Historical Data Regarding the Experiences with Coumarin Anticoagulants at the University of Wisconsin Medical School

By Ovid O. Meyer, M.D.

It was 1938, 20 years ago, when, in conversation with Professor R. A. Brink of the Department of Genetics at the University of Wisconsin, that I first heard of the work being done in the Department of Agriculture to identify the substance in spoiled sweet clover accountable for hemorrhagic disease in cattle. This had been initially undertaken in 1934 at the Wisconsin Agricultural Experiment Station by Professor Karl Paul Link and his associates. This group of workers, including Campbell,1 Stahmann and Huebner,2 finally isolated the anticoagulant, a coumarin derivative, and established its chemical characteristics. The yield was about 1 Gm. per ton of clover, an amount which was not practical for clinical usage. However, by April 1940, these investigators had synthesized a 3-substituted-4-hydroxyeoumarin which was chemically, physically, and biologically identical to the naturally occurring substance. This could be prepared cheaply and in abundant quantities. The potential significance in the treatment of thromboembolic disease was then obvious, and hence we were happy when a supply was made available to us for basic studies in September 1940. The anticoagulant for clinical purposes was given the name Dicumarol.

My early associates in the field included James B. Bingham, now in Seattle, Dr. Frederick J. Pohle, deceased, Dr. John McCarter, now of Boise, Idaho, Dr. Charles T. Thill of Chicago, and Dr. Maryloo Spooner Schallek of Nutley, N. J. It was promptly established that this anticoagulant was a potent hypopro-

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One of the first lessons in the use of the early Dicumarol was that the substance was not active in quantities of 1% or less, and that 2 or 3% proved most desirable. It became immediately clear that if this agent would work at all it was likely to work best in combination with other agents, and that it was not antagonistic to the use of gelatin capsules. The next and perhaps most important lesson was that Dicumarol in the starting dose of 1 mg. per pound of body weight was not satisfactory. A dosage of 10 mg. per pound was required for adequate anticoagulant action. The administration of Dicumarol in gelatin capsules was the only practical method of administration for clinical use.

The anticoagulant properties of Dicumarol could be demonstrated in dogs. However, it was important to establish that the agent was hypoprothrombinic in vivo in dogs and without effect in vitro. Our original experiments were set up to elucidate the morphologic changes that might occur in dogs when so-called therapeutic and toxic doses were given, to establish the range between the effective therapeutic dose and the minimal lethal dose, to determine whether or not this anticoagulant reduced the prothrombin in human beings as it had been shown to do in cattle, rabbits, rats, mice, guinea pigs, and dogs, and to demonstrate whether administration of this dicoumarin in safe dosage would actually prevent or prolong the time of intravascular clotting.

The final and most important objective, of course, was to establish whether or not the anticoagulant would prevent the development of thromboses in human beings. Investigation of the above effects was mainly directed toward this major aim, which obviously could be settled "only by extensive investigations of the future."3

Our first published report3 established that the administration of oral (the powdered substance given in a gelatin capsule)4 or intravenous administration of Dicumarol produced, after a usual latent period of 24 hours, prolongation of the prothrombin time (and coagulation time if measured at room temperature but not if properly measured in a water bath at 37-38 C.). It was further demonstrated that therapeutic and even fatal doses did not produce significant pathologic changes in the liver or other parenchymal organs. It was shown5 in dogs, however, that excessive or fatal, but not therapeutic, doses produced

*3,3'-methylenebis (4-hydroxyeoumarin) is highly insoluble in water. At a pH of 10 or more the sodium salts are soluble but the solutions are unstable and must be used promptly after being prepared.
hemorrhages, gross or microscopic, toxic lesions, and marked dilatation of small arteries, arterioles, capillaries, venules, and small veins, acute renal glomerular swelling, and toxic lymphoid degeneration. These effects are emphasized, since several authors, at least by implications, have indicated that Dicumarol is a vasodilator, which it is not unless toxic doses are administered. We have never observed vasodilatation when proper doses are employed.

After gathering, with a less than ideal method, some suggestive experimental evidence that Dicumarol did prevent some intravascular (jugular) clotting in dogs and after establishing the safety of the drug in animals and an approximately proper dosage, we cautiously administered it to human beings to achieve the data needed for clinical use. The first 12 patients who received the drug were, with 1 exception, patients with advanced malignancy. The patients, save 1, demonstrated no definite clinical evidence of involvement of the liver. The very first patient received a total dose of 10 mg. and the other 11 patients received doses of 50 to 100 mg. (0.75 to 2.0 mg. per Kg.). In 5 of these 11 the prothrombin time was slightly prolonged. It was then promptly established in additional patients that a dose of 4 mg. per Kg. was safe and could produce significant hypoprothrombinemia. Still later it was found that, in our hands, the most satisfactory therapy entailed the use of an initial oral dose of 5 mg. per Kg., followed by doses of 1.5 mg. per Kg., on those days when a dose could be given to maintain the prothrombin at 50 to 25 per cent. As is well known, subsequent studies by many others as well as ourselves have established that still lower levels of prothrombin are better.

The first public report of our experiences with this anticoagulant was made in the discussion of a paper presented by Professor Link before the University of Wisconsin Medical Society, February 27, 1941.

By early winter, 1942, we had more clearly demonstrated, as had others, the permissibility of giving the anticoagulant for as long as 5 weeks without toxic effect and the absolute need for daily or at least frequent prothrombin time determinations if the drug was to be safely administered. We found that blood transfusions appeared to be effective in controlling excessive hypoprothrombinemia and that vitamin K was ineffective, but we used doses no larger than 10 mg. given orally or intramuscularly. However, Shapiro et al. demonstrated that vitamin K in relatively large amounts did counteract Dicumarol-induced hypoprothrombinemia and Cromer and Barker found that large doses, 64 mg. of menadione bisulfite intravenously, usually were effective in correcting excessive hypoprothrombinemia due to administration of Dicumarol.

