**Introduction**

It is more than six decades since warfarin came into clinical use, and it is interesting to note that the drug is still used in various clinical scenarios. Even more fascinating is the story of how a “rat poison” later on became a powerful oral anticoagulant, which saved endless human lives. Since we are entering an era of newer oral anticoagulants, it is good to look back into the discovery and development of warfarin, a drug that initiated the long journey of oral anticoagulants.

**Sweet-clover Disease**

In the winter of 1921, a number of cattle in Alberta and North Wisconsin, North America, were dying from an unknown disease. Autopsies showed that these animals had suffered from internal bleeding and extensive bruising. In some areas, entire herds were affected, with animals dying within a few days of the onset of symptoms. Livestock was one of the most important industries in these areas and hence, farmers were more financially affected. Since no recognizable infection or nutritional deficiency could be identified, the interest was turned toward the diet of these cattle.[1] Frank Schofield and Lee Roderick, local veterinary surgeons, independently demonstrated that the disease occurred in cattle which fed on damp sweet-clover hay (*Melilotus alba* and *Melilotus officinalis*), and hence, the condition was called as “sweet-clover disease.” Even though the cause of the problem was identified, the only advice the veterinarians could give to the farmers was to find an alternative source of hay, which the farmers could not afford due to financial constraints.[2,3]

**Karl Link and Isolation of Anticoagulant**

On a Saturday in February 1933, Ed Carlson, a local farmer who had already lost most of his livestock to this hemorrhagic disease, loaded his truck with a dead cow, milk can with unclotted blood, and about 100 pounds of rotting sweet clover. He traveled a 200-mile journey to visit the Agricultural Experiment Station to get some answers, since he had no faith in the theory of sweet-clover disease. After all, they had fed the cows with the same type of hay for generations and there was no ill effect. However, when he arrived, the department was closed. As a result, he was frustrated and tried to find somebody to help when he found one unlocked door, which took him to the research laboratory of Karl Link. Then, Link told him that his cattle had sweet-clover disease and the only thing he could do was stop feeding them that hay. The meeting with Carlson had a major impact on Link, and he started focusing on isolating the chemical in sweet clover that caused hemorrhagic disease in cattle. It took Link and his team 6 years to find the chemical responsible for sweet-clover disease. It proved to be 3,3’-methylenebis[4-hydroxycoumarin] or dicoumarol which when mixed with rabbit blood prevented clotting.[4,5] Dicoumarol was introduced for clinical use in the early 1940s. The early reports of its use initially created excitement among clinicians, but later on, concerns over complications due to bleeding and with early reports suggesting that Vitamin K does not have antidote effect created only a lukewarm response among the clinicians.[1]

**Introduction as “Rat Poison”**

In 1948, Link proposed that coumarin derivative should be used as a rodenticide. Among various modified forms of dicoumarol, compound 42 was found to be more effective and was named as “WARFARIN” – named from Wisconsin Alumni Research Foundation and the “arin” from coumarin. This poison caused internal hemorrhage within the rats, resulting in their death. Warfarin soon became the best-selling rat poison in America, and similar chemicals are still used in most mouse and rat poisons around the world.[1,4]
**Transition into Clinical Use**

In 1951, a young naval officer attempted suicide with multiple doses of warfarin and was admitted to the Naval hospital. He had consumed multiple doses of the drug over a 5-day period. He made an uneventful recovery after treatment with Vitamin K. Studies then began on the use of warfarin as a therapeutic anticoagulant. Other anticoagulants were available from clinical use at that time, such as heparin was required as parenteral administration, and dicoumarol had a long lag period before the onset of a therapeutic effect. The main advantages of warfarin are high oral bioavailability and high water solubility; it was more potent than dicoumarol, but its effect could still be reversed by Vitamin K. Therefore, warfarin transitioned into clinical use under the trade name Coumadin and was approved for use in humans in 1954.[6,7]

**Treating a President with Warfarin**

In 1955, the President of the United States of America, Dwight D. Eisenhower, developed acute chest discomfort and was diagnosed with myocardial infarction. Eisenhower was initially treated with heparin and then started on warfarin at a dose of 35 mg/week. This incident also added more popularity to the drug, and it was said that “what was good for a war hero and the President of the United States must be good for all, despite being a rat poison!” Later on, various clinical trials pointed out the efficacy of warfarin’s use in various clinical conditions such as deep-vein thrombosis, atrial fibrillation, and postprosthetic valve replacement surgery.[11]

**Conclusion**

If we look into legacy of warfarin, it is fascinating how it started from sweet-clover hay to rat poison and then went onto become the most used oral anticoagulant in the world. Currently, in an era of newer oral anticoagulants, warfarin’s clinical use may be reduced in the future, but its discovery remains one of the greatest medical breakthroughs of the century.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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