Historical Notes on the Early Development of Anticoagulant Therapy with Dicumarol in Sweden

By Jörgen LehmANN, M.D., Ph.D.

The interest in anticoagulant therapy of thromboembolic diseases was stimulated in Sweden during the years 1935 to 1937 due to the work of Jorpes and co-workers on heparin. The author’s participation in this field was facilitated when he was appointed in 1938 as director of a newly erected central laboratory for clinical chemistry in the city hospital of Gothenburg-Sahlgrens Hospital. A new laboratory building, equipped with animal rooms, operating room, etc. for work in experimental medicine, was opened on September 1, 1940. A few days before this celebration, a big truck turned up at the front side of the laboratory building, loaded with hay of sweet clover (Melilotus albus) harvested at the dustyard at Hisingen, outside Gothenburg. At the top of this load the assistant doctor of the laboratory, Johan Mårtensson, was seated, and the truck was followed by the author, riding a bicycle. Astonished and wondering laboratory technicians gathered at the windows at this peculiar appearance—this was something unusual.

The hay was brought into a small, closed room of the laboratory and left for spontaneous molding, after which it was fed to rabbits. The aim was to see if the hemorrhagic disease described in cattle by Schofield and Roderick, mentioned in a paper by Quick, could be reproduced. This would be of interest, as the toxic principle in the hay might be extracted and purified for clinical use in thromboembolic diseases. It was suspected to be a derivative of coumarin. This anticipation was based on a personal communication during the summer of 1940 from Dr. Göte Turesson, Professor of Plant Systematics and Genetics at the Royal Agriculture College in Upsala, whom the author had told about the bleeding disease in cattle. Dr. Turesson mentioned the high concentration of coumarin in sweet clover and the efforts in Canada of producing new coumarin strains which might produce a better food for the cattle. We looked up the structural formula of coumarin, and the author was struck by the close relationship between coumarin and naphthoquinone, the essential part of the recently synthesized vitamin K (Fieser and Doisy). This relationship might possibly explain the mechanism by which the toxic principle was active, namely, as a competitive inhibitor of vitamin K, thereby depressing the synthesis of prothrombin in the liver and producing a lowered coagulability of the blood.

The author was familiar with such substrate inhibitions of enzyme activity from many years of work on dehydrogenases in Thunberg’s laboratory at the University of Lund, and especially from the work of Quastel and Wheatley on the specific inhibition of the oxidation of succinic acid by the closely related malonic acid.

The relationship between coumarin and vitamin K brought the sweet clover experiments in touch with earlier experiments of the same year (1940) in which preliminary experiments with naphthoquinone as a vitamin K inhibitor had been performed—but in vain.

Other methods of producing inhibition of the coagulation process were then tried (July 1940) with Benzoechtrosa (Kahlson and Landby) but were found to be not applicable in the clinic.

After the visit to Dr. Turesson in Upsala the author’s interest was directed toward coumarin. Even before the experiments with molded sweet clover were started, coumarin was tried as an anticoagulant in rabbits, given intramuscularly in doses of 0.15 to 0.20 Gm., dissolved in sesame oil, and 0.5 Gm. dissolved in 6 ml. of 30 to 45 per cent (v/v) ethanol.
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and given by stomach tube. With the last doses definite prolongation of the prothrombin time, but not of the spontaneous coagulation time, was achieved (August 15 to 21, 1940). These experiments were considered as unpromising and given up.

Experiments with spontaneously molded sweet clover hay were begun in rabbits (October 11, 1940). No fully conclusive results were obtained. The experiments were continued in 1941, when the hay was molded with Asperigillus niger and Asperigillus fumigatus, kindly supplied by Dr. Rennerfeldt at the Botanical Institute of Gothenburg and known to be active in producing the "toxic" substance. On March 23, 1941, a successful series of experiments was started, succeeded by preliminary extraction experiments. However, the papers of Dr. K. P. Link and his co-workers on the isolation and synthesis of the active principle in spoiled sweet clover hay appeared in the Journal of Biological Chemistry, and these experiments were therefore stopped (May 1941).

