Letter by Mitchell et al., Regarding Article "Urinary Prostaglandin Metabolites An Incomplete Reckoning and a Flush to Judgment

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Dear Editor,

We would like to thank Drs. Grosser, Naji and FitzGerald[1] for their continued interest in our work. While we may not agree with their arguments or their opinions of our study[2] we welcome debate in this extremely important area. We take this opportunity to address the points that they raise.

First, while urine may well be a convenient compartment within which to measure markers of prostacyclin and thromboxane A_2, numerous observations[3-10], of which ours is only the latest[2], indicate that they poorly reflect production within the circulation and the reactivities of endothelial cells and platelets.

Second, the literature that Grosser et al. cite is somewhat selective and in places inaccurate. For example, reference 3[11], which the authors cite to substantiate the statement '*Most insights into the in vivo biology and pharmacology of the prostaglandin pathway have derived from the measurement of metabolites, particularly in urine'* refers to a paper published in 1975 which makes no references to prostacyclin, PGIM, thromboxane, or TXM, being published before the discovery of prostacyclin[12].

Third, the studies selected to substantiate the point that *'there is a striking discordance between the capacity of cells to make these lipids and their actual formation in vivo'* referring to platelet thromboxane A_2 and urinary TXM, in fact, serve to corroborate the view that urinary prostaglandin metabolites do not necessarily reflect levels produced by vessels or platelets in the circulation. Indeed, Dr Fitzgerald's own work shows that orally administered aspirin inhibits the formation of thromboxane by clotting blood ex vivo (which is driven by platelets) much more readily than it reduces the levels of urinary thromboxane metabolites [5]. The simplest explanation for such results is that TXM does not reflect formation of thromboxane by platelets under physiological conditions and rather, as our study shows, can originate from the kidney[2].

Fourth, we were pleased to note that the authors provide no counter arguments to our conclusions regarding the origin of urinary PGIM in humans[2]. Instead the authors suggest that reduced PGIM in the urine of vascular COX-2 knock out mice[13] supports their position. However, this does not prove that COX-2 drives prostacyclin in the circulation and is more simply explained as prostacyclin generation by vascular cells within the kidney, an organ where COX-2 expression is very well-characterized[14, 15]. Indeed, as we[4, 10] and others have shown repeatedly, it is COX-1, not COX-2, that is generally expressed in systemic blood vessels; the kidney is an exception where COX-2 is expressed.

Finally, and most importantly, in direct contrast to before surgery where the patient we describe did have chronic renal failure which progressed to severe renal failure necessitating 4 hours of hemodialysis 3 times per week and passing less than 500ml/day urine, after the kidney transplant the patient had (i) normal renal function with estimated glomerular filtration of greater than 70 ml/min, (ii) was not in renal failure and (iii) had no signs of inflammation measured as both low plasma C-reactive protein (<5) and absence of cellular infiltration in renal biopsies taken at 3 months post transplant.

In summary, following transplantation of a healthy kidney to an individual lacking in $cPLA_2\alpha$ and in the complete absence of any signs of renal inflammation or dysfunction, the levels of urinary PGIM and TXM fall within the normal range. The simplest explanation is that the kidney forms PGIM and TXM.

Authors conflicts of interest
Authors report no conflicts of interest.

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