

This Week's Citation Classic®

Rotruck J T, Pope A L, Ganther H E, Swanson A B, Hafeman D G & Hoekstra W G. Selenium: biochemical role as a component of glutathione peroxidase. *Science* 179:588-90, 1973.

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This paper was the first to demonstrate a specific biochemical role for selenium in mammals. Specifically, the data show that selenium is an integral part of the enzyme glutathione peroxidase. [The *SCI*® indicates that this paper has been cited in over 680 publications.]

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December 7, 1987

This work was conducted while I was a graduate student in W.G. Hoekstra's laboratory at the University of Wisconsin's Department of Biochemistry. As is often the case in scientific discoveries, there were a number of fortuitous incidents that eventually led to this work. From a personal standpoint, the most important development was my assignment to Hoekstra's laboratory. Initially, I was assigned to a different professor, who subsequently left the country on sabbatical. At this point I changed professors but wanted to continue working in the same research area, which was selenium. While selenium was not Hoekstra's primary focus, he was familiar with the whole field of trace mineral research and, fortunately for me, had an opening for an additional graduate student.

While attempts to understand selenium's mode of action had focused on its potential role as an antioxidant, these theories had not been uniformly accepted. Although it is easy to have 20-20 vision in hindsight, it seemed logical that an understanding of selenium's biochemical role would help explain its nutrition-

al interactions with the sulfur amino acids and vitamin E and that it should somehow be intertwined with glutathione metabolism.

Being an enthusiastic graduate student, I read the literature in these areas, especially that on glutathione biochemistry. One of these papers, by R.E. Pinto and W. Bartley,¹ was on the effect of age and sex on glutathione peroxidase and glutathione reductase. This paper presented a pathway of glutathione metabolism that connected glutathione with the enzyme glutathione peroxidase and led me to the hypothesis that selenium could exert "antioxidant activity" as a part of glutathione peroxidation. In essence, a role for selenium in glutathione peroxidation offered an enzymatic approach to thinking about selenium's antioxidant activity. The paper also led me to spend most of the afternoon in the library reading the then scant literature on glutathione peroxidase. The same afternoon I wrote a research proposal (unpublished, August 1968) and presented it to Hoekstra. To the best of our knowledge, this was the first proposal of an involvement of selenium with glutathione peroxidase.

Hoekstra reacted positively to my proposal that same afternoon and seemed to intuitively know that it was a good approach to pursue. However, other experts and professors were not nearly as enthusiastic, and in fact some discouraged us from pursuing this line of research because they didn't think it was possible that selenium could be part of an enzyme. Still, with Hoekstra's encouragement, I began pursuing this line of research, which ultimately led to the discovery that selenium is an integral part of glutathione peroxidase.

I think that this paper is frequently cited because it provided the first data showing that selenium is an integral part of the enzyme glutathione peroxidase. In addition, this discovery offered a way to think about the dietary relationships of selenium, vitamin E, and the sulfur amino acids.

Since the publication of this paper, numerous other investigators have confirmed the presence of selenium in glutathione peroxidase and have used this enzyme as a tool to investigate selenium deficiency. It has been particularly satisfying to see selenium and glutathione peroxidase impact on human health.²

1. Pinto R E & Bartley W. The effect of age and sex on glutathione reductase and glutathione peroxidase activities and on aerobic glutathione oxidation in rat liver homogenate. *Biochemical J.* 112:109-15, 1969. (Cited 110 times.)
2. Combs G. The nutritional biochemistry of selenium. *Annu. Rev. Nutr.* 4:257-80, 1987.

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