A new epoch opened for us when 3,3'-methylene-bis (4-hydroxy-coumarin) was synthesized by Mr. Rosdahl at the Ferrosan Company, Malmö, Sweden. The first sample was received on June 26, 1941. Animal experiments began on June 30 in 13 rabbits and a few dogs and were finished on August 14. The reversibility of the prolongation of the prothrombin time and coagulation time was demonstrated. No liver injury could be demonstrated by microscopic examination even after long-term treatment of the animals. The antagonistic effect of blood transfusion was shown. Synthetic vitamin K was also tried in a dose of 5 mg. to a rabbit but did not inhibit the effect of Dicumarol (July 12, 1941). This was a great disappointment, as the anticipated competitive inhibition of vitamin K was thereby questioned. However, later in a critical situation with an oozing bleeding from the intestinal mucosa of the anus in a young woman, 200 mg. of vitamin K (2-methyl-1,4-naphthohydroquinone disulfate) was given with immediate effect (Jan. 5, 1942, Surg. Dep. II, Jl.Nr 3347/41).

When the animal experiments were finished, the author was very much in doubt if they should be published at once. In spite of the fact that they were promising as an anticoagulant treatment for thrombotic diseases, which was the aim of the experiments, it was decided not to publish any experiments before the effect had been demonstrated in patients suffering from thromboembolic disease. The main argument for this decision was the critical attitude which clinicians in Scandinavia often had shown against animal experiments as a guide to human therapy. Premature conclusions would presumably hurt the future development of the experiments. The author was even cautious in keeping the experiments secret within the laboratory as well as within the hospital. In the animal protocols Dicumarol was signed as "X-substance."

The details of the early clinical use of Dicumarol in Gothenburg have been published elsewhere. The care of the patients with thrombosis during the first years was assigned to the author, who is especially grateful to Dr. Gustaf Pettersson, Surgical Department II, the first doctor in the hospital to whom the Dicumarol experiments were mentioned, and whose patients were the first to be treated. (The first patient suffering from thrombosis was treated on October 11, 1941. Surg. Dep. II, Jl.Nr 2619/41.)

After the first presentation of the clinical results November 29, 1941, in Stockholm (published in Svenska Läkartidningen, January 9, 1942), the author was confronted with the problem of how to get a paper published in the international literature. All regular communications with England and America had stopped because of the war. The only communications with England were irregular and by planes during the night. These were often heavily attacked by German planes. However, the British Consul General in Gothenburg was kind enough to take care of a paper for Lancet (December 23, 1941).

Nothing was learned about the fate of the paper until a letter arrived from Dr. Link,
dated April 20, 1942. With Dr. Link’s permission the letter is here published.

Dear Dr. Lehmann,

I was very glad to see your account in the Lancet entitled Hypo-prothrombinaemia produced by Methylen-Bis-(Hydroxybenzoin) 3/14/42.

It is clear from this excellent and highly condensed note that you have made very substantial progress toward evaluating the possible therapeutic potentialities of the substance. I would be very glad to have reprints of your work as it appears.

By separate post I am sending you reprints of our work which has appeared in print to date. The following papers are in press:


IX. The effect of diet and Vitamin K on the Hypoprophrombinaemia induced by 3,3'-methylene-bis (4-hydroxybenzon) in the rat.

A critical study on the role of l-ascorbic acid in the rat and guinea pig in so far as it affects the dieumarin has been completed and will be ready shortly.

We were very much impressed by the fact that your reasoning on the action of l-ascorbic acid and the possible antagonistic action of vitamin K paralleled our thinking. Furthermore I think in figure 1 of paper VII and the first figure in your Lancet article bear a striking parallelism.

With best wishes and kindest regards,

Karl Paul Link

None of the papers from Dr. Link was ever received. From the author’s answer to Dr. Link, dated July 13, 1942, the following is quoted.

Dear Dr. Link,

Very many thanks for your kind letter of 4/20/42, which I received 6/25/42. It was the first announcement to me, that my paper had been printed in the Lancet. I sent it to the editor 12/23/41 and have not heard anything about the fate of the paper until I received your letter. We have only air mail connection with England and the sendings are therefore very restricted. We can’t get the Lancet here in Sweden. Therefore, Dr. Link, your letter was especially welcome. I have now asked the editor for a few reprints and I will send you one as soon as I have got it. It contained a summary of my other papers, which are written in Swedish. It will be of great interest to me to read the papers mentioned in your letter. They have not arrived yet.

