Serum Bilirubin May Serve as a Marker for Increased Heme Oxygenase Activity and Inducibility in Tissues – A Rationale for the Versatile Health Protection Associated with Elevated Plasma Bilirubin

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In individuals with normal hepatic function, elevated plasma bilirubin levels have been correlated with decreased risk for a number of health disorders, including coronary heart disease.[1-8] This protection is particularly notable in subjects with Gilbert syndrome, who for genetic reasons maintain plasma bilirubin above 20 μM. People with this syndrome are usually found to have a genetically diminished capacity to conjugate bilirubin in the liver, reflecting the fact that they carry variant alleles of the conjugating enzyme UGT1A1 associated with diminished expression or activity. Most commonly, Gilbert subjects are homozygous for a promoter polymorphism in the *UGT1A1* gene (UGT1A1*28) such that diminished amounts of a normal protein are expressed.[9, 10]

Bilirubin can act as an oxidant scavenger, and unconjugated bilirubin binds to albumin in such a way that it can function efficiently as an antioxidant for plasma and the extracellular space; indeed, the pool of albumin-bound bilirubin accounts for much of the oxidant scavenging activity of plasma.[11, 12] For this reason, it has usually been presumed that the health protection associated with elevated plasma bilirubin reflects the fact that free unbound bilirubin in plasma is fluxing back into cells to act as an oxidant scavenger. However, this view has never had much credibility, inasmuch as the plasma concentration of free unbound bilirubin - the fraction capable of entering cells – is less than 0.01% of total plasma bilirubin, and hence in the very low nanomolar range.[13] In contrast, intracellular levels of the effective oxidant scavengers glutathione and ascorbate are in the low millimolar range – essentially a millionfold higher; how could low nanomolar levels of bilirubin add meaningfully to their scavenging power? (The fact that some bilirubin that has been oxidized intracellularly may be reduced back to its native form,[14] does nothing to counter this logic.[15]) However, it is now known that, in submicromolar concentrations, bilirubin can inhibit certain isoforms of NADPH oxidase[16-20] – a key source of pathogenic oxidative stress in many disorders.[21] Moreover, there is other recent evidence that bilirubin may exert anti-inflammatory immunomodulatory effects that likely are independent of its antioxidant activity.[22-24] These findings cast a fresh light on the situation, and render more plausible the notion that the plasma bilirubin pool could be providing antioxidant protection to the body's cells, or working in other ways to dampen inflammation.

However, recent Mendelian randomization analyses focusing on polymorphisms of the UGT1A1 gene contradict the view that plasma bilirubin protects the vasculature.[25, 26] Variant alleles that clearly associate with increased plasma bilirubin, were *not* found to be associated with diminished risk for coronary disease, or with certain cardiovascular risk factors that typically correlate inversely with plasma bilirubin. It therefore appears that, at least in most individuals, plasma bilirubin is a marker for risk, but not a mediator of it.

Bilirubin arises within cells when heme oxygenase degrades heme to generate biliverdin and carbon monoxide; the derived biliverdin is rapidly reduced to bilirubin by the ubiquitously expressed enzyme biliverdin reductase.[27] (Since oxidative stress promotes induction of heme oxygenase-1 via nrf2

activation, this can be viewed as a homeostatic feedback mechanism whereby oxidative stress stimulates generation of bilirubin, which then inhibits a key source of that oxidative stress.[19, 28]) Polymorphisms of heme oxygenase-1 (HO-1) are common. In particular, variations in the length of GT repeats in the promoter of the HO-1 gene are observed which have a marked impact on the inducibility of HO-1; a relatively short GT repeat region correlates with increased inducibility, whereas relatively long TA regions diminish expression.[29] Quite a number of studies – albeit not all – have concluded that individuals carrying short GT repeat alleles are at lower risk for cardiovascular disease than those carrying long GT repeat alleles – consistent with the thesis that efficient production of bilirubin and/or carbon monoxide in cells subjected to oxidative stress is protective for vascular health, a highly plausible conclusion.[30-45]

I suggest that plasma bilirubin can serve as a marker for the level of expression, or the efficiency of inducibility, of heme oxygenase in the body's tissues, and that this largely accounts for correlations between plasma bilirubin and favorable healthy outcomes. There is in fact one report concluding that serum bilirubin is higher in individuals carrying the short repeat alleles of HO-1, as opposed to those carrying long repeat alleles.[40] However, it is almost certainly true that a number of other genetic variants can influence heme oxygenase expression and inducibility (variants in the nrf2 induction system, for example, or variants impacting the translation or degradation of heme oxygenase) – and these likewise could be expected to impact plasma bilirubin level. In this interpretation, the health protection associated with elevated plasma bilirubin is in fact mediated by increased generation of bilirubin and possibly carbon monoxide within the body's cells.

