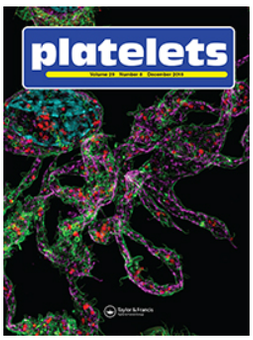

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SPECIAL REVIEW: GUS BORN

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Gustav Born: pioneer in imaging platelet and leukocyte biology

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Abstract

Gustav Born achieved scientific fame for his application of light transmission aggregometry to the study of platelet function, but also led interdisciplinary research teams in pioneering quantitative *in vivo* imaging studies of platelet aggregation and leukocyte adhesion, and in conducting the first research into the biomechanical factors underlying atherosclerotic plaque rupture. Gus Born also communicated both current research findings and an integrated understanding of cardiovascular biology to a wide audience through acting as scientific advisor on several television productions. Using footage from two of these films, we discuss Gustav Born's scientific achievements and legacy.

Keywords

Gustav Born, platelet, leukocyte, intravital, prostacyclin, imaging

History

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Introduction

Gustav Born (1921–2018) is best known in platelet research for the development of the light transmission aggregometer [1,2] (Figure 1) and for a lifetime of major research contributions in platelet and cardiovascular biology [3–6]. Born's research directly contributed to the development of drugs which have led to the extension and improvement of thousands of lives, a huge healthcare impact even putting aside the diagnostic improvements and scientific advances enabled with use of the light transmission aggregometer to study platelet biology.

Born was Professor of Pharmacology at King's College London from 1978 to 1988. One of the authors (CPP) had the privilege of being appointed to his first academic post as a Lecturer in Pharmacology in 1986 by Born, starting an interaction which continued into the latter stages of Born's career, well beyond his official retirement. After his retirement from King's, Born gave his collection of original Ciné film reels and VHS tapes of experiments on platelets and leukocytes, as well as studio productions using research footage, to CPP. On watching this mixture of documentaries, infomercials, and primary research footage, we were reminded of major contributions that Born made during his career beyond the study of platelet aggregation, notably in intravital microscopy, interdisciplinary research into cardiovascular disease, and in making scientific findings accessible to people outside of laboratory research.

Making Dynamic Biology Visual and Making Dynamic Visuals into Science

This material produced by Born and his colleagues shows hemostatic thrombosis following severance of small blood vessels (Figure 2), and thrombosis resulting from intravascular activation of platelets [7], primary research footage from which remarkably remains in current use in the field of thrombosis modelling [8]. Born also captured on camera the adhesion of single platelets to endothelium *in vivo* [9], a phenomenon which the present authors can attest is still a challenge to investigate even with twenty-first-century technology [10].

The engineering required to produce quantifiable video footage, acquiring in darkness onto 16-mm Cine film reels, and the physical and mathematical understanding required to use recordings to better explain platelet activation rates, endothelial shear stress, and blood rheology [11,12], are a testament to Born's broad scientific understanding and recognition of the importance of interdisciplinary research teams.

As well as imaging platelet aggregation *in vivo*, Gustav Born and Anne Atherton are acknowledged as the first scientists to use intravital microscopy to quantify leukocyte adhesion in an inflammatory response [13–16], with quantification enabling the identification of different mechanisms determining the respective movement of platelets and leukocytes from freely flowing in the bloodstream, to becoming adhesive to endothelium. Born identified sialic acid residues on cell surfaces as being important in the regulation of leukocyte adhesion, and he recognized that surface charge could be a biophysical basis underlying this regulatory role. Following on from this strand of Born's research, intravital microscopy techniques are still in current use to study both platelets and leukocytes in our laboratories at King's, with the study of individual sialic acid and charge-bearing molecules now possible [17–20]. The relative contributions of adhesion molecules in different inflammatory and organ contexts, and the extent to which bulk electrical charge density of membranes versus adhesion molecule ligand-binding availability regulates endothelial adhesiveness, are still a research area under intense debate and investigation [21,22].

