The Discovery of Dicumarol and Its Sequels

By Karl Paul Link, Ph.D.

The story of Dicumarol* has been told several times by me in the past 17 years, and often by others. Like any good story it need not be told in exactly the same manner each time. In Wisconsin it has become a kind of legend. I shall consider only the high water marks of certain chapters.

Fortunately the basic scientific facts on the discovery and development have already been thoroughly recorded1-6 so that little new information on Dicumarol and its sequels needs to be revealed here. However, when I do introduce new material it will be restricted to that which is documented or sustainable via memoranda or letters.

The story begins some 36 years ago on the prairies of North Dakota and in Alberta, Canada. In the 1920's a new malady of cattle involving fatal bleeding showed up almost simultaneously in these areas. The veterinarians, Schofield and Roderick, were forced to conclude that the cause of the disease was neither a pathogenic organism nor a nutritional deficiency. The origin of the new malady was traced to stacks of sweet clover hay mysteriously gone bad. Hence the disease became known in veterinary practice as "sweet clover disease" and it was found that it was caused only by improperly cured hay made from the common varieties of sweet clover. When first observed this disease was in a sense without parallel in animal pathology or human medicine. When cattle or sheep ate the spoiled hay the disease slowly became manifest by a progressive diminution in the clotting power of the blood (about 15 days) and resultant internal hemorrhage which usually became fatal in about 30 to 50 days.

From the Department of Biochemistry, University of Wisconsin, Madison, Wis.

Given February 25, 1938 at the New York Academy of Medicine under the auspices of the Section of Medicine and the New York Heart Association, on the programme, "The Historical and Physiological Aspects of Anticoagulants."

It was recognized by Schofield and Roderick that the disease was reversible. It could be controlled in cattle by the withdrawal of the spoiled hay from the diet and by transfusion of blood freshly drawn from normal cattle, provided the hemorrhagic extravasation had not proceeded too far. Indeed, they showed that even in desperate cases, recovery could be hopefully anticipated after transfusion and change in diet (good hay).

In a comprehensive and thorough study of the pathology and physiology of the disease Roderick in 1931 emphasized that the delayed or abolished coagulability of the blood was due to a "prothrombin" deficit. Indeed he showed that the severity of the hemorrhagic condition paralleled the reduction in "prothrombin content or activity." He did this by using the technic developed by that great American pioneer of blood coagulation, the late Professor W. H. Howell. Solutions of what was then called "prothrombin" prepared by precipitation of normal bovine plasma with Howell's acetone method when added to the "sweet clover blood" promoted coagulation. In contrast, preparations of "prothrombin" made in a parallel manner from "sweet clover blood" did not produce coagulation. The other constituents for the maintenance of normal coagulability known at that time (fibrinogen, calcium, platelets, and inhibitory substance) appeared to be unaffected.

I first learned about the hemorrhagic sweet clover disease of cattle in December 1932 through the late Ross A. Gortner, who then

*Dicumarol is the trademark for 3,3'-methylenebis-(4-hydroxyecoumarin). The anticoagulant was made available in 1940 and 1941 for clinical use by the cooperative efforts of the Wisconsin Alumni Research Foundation, Madison, Wis., the Abbott Laboratories, North Chicago, Ill., Eli Lilly and Company, Indianapolis, Ind., and E. R. Squibb and Company, New Brunswick, N. J. The official U.S.P. name is bishydroxyecoumarin.
headed the Biochemistry Department of the University of Minnesota. He had offered me a post and I had come to St. Paul to consider it. Since the “sweet clover disease” was also a problem in Minnesota it was one of the projects open for study if I chose to accept. It was Gortner who supplied me with the original publications of Roderick. Some attempts had been made in Gortner’s department to extract the hemorrhagic agent but they, like those of Roderick and others, had failed.

Curiously, the “‘official start of our work in January 1933 in cooperation with Professor R. A. Brink and W. K. Smith of our Genetics department was on a different aspect of the sweet clover problem. They sought to develop a strain of sweet clover suitable for Wisconsin climatic conditions low in, or free from, coumarin. Though coumarin was sweet (the characteristic smell of new mown hay is due to its presence) it tastes bitter, and it was known that the bitter taste of green sweet clover plants, Melilotus alba and M. officinalis, paralleled the total coumarin content. In actual practice it was observable that cattle (or rabbits) would eat the less bitter plants first.

**Tragedy out on the Farm**

Quite apart from the “‘official’ start concerned primarily with the palatability question my laboratory had a direct catalytic hit from agricultural practice.