But if intracellular bilirubin is indeed largely responsible for this protection, why doesn't elevated plasma bilirubin *per se* exert comparable protection via back flux into cells? I propose that, within cells, heme oxygenase gravitates to microenvironments where it is close to a key target of its bioactivity, NADPH oxidase. Indeed, there is evidence that both HO-1 and NADPH oxidase tend to localize in caveolae; moreover, biliverdin reductase, crucial to HO-1's antioxidant efficacy, is also found in caveolae.[46-54] Conceivably, HO-1 and NADPH oxidase may co-localize in other cellular microenvironments as well. If this is the case, then the concentrations of free bilirubin produced in the microenvironment of NADPH oxidase are likely to be notably higher than those in the overall cytoplasm or in plasma – in which case back flux of plasma bilirubin might be expected to have little impact on NADPH oxidase activity (unless plasma bilirubin is exceptionally high). This thesis is not unreasonable in light of the fact that, as noted above, the concentration of free bilirubin in plasma, unbound to albumin or other plasma proteins, is in the very low nanomolar range.[13]

It should be noted that people with Gilbert syndrome, although they are usually found to express reduced activity variants of UGT1A1 (most commonly, homozygosity for the UGT1A1*28 promoter allele), are almost certainly *also* endowed with an increase in the activity or inducibility of heme oxygenase. This can be deduced from the fact that the average plasma bilirubin in subjects homozygous for UGT1A1*28 is in the range of 10-15 μM[9] – whereas bilirubin in excess of 20 μM is traditionally required to qualify for a diagnosis of Gilbert syndrome. I propose that it is this increase in heme oxygenase activity – *not* the diminished activity of UGT1A1 – that is primarily responsible for the health protection that they enjoy. Individuals with comparably increased heme oxygenase activity – but who carry the high expression form of UGT1A1 – could be expected to enjoy comparable levels of health protection.

Clearly, there is some sufficiently high level of plasma bilirubin that can exert direct antioxidant effects on tissues. Gunn rats – a model of Crigler-Najjar syndrome, in which hepatic UGT1A1 activity is absent – enjoy protection from atherosclerosis, hypertension, and diabetic nephropathy that seems likely to reflect bilirubin's antioxidant activity.[55-58] Furthermore, when diabetic patients were treated with a high dose of the protease inhibitor atazanavir that increased their plasma bilirubin 9-fold (to an average of 64 μM), a significant improvement of endothelial function was noted.[59] (Atazanavir can inhibit UGT1A1.) These findings suggest that, in some Gilbert syndrome subjects with exceptionally high plasma bilirubin, back flux of plasma bilirubin may indeed exert a meaningful antioxidant effect within cells.

It is also important to note that there likely are other reasons why elevated plasma bilirubin may correlate with improved health outcomes. For example, obesity tends to associate with decreased plasma bilirubin, whereas bilirubin tends to rise after weight loss, for unknown reasons.[60] Hence, plasma bilirubin may serve as a marker for obesity. Oxidative stress, such as that imposed by cigarette smoke, can decrease bilirubin by directly oxidizing it (though, conversely, oxidative stress in tissues would be expected to increase bilirubin generation by inducing HO-1).[61] Of course, many if not most of the epidemiological analyses which correlate plasma bilirubin with health outcomes have used multiple regression to factor out the role of body mass or smoking – and protective associations are often still noted. So whereas plasma bilirubin can serve as a marker for certain well established risk factors, this cannot fully account for the protection associated with elevated bilirubin levels.

The model proposed here is fully consistent with the thesis that intracellular bilirubin provides protection from the range of health disorders that tend to correlate inversely with plasma bilirubin – and that measures which either boost intracellular bilirubin (e.g. administration of biliverdin or of HO-1 inducers) or mimic its activity (administration of phycocyanobilin, the biliverdin-derived spirulina chromophore that shares the ability of biliverdin/bilirubin to inhibit NADPH oxidase) have tremendous potential for health promotion.[62-70]

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