From a personal point of view (CPP), having Born as a Head of Department was sometimes challenging as he was never convinced by a radiolabeled platelet tracking technique developed as part of my PhD which I referred to as "*in vivo* aggregometry" [23], although this is a method which has since been used by several research groups to study platelet biology *in vivo*

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/iplt.

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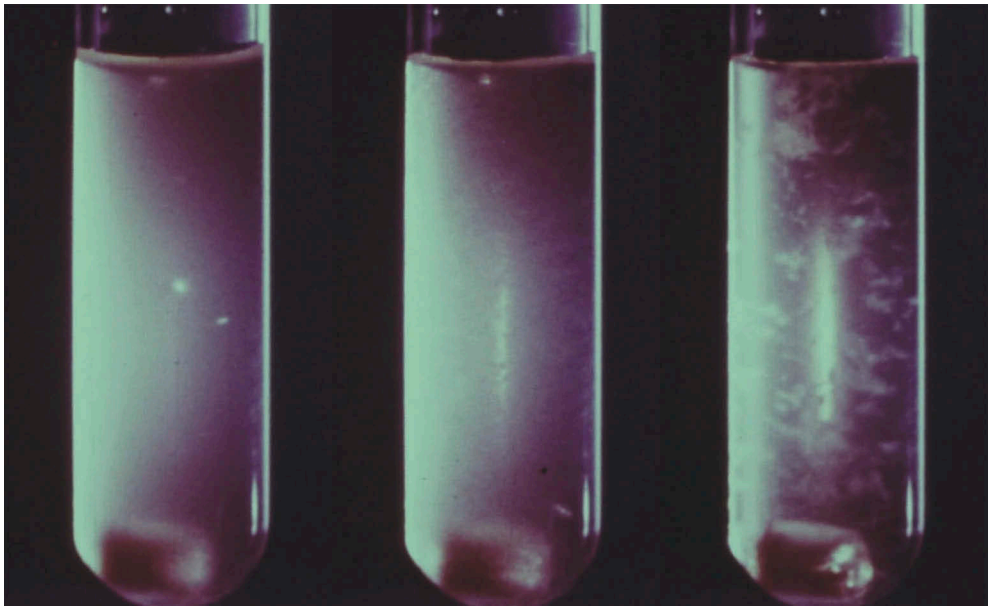

Figure 1. A video demonstration of light transmission aggregometry from the documentary *"Platelets"* (MSD, 1971). As platelets aggregate over time (moving from left panel to right) in a stirred suspension of platelet-rich plasma, light scattering decreases and light transmission increases.

[24–31] and leukocyte [32]. He was also skeptical of our early work investigating the non-hemostatic functions of platelets, although after leaving King's, Born became more interested and indeed supportive of this aspect of platelet biology [6] and our work exploring the contributions of the platelet beyond its important role in hemostasis and thrombosis, including roles in inflammation [19,33–36], bronchoconstriction [37,38], and host defense [39].

As well as contributing to the scientific literature, and making acting appearances as a French onion seller and as a PhD supervisor in the 1961 Royal College of Surgeons spoof film *A Career in Pharmacology*, Born was a prolific scientific advisor on films for science communication and public engagement, with research footage from his laboratories and others achieving broader impact in a variety of documentaries and infomercials. A prime example is "*Platelets*", a 1971 film by Norman Schenker produced for Merck Sharp & Dohme. This video still makes informative and enjoyable viewing for platelet biologists and hematologists, showing biological concepts (hemostasis and thrombosis) (Figure 2), and research methods (aggregometry [Figure 1], clot retraction, and bleeding time assays), together with clinical conditions (trauma, myocardial infarction, congenital platelet disorders, and thrombocytopenia). A summary of these videos and Born's experimental material have been made available on the website of the British Pharmacological Society (www.bps.ac.uk).