Indeed on a Saturday afternoon in February 1933 following the first conferences with Brink, while a blizzard was howling and the mercury was hovering near zero, a farmer from the vicinity of Deer Park, Wisconsin, some 190 miles from Madison appeared with what the late Professor A. J. Carlson might have called “the evidence.” Curiously the farmer’s name was Ed Carlson. The hemorrhagic sweet clover disease of cattle was rampant on his farm. He had fed sweet clover hay for years previously without encountering any difficulties and he doubted the veterinarian’s diagnosis. Accordingly he was advised to go to the Agricultural Experiment Station authorities to get the facts. The office of the State Veterinarian had closed and pure chance had brought him to the Biochemistry Building.

Farmer Carlson’s multiple evidence was a dead heifer, a milk can containing blood completely destitute of clotting capacity, and about 100 pounds of spoiled sweet clover—the only hay he had to feed his cattle.

His account of the over-all course of the disease coincided perfectly with the classical “sweet clover poisoning” picture. Late in December he had lost 2 young heifers. In January 1 of his favorite old cows had developed a massive hematoma on a thigh and following a skin puncture fatal bleeding set in rapidly. Finally 2 young cows had died on Friday and the bull was oozing blood from the nose. So he took off for Madison in a blizzard.

I immediately had to tell farmer Carlson that we could do no more at this time than to recommend the teachings of Roderick and Schofield. He had to stop feeding that hay, and possibly transfuse those desperately sick cattle, if he wanted to save them. Eventually it might become possible to make some usable recommendations to avoid such disasters, but not now.

I can still see him take off for home about 4:00 p.m. Those 190 miles of drifted roads between our laboratory and his barn must have appeared to him like a treacherous and somber ocean.

I cannot take the time to tell all the details of this slice of the Dicumarol story, but I can assure you its impact on me was immense. I will relate a part of it exactly as I did in my first lecture on Dicumarol given at the Mayo Clinic on March 12, 1942.

When farmer Carlson came to see us, my senior student and old man Friday was Eugen Wilhelm Schoeffel, a volatile Schwabian who came to the U.S. in 1926 with a diploma in Agricultural Chemistry. After serving a 2-year apprenticeship in the Chicago Stock Yards he began to study with me in 1929. Schoeffel is interesting, energetic, and loyal. He was then and still is, somewhat of a mystic and inclined in ordinary conversation to quote freely from Goethe’s Faust, Shakespeare, and the Bible, as well as other primary sources. In 1933 his spoken English was not only strongly guttural, but also very earthy, punctuated frequently with Schwabian German.
After farmer Carlson left, Schoeffel stormed back and forth in the laboratory shouting, “Vat da Hell, a farmer shrugs nearly 200 miles in dis Sau-wetter, driven by a shpeeter and den has to go home vit promises dat might come true in five, ten, fifteen years, maybe never. Who knows? ‘Get some good hay—transfuse.’ Ach!! Gott, how can you do dat ven you haf no money?’” he snarled.

He dipped his hands into the milk can repeatedly and while rubbing them muttered, “Dere’s no clot in dat blok! BLUT, BLUT VERFLUCHTES BLUT. ‘Die Menschen dauer-mich in ihren Jammertagen.’” (Faust Prolog., line 297) and then, “Vat vil he find ven he gets home? Sicker cows. And ven he and his good woman go to church tomorrow and pray and pray and pray, vat vil dey haf on Monday? MORE DEAD COWS!! He has no udder hay to feed—he can’t buy any. And if he loses de bull he loses his seed. Mein Gott!! Mein Gott!! Vy didn’t ve anti-shi-pate dis? Ya, ve should haf anti-shi-pated dis.’”

We took the blood and hay and played about with them until about 7:00 p.m. when I headed for home. As I left the laboratory, Schoeffel grabbed me by the shoulders, looked me squarely in the face and said, “Before you go let me tell you something. Der is a desh-tiny dat shapes our ends, it shapes our ends I tell you! I will clean up and gif you a document on Monday morning.”

Development of the Bioassay

Two fundamental issues confronted us. First there were no chemical criteria available to establish the presence of the hemorrhagic agent. Therefore, a bioassay involving a small experimental animal (rabbits) offered the only practicable means of appraising the anticoagulant activity of test hays and extracts prepared therefrom.