An attempt was even made in April 1942 to have a paper published in Science in the U.S.A. as elucidated from the following letter to a friend of the author, Dr. Frederick Bernheim, Duke University School of Medicine.

Göteborg, April 11th, 1941.

Dear Frederick,

A friend of mine, captain on a Swedish boat,* has promised me to forward this letter to you, when coming to your continent. I enclose parts of a paper, which I think will be of interest for you. When I had finished the paper in 1941 I had written a summary for Science, but just as I was going to send it, the post for U.S.A. was stopped. If it is possible I should be glad if you would forward it to Science. For such a case, please correct it and make a choice of the figures. I am sorry not to be able to send the figures to paper 2 (in print), but I think it can be printed without the figures. I have heard of a friend of mine, that some doctors at the Mayo clinic (H. R. Butt, E. V. Allen. a. J. L. Bollman) have been working on the same subject. Would you kindly send them paper II when having used it for Science. I send them the summary of paper I. (They are working at the Mayo clinic, Rochester, Minn.)

Even the fate of this paper was unknown to the author for about a year. From a letter to Dr. Bernheim February 28, 1943, it is evident how the author received information about its publication October 9, 1942.

Dear Frederick,

Very many thanks for your letter of November 3, 1942, which I received February 26, 1943. For a week ago I heard from the Swedish-American News Information in Stockholm that a paper of mine in Science had been mentioned in Science News Letter and from that I understood that you had got my letter and been kind to send a note about it to Science. I am awfull glad for your kindness.

The poor communication between Gothenburg and U.S.A. during the war is shown by

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*The boat Svarajit was torpedoed on the next sailing, and the captain and most of the crew were drowned.
the following letter, dated June 1, 1943, to Dr. Bernheim.

Dear Frederick,

. . . Further I should be glad to know if any papers have appeared in U.S.A. on the use of the dicoumarin in thromboembolic diseases and their results. In the Lancet May 15, 1943 my clinical results for 1942 have been published. The dicoumarin is now in use in many hospitals in Sweden and so far I know with good results.

The last phase in the development of the use of Dicumarol was the treatment of coronary infarction. The first case, complicated with a thrombosis aneurysis, was treated November 7, 1941, (Dep. Vasa. . . Julia M-g, admitted November 2, 1941). On proposal of, and in cooperation with, Dr. Bo Ewert, Medical Department I, a more consistent but cautious treatment of selected cases was started in 1942. Of 47 cases, 16 were treated with 0 per cent mortality as compared with 45.1 per cent of the untreated group. During 1943 the corresponding figures were 31, of which 16 were treated, with 25 per cent mortality as compared with 64.2 per cent in the untreated group. During 1944, 57 cases were treated of a total of 76, with 25.9 per cent mortality as compared with 47.3 in the untreated group, and in 1945 (January 1 to June 30) 43 out of 46 were treated, with a mortality of 20.9 per cent. Since then nearly all cases have been treated with Dicumarol, often combined with heparin. (The figures mentioned above have been compiled by Dr. Albert Larsson, and read before the Swedish Society for Internal Medicine, September 8, 1945, but this paper has as yet not been published.)

After 1945 the treatment of thromboembolic patients as well as of patients with coronary infarction in Sahlgrens Hospital was taken over by the physicians of the different departments. In many hospitals in Sweden Dicumarol was then in use. Especially at the University clinic in Lund a careful study was made of the prophylactic and curative use of Dicumarol in surgical patients.

This review of the early events in the use of Dicumarol in Sweden can best be finished by quoting a letter from the author to Dr. Link dated June 13, 1942.

It was surprising but a striking fact, that the year 1941 was mature for a more detailed study of the toxic agent in sweet clover hay as it was studied at the same time in your laboratory and here. I have now treated nearly 200 patients with the dicoumarin and the results are even as good as those from patients treated with heparin.

I hope I will be able to meet you once in the future, when the world has found itself again. I was working 14 months 1935-1936 in the Rockefeller Institute in New York (Neuro-physiology by Dr. Gasser) where I spent some of the most interesting time in my life and I do hope I will get time for another trip to U.S.A.

With kindest regards,

Sincerely yours,

Jørgen Lehmann

REFERENCES


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