Real Life and Real Death in Cardiovascular Disease

Born was also active in public engagement and was not afraid to challenge dogma. Both of these attributes are displayed in an excellent documentary which covers platelets, cardiovascular disease, and the discovery of prostacyclin by researchers at the Wellcome Research Laboratories. This video closes with distinct views of varying optimism posed by Born and Sir John Vane (Figure 3), a friend of Born's from their time at Oxford University and the Royal College of Surgeons who would go on to win the Nobel Prize in Physiology or Medicine, and who would later appoint Born as an Emeritus Research Professor at his William Harvey Research Institute following Born's retirement as Professor of Pharmacology at King's College London. Vane says:

> *We think that perhaps there will be a utility of prostacyclin after a heart attack*

whereas the more skeptical Born states that:

> *it is possible that the mechanism is so much more complicated that even prostacyclin isn't going to take care of it.*

Born also emphasized this skepticism in an "Afterword" in the book *Platelets in Health and Disease* [40], for which one of us (CPP) was an Editor. Born wrote:

> *…our findings do little to support the claims of functionally significant interchanges of prostaglandin precursors between platelets vessel walls, nor of the so-called prostacyclin-thromboxane balance hypothesis which claimed that these two mutually antagonistic agents play a major role in acute coronary thrombosis. The hypothesis, attractive by being simple, was accepted uncritically for many years. But every medical student sees for himself in the postmortem room the gross damage caused by coronary plaque rupture, which makes it inconceivable that these evanescent agents could possibly have any significant effects on the overwhelming thrombogenetic sequelae. The lesson is to stay in touch with real life or, in this case, real death.*

Although Born later qualified in a Letter to *Platelets* that he did not intend to rule out a role for thromboxane A2 in thrombogenesis and was referring only to the prostacyclin–thromboxane balance in the context of "gross damage" [41], he was probably right about the limited clinical utility of prostacyclin in preventing thrombosis. However, the vasodilatory effects of prostacyclin which were considered a challenge in the assessment of this substance as an anti-platelet agent [23,42] later proved to be a useful pharmacological effect when prostacyclin was successfully used for the treatment for pulmonary arterial hypertension [43]. However, selective

