therapy.

The possibility of long-term prophylactic and therapeutic anticoagulant therapy was a natural sequence to its successful use for acute thromboembolic conditions. It did necessitate a marked revision in both the technical and the philosophical approach to such conditions as recurrent thrombophlebitis, myocardial infarction, auricular fibrillation which was responsible for multiple emboli, and numerous other thromboembolic conditions. From a static and resigned approach in which the patient and physician alike awaited apprehension the possibility of a series of serious or even fatal developments, it was conceivable that a dynamic attack might be at least considered, with physiologic and psychologic advantages to the patient.

In 1946 we reported our preliminary experience with Dicumarol for long-term management of patients with rheumatic heart disease with auricular fibrillation and multiple emboli. It is of interest that of the small number of patients then reported on, several of them are still alive and in reasonably good health. An outstanding example is a woman who had suffered a total of 21 recognized emboli prior to her anticoagulant therapy. She had nine emboli of sufficient significance to be recognized clinically; some of the resulting episodes were serious in the 10 days before anticoagulant therapy was inaugurated. She is still alive and active. She was placed on anticoagulant therapy on Nov. 6, 1946. The only embolus that has been recognized from that date until the present was one which occurred in June of 1950, after 30 days without anticoagulant therapy. About June 1, 1950 she decided that she was probably safe from the danger of emboli although she was still fibrillating. She was bored and tired of prothrombin tests at weekly intervals and discontinued the therapy. Just 30 days later she had a saddle embolus. Fortunately, this disintegrated. The fragments descended into the small vessels and serious consequences were averted. She then decided to resume therapy and has suffered no further emboli.

Subsequently, Nichol and Fassett have reported experiences with long-term therapy in an attempt to forestall acute myocardial infarction and we have published additional observations on larger groups of cases. Also Sprague and Jacobson of Boston, Cosgriff of New York and Askey and Cherry of Los Angeles have reported experience with this form of therapy. While the data regarding such long-term therapy are difficult to evaluate because of the countless variables that are introduced by the active lives of individuals, those who have watched these cases have been impressed with the probability that the course of these patients has usually been favorably affected. It has been clearly demonstrated, furthermore, that long-term therapy is practical. It is entirely feasible with certain provisions, and patients on long-term anticoagulant therapy can in many instances be self-supporting and productive citizens.

After our experience has multiplied with the passage of years, Dr. Tulloch summarized our observations on 227 patients cared for in private practice or in the Ambulatory Clinic at the New York Hospital. This study represented a total of 180 years and 124 days of anticoagulant therapy. One hundred and

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Based on a peripheral vascular disease conference held on Wednesday, Oct. 14, 1953.
eighty-two patients received Dicumarol for 59,104 days and 53 patients received Tromexan for 6,700 days. This experience is sufficient to be of some interest. Since Tulloch compiled these data we have increased our experience so that the total now approximates 300 such patients. A report dealing with this experience has been accepted for publication by this journal.

There are certain indications for long-term anticoagulant therapy, but each case must be subject to the decision of the physician.

**Indications**

I. Multiple embolization in patients with rheumatic heart disease and auricular fibrillation.

II. Recurrent thrombophlebitis, especially if the recurrences occur at very short intervals of time.

III. Multiple arterial occlusions, if it is believed that thrombosis or embolism is playing the causative role.

IV. Recurrent myocardial infarction, especially if thromboembolic complications are evident.

V. Idiopathic or familial thrombosing conditions.

VI. Idiopathic and recurrent pulmonary embolism or thrombosis in which the original site of thrombus may never be known.

VII. Less well-defined indications include recurrent angina pectoris, which suggests impending coronary occlusion. This applies to the person who is unable to be active without suffering anginal pain which is becoming sufficiently frequent and severe to convince the physician that there is danger of a coronary thrombosis. Another less well-defined indication is with recurrent evidence of cerebral vascular spasm or multiple small thromboses.

