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Turning Catabolism into Usefulness—A Jaundiced View

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Featured Article: Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science 1987;235: 1043–6.[2]

My interest in bilirubin, a product of heme catabolism in mammals, was sparked by 2 momentous and interrelated events in 1983. The first was the premature birth of my eldest daughter, Sophie. The second was her treatment with "blue light" therapy for jaundice, which was successful despite my initial fears of its potential harmful effects. However, it was not until I joined the Bruce Ames laboratory at the University of California, Berkeley, in early 1986 that I was presented with the opportunity to work with this golden bile pigment as a postdoctoral scientist. At that time, natural antioxidants were a major interest of Bruce Ames in the context of cancer prevention *(1)*. His close colleague, Alex Glazer, who carried out fundamental work on phycobiliproteins in a photosynthetic antenna *(2)*, put forward a general hypothesis that end products of degradative metabolic pathways may play important roles as protective agents and that in this context bilirubin is a likely candidate for such a role. I immediately volunteered to test this hypothesis.

Two other important factors played a crucial role in the discovery of bilirubin as an antioxidant of potential physiological importance. First, Yorihiro (Junkan) Yamamoto was also a postdoctoral scientist in the Ames laboratory. This was extremely fortuitous because Junkan introduced me to the use of azo initiators for the controlled peroxidation of unsaturated lipids. This experience provided me with the necessary technology and methodologies to quantitatively investigate the radical-scavenging properties of bilirubin.

Second, I contacted one of the inventors of the blue light therapy, Antony McDonagh, at the University of California, San Francisco. Being a keen lunchtime runner, Tony had just discovered that sunlight induced the isomerization of bilirubin, just as blue light did, suggesting that this "mutation" of bilirubin was a physiological process *(3)*. We jointly set out to test whether photoisomerization altered the antioxidant property of the bile pigment. Although we eventually learned that different configurational bilirubin isomers have comparable antioxidant activities, collaborating with Tony afforded an insight into the chemistry and properties of bile pigments, without which a meaningful assessment of their antioxidant activity would not have been possible.

Crucial steps for the discovery were taking the test system from homogeneous solution to liposomes and lowering the oxygen tension to a physiologically relevant 2%. Under these conditions, bilirubin surpassed the lipid peroxidation–inhibiting activity of α-tocopherol, considered to be the most effective lipid-soluble antioxidant in humans. In view of these observations and the fact that the bile pigment associates strongly with membranes, our work suggested that one beneficial role of the waste product bilirubin may be to act as a powerful biological chain-breaking antioxidant.

The scientific importance of the work is that it opened a now blossoming area of research on the beneficial effects of heme catabolism initiated by heme oxygenase *(4)*. This research has extended to the direct product of heme oxygenase enzymatic activity, carbon monoxide (CO). Indeed, there is now growing interest in bile pigments and CO as therapeutics, with CO being investigated in a clinical trial to improve kidney function after transplantation, and bilirubin and its precursor biliverdin having been reported to protect against vascular diseases *(5)*.

Arguably, the work has had an even more important impact at a personal level. I am forever grateful to Bruce Ames for the unique opportunity he gave me at that early stage in my career. I am also indebted to him and the other authors of the *Science* report for their ongoing friendship that is alive nearly 30 years later. And my daughter Sophie? She is now doing postdoctoral work at UC San Francisco and is lucky to count Tony and Bruce among her friends.

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