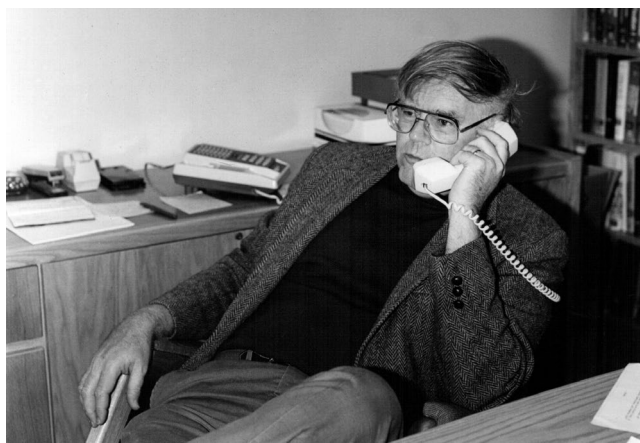


## OBITUARY

## Obituary for John W. Suttie



John W. Suttie.

We sadly report that John Suttie died on December 21, 2020, at the age of 86. John made vital contributions to the field of hemostasis and thrombosis. His early work was key to showing the action of vitamin K on the subset of coagulation factors known to require vitamin K for activity. Subsequently, John led in studies of  $\gamma$ -glutamyl carboxylase and vitamin K oxidoreductase required for vitamin K-dependent carboxylation, inhibition of the reductase by coumarin anticoagulants, and nutritional needs for vitamin K in newborns and the elderly.

John grew up on a dairy farm amidst the beautiful ridges and valleys of Trempealeau County, Wisconsin. He received undergraduate and graduate degrees in biochemistry from the University of Wisconsin-Madison. His PhD thesis was on fluoride toxicity, which was recognized first in cows fed phosphate contaminated by fluoride and then associated with proximity to smelting of aluminum. Upon graduation in 1960, John was offered a faculty appointment in the university's Department of Biochemistry. As was the tradition in the department, he first went abroad for a fellowship and spent a year at the Mill Hill campus of the English National Institute for Medical Research, where he contributed to the early characterization of protein synthesis by isolated mitochondria.<sup>1</sup> Back in Madison, John returned to fluoride toxicity studies utilizing a herd of dairy cows established on campus for that purpose. He worked with industry and farmers to establish safe levels of fluoride in ambient air and on vegetation and a scoring system based on altered dentition that allowed identification of affected herds and indemnification of the animals' owners.

What led John to venture from the fluoride field in which he had such a firm foothold and large impact to work on vitamin K? He described his thinking in 2011.<sup>2</sup>

"I had developed an interest in protein synthesis at Mill Hill and was looking for a good problem to study. By the early 1960s the basic pathway of protein synthesis in animals was understood, and scientists were attempting to understand how the syntheses of specific proteins were regulated. I spent most of a couple of weeks in the library and found a number of areas that were very active. Glucocorticoids were being shown to influence the synthesis of a number of proteins, and alterations in the nutrient content of diets were being shown to impact the activity of specific enzymes. I became rather interested in the ability of alterations in iron intake to regulate ferritin production, but in retrospect I think that the leader in this field, Hamish Munro, would have squashed me. The activity of the procoagulant prothrombin was known to be dependent on sufficient vitamin K, but the metabolic role of the vitamin in regulating it was not known. As the action of vitamin K could be antagonized by warfarin [developed in the Department of Biochemistry by K.P. Link], it seemed to me to be an approachable problem, and I decided to give it a try. At this point, in mid-1964, I wrote an NIH grant entitled 'Regulation of Prothrombin Synthesis by Vitamin K' and asked for \$17,417 a year. I received this amount and was probably the luckiest person to have ever received an NIH grant. I knew nothing about coagulation, did not know any hematologists working in this field, and had never done an experiment in this area."

