My Early Experience with Bishydroxycoumarin (Dicumarol)

By Edgar V. Allen, M.D.

"... leaven to quicken the blood that ran..."
A. C. Swinburne, 1878

In the last of March 1941, my associate at the Mayo Clinic, Dr. H. R. Butt, gave a lecture at the weekly meeting of the staff of the Mayo Clinic on the use of vitamin K to correct deficiency of prothrombin associated with jaundice and disease of the liver. In the course of that lecture he mentioned a compound that had been prepared which was capable of producing a deficiency of prothrombin in animals. This state apparently could not be corrected by the administration of vitamin K. After the lecture I asked Dr. Butt about the new preparation, and found that he had read about it only a few days previously in the Journal of Biological Chemistry. The work had been done by Dr. Karl P. Link and his associates at the University of Wisconsin. Dr. Butt had been working with vitamin K and measurements of prothrombin for several years, and he was greatly interested in this new discovery.

A request was sent to Dr. Link for a supply of some material for clinical use. We discussed at some length the possible clinical uses of this material but, to the best of our knowledge, it never had been administered to a human being, so all we could do was to speculate. We did have high hopes. Dr. Link and his associates very promptly sent to us some bishydroxycoumarin (Dicumarol). A study of the effect of this compound on dogs was begun by Dr. J. L. Bollman about the middle of April 1941. The results of his studies confirmed the observations of Link and his associates.

My associates and I who were interested in intravascular coagulation had used heparin for a number of years. Heparin was known to be valuable in the treatment of vascular thrombosis and embolism, but it had disadvantages, specifically in its short action, its need for parenteral administration, and its considerable cost. I had believed for some time that another preparation could be used that would abolish these objections and that would be beneficial in the care of patients with vascular thrombosis and embolism.

On May 9, 1941, Dr. Butt and I administered Dicumarol to an organically sound young man who was 19 years old and who weighed 80 Kg. We had no alternative but to guess at the proper dose; we gave too much, that is, 1.8 Gm. in 5 days. On the sixth day after our patient first swallowed the Dicumarol, Miss Margaret M. Hurn, who was determining prothrombin activity in the blood, called me, with some concern, to say that our patient had almost no prothrombin in his blood (fig. 1). Moreover, the coagulation time of the blood was prolonged (fig. 2). Dr. Butt and I shared Miss Hurn's concern, for we were conscious of the possibility of severe hemorrhage.

Although at that time vitamin K was considered to lack the ability to increase prothrombin activity when deficiency of prothrombin was induced by Dicumarol, we gave the patient 20 mg. of synthetic vitamin K intravenously, at the suggestion of Dr. Butt. The prothrombin time decreased from 140 to 87 seconds within 24 hours, but at the end of another 24 hour period the prothrombin time was 161 seconds. It was only many months later, when reviewing the clinical record of the patient, that we recognized that there had been substantial increase in prothrombin activity attributable to the use of vitamin K. Until that time we had believed that the recorded change in prothrombin activity had been a "normal fluctuation." When we finally recognized, in retrospect, the specific effect of vitamin K on the blood of our patient, it had already been demonstrated that large doses of

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ANTICOAGULANTS: A HISTORICAL SYMPOSIUM

Fig. 1
Conagulation Time (Minutes)

300 mg

600 mg

300 mg

200 mg

100 mg

0 mg

Fig. 2
vitamin K enhance prothrombin activity when deficiency of prothrombin has been induced by the use of Dicumarol, although small doses fail to do so.

We protected our first patient from injury, and within 20 days the prothrombin activity and the coagulation time of the blood had returned to normal (figs. 1 and 2). His health had not been impaired in any way.

At that time Dr. Butt and I believed that we were the first to administer what since became known as Dicumarol to a human being, but Dr. Link said in his Harvey Lecture, delivered on January 20, 1944, that the anticoagulant had been given to the clinical group at the Wisconsin General Hospital, Madison, in September 1940. Dr. Ovid O. Meyer subsequently told me that he and his associates had first given Dicumarol to human patients in December 1940 or in January 1941. However, the first patient received 10 mg. of Dicumarol on the first, third, and fifth days, 25 mg. on the sixth day, and 50 mg. on the tenth day of observation. Eleven additional patients, with one exception, received single doses ranging from 50 to 100 mg. of Dicumarol. Study of the blood of these patients showed that in 5 instances there was prolongation of the prothrombin time from an average control level of 10 seconds to an average maximal level of 12 seconds.

When I was attending the annual meeting of the American Medical Association in 1941 I received a telegram from Dr. Butt relative to some aspect of the problem. Shortly afterward I told Dr. Irving S. Wright, of New York City, that we were carrying out studies that might have great importance. I told him I did not wish to disclose the nature of the studies because they were in a preliminary stage. He replied that he also was anticipating carrying out studies of interest, but declined to give information for the same reason I had declined. It was not until some time later that it was disclosed that both of us had Dicumarol in mind.

In the issue of the Proceedings of the Staff Meetings of the Mayo Clinic for June 18, 1941, Dr. Butt, Dr. Bollman, and I published the first report of the administration of Dicumarol to man.

Of this report Dr. Link wrote in his Harvey Lecture, "Boldness, a combination of right talent and an objective point of view . . . enabled them to publish the first preliminary clinical report . . .," and that "Messrs. Butt and Allen gave it in full therapeutic doses to six human subjects."

The editorial comment on our report in the September 13, 1941, issue of the Lancet was given the title, "Heparin and a Rival." On May 4, 1942, the presentations on behalf of the speakers and their associates were by Dr. Irving S. Wright, of New York City, Dr. Ovid O. Meyer, of Madison, Wisconsin, and by myself before the American Society of Clinical Investigation. At the annual meeting of the American Medical Association in June 1942, 3 more detailed presentations were made before the meeting of the Section on Experimental Pharmacology and Therapeutics.

Needless to say, Dicumarol and similar substances have proved of great value in clinical practice; the use of them has saved many lives. The story which I have related, based on my personal participation in it, is the story, "From the Haystack to the Human,"* for treatment of diseases of man with Dicumarol resulted from original studies by Link and his associates on the cause of hemorrhagic disease of cattle which occurred when they ate spoiled sweet-clover hay.

There is another chapter yet to be written. Identical amounts of Dicumarol and substances that have a similar action produce diverse effects on the prothrombin activity of different persons, and on the prothrombin activity of the same person at different times. Hence, an effect that is constant in quality cannot be anticipated accurately. What is urgently needed is a preparation which, when administered in the same amount, always produces the same effect. Such an accomplishment seems improbable and perhaps impossible, but we are bound to remember that in 1939 Dicumarol also was "impossible."

*The designation of a newspaper reporter.
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