**Technic**

The technic we have used is somewhat as follows: The patient is preferably admitted to the hospital where an endeavor is made to standardize his dosage requirements, whether he uses Dicumarol, Tromexan, Cyclocumarol, Hedulin, or any of the new anticoagulants. After 7 to 10 days he can usually be controlled by the use of prothrombin-time tests taken once a week. Occasionally a patient requires a test twice a week if his prothrombin time tends to fluctuate very much. With Dicumarol the dosage has been from 25 mg. to 125 mg. a day. It is impossible to predict how much a patient will require for proper control. The dosage requirement will vary from time to time, but over a period of several years the average for a specific patient will remain fairly constant in most instances. The desirable levels of prothrombin time for patients on long-term therapy are between 23 and 33 seconds (50 to 25 per cent prothrombin activity) because a person who is ambulatory is more subject to trauma and dietary disturbances, which may affect anticoagulant utilization, than the patient who is under complete hospital control.

**Contraindications**

It should not be forgotten that there are certain contraindications, or indications for the cautious use of these substances. They include: (1) hypoprothrombinemia due to vitamin K deficiency or severe hepatic disease; (2) vitamin C deficiency (until this is remedied); (3) renal insufficiency of a marked degree; (4) blood dyscrasias with bleeding tendencies; (5) surgical and other trauma which leave large, open, raw surfaces, exposure of the brain or spinal cord and operations in the presence of obstructive jaundice or severe liver disease; (6) ulcerations or cancer of the gastrointestinal tract, the genitourinary tract, or other sites at which bleeding may be easily induced; (7) subacute bacterial endocarditis, although as Dr. Huebner pointed out recently,

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Optimal therapeutic range for long-term anticoagulant therapy is considered to be between 23 and 33 seconds or approximately 50 to 25 per cent of prothrombin activity.
this subject has not been fully re-evaluated in recent years.

These are general contraindications for either acute or chronic anticoagulant therapy. There are additional contraindications which pertain to long-term therapy: (1) Marked hypertension. A level above 200/110 is an indication for great caution if the drug is used at all. Even lower levels of pressure may be equally important if there has been any evidence of vascular damage. (2) An irresponsible or mentally incompetent patient. Once the patient leaves the hospital the physician no longer has control over whether he does take the drug when he is expected to, whether he comes for his tests of prothrombin time when he is supposed to, or other factors which may enter into the picture such as alcoholic bouts and deprivation of proper food, and so forth. (3) A physician who is not well trained in this work or who does not wish to assume the responsibility for this rather demanding and meticulous form of therapy.

It may be said that while there appears to have been a marked diminution in the number of thromboembolic complications in our patients on long-term therapy, thromboembolic episodes have occurred at all levels of prothrombin time. They have occurred at levels below 20 seconds; they have occurred at levels between 20 and 24 seconds; they have occurred between 24 and 40 seconds; and they have even occurred at prothrombin times above 40 seconds. This is evidence that there is great complexity and variation in the mechanism concerned in thromboembolic tendencies, and, whereas with these drugs we may take care of the prothrombin and perhaps factor VII and V, there are still other aspects of the clotting mechanism which may outweigh these factors from time to time in a given patient. Actually, while on anticoagulants only 26 patients of our rather large series had a total of 40 clear or doubtful thromboembolic complications; of the latter 16 were very doubtful.

Hemorrhages also occurred at all prothrombin levels. Bleeding should not always be attributed to anticoagulants simply because a patient happens to be taking them at the time. Control groups of patients not on anticoagulants also have hemorrhages, although this fact is often overlooked. With pulmonary emboli they have hemorrhages from the lung; with renal emboli they have urinary bleeding; with emboli to the wall of the gut they may have a hemorrhage from their bowels. In other words, all hemorrhages which occurred in this series were not necessarily due to anticoagulant therapy, but we have so listed them nevertheless. The majority of these hemorrhages occurred at prothrombin levels over 25 seconds, and there is a much higher incidence above 40 seconds. There has been one death in this series which we believe have been due to anticoagulant therapy. This was a cerebral hemorrhage in a patient with hypertension, but since the indications for anticoagulant therapy were very strong, a calculated risk was assumed.

