

Effect of Cecectomy and Succinylsulfathiazole on Vitamin K Synthesis.*

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Great interest is centered on the synthesis of essential nutrients by microorganisms of the digestive tract.¹⁻⁶ The cecum, aptly referred to as a "fermentation vat,"⁶ is generally regarded as the principal site of this important function in the rat.

Although quite a few reports have been made concerning the inhibitory effects of certain sulfonamides on the enteric synthesis of various vitamins very little experimental work has been done on the role of the cecum as a favorable site for such activity. The latter studies have been concerned only with the synthesis of B-complex vitamins⁷⁻⁹ and the utilization of phytin phosphorus.¹⁰

During the past year our investigation of factors affecting vitamin K synthesis in the intestinal tract¹¹ has included observations on cecectomized rats. The timeliness of certain of our findings prompts this short communication.

Stock rats about 35 days old were started on a vitamin K-free diet of the following composition: casein (Smaco, vitamin-free) 18, glucose (Cerelease) 66, salt mixture 4, ether-extracted brewer's yeast 7, corn oil 3, cod liver oil 2, and choline chloride 0.04. After one week these animals were cecectomized and

two days after the operation succinylsulfathiazole was added to the vitamin K-free diet at a level of 1% replacing an equal amount of glucose. Four weeks after cecectomy determination of the plasma prothrombin clotting time was started at biweekly intervals using a modification of Quick's method.¹² The blood was obtained by cardiac puncture under ether anesthesia.

Severe hypoprothrombinemia occurred in 14 out of 17 cecectomized animals fed the vitamin K-free diet containing succinylsulfathiazole. Within 3 months nearly all had died from hemorrhage due to severe hypoprothrombinemia. Seven out of 9 littermates cecectomized at the same time and fed the diet without succinylsulfathiazole had normal prothrombin clotting times. The remaining 2 showed only a slight increase in prothrombin time. Similarly, unoperated (not cecectomized) rats fed the vitamin K-free diet containing succinylsulfathiazole had only an occasional and very mild hypoprothrombinemia.

In cecectomized rats fed succinylsulfathiazole the elevated prothrombin clotting time consistently returned to normal upon the addition of 2-methyl-1,4-naphthoquinone to the

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diet. This is additional evidence that vitamin K deficiency had been produced.

Over half a million pounds of sulfonamides were used in 1940,¹³ and as a result of the proven usefulness of these drugs more may be used in the future. However, certain harmful effects cannot be ignored. In addition to other reported injurious consequences, we have noted a hemorrhagic tendency occurring under the influence of the sulfonamide derivatives which, because of low solubility and very slow absorption, remain in the lumen of the intestinal tract and act as efficient bacteriostatic agents. At the same time they interfere with the bacterial synthesis of vitamin K in the intestinal tract and, if administered for several weeks, may reduce the prothrombin content of the blood when the diet is extremely restricted.

At the beginning of our studies most of the animals died of hemorrhage about the third postoperative day. These rats had been fed the vitamin K-free diet containing succinylsulfathiazole for over a week prior to cecectomy. Their death was attributed to low plasma prothrombin resulting from K-avitaminosis. Such an outcome was subsequently avoided by performing the cecectomy before administration of the sulfonamide, or by administration of vitamin K.

These findings demonstrate that rats fed a vitamin K-free diet containing yeast suffer from severe and often fatal hypoprothrombinemia when succinylsulfathiazole is added and the volume of the lower bowel is greatly

reduced by cecectomy. However, cecectomy in the absence of succinylsulfathiazole may lead to only a slight increase in prothrombin clotting time, if any, suggesting appreciable vitamin K synthesis in other parts of the digestive tract under normal conditions.

Gatch and his assistants¹⁴ noted postoperative hemorrhage in a few patients given succinylsulfathiazole pre- and post-operatively and alleviated the condition by administration of synthetic vitamin K.

In the light of the above experimental and clinical observations surgeons should keep in mind the possibility that patients given succinylsulfathiazole or closely related compounds over long periods of time may develop hemorrhage as a result of the bacteriostatic effect which thus reduces vitamin K synthesis in the intestinal tract, and that the administration of vitamin K alleviates the hypoprothrombinemia and prevents the post-operative hemorrhage resulting therefrom. However, the amount of succinylsulfathiazole used and the length of the period of its administration pre- and post-operatively influence the occurrence of hypoprothrombinemia and the consequent hemorrhagic tendency. Large amounts used over a long period of time are more liable to cause hypoprothrombinemia, especially if the diet is so restricted as to contain insufficient amounts of vitamin K or none at all, but small amounts of the drug or a short duration of its administration is not as likely to cause hypoprothrombinemia.

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