In 1943 we observed that the rectal administration of Dicumarol in suppositories was not regularly effective. Miss Maryloo Spooner, while a graduate student at the University of Wisconsin, established, using the method of Helen Wright, that Dicumarol decreased the adhesiveness of platelets without affecting the platelet count per se.

By 1943 there were several workers investigating coumarin anticoagulant therapy, and the practicality and usefulness of this drug became increasingly evident. It has been widely established that the only hazardous effect of this treatment was hemorrhage, and this was likely, of course, in patients who had ulcerative lesions, a hemorrhagic tendency, significant liver disease, or in the rare patient who was unusually sensitive to the drug in ordinary dosage. Some rare individuals were unusually resistant and required large doses. However, we sought a more ideal anticoagulant, a fixed dose of which would produce a fixed proportional hypoprothrombinemic effect, in order to avoid, insofar as possible, the need for frequent, troublesome, costly, and sometimes unavailable prothrombin time determinations.

Hence we were pleased to test another coumarin compound, 4-hydroxycoumarin no. 63, made available to us by Professor Link and Dr. Lester D. Scheel in May 1949. This synthetic chemical, 2-methyl-2-methoxy-4-phenyl-5-orodihydropyrano-(3-2e)(1) benzopyran,
was first tested in dogs, a dose was established, and it was later tested in human beings. The results indicated that this anticoagulant was 2 to 3 times as potent as Dicumarol and that lethal doses in dogs did not produce the toxic lesions in the small blood vessels that occurred with excessive administration of Dicumarol. Although it appeared from these and later studies that a greater stability of hypoprothrombinemic maintenance seemed possible with this drug (cyclocumarol) and that it had no apparent disadvantages, it never became popular, and in our own clinical work it was subsequently replaced when warfarin sodium was introduced. While testing this latter anticoagulant, we first observed that vitamin K₁ and vitamin K₂ oxide were very effective antidotes for excessive hypoprothrombinemia due to this and the other coumarin anticoagulants. James et al. had previously reported this observation for vitamin K₁ oxide. Obviously this was an important addition to our armamentarium, since it appreciably lessened the hazard of coumarin anticoagulant treatment.

While testing this anticoagulant, we inadvertently learned of another hazard in this type of therapy. In retrospect, it seems humorous, but it was not funny at the time and it might have been tragic. Two patients of the same name were on the same hospital ward. One was receiving the 4-hydroxycoumarin anticoagulant, and the prothrombin time determinations were carried out daily on the blood of the other. Since the former patient appeared to be resistant to this drug and the daily prothrombin of the latter was 100 per cent, the dosage was progressively increased, and only when subcutaneous bleeding developed at the site of hypodermoclysis needle punctures in the patient receiving the anticoagulant was the error realized and corrective measures taken. This was the fifth of 200 patients who demonstrated gross hemorrhagic side effects attributable to cyclocumarol.

The ideal anticoagulant had still not been discovered, nor has it yet. The toxicity of those available was low, and effectiveness was demonstrated. Nevertheless, it was still hoped that an anticoagulant with more regular response in prothrombin reduction to any given dose and with greater stability of levels of prothrombin might become available so that less frequent prothrombin determinations might be possible.

Synthesis of the 3-substituted-4-hydroxycoumarin anticoagulant no. 42, 3-(a phenyl-β-acetylethyl)-4-hydroxycoumarin, was first accomplished and its action studied in Professor Karl Paul Link’s laboratory. This compound was named warfarin, and its readily water-soluble sodium salt was warfarin sodium. This anticoagulant was first kindly supplied by Professor Link and later by Dr. Samuel B. Gordon of Endo Products, Inc., Richmond Hill, N. Y. Initially in 1953 we used both warfarin and warfarin sodium, which are more potent than the other 2 anticoagulants. Later, since the former had no advantages, we continued our studies with only warfarin sodium, which we have found subsequently can be used intravenously and intramuscularly with safety, as well as orally. To my knowledge, no other coumarin anticoagulant can be satisfactorily employed parenterally. In 1956 we found that, unlike Dicumarol, warfarin sodium was consistently effective when administered rectally. Our investigations demonstrated that this anticoagulant was superior, not only because it could be given parenterally if the need existed, but because the latent period, which was the same for oral and parenteral administration, was shorter than for either Dicumarol or cyclocumarol (Cumopyran). Even more important, with warfarin and warfarin sodium it has been easier to maintain the prothrombin level steadily within the therapeutic range. Hence, the staff throughout our hospital has found it generally easier to manage the patients requiring anticoagulant therapy. The hazards of anticoagulant therapy are the same for warfarin sodium as for other coumarin compounds, though perhaps somewhat lessened, and vitamin K₁ has been found to be a satisfactory antidote for the excessive hypoprothrombinemia which could result. In our
institutions for the past 3 years Dicumarol and cyclozearol have been almost entirely superseded by this newer coumarin compound.

This concludes my remarks, limited to the contribution of the investigators at the University of Wisconsin Medical School. These historical facts are related as accurately as possible in order to make our segment in the final historical profile complete and graphic. The total picture will point out the numerous contributions of many investigators in the elucidation of this very interesting subject. Once more there is emphasized the importance of fundamental progress from the laboratory of the scientist making the original discovery to the final successful clinical application. Obviously many unanswered problems remain in this field, and there is much opportunity for other workers to perfect the applications of the present information and to augment these facts with additional, much needed information.

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