In the event of major hemorrhage the patient was given either one or two transfusions of 250 to 500 cc. of whole fresh blood or 250 mg. to 500 mg. of vitamin K. For minor bleeding, discontinuance of the anticoagulant and the administration of 70 to 150 mg. of water soluble vitamin K was usually sufficient.

These patients on long-term anticoagulant therapy have survived accidents and surgery successfully. Before a surgical procedure is undertaken, it is advisable to reduce the dosage of the anticoagulant for a day or two, or by other means bring the prothrombin time down to a normal or nearly normal level. Surgery is not contraindicated during the type of treatment we are discussing provided that the proper steps are taken to prepare the patient; the prothrombin time should be normal.

The first case to be presented this afternoon is a case of recurrent myocardial infarction which will be presented by Dr. Rene Bourgain.

DR. RENE BOURGAIN: Mr. A. J., an orderly in this hospital, is a 47 year old white man. His past history is not significant. His father suffered from diabetes.

The patient was symptom-free until December, 1944, when, after seven days of substernal discomfort, he suddenly experienced a severe stabbing pain in the same area. There was no previous history of angina. He was admitted to this hospital, the electrocardio-
gram revealing an acute anterior myocardial infarction. The white blood cell count was 24,000 and the blood pressure 145/90. The patient did not complain of further pain and he made an uninterrupted recovery. He was discharged in February, 1945, without any signs of cardiac failure. His blood pressure was 120/80. He was followed in the Cardiac Clinic and received aminophylline and nitroglycerine. An electrocardiogram taken later showed that T1 had become positive. He was free of symptoms until August, 1949, when he suffered two anginal episodes, each of about five minutes duration. An electrocardiogram taken at this clinic showed minor posterior-wall changes and a second electrocardiogram taken about three days later revealed a definite pattern of acute infarction of the posterior wall of the left ventricle, and he was therefore readmitted. On physical examination at this time he had rales at the base of the left lung, and the blood pressure was 120/70. Two weeks after his admission, and after consultation with the vascular clinic team, it was decided that the patient should receive anticoagulant treatment, and he was started on Dicumarol. This was continued for nearly a month and the maximum prothrombin time noted was 42 seconds.

He was free of symptoms for about 18 months and an electrocardiogram made in December, 1950, revealed no signs of further myocardial infarction, T1, T2 and T3 being upright. In January, 1952, he again complained of severe localized left anterior chest pain accompanied by severe dyspnea. He was admitted for the third time. His blood pressure was 130/70 and there were rales at both lung bases. The electrocardiogram was characteristic of anterior wall infarction. There was a small Q1 and deep Q in V5 with negative waves in leads I, V4 and V6. After about three days his pain subsided. He was again placed on anticoagulant therapy for one month. During hospitalization he developed a perianal abscess which subsided without complications. He was discharged on Feb. 7, 1952, with a blood pressure of 120/70.

After discharge he was free of symptoms again, but only for six days, when he was admitted for the fourth occasion with severe pain and a negative T1 in the electrocardiogram. It was then decided to institute long-term anticoagulant treatment with Dicumarol. The maximum prothrombin time during hospitalization was 45 seconds. He was discharged in February, 1952, and has been continuously on anticoagulant treatment except for five days during August, 1952, when he was again admitted with a chill, fever and diarrhea with bloody stools. Diagnoses of Salmonella enteritis and pneumonia were among those considered. Stools were negative on culture and the only positive finding was a bilateral maxillary sinusitis on radiologic examination. Anticoagulant treatment was started again five days after admission and has been continued to date.

The patient was discharged in August, 1952, his prothrombin time being 27 seconds. On four occasions since long-term therapy was started his prothrombin time has reached 45 seconds or more. He was admitted for surgical drainage of his perianal abscess in August, 1953. The patient’s general condition is good, but he has developed an anxiety state. He occasionally has anterior chest pain, but not typically anginal in character.