John's breakthrough was to show that cycloheximide failed to inhibit the burst of active circulating prothrombin that appeared after giving vitamin K to vitamin K-deficient rats.<sup>3</sup> John then demonstrated a pool of prothrombin lacking procoagulant activity in the microsomal fraction of the liver of vitamin K-deficient rats.<sup>4</sup> Showing that vitamin K works post-ribosomally set off a race to determine the protein change that required vitamin K. The race ended at a small meeting at Leiden's Rijksmuseum Boerhaave in 1974. As described by John:<sup>2</sup> "Following a reception and dinner and a lengthy comparison of Oude (old) and Jonge (young) Genever, Johan [Stenflo] informed a few of us that he had demonstrated the presence of a new amino acid,  $\gamma$ -carboxyglutamic acid (GLA), in prothrombin, but not in the biologically inactive form of the protein present in warfarin-treated cattle." The presence of GLA was quickly confirmed by Gary Nelsestuen at the University of Minnesota in a prothrombin fragment that he had isolated as a fellow with John,<sup>5</sup> and John and Chuck

Craig M. Jackson is retired.

Esmon demonstrated Vitamin K--dependent incorporation of radioactive CO<sub>2</sub> into prothrombin<sup>6</sup> and established an assay that allowed the carboxylase to be characterized.<sup>7</sup> In 1975, Johan joined John's lab for a year, bringing with him protein C isolated as a by-product of prothrombin purification. Chuck and Johan found that upon cleavage protein C became a serine protease that bound to phospholipid vesicles<sup>8</sup> and thus initiated the explosion of research on activated protein C as a regulator of blood coagulation.

These breakthroughs raised many questions that John investigated working with students, fellows, and Dhami Shah, a longtime associate. The lab was a place of great collegiality that produced important advances. Papers described the nature and enzymology of  $\gamma$ -glutamyl carboxylase and vitamin K oxidoreductase, the metabolic cycle of vitamin K, how coumarin anticoagulants work, how best to evaluate vitamin K deficiency and sufficiency, and roles of vitamin K--dependent proteins that are not coagulation factors. The demonstration that GLA-less prothrombin accumulating in the liver is larger than GLA-less prothrombin in the circulation<sup>9</sup> allowed John to place a final piece in the prothrombin synthesis puzzle. John seized on the finding that cDNAs of K-dependent factors encode "pre" sequences N-terminal to the glutamyl residues that undergo  $\gamma$ -carboxylation and designed experiments that supported the hypothesis that the "pre" sequence is a recognition site for  $\gamma$ -glutamyl carboxylase.<sup>10</sup>

John was a master at disseminating knowledge. He expanded his undergraduate teaching notes into *Introduction to Biochemistry* (Holt, Rinehart & Winston, 1977 and 1979). He regularly prepared updated reviews of vitamin K and vitamin K-dependent proteins. He hosted Steenbock Symposia at the University of Wisconsin on "Vitamin K Metabolism and Vitamin K-Dependent Proteins" in 1979 and "Current Advances in Vitamin K" in 1987. In 2009 he published *Vitamin K in Health and Disease* (CRC Press), which comprehensively covers vitamin K and will be a valuable resource for years to come.

John also was a tireless organizer and advocate for science. He served as chair of the university's Department of Nutritional Sciences, president of the American Society for Nutritional Sciences, president of the Federation of American Societies for Experimental Biology, editor-in-chief of the *Journal of Nutrition*, and member of a number of advisory committees. He received multiple awards and was elected to the National Academy of Sciences in 1996.

We remember John as a consummate schmoozer who called us by our last names. One of us (Jackson) worked with John as he entered the field and fondly recalls conversations at the 1977 ISTH meeting in Paris and writing a joint review on prothrombin activation and biosynthesis.<sup>11</sup> Mosher and Schwartz shared a National Institutes of Health grant with John and benefitted from John's unique blend of high standards and pragmatism. We especially remember social

gatherings organized by John and Leone, his wife for 65 years. We will miss John greatly.

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