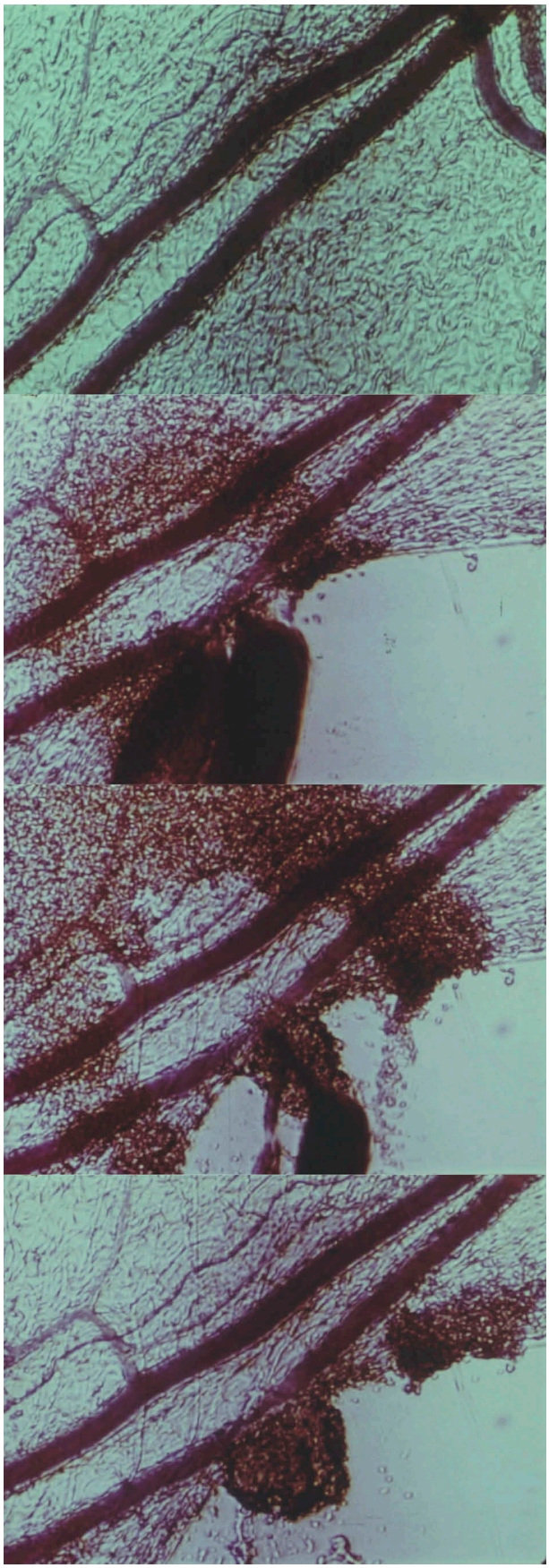

Figure 2. Bright-field intravital microscopy image sequence featured in the documentary *"Platelets"* (MSD, 1971), showing blood vessels in an intravital preparation, cut, and the formation of a hemostatic plug which eventually causes cessation of bleeding.

thromboxane receptor antagonists were also developed but gave disappointing results in late-stage clinical trials [44].

The effectiveness of low-dose aspirin in secondary prevention of cardiovascular events builds on the work of Vane and others, particularly Carlo Patrono, as well as the early work of Born and colleagues, and Born would later concede in a review coauthored with Patrono [5] that:

> *the (prostacyclin-thromboxane balance) concept has been substantially validated by the recent discovery of cardiovascular toxicity associated with COX-2 inhibitors.*

Rather than focusing on the factors released by healthy endothelium, in the later part of his career, Born chose to focus his studies on atherosclerotic plaques, part of which was another interdisciplinary collaboration highly valued by Born [45]. Together with the cardiac pathologist Michael Davies, the mechanical engineer and physicist Peter Richardson, and pharmacology graduate student Corinne Lendon, Born worked on the first studies directly relating mechanical properties of atherosclerotic plaques to biochemical and histological factors in order to guide treatment and prevention of cardiovascular disease [46–49]. During this period, Born and colleagues also made discoveries relating to the biochemical [50], dietary [51,52], and pharmacological [53–55] determinants of the uptake of lipids and fibrinogen into blood vessel walls.

Targeting vulnerable atherosclerotic plaques to prevent cardiovascular mortality has proved to be just as complex and surprising as the exploitation of "evanescent agents" released from the endothelium. Three major prospective studies found that "vulnerable" plaque features had low positive predictive value as a cardiovascular disease risk factor, leading to the questioning of the whole concept of plaque vulnerability [56,57]. It is possible that the biomechanical nature of plaques has shifted since they were studied by Born and Richardson [56], and the puzzle remains as to why 37% of plaque ruptures occur in the center of the fibrous cap, rather than at the fibrous cap "shoulders" which were identified as more vulnerable to rupture by Born and others [58]. Still, some clinical validation of Born's association of monocyte/macrophage infiltration with regions prone to rupture has recently been produced, in the form of reductions in cardiovascular (although not all-cause) mortality through targeting interleukin (IL)-1β innate immunity pathway with the anti-IL-1β monoclonal antibody canakinumab [59].

Conclusion – Lessons From Gustav Born

Gustav Born leaves behind a scientific legacy that extends well beyond the platelet aggregation, as well as outside of laboratory research. Born's research outputs and contributions to scientific films are reminders of the importance of:

(1) capturing dynamic biological processes in action using imaging techniques and using resultant movie footage for both quantitative research and the communication of science to wider audiences
(2) challenging dogma, but being prepared to change one's mind in the face of new evidence, and
(3) bringing researchers from a variety of backgrounds together to work on solving fundamental problems in medical research.