To summarize, we have presented a patient who has had four recognized episodes of acute myocardial infarction and has been under long-term anticoagulant therapy since 1952 without any further thromboembolic complications.

(Patient comes in.)

Dr. Wright: How are you feeling?

Patient: Very well.

Dr. Wright: Do you have any pain?

Patient: Not now, sir.

Dr. Wright: We have nothing particular to demonstrate. You have had four attacks?

Patient: Yes, sir.

Dr. Wright: When was the last one?

Patient: January ’52.

Dr. Wright: You work as an orderly?

Patient: Yes, sir.

Dr. Wright: You are able to shift patients about?

Patient: I do the best I can, sir.

Dr. Wright: Are there other questions anyone would like to ask Mr. J.? (Patient leaves.) Dr. Foley, do you have some comments about this problem of the use of anticoagulants
in the treatment and prevention of recurrent myocardial infarction?

Dr. William T. Foley: This problem presents a challenge to the medical profession and there had been no previous treatment offered that could possibly prevent recurrence of coronary artery thrombosis. With this in view Dr. Wright and I initiated long-term anticoagulant therapy in a series of patients. A preliminary report appeared in February, 1948. Of the original five patients who were placed on this form of therapy because of recurrent myocardial infarction, four are still living after a minimum of six years. Since that time we have maintained an additional 10 patients, bringing the total number to 15, all of whom have been on anticoagulant therapy for a period now which averages five years for each person. In this entire group there have been three deaths. One of the group had to abandon therapy because of bleeding in the urinary tract, and genitourinary investigation disclosed a congenital abnormality of the kidney. One of the patients abandoned treatment because of difficulty in having his prothrombin time tested. One month after abandoning therapy he died, apparently of coronary thrombosis. There have been no major problems with the rest of the group. There have been minor incidences of hemorrhage but no hemorrhage requiring hospitalization or requiring more than temporary withdrawal of the drug.

Dr. Wright: Are there other questions?

Dr. Bourgain: We all know that some cardiovascular conditions, especially coronary disease, are accompanied by hypercoagulability of the blood. At the time that the patient, Mr. J., complained of a severe pain in the chest, the electrocardiogram showed posterior wall changes. Although not unequivocally diagnostic of infarction, this electrocardiogram showed alterations not present in the previous electrocardiogram. I believe that at that time treatment by heparin was indicated. Do you agree?

Dr. Wright: That brings us to a very important point in this discussion. If a person develops an acute thromboembolic episode of whatever nature, and you wish to obtain the maximum effectiveness in the shortest period of time, heparin should be used to initiate therapy. That is the great advantage of heparin. It cannot be continued effectively over a period of years. I believe, with Dr. Bourgain, there was a definite indication for heparinization at the time of the premonitory symptoms in this case. It is, however, difficult to know with certainty whether the course of the individual patient has been altered by this approach.

In a specific case one may question whether the patient has had an actual thrombosis. The more than 90 cases autopsied and studied very carefully for the Committee on Anticoagulants of the American Heart Association indicated that more than 70 per cent of all myocardial infarctions resulted from coronary thrombosis.6 Frequently the indications are more clear-cut than they are with the patient we are discussing. We have followed a patient who had four very severe myocardial infarcts within a period of six months, following which he was placed on long-term anticoagulant therapy. He has never had a recurrence of myocardial infarction. He leads an extremely active life as both the president and chairman of the board of one of the nation’s largest corporations. He flies in company planes from one part of the country to another visiting plants, but he continues his anticoagulant therapy. He has physicians in most of the cities that he visits who are well trained in the field, and he goes once a week to have a prothrombin time taken; he can now adjust his life and his anticoagulant therapy accordingly. I mention this patient to indicate the feasibility of an active life on such a regimen.

The next patient has suffered from recurrent thrombophlebitis with pulmonary emboli.

Dr. McDevitt will present this patient.

Dr. McDevitt: Mr. V. J. is a 50 year old postal clerk who was essentially well except for bronchial asthma which recurred yearly. In 1947, at the age of 44, three months after a right hemiorrhaphy, he developed a right saphenous thrombophlebitis which necessitated six weeks’ rest in bed. Following ambulation he wore an elastic stocking. In 1948 he had a
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recurrence of thrombophlebitis in the same leg, and in 1949 he had two episodes of thrombophlebitis involving the same extremity. This patient was first seen in the New York Hospital in March 1950. Three weeks following the onset of pain, swelling and redness in the right extremity, and one week prior to admission, he experienced a sudden onset of sharp pain in the right chest, and one day prior to admission he had hemoptysis. On admission his vital signs were within normal limits. The temperature was 37.4 C., respirations 20, pulse 80, blood pressure 135/80. The positive findings included diminished breath sounds at the base of the right lung and a swollen, red, tender right lower extremity. He was started immediately on heparin and Tromexan; he made a fairly satisfactory recovery and was discharged but was not maintained on anticoagulants.

Twenty-three days after his discharge, on May 2, he was readmitted to this hospital because of recurrence of the thrombophlebitis in the right leg. At this time there was no chest pain. He was restarted on anticoagulants, and it was decided at that time to maintain him on long-term anticoagulant therapy. He was followed in the Anticoagulant Clinic until September 18 of that year, approximately three months later, when he developed an episode of rectal bleeding which was thought to originate in external hemorrhoids. He was seen in the emergency clinic, in this hospital, and the anticoagulant therapy was discontinued. The prothrombin time was 37 seconds. Approximately three days after the anticoagulant was discontinued he experienced sudden, sharp pain in the left chest associated with hema- temesis. He was readmitted to the hospital. On this occasion he was febrile for two weeks, and on one occasion his prothrombin time reached 91 seconds following an accidental overdosage of Dicumarol. This prothrombin time was quickly brought under control by using 72 mg. of water soluble vitamin K. He was discharged on Nov. 1, 1950, and he has been maintained since that date on Dicumarol. His average dose is 50 mg. a day and his prothrombin times have ranged between 24 seconds and 41 seconds. On three occasions when he has been out of town for three weeks his times have dropped to around 19 seconds, but they have very quickly been restored to their average level, and he has had no recurrence of the thrombophlebitis. You will note that he had seven episodes of thrombophlebitis prior to the institution of long-term treatment.

DR. WRIGHT: Bring the patient in. (Patient comes in.) Have you had any trouble lately?

PATIENT: None with my legs since 1950.

DR. WRIGHT: Do your legs swell at night?

PATIENT: No.

DR. WRIGHT: No pains or tenderness? Do you have any pains when it rains?

PATIENT: No.

DR. WRIGHT: A great many people after severe thrombophlebitis do have pains with changes in the barometric pressure. I call them weather “veins,” a rather poor pun but not without point.

PATIENT: It does not seem to affect me that way.

DR. CLARA GROSS: Do you wear elastic stockings?

PATIENT: Yes.

DR. WRIGHT: On both legs?

PATIENT: Only the right leg.

DR. WRIGHT: Are there any other questions? Thank you very much for coming. (Patient leaves.)

This has been a very difficult syndrome in the past because there seemed to be no way of preventing these individuals from having recurrent thrombophlebitis. Some individuals have had 40 or 50 attacks over a period of many years. Each attack has incapacitated them temporarily to a marked degree and left its long-term scar in an accumulative diminution of the active venous system. As a result they develop chronic edema, ulcerations of the ankle, various types of eczematoid reactions and other painful disabling lesions. It was found that if the thrombus occurred peripherally in the saphenous system, ligation might prevent pulmonary emboli, but ligation does not prevent recurrent attacks of thrombophlebitis.

We have studied for six years a retired army colonel who first had saphenous ligation, then
a femoral ligation, and finally an inferior vena cava ligation. He still continued to have recurrent thrombophlebitis of the veins of his legs and pulmonary emboli. Anticoagulant therapy controlled his situation.

We have recently had another patient in the hospital who has had recurrent pulmonary emboli following an inferior vena cava ligation performed after many episodes of thrombophlebitis. In other words, if there is a thrombosing tendency in the blood, it is not necessarily confined to the vessels of the lower extremities, although they are the most frequently involved. So it seems physiologically and pharmacologically sound to attempt to weigh the balance of the thrombosing mechanism against ease of anticoagulation, and yet try not to produce a hemorrhagic state. This we can now do with anticoagulants. Many such patients have now been followed for periods of years. It is of note that even after several years, if prothrombin times are allowed to return to normal, thrombophlebitis may become active again. In certain patients thrombophlebitis will develop if the prothrombin time shortens to under 23 or 24 seconds. At levels of 30 seconds or higher, they are safe from this risk. We do not understand why their blood has this thrombosing tendency. Even rather detailed surveys of many of the clotting factors may fail to reveal any significant alterations from the normal. This merely emphasizes the limitations of our technics.

Dr. Foley: This patient presents one of the key problems in ambulatory anticoagulant therapy, namely, at what level to maintain the prothrombin time. When his prothrombin time was only 33 seconds, he had rectal bleeding. When it was shortened to below 25 seconds, he again developed thrombophlebitis. There are a few patients who must be maintained within a very narrow range. These represent a real challenge to the clinician, but they are usually in serious danger if untreated, so the calculated risk must be taken.

Dr. Burke: Drs. Overman and Link7 were able to protect rats better from hemorrhage by having them on small doses of vitamin C. Should our patients on long-term therapy, even though they have no evidence of a sclerotic state, receive supplementary vitamin C?

Dr. Wright: That might be taking every precaution, although where there is no evidence of vitamin C deficiency its supplementary administration might not have a very valid scientific basis. It is reasonable and safe to give any patient with any abnormal bleeding tendency rather large doses of vitamin C, such as 600 mg. of ascorbic acid a day, which frequently exceeds their requirements but is harmless.

Dr. Gross: Following a single episode of thrombophlebitis, how long would you continue anticoagulants?

Dr. Wright: Usually until all evidence of thrombophlebitis, such as redness, heat, tenderness and local swelling (except perhaps a remnant of a hard cord which may remain for many months) has subsided, until the pulse rate has returned to normal, and until the sedimentation rate is normal. This usually takes from 10 days to three weeks. For rather severe bouts of thrombophlebitis we may continue anticoagulants for an extra week or so after the patients are up and about and even after they leave the hospital. For recurrent thrombophlebitis, long-term anticoagulant therapy must be considered.

A Physician: Is there any valid evidence that when anticoagulant therapy has been stopped, the patient has a greater risk of a recurrence of thrombophlebitis than a patient who has never been on it?

Dr. Wright: This hinges on the question whether there is an overswing when the blood prothrombin level approaches normal. I think the evidence on this is rather meager. There are patients who have been on anticoagulants for a long time who had thrombi or emboli after anticoagulants were stopped, but usually this occurred from two weeks to two months later. That seems a long time for an overswing to be effective. We have never been able to measure the overswing from coumarin compounds satisfactorily. With heparin a temporary overswing seems a little more likely. More probably this is a manifestation of the former tendency to thrombosis which has now
been released by the elimination of the anticoagulant therapy.

There are many drugs and other factors which affect the dosages of anticoagulants of the coumarin type. For example, if the patient on anticoagulant therapy receives gut-sterilizing antibiotic therapy (Aureomycin, for example) the dosage of Dicumarol or Tromexan may have to be substantially reduced. The theory for this phenomenon is not established beyond doubt, but it is quite likely that the sterilization of the gut interferes with the production of vitamin K, which ordinarily may act as a buffer substance against the coumarins.

We will now consider the last patient, a woman with rheumatic heart disease with auricular fibrillation and recurrent emboli. This is to be presented by Dr. Eugene Simon.

**DR. EUGENE SIMON:** The patient, Mrs. B. J., is a 43 year old housewife. Her history of rheumatic disease began at the age of six years when she had an episode of chorea. At the age of 13 the patient learned of a heart murmur. She first developed signs and symptoms of heart failure at the age of 21, during her first pregnancy. She was first seen in the New York Hospital Cardiac Clinic at the age of 28. At that time the diagnosis was rheumatic heart disease with mitral stenosis, mitral insufficiency and aortic insufficiency. There was a normal sinus rhythm. Slight cardiac enlargement was noted.

The patient was treated at the age of 31 for an episode of acute rheumatic fever. Between the ages of 33 and 38 she was seen regularly at New York Hospital and she was continued on digitalis because of persistent symptoms of heart failure. During this period normal sinus rhythm was consistently reported. Between the ages of 38 and 41 the patient was not seen at New York Hospital.

Late in 1951, when the patient was 41 years old, she reappeared, complaining of left hemiparesis and left hemihypesthesia with severe headache. At this time for the first time auricular fibrillation was noted. The neurologic diagnosis was considered to be cerebral embolus. The patient was treated with Dicumarol and the symptoms of paresis and hypesthesia subsided fairly promptly. The Dicumarol was discontinued after a few weeks. About seven months later she complained of sudden onset of severe right costovertebral angle pain. This pain was similar to that which one might expect in renal colic and was accompanied by hematuria. Urologic studies revealed no function in the right kidney, and there was a great deal of doubt about the actual diagnosis in her case. Because of the presence of rheumatic heart disease with auricular fibrillation and because of the evident inability to visualize any obstructions in the right kidney, the most likely diagnosis was considered to be embolus to the right kidney. The patient was therefore restarted on anticoagulants. There was a gradual reappearance of function in the right kidney, and it seemed fairly certain at the time of her discharge that she actually had had a large renal embolus. It was felt that this was an appropriate case for long-term anticoagulant therapy because of her having had two serious episodes of embolization in the course of one year and because of the persistence of the factors that seemed to be conducive to her thromboembolic tendency, namely, the mitral heart disease, and rheumatic heart disease and auricular fibrillation. Since the time of her 1952 admission, somewhat more than one year ago she has been maintained on Dicumarol. During this past year she has taken approximately 50 mg. of Dicumarol per day. Her prothrombin times have been determined at either one- or two-week intervals and they have usually been between 25 and 35 seconds. There have been no other complaints or symptoms to suggest any other embolic phenomena. There have been no hemorrhages. In addition to Dicumarol she is receiving digitoxin and Thiomerin. She is able to perform her duties as a housewife and at times has engaged in part time work outside of the house.

**DR. WRIGHT:** Will you bring in the patient? *(Patient comes in.)*

**DR. WRIGHT:** How are you feeling?

**PATIENT:** All right.

**DR. WRIGHT:** Are you able to do your housework?

**PATIENT:** With help.
Dr. Wright: Do you wash your dishes?
Patient: Oh, yes!
Dr. Wright: Make the beds and sweep the floors?
Patient: Yes.
Dr. Wright: I hope that you do not move heavy furniture?
Patient: No.
Dr. Wright: Do you do your shopping?
Patient: Yes.
Dr. Wright: Do you have to walk up to your apartment?
Patient: One flight.
Dr. Wright: Do you have any trouble doing that?
Patient: No.
Dr. Wright: Thank you very much for coming. (Patient leaves.)

This patient presents a most interesting set of problems. One of these is the question, which is often presented, whether all patients with auricular fibrillation should be placed on anticoagulant therapy. We have taken the position that, with anticoagulant therapy as complicated as it is, it is probably not advisable. If anticoagulant therapy becomes very much simpler it may be acceptable. The reason that we do not recommend anticoagulant therapy for all cases is that many patients have auricular fibrillation for 15 or 20 years and never have an embolus. The chances are they will at sometime, but many do not. We do advise this therapy for patients in fibrillation with a history of one or more emboli. Even a single embolus may be a doubtful indication. The only difficulty with this type of reasoning is that the first embolus may be a very serious one which produces a permanent hemiplegia or results in the loss of a leg. Therefore, we are not on very firm ground. On the other hand, the difficulties and economics involved in keeping patients for years on anticoagulants when they may never have a thromboembolic episode are to be given serious consideration. At present if the patient has had two emboli or more, it seems as though long-term therapy is indicated. One embolus may be a sufficient indication, but without any emboli I doubt that we are justified in using anticoagulants. This must, however, rest with the discretion and judgement of the physician who is caring for the patient.

The second point of particular interest with this patient is this question of the renal embolus: an embolus to the renal artery with what appears to have been a restoration of function! Following severe pain in the flank there was no evidence of function in the right kidney. In this patient that was fairly strong evidence in favor of an interference with the arterial circulation, and gradually the function of the kidney was restored. It is now known that anticoagulant therapy does encourage the early restoration of the patency of vessels blocked by clots. This was not understood a few years ago, but the work of Helen Payling Wright in London demonstrates that there is no doubt about this, especially if anticoagulants are administered shortly after a clot is formed or even before, when the clot has not become very firmly fibrosed. It is felt that this is not due solely to the action of the anticoagulants, but rather that these drugs allow the enzymes in the blood to act upon the clot directly.

Dr. Jerrold Lieberman: When patients with rheumatic or other heart disease eventually go into heart failure there is some change in liver function and at this time it is usually quite important to watch the anticoagulant dosage very carefully.

Dr. Wright: That is correct. This is also true especially if a patient has an episode, either in terms of embolism or myocardial infarction, which results in shock which, in turn, may produce changes in both liver and renal function. In such a patient small doses of anticoagulants may produce exaggerated elevations of the prothrombin time. The physician must be alert to these possibilities.

Dr. Symons: Is there ever any trouble from menstrual irregularities arising during anticoagulant therapy?

Dr. Wright: In normal women I should say rarely, if ever; but we have uncovered a number of pathologic conditions of the cervix and uterus such as polyps, erosions and even carcinoma because the patient at a fairly satisfactory level of prothrombin time bled unexpectedly. It might be pointed out that this constitutes a signal for investigation, wherever
the bleeding may come from in the body. We have detected a number of cases with carcinoma of the bowel, ulcer of the bladder hitherto unsuspected, duodenal ulcers, and, as I said, lesions of the uterus because bleeding occurred at what might be called routine therapeutic levels. Never assume that such bleeding is due to the anticoagulant alone, but be certain that the patient does not have a lesion which the thrombosing mechanism of the body was formerly preventing from bleeding. When that protection was removed by the use of anticoagulants, bleeding became possible. This is a very important consideration because of the number of patients in whom the physician will be able to detect real pathology which hitherto had been missed.

Dr. HUEBNER: Dr. Wright, in your opening discussion, you mentioned two uses for anticoagulants where the indications were not clearly defined, the recurrence of severe angina and cerebral spasm. I wonder if we might not add to that group those elderly patients with arteriosclerosis obliterans of the lower extremities who are having progressive occlusive episodes in the arteries. Some of them have impending gangrene of the toes or feet.

Dr. WRIGHT: I think they might be well included, at least with a question mark. Many of them have their occlusions practically entirely on the basis of atherosclerotic plaques, but the final step is almost always a thrombus that develops in the narrowed lumen.

Conclusion. We have indicated that there are many unanswered questions regarding long-term anticoagulant therapy and that it does not lend itself to the precise statistical analysis which was used for a six weeks' study under controlled conditions for myocardial infarction. Nevertheless there is increasing evidence that for some patients it represents the only hope of preventing or treating devastating continuing disability, and it may delay or prevent a fatal conclusion due to a thromboembolic episode.

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Long-Term Anticoagulant Therapy
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