Experience with Anticoagulants

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THE GREAT STUDIES of Schmidt, Morawitz, Virchow, Rokitansky and others on the pathogenesis of thrombosis and embolism produced no specific clues leading to a sound method of treatment for these deadly and disabling complications of disease.\(^1\) Just 24 years ago Morawitz made the following statement. "Even today it is still a thankless task to discuss the problem of thrombosis on the sickbed; thrombosis has lost none of its danger; it is still a fearsome disease, a frightening spectre to the surgeon and the physician. We still seek vaguely hither and thither for prophylactic and therapeutic measures." To one working in the field of cardiovascular diseases, the lack of agents with which to combat the thrombosing process was a constant source of frustration. Heparin was theoretically available after McLean’s\(^2\) discovery and Howell’s early work\(^3\) but actually this was not true because of the difficulty of preparation, the impurity of the product, the severe reactions which forbade its use in man, and the great expense involved in producing small amounts. It was therefore an interesting tool for the laboratory but not safe for man. Best, Scott, and Charles had taken the first major step toward producing a heparin suitable for use in man in 1934, but it was not available for general use for another 5 years. When, therefore, in 1938 I lay in bed for 4 months harassed by a severe thrombophlebitis which occurred after an appendectomy, and which finally burned itself out after producing almost daily fevers of 102 to 103° F. and a total loss of 60 pounds in weight, I had both time and special cause for contemplation on this subject. The same year we learned that Best and his co-workers\(^4,5\) had succeeded in producing satisfactory heparin in sufficient quantities so that it could be used in the treatment of thrombosis in man without the risk of severe reaction, provided careful control of the clotting time was observed.

In the fall of 1938 a young man (A. S.), aged 31, was seen in consultation with Drs. Leo Mayer and Jerome Marks. He had been suffering from an intractable and migrating thrombophlebitis which had involved the veins of the legs and the superficial veins of the trunk. In addition, there was clinical evidence of involvement of the mesenteric, splenic, renal, and probably pulmonary venous systems. Available treatment had failed to change the progressive course of this disease. Drs. Best and Murray generously agreed to come to New York, sharing some of their limited supply of heparin, and to help us set up the continuous intravenous infusion with suitable controls of the clotting time. For 16 days and nights during which all concerned were constantly apprehensive, the infusion continued with clotting times being taken at 2 to 4 hour intervals. There were no untoward incidents. The temperature, which had been elevated daily for months, remained normal throughout and the existing lesions subsided. No new lesions developed. This was most encouraging. At the end of that period our supply of heparin ran out and Dr. Best had no more to give us. Unfortunately, shortly thereafter the patient’s fever returned and the course of the disease continued uninterrupted until some months later, when he contracted mumps from one of his children, became very ill, and developed a fever that reached 106° F. This fell to normal by crisis, after which the phlebitis disappeared and did not recur for several years. This was never explained, but the experience with heparin was sufficiently interesting for us to use it in additional patients. This was believed to be the first patient treated with the improved heparin in the United States although a few had received it in Canada.

As we were able to obtain additional supplies of heparin, we tried it on other patients, but the cost and difficulty of maintaining continuous intravenous infusions, the only method recommended at that time, was such that it

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Footnotes:

1. From the Department of Medicine, Cornell University Medical College, New York, N. Y.

2. T. W. Schmidt, Virchow’s Arch. 236:204, 1925.


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was not very practical for general use. The need for an anticoagulant that could be administered orally and that was not too costly became increasingly apparent.

Meanwhile, Karl Paul Link and his co-workers had been working for some years in an attempt to isolate the compound that was present in spoiled sweet clover. This factor had been recognized by the 2 veterinarians, Schofield and Roderick separately, as the cause of a hemorrhagic disease in cattle. The substance responsible for this phenomenon had never been isolated. Link's experiences will be found in his paper in this symposium.

Beginning in 1940, Karl Paul Link and his co-workers began to publish a classical series of papers on this subject and this was capped in April 1941 by the report of the identification and synthesis of the hemorrhagic agent. This was truly exciting and we immediately wrote asking Dr. Link for supplies of this new synthetic agent as soon as he could spare some. His response was prompt and generous and shortly thereafter we began to receive supplies of the first oral anticoagulant, which was suitable for use in man, Dicumarol. Link had, previous to his publication, supplied some Dicumarol to O. O. Meyer, J. B. Bingham, and F. J. Pohle at the University of Wisconsin where he worked, and to H. R. Butt, E. V. Allen and J. L. Bollman at the Mayo Clinic. On February 27, 1941, Meyer presented the first report on its use in man at the University of Wisconsin. In June 1941, Butt, Allen, and Bollman published a preliminary study of its use in dogs and in a series of 6 human beings. In October 1941, we presented our preliminary experiences with its use in 20 human beings.

Immediately upon receiving the first shipment of material from Dr. Link, Dr. Andrew Prandoni, who was working with me as a research fellow, and I set up a program to test it in man at the Goldwater Memorial Hospital. While recognizing the potential risk as seen in animals, neither of the previous groups had reported any hemorrhagic complications in man. We soon encountered some of considerable severity. For example, one patient who leaned out of bed developed a subcutaneous hemorrhage on 1 flank about 8 inches in diameter. Others developed hematuria. This was naturally alarming and both Dr. Prandoni and I lost much sleep over this, but resolved to continue the studies. As it turned out, this was a significant observation, since several pharmaceutical houses were then ready to release large amounts of this substance on the market without adequate understanding or warning regarding the risk and with no detailed knowledge of how to handle such complications if they occurred in man. This would have made it available to physicians without proper training for this form of therapy who would in turn have been dependent on laboratories where the tests for prothrombin time were totally inadequate for measurement of the activity of this potent but potentially dangerous new drug. With the cooperation of the Council of Pharmacy of the American Medical Association and the pharmaceutical houses, the release was delayed until further studies could be carried out. This was actually a matter of more than a year. It is probable that many tragedies were averted by this cautious step. Why did our patients develop hemorrhages whereas the others had not thus far encountered this complication? We finally concluded that this was because we used the Russell Viper Venom technic for our prothrombin tests. This was an accepted method at that time but was not sensitive enough to measure early changes in factor VII and prothrombin activity and since the dosage of Dicumarol in man was uncertain, this presented real danger. Another disturbing factor was finding that the dosage of Dicumarol could not be determined on the basis of the weight of the patient. Lastly, we found that the poorly nourished, often cachectic, patients we worked with did not react to Dicumarol in the same way as the well nourished patients of the Wisconsin and Minnesota groups.

Communication with Drs. Meyer and Allen made it possible for us to cross check our results. On May 4, 1942, Drs. Meyer and Allen and I, each representing our respective teams, presented data before the American Society for Clinical Investigation and this
was repeated in greater detail before the Section on Experimental Medicine and Therapeutics of the American Medical Association in June 1942.\textsuperscript{10-12} The experiences were so similar and encouraging that coming from 3 separate institutions the impact was such as to stimulate others to initiate broader studies. We had an effective antieclotting agent which could be administered by mouth, but now the challenge was to determine the indications and contraindications for its use in the care of patients. The experience in numerous hospitals with its use for the prevention and treatment of thrombophlebitis and pulmonary embolism was rapidly and favorably developed. In May 1942 we started to use it cautiously in patients with heart disease, first for myocardial infarction with embolization, then with rheumatic heart disease with embolization. The patients tolerated the drug well and the clinical impression was encouraging but the material was limited because of the lack of confidence in this form of therapy by others as well as ourselves.

World War II then entered into the picture and undoubtedly delayed the development and acceptance of anticoagulant therapy, since many who were active in this field entered the armed forces. Although we could not obtain official approval from the Surgeon General's Office to stock Dicumarol in Army pharmacies until later, we did succeed in getting tacit permission to continue our studies first at the Army and Navy General Hospital in Hot Springs, Arkansas, and later in numerous army hospitals in the Midwest and Far West where I served as consultant. Dr. Prandoni also continued to increase his experience with anticoagulants on the Medical Service at the Walter Reed Hospital.

By 1945 we had accumulated data based on the treatment of 76 patients suffering from acute or recurrent myocardial infarction, and this was reported before the California Heart Association on October 18, 1945.\textsuperscript{13, 14} Meanwhile, E. S. Nichol and S. W. Page of Miami, and H. R. Peters, J. R. Guyther, and C. E. Brambel of Baltimore had been accumulating series of patients suffering from myocardial infarction treated with Dicumarol. Their experiences were published early in 1946 and were in agreement with ours.\textsuperscript{15, 16} This was encouraging but the data were not conclusive and we therefore proposed the cooperative study which was carried out by the Committee on Anticoagulants of the American Heart Association. The report of this committee includes the details of its work. This large project enlisted the resources of 16 leading medical institutions with teams of workers each headed by an outstanding cardiologist. A central laboratory and statistical center at the New York Hospital acted as the coordinating agency. Cases admitted on alternate days were admitted to treated and controlled series. Master forms were compiled in detail and analyzed by Dr. Dorothy Beck, Chief Statistician, and her staff. In 2 years the case records of 1,031 patients were secured. Preliminary reports were issued, but the final report took more than 6 years to complete.\textsuperscript{17, 18} Following the publication of this report the use of anticoagulants for the treatment of myocardial infarction was adopted widely in many countries as well as in the United States. Although there still exist some differences of opinion regarding the selection of suitable cases, there have been more than 60 confirmatory reports published from medical centers in this country and abroad and the wide use of this form of therapy seems to be accepted for the foreseeable future.

There are now many anticoagulants of the coumarin and phenylindandione groups available. We have evaluated a number of them. They vary somewhat in onset and duration of action but present few advantages over Dicumarol and phenylindandione as they were first made available for general use.

As indicated above, in 1942 we began the treatment of patients with multiple embolization from old rheumatic heart disease and myocardial infarction. Thus evolved the conception of long-term anticoagulant therapy. Some of these patients had developed cerebral emboli and it seemed logical to attempt to interrupt a tragic series of events leading to death or perhaps even worse, complete invalidism. From these experiences we were encouraged to treat patients with cerebral
thrombosis including carotid artery and basilar artery thrombosis. This was seriously embarked upon in December 1946 and the results have been reported at intervals since that time. This work has expanded and is now being submitted to analysis in several cooperative long-term studies in which our group is actively participating. Great credit is due to Dr. William T. Foley and Dr. Ellen McDevitt for their consistent work in this field during the past decade. The final evaluation of the indications and contraindications for the use of anticoagulants in the treatment of cerebral thrombosis remains to be concluded during the coming years.

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