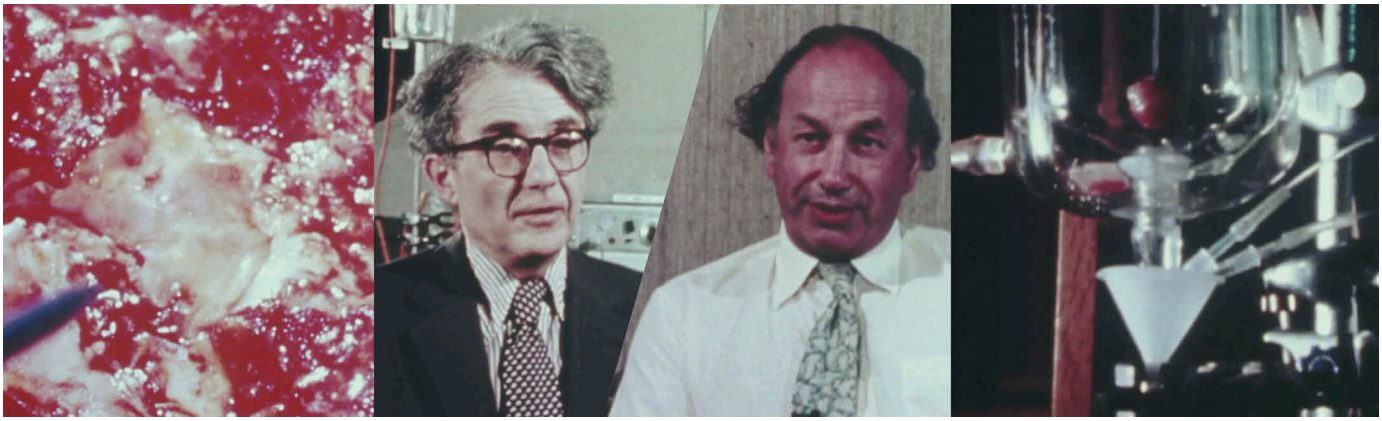

Figure 3. Gustav Born (left) and Sir John Vane (right) disagreed over whether clinical outcomes after thrombosis resulting from rupture of atheromatous plaques (left) could ever be improved by molecules like prostacyclin (then studied using superfusion cascade organ bath systems, right).

Disclosure Statement

The authors report no conflict of interest related to this article.

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References

1. Born GVR (1962b). Quantitative investigations into the aggregation of blood platelets. In Proceedings of the Physiological Society, 23–25 March 1962, University College London Meeting: Communications (J Physiol), 67–68P.
2. Born GVR. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 1962a;194:927–929. doi:10.1038/194927b0
3. Born GVR, Honour AJ, Mitchell JRA. Inhibition by adenosine and by 2-chloroadenosine of the formation and embolization of platelet thrombi. Nature 1964;202:761–765. doi:10.1038/202761a0
4. Born GVR, Cusack NJ, Darwin C, McClure M. Prolongation of bleeding time in rats by ADP receptor antagonists. J Physiol 1986;381:22P.
5. Born G, Patrono C. Antiplatelet drugs. Br J Pharmacol 2006;147:S241–S251. doi:10.1038/sj.bjp.0706401
6. Reynolds LA, Tansey EM, Wellcome Trust (London, UK, and Wellcome Trust Centre for the History of Medicine at UCL). (2005). The recent history of platelets in thrombosis and other disorders (Wellcome Trust Centre for the History of Medicine at UCL).
7. Begent N, Born GV. Growth rate in vivo of platelet thrombi, produced by iontophoresis of ADP, as a function of mean blood flow velocity. Nature 1970;227:926–930. doi:10.1038/227926a0
8. Wu W-T, Jamiolkowski MA, Wagner WR, Aubry N, Massoudi M, Antaki JF. Multi-constituent simulation of thrombus deposition. Sci Rep 2017;7:42720. doi:10.1038/srep42720
9. Kortenhaus H, Schröer H, Born GV. Quantification of the adhesion of platelets in hamster venules in vivo. Proc R Soc London Ser B, Biol Sci 1982;215:135–145. doi:10.1098/rspb.1982.0033
10. Riffo-Vasquez Y, Somani A, Man F, Amison R, Pitchford S, Page CP. A non-anticoagulant fraction of heparin inhibits leukocyte diapedesis into the lung by an effect on platelets. Am J Respir Cell Mol Biol 2016;55:554–563. doi:10.1165/rcmb.2015-0172OC
11. Schmid-Schönbein, H., Born, G. V, Richardson, P.D., Cusack, N., Rieger, H., Forst, R., Rohling-Winkel, I., Blasberg, P., Wehmeyer, A. Rheology of thrombotic processes in flow: the interaction of erythrocytