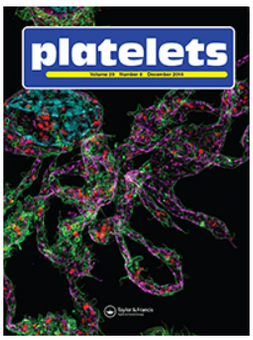

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SPECIAL REVIEW: GUS BORN

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Gustav Born and life as "a series of ripples widening out from an original centre"

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Keywords

Gustav Born, platelet aggregation, aspirin

Although the intravascular aggregation of platelets had been recognized at the time of their discovery by the Italian pathologist Giulio Bizzozero in 1881, elucidation of the phenomenon made little progress until it could be investigated *ex vivo* by the technique of optical aggregometry [1–3]. This technique was developed for quantifying and analysing platelet reactions *in vitro*. The idea came to Gustav (Victor Rudolph) Born after making turbidimetric measurements of ribonuclease activity in *Streptomyces* culture filtrates carried out for the Oxford PhD degree [4]. Appropriate adaptations were made for measuring platelet aggregation in plasma. The new method, first described in a 1962 *Nature* paper [1,2], is remarkable in its simplicity, and basic observations were published during the following year [3]. Platelet aggregation was characterized with respect to velocity, temperature and pH dependence [3]. The relation of aggregate formation to the optical changes was later quantified and accounted for on classical light-scattering theory [4].

The rapid shape change of platelets, which is the first visual evidence of their activation, was quantified and shown to conform to Michaelis–Menten kinetics [5]. The results suggested that platelet agonists such as ADP react with specific membrane receptors leading to structural changes. Two essential cofactors of platelet aggregation were discovered, i.e., calcium and fibrinogen [6]. The brilliant intuition that fibrinogen forms "bridges" linking aggregating platelets [7] was later confirmed at the electron microscopic and molecular levels [4]. Optical aggregometry led to the discovery of the first platelet inhibitors, i.e., ATP and adenosine, considered at first because of their close chemical relationship to proaggregatory ADP [8]. Soon it was shown that these and other aggregation inhibitors are also effective *in vivo*, by stopping the formation and embolization of platelet thrombi in injured arterioles and venules [9]. The last paragraph of the 1962 *Nature* paper reads: "If it can be shown that ADP takes part in the aggregation of platelets in blood vessels, it is conceivable that AMP or some other substance could be used to inhibit or reverse platelet aggregation in thrombosis" [2].

By 1965 the foundations had therefore been laid for the development of antiplatelet drugs as a new class of therapeutic agents, but it took more than two decades before the mechanistic understanding and clinical pharmacology of its antiplatelet effect were sufficiently advanced for the introduction of aspirin as the first antiplatelet drug to prevent coronary and cerebral atherothrombosis [4].

By the time I went to King's College London to spend a sabbatical year (1985–1986) with Gustav, I had developed a whole blood assay of platelet thromboxane (TX)A_2 production to investigate the effects of aspirin (and other cyclooxygenase [COX]-1 inhibitors), by replacing the electrical signal of optical aggregometry with a highly specific immunological signal detected by a radioimmunoassay of serum TXB_2 *ex vivo* [10]. This new assay was instrumental in demonstrating the cumulative nature and biochemical selectivity of platelet COX-1 inactivation by low-dose aspirin in health and disease [11]. Moreover, together with Garret FitzGerald, we had characterized the metabolic fate of TXB_2 in the human circulation [12] and developed a radioimmunoassay for its major urinary metabolite, 11-dehydro-TXB_2, as a non-invasive biomarker of platelet activation *in vivo* [13]. When I proposed a research project for my sabbatical based on these analytical approaches, Gustav had no objection despite clinical investigation of platelet activation in unstable angina being miles away from his research interests. He was an intellectually generous and genuinely curious scientist. Through my joint appointment in the Cardiovascular Unit of Hammersmith Hospital, headed at the time by Attilio Maseri, we embarked in a rather complex study of TXA_2 biosynthesis during recurrent episodes of transient myocardial ischaemia in patients with unstable angina undergoing various pharmacological treatments [14]. Much to our surprise, we found that low-dose aspirin reduced but did not abolish episodes of transient platelet activation in this setting [14], perhaps a first example of aspirin-insensitive platelet activation (later to become more fashionably termed "aspirin resistance") [15]. I remember Gustav saying that this was by far a more interesting observation than what we had anticipated, reflecting his intellectual freedom and scientific interest for the unexpected. His free spirit and scientific acumen were not hampered by ageing, and 20 years after his "forced" retirement from the Chair of Pharmacology at King's College London (where he unpretentiously sat on a very old chair belonging to Albert Einstein, a frequent visitor to the home of Max Born, Gustav's father) I had the opportunity of spending a long weekend with him and our wives on the island of Ischia. There we had our last scientific conversation about novel research interests, some kind of "ripples widening out from an original centre": Gustav

Quoted by Catherine Heaney in Seamus Heaney, *100 Poems*, Faber & Faber, London, 2018.

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was trying to understand why skeletal muscle is rarely a site of malignant metastasis, I was interested in understanding the mechanism of action of aspirin in protecting against gastrointestinal cancers. Gustav was intrigued with, but not surprised by the idea that platelet activation at sites of intestinal mucosal lesions might be involved in early colorectal carcinogenesis, an idea that Paola Patrignani and I had put forward a few years earlier [16]. Our current review on "Aspirin, Platelet Inhibition and Cancer Prevention" [17] is intended as a celebration of the extraordinary person who gave us intellectual support and inspiration.

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