It was clear from the pioneer papers of Roderick that the sweet clover disease was completely reversible. The eating of spoiled hay, even over long periods, caused no permanent functional change, no demonstrable morphologic change, and no detectable pathologic change of the liver, the assumed primary site of prothrombin synthesis. Nevertheless, the immediate prospects of developing a reliable and simple bioassay were not bright; indeed they were dark, “dark like the inside of a cow.” We had not had previous experience with that complex problem—blood coagulation.

Schoeffel and Roberts first showed that the Howell method for estimating prothrombin activity did not have the precision required. Smith and Roberts showed that the whole blood coagulation time was too variable, and that the Quick 1-stage method using whole plasma left much to be desired. Smith also showed that there was a wide variation in the response of individual rabbits to the standard dose of 50 Gm. of the spoiled hay. So Campbell and Smith bred and reared a susceptible rabbit colony specifically for the assay.

At that time, 1935-1938, a bloody and amusing polemic raged among the coagulation specialists on how to estimate “prothrombin concentration or activity”—whether it should be done by the 1-stage method of Quick* or the 2-stage method of H. P. Smith and coworkers.† We tried to keep out of that brawl. In 1938 Campbell finally got over the chief obstacles. He adapted the Quick 1-stage method to our conditions, primarily by relying on the clottability of diluted plasma within the concentration range 12.5 to 8.34 per cent. He eliminated some of the inherent daily variations by fasting the assay rabbit 24 to 36 hours before feeding any preparation under test, by making the plasma clottability tests promptly after drawing the blood, and by comparing the test plasma against the normal plasma of each rabbit.

Through the use of individually standardized rabbits (the standard response being that

*The intricacies of the blood coagulation phenomenon are outside the scope of this discourse. Suffice it to state that it is now accepted by most “coagulationists” that a prolonged Quick 1-stage “prothrombin time” (when the fibrinogen is normal) induced by Dicumarol and the like is a primary deficiency in factor VII and prothrombin. See British Medical Bulletin, vol. II, no. 1, Blood Coagulation and Thrombosis, Medical Department, The British Council, London, November (1955), and the lectures by Owen P. A. on Congulation of Blood, etc., Northwest Medicine, January, pp. 31-39, February, pp. 159-166, and March, pp. 298-307, 1957.
induced by the anticoagulant in 50 Gm. of spoiled hay) and by having the assay on a strictly differential basis the ever present problem of biologic variation was greatly reduced.

Some side observations were made by Campbell on the plasma of rabbits fed the spoiled hay or fractions thereof that were later reported by others. A plasma factor beyond that needed by the classical blood coagulation expression of Morawitz-Field and Spero was hinted at in one of Campbell’s reports. But these hares were not hunted. Our goal was to make real a substance that abolished the clottability of cattle blood in agricultural practice. To use the vernacular, the bioassay using the 1-stage plasma clottability was altered so that “it worked,” and few of the valuable assay rabbits were lost in the process. One of them known as Bess Campbell was used for about 200 individual assays, over a period of 5 years.

*Isolation, Crystallization, Identification, and Synthesis of Dicumarol*

Between that fateful Saturday in February 1933 and June 1939 a long and arduous trail was followed by Smith, Roberts, and especially Campbell, to lay the anticoagulant out on the bench. I would like to detail some of the chemical extraction, separation, and isolation problems that the spoiled sweet clover hay presented. This hay was indeed a kind of biochemical grab-bag and yielded many inactive products, some new, most of them old. But suffice it to state that many a seething and simmering hope did not become reality. At times the hemorrhagic agent appeared to hover before us like thistle down only to elude us like the will-o-the-wisp. At one time it was thought to be a porphyrin-like substance, a pheophytin resulting from the degradation of the chlorophyll in the spoiling process.

Finally in the dimness of dawn on June 28, 1939, after working all night, Campbell saw on a microscope slide what turned out to be crystalline Dicumarol. Two hours later he had collected about 6.0 mg. of it.

When I reached the laboratory that morning Campbell was asleep on the laboratory couch; the door to the room was guarded by one Chet Boyles, a soldier of fortune on the W.P.A. relief roles, who assisted Campbell with the bioassays. Boyles was an excellent handler of animals for he had served 2 years as helper to a veterinarian before he came to us.

As I walked into the room, Boyles was taking a nip from the contents of a bottle whose bottom layer consisted of carpet tacks, the upper layer of 95 per cent ethanol. Without the flier of an eyelash Boyles said to me, “I’m celebrating, Doc. Campy has hit the jack-pot.” (As though I didn’t know that he had been hitting that bottle for months.)

But Boyles’ surmise was correct this time. Campbell did have Dicumarol and the first bioassay to establish its anticoagulant potency was already in process!

Campbell avoided me for 2 days—until the results of the assay were available—and then he came in to report.

There is a bed-rock of matter-of-fact common sense in Campbell’s makeup. He was not inclined to show his emotions, but it was apparent that he was secretly as happy as a boy who had just caught his first big fish. He passed the vial to me and said, “This is H. A.!” (H. A. was the laboratory code for hemorrhagic agent.) I did not disclose that Boyles had given me the tip-off. I told Campbell that I knew a couple of lines of German poetry that fitted the occasion, and I recited to him,

“So halt’ich’s endlich denn in meinem Händen
Und nenn’ es in gwissen Sinne mein.”

We sent a short wire to Schoeffel, who was then in the control laboratory of the American Medical Association in Chicago. He responded at once with a 200-word reply wherein he expressed his complete confidence in Nature, Fate, and us.

Mass isolation was started at once, and a stock of about 1,800 mg. of the crystalline anticoagulant was accumulated (Stahmann).
ANTICOAGULANTS: A HISTORICAL SYMPOSIUM

The problem of determining its structure fell to the sensitive, brilliant, and deft C. F. Huebner, who with some assistance from his lively imagination made the correct structural diagnosis as 3, 3'-methylenebis (4-hydroxycoumarin). He set the sights for the synthesis, which was achieved on April Fool’s day, 1940. The synthetic and the natural product were shown to be chemically identical. Subsequently, Overman and Sullivan, through carefully conducted tests on the rabbit, rat, guinea pig, mouse, and dog, hall-marked the natural and synthetic products as biological equals.

The determination of the structure of the anticoagulant as a 3-substituted derivative of 4-hydroxycoumarin makes it appear that both of the undesirable aspects of the common sweet clovers—their unpalatability (bitterness) in the green state and the tendency of the hays to cause hemorrhage when improperly cured—have a common basis in the coumarin molecule. The biological synthesis during spoilage can be rationalized as an oxidation of coumarin to 4-hydroxycoumarin which upon coupling with formaldehyde leads to Dicumarol.

Physiologic Action of Dicumarol

After synthetic Dicumarol became available in quantity the essentials of its physiologic action were quickly established. It was shown that there is a lag in response, a variation in the intensity and duration of the hypoprothrombinemia (plasma prothrombin clotting time), depending on the size of the dose. In each species tested a certain single dose level gives the most efficient response. Below this level the efficiency of action is decreased by a threshold effect and at high levels by incomplete absorption of the drug.

Due to the latent or lag period of 12 to 24 hours before the drug’s action becomes apparent, there is a cumulative effect following repeated administration. Thus it was anticipated that in clinical practice this action will vary with the individual and because of this variation optimal therapeutic effects without hemorrhage would be obtained only when the dosage is individualized.

A brief summary1-3 of the details follows:

1. There is a wide species difference in the response induced in the rabbit, rat, guinea pig, mouse, dog, cat, and chicken, and this varies with the age and sensitivity of each individual. Broadly speaking, the rat and mouse are the most sensitive, the cat and dog intermediate, and the rabbit, the cow, and the chicken the least sensitive.

2. The vitamin K and C levels in the diet affect not only the intensity but also the duration of the anticoagulant action. I propose to elaborate on this later.

3. The nutritional status of the animal affects the anticoagulant response—fasting generally enhances it in all species.

4. Any pre-existing hypoprothrombinemia like that inducible by the salicylates (aspirin), the sulfa drugs, or mild chloroform anesthesia augmented the response.

5. The hepatic and renal function influences both the intensity and duration of the response.

6. The presence of drugs that affect the total functioning capacity of the liver, like the methylxanthines (theophyllin) and the digitalis drugs, have a mild but definitely detectable counter action.

7. Pregnant or lactating females show a slight resistance to the drug’s anticoagulant action.

These observations did not exhaust the conditions that can influence Dicumarol’s action but they cover the essential points. Finally, it should be added that in Dr. Best’s department at Toronto, Dale and Jaques first9 and later Meyer and co-workers10 at Wisconsin General Hospital, and others11-15 were able to show that a primary relationship exists between thrombus formation and the clotting mechanism of the blood. These studies established for the first time that an effective reduction of extravascular and intravascular thrombus formation parallels the diminished hypocoagulability induced by Dicumarol. It
was also shown by Spooner and Meyer\textsuperscript{14} that, when Dicumarol is given to dogs in safely usable therapeutic doses, it definitely decreases platelet adhesiveness; at the same time Quick showed that it also reduced platelet agglutinability.\textsuperscript{15} Thus the clinical use of the anticoagulant as a prophylactic agent for (against) thrombosis rested on a sound experimental basis.

\textbf{Breaking the Bonds of the Usual Pattern of Thought}

When we turned Dicumarol over to the clinicians in the years 1940 to 1942, one significant point, clearly established by our work, was at first missed, in fact denied.\textsuperscript{6} I have reference to the capital fact that vitamin K (all forms—some better than others) can counteract the action of Dicumarol.\textsuperscript{*} I emphasized this in letters, personal conversations, and in my first lecture on Dicumarol at the Mayo Clinic and at Wisconsin General Hospital. In spite of these efforts the first clinical reports carried the statement that “vitamin K has no effect as an antidote to the administration of Dicumarol.” The editorial and annotation writers for the medical journals, those who only “think” but “don’t try,” innoently reiterated this statement.\textsuperscript{1, 2} While in error, the clinicians were in good company, for an authority on blood coagulation\textsuperscript{16} had written in 1937, and again in his book published in 1942, that “vitamin K will not restore the prothrombin concentration” depleted by Dicumarol.\textsuperscript{17}

Originally these denials made me very unhappy. The misfortune of being accused of error was not the primary basis for the unhappiness, for we were certain that the antidotal capacity of vitamin K would in time be sustained in the clinic. What did disturb me was the needless induction of the hemorrhagic “sweet clover disease” in man and the stigma temporarily attached to Dicumarol, that it was a dangerous drug.\textsuperscript{18} And this did happen.

A feature of science that has always appealed to me is that sooner or later, and usually sooner, “the truth will conquer.”

Dr. Shepard Shapiro in New York City was the first clinician (February 1942) to sustain our claims that vitamin K can counteract the anticoagulant action of Dicumarol in man when liver function is adequate.\textsuperscript{5, 20} Subsequently he was independently supported by Townsend and Mills in Canada,\textsuperscript{21} Lehman in Sweden,\textsuperscript{22} and finally by Cromer and Barker\textsuperscript{23} at the Mayo Clinic, as well as others. Today it is accepted that the water-soluble forms of vitamin K or vitamin K\textsubscript{1} given orally can successfully antidote overdosing with Dicumarol, provided they be employed when reversal is still possible.

Let us briefly examine why the error arose. The clinicians did not use a 1-stage prothrombin assay as sensitive as the one Campbell developed for our experimental animals. They were originally conditioned to the low levels of vitamin K effective in obstructive jaundice, biliary fistula, cholemic bleeding, etc. It was also thought that the menadione form of vitamin K might be toxic. Over 10 years were required to wipe out this error from clinical practice.

To summarize, surmise, faulty thinking, and not enough trying kept vitamin K from being the corner building stone in Dicumarol therapy that it deserved to be from the outset.

In 1950 Marple and Wright (pages 149 and 181)\textsuperscript{6} wrote, “When bleeding occurred from the clinical use of Dicumarol the fault rested with the physician who administered the drug.”

\textbf{Enthusiasm—Muddle—Consolidation}

Within 2 years after Dicumarol was synthesized, over 100 related 3-substituted 4-hydroxycoumarins were prepared in my lab-
ANTICOAGULANTS: A HISTORICAL SYMPOSIUM

oratory. Synthesis ran substantially ahead of biochemical appraisal. Accordingly, when I gave the Harvey Society lecture on "The Anticoagulant from Spoiled Sweet Clover Hay" in January 1944 it was indicated that "it would not be valid to conclude from the relative appraisals on activity made with the rabbit—thatDicumarol is the most desirable compound for clinical use." It was indicated that "In the course of the routine appraisal of the many compounds tested it was learned that some of them exhibited a slower but more sustained hypoprothrombinemic action, while the action of others is of shorter duration. It will take some time before final judgment can be passed on this subject. From the experience gained with other pharmacological agents it is abundantly clear that the final test is the action in man under a variety of conditions. The unpredictable can be surprising, so, as we see it, we might now be at the beginning of things and not at the end in this field of study."

Being an agriculturist I have little confidence in predictions, including my own. The situation can now be appraised in the light of wisdom after the event. Bear in mind that the statement quoted was made less than 4 years after Dicumarol became known to us and before extensive clinical information on the response in man was available. About 50 reports on the clinical use of Dicumarol had appeared between 1941 to 1944.4, 6

The appearance of any new drug creates an interesting cycle of events, and Dicumarol went through that cycle quite rapidly. The first preliminary reports indicated that an atmosphere of optimism prevailed. They evoked prompt favorable editorial comment in the Lancet (September 13, 1941) under the title, "Heparin and a Rival." Then came the second period—a period of muddle. Enthusiasts and skeptics for anticoagulant therapy with Dicumarol were created, and it can be stated that some of the skeptics condemned the drug in no uncertain terms, though they were largely armed with surmise, faulty, or no prothrombin clotting time determinations and they used the antidote vitamin K inadequately. Then came the third period of consolidation, from which it can now be concluded that a better anticoagulant of the Dicumarol type was desired.

Since Dr. Wright asked for aspects of human interest, let me add another slice from the Dicumarol story. Early in September 1945 I was fed up with laboratory work, etc., and I went off on a canoe trip with my family. On this trip we were caught in a cold rain storm. I got soaked and overexhausted. Two weeks later I came down with what I had had once before—after a similar heavy physical bout, as a student in Switzerland—wet pleurisy. At first my doctor thought I had pneumonia; then I told him about my previous bouts of tuberculosis; so the diagnosis was changed to reactivated pulmonary tuberculosis. I spent 2 months at Wisconsin General Hospital and then was transferred to Lakeview Sanatorium headed by the double cross of Lorraine. Here I was supposed to vegetate like a topped carrot. I did rest there, physically for 6 months, took nothing stronger than cod liver oil and 3 bottles of beer a day, but kept the aged tuberculosis out of my mind by studying laboratory records and reading the history of rodent control from ancient to modern times.24, 25

A "Janus" in the Coumarin Family

Now brace yourselves, for I propose to shift from a "cow poison" that had become a drug of substantial clinical usefulness, to a "rat poison" converted to a drug, which has I believe most of the desirable features that can be expected from an anticoagulant to be given primarily via the oral route.
The many coumarins synthesized between 1940 and 1944 were listed by numbers in logical groups based on their chemical structure. While I was in the sanatorium in 1945-1946 the laboratory work was practically at a standstill. There were few students available, since most of them were still in the armed forces. So I had ample time to reexamine all the chemical and bioassay data available. Upon the return of L. D. Scheel from service in the spring of 1946, he was assigned to the task of reappraising the anticoagulant activity of the compounds numbered from 40 to 65. They were made by Ikawa in 1942-43. Instead of using only rabbits for the bioassays Scheel also used rats, mice, and dogs. In 1946-1948 he defined coumarin numbers 42 and 63 as being much more potent than Dicumarol in the rat and dog, as capable of producing a more uniform anticoagulant response, and as having the quality of maintaining a more severe state of hypothrombinemia without inducing visible bleeding. Certain chemical properties were also considered: the degree of purity readily attainable (absence of taste and odor), the cost of making them, and the property of being convertible to stable water-soluble salts.

Back in 1940 to 1942, Overman, Field, and my colleague, C. A. Bauman, had studied extensively the action of Dicumarol in the laboratory rat, and the effect of diet on the response, specifically the influence of vitamin K and foods rich in it. Later in 1942 I personally, with the help of good old Schoeffel, set up field trials to ascertain the suitability of Dicumarol for rodenticidal purpose. It was concluded that the activity of Dicumarol in the rat was not high enough to make it practical for rodent control. This was found to be largely due to the vitamin K content of mature grains and the availability of green foods with a high vitamin K content. It was shown that rats could tolerate a daily intake of 2.0 mg. of Dicumarol for 60 or more days due to the vitamin K content of the natural foods available. On a semisynthetic diet essentially free from vitamin K the survival time was about 15 to 23 days. When 5 mg. of vitamin K per day were added to the artificial diet, the rats also tolerated 2.0 mg. of Dicumarol daily for over 60 days.

Early in 1948 I told Scheel and Dorothy Wu that I wanted to propose no. 42 for rodenticidal use. This proposal shook the laboratory. I can sum up by stating the consensus of opinion "the boss has really gone off the deep end this time." Scheel favored no. 63 for clinical purposes. They are chemically closely related, no. 63 being a direct derivative of no. 42. To make a long story very short, early in 1948 no. 42 was promoted for rodent control under the auspices of the Wisconsin Alumni Research Foundation through the able, enthusiastic, and public-spirited Ward Ross, General Manager of this organization. Within a short time this effort revolutionized the art of rodent control (multiple doses as opposed to the single dose of the highly toxic poisons), and warfarin rapidly became and still is the leader in the rodenticide field. The name Warfarin was coined by me by combining the first letters of the Wisconsin Alumni Research Foundation with the "arin" from coumarin—and it is now a household word throughout the world.**

Between 1948 and 1952 Dicumarol was, so to speak, being squeezed by chemical kin stemming primarily from European studies. Curiously, one of them, a derivative of Dicumarol, trade-named Tromexan, was not seriously considered by us as early as 1940. Though it acted somewhat faster than Dicumarol, it required substantially larger doses

*Just as cattle eat hemorrhagic sweet clover hay until they die without visible sensory responses, the rat eats warfarinized cereal grain bait until fatal hemorrhage sets in. Neither bait refusal nor bait shyness develops. Indeed, the rodent's departure is biblical "death without stinging." In Maxwell Anderson's drama, Elizabeth the Queen says, "To the end of time it will be so... the rats inherit the earth." Since warfarin has become available, this need not be so. Furthermore, via the water-soluble warfarin sodium the rat can drink unto death.

**Warfarin is the safest rodenticide known. Up to now, in the United States there is no recorded case of a warfarin-induced fatality in man, although over 140,000,000 pounds of warfarin containing bait (0.025 per cent) have been distributed since 1950.
to get the equivalent anticoagulant action.* The second, Marcumar, a close kin to warfarin, was also passed by us, since its water-soluble sodium salt is less stable than warfarin sodium. Milligram for milligram, Marcumar is more active than warfarin and its action is also more prolonged. But as a result of the claims made about Tromexan and Marcumar

*IThe clinical promotion of Tromexan (bis-3,3'-4-
oxycoumarinyl) ethyl acetate, referred to as B.O.E.A. in the article by Burt, C. C., Wright, H. P., and Kubik, M., Brit. M. J. 2: 1250, 1949, precipitated interesting editorial comment under the heading, "Dangers of Dicumarol" (pp. 1279-1280). In this editorial it was suggested that since Tromexan seemed to be superior to Dicumarol 'owing to its shorter-lived action . . . ' and in view of recent reports of the drug's (Dicumarol's) efficiency as a rat poison, but may be that Dicumarol will ultimately be more useful for that purpose."

Unfortunately the significance of our paper on the action of Dicumarol in the rat dealing specifically with the effect of diet and vitamin K on the anticoagulant action (J. Nutrition 23: 589-602, 1942) was not appreciated by O'Conner, J. A., Research 1: 334, 1948, who suggested the use of Dicumarol for rodent control. Had O'Conner read our paper carefully, he would not have made this suggestion. The critical issue is that Dicumarol's anticoagulant action in the rat subsisting on natural grain foods is too slow to be practical. The level of Dicumarol in the bait has to be set so high that other animals (cat, dog, and children) would be vulnerable.

It was the inefficiency and slowness of Dicumarol to kill rats under practical field conditions that caused me not to suggest its use as a rodenticide in 1941-1943 (letter, Link, K. P., to the National Defense Research Council, Washington, D.C., dated March 10, 1943, and confidential disclosures, 1942-1943, to the late Professor Homer Adkins and Professor H. Gilman, official investigators and project leaders of N.D.R.C. and O.S.R.D. (confirmatory letter of Gilman to Link, June 11, 1952). Instead of Dicumarol the much more potent and efficient (no. 42) warfarin was recommended. Nevertheless, O'Conner's paper served a useful purpose in rodenticide control circles, and he must be accredited with being the first one to stimulate, via the printed page, the backward pest control workers by pointing out the possibilities of anticoagulants (Link, K. P., letter December 6, 1948, to U.S.D.I. Fish and Wildlife Service, Denver, Colo.). I had attempted to create an interest in warfarin via letters and memoranda, which at first failed to reach the objective (see reference 24 and particularly reference 25). A complete history of the warfarin development based on 10 years of practical field experience is in the process of being prepared.

I took another good look at the mass data in the light of what clinicians were seeking, namely an anticoagulant that could be used via any route with the retention of the virtues of Dicumarol but without its limitations.

Based in part on the supposition that the response of the rat to warfarin (no. 42) was a very reliable index of how man would respond, late in 1950 I told Dr. S. Shapiro and Dr. O. O. Meyer that the water-soluble sodium salt of warfarin should be tried on man. In 1941 the clinicians had literally snatched the "cow poison" from us, but the transition to a substance originally promoted to exterminate rats and mice was a bit more than they could accept with real enthusiasm. Then, on April 5, 1951, we were informed by Captain J. Love (MC) in the U.S.N. at Philadelphia that an army inductee was admitted to the Naval Hospital who had taken over a period of 5 days a concentrate of warfarin designed for rodent control.27 The package contained 567 mg. of warfarin in corn starch. The inductee had followed the multiple dose directions on the package. It became clear to him that warfarin was not an efficient agent "to shuffle off" this "mortal coil." It allowed too much time for thinking—so he went to the hospital with a fully developed case of hemorrhagic "sweet clover disease." He was treated per the directions—blood transfusion and large doses of Vitamin K—and made an uneventful recovery.28

This incident acted as a catalyst. Shapiro29 and Meyer30 both concluded from their carefully done work with warfarin sodium that it did possess certain properties not inherent in Dicumarol or the other anticoagulants they
had tried. After Collin Schroeder perfected the process of making warfarin sodium, I induced my long-standing friend, Dr. S. M. Gordon, of the Endo Laboratories, Richmond Hill, N.Y., to make it available for clinical use. This he did, under the trade name Coumadin Sodium. Today it would appear, from the 15 to 20 clinical papers on warfarin sodium that have been published (see reference 32), that most of the drawbacks of Dicumarol have been overcome. Warfarin sodium is at least 5 and possibly 10 times more potent than Dicumarol. It is the only synthetic anticoagulant available today for therapeutic anticoagulation that can be given orally, intravenously, intramuscularly, or rectally.\(^3\)\(^2\) The rate of absorption is almost the same, irrespective of how it is administered. No other anticoagulant of the Dicumarol type has all these virtues. Of course, an overdose can be readily corrected via vitamin K. It acts faster than Dicumarol, and fewer prothrombin times are required in its routine use. To use the words of both Shapiro and Meyer, "It is easier to handle clinically." It is my firm belief that in time it will replace Dicumarol on the basis of its performance over a wide variety of conditions and that other anticoagulants of the Dicumarol type will not be superior.

It always seems appropriate to me to visualize successful anticoagulant therapy with the Dicumarol-type drugs as being shaped like a triangle with accurate "prothrombin assays" at one corner, vitamin K at another, and sound clinical judgment at the third.

Each corner is linked to the other by way of the connecting sides. There should be no separation, each is vitally dependent on the other two. Though the clinical judgment be good and the "prothrombin time" accurate, the vitamin K corner might still have to be evoked, since each individual patient is essentially "an unstandardized biologic entity," errors in dosage can be made by the hospital service, the patient might have a silent ulcer, or the functioning of the liver or kidney might unknowingly be penumbral.

On September 29, 1955, I got a card from a former Wisconsinite working in Fitzsimons Army Hospital in Denver, Colorado which read, "The President is getting one of your drugs and it's not Dicumarol." A day later press secretary J. C. Hagerty announced, "We had the heparin which was used initially as the anticoagulant has been replaced by a drug of the Dicumarol type. The present prothrombin level has been well maintained." I knew of Colonel Pollock's paper, "Clinical experience with warfarin (coumadin sodium a new anticoagulant)", read before the first annual meeting of the American College of Angiology Atlantic City, N.J., on June 4, 1955, and I surmised that the most important man in the world today was being anticoagulated via warfarin sodium.\(^3\)\(^4\) This surmise proved to be correct and since then it is an open secret that warfarin sodium was being used. "The unpredictable can be surprising."

In closing I wish to indicate that what my laboratory has achieved in the past 2\(\frac{1}{2}\) years represents the combined effort of many students. It is fun to be the reporter or narrator of this highly successful adventure. To use the words of the late Allan Gregg,\(^3\)\(^5\) my students represented much "emergent ability." I think the secret of their success is 3-pronged: they never ceased to wonder, they kept on trying, and they were on a project directed toward doing mankind some good instead of trying to destroy it.

REFERENCES

1. Link, K. P.: The anticoagulant from spoiled sweet clover hay. Harvey Lectures Series 34: 162, 1943-44.
ANTICOAGULANTS: A HISTORICAL SYMPOSIUM

17. —: The Hemorrhagic Disease and the Physiology of Hemostasis. Springfield, Ill., Charles C Thomas, 1942.
The Discovery of Dicumarol and Its Sequels
KARL PAUL LINK

Circulation. 1959;19:97-107
doi: 10.1161/01.CIR.19.1.97
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1959 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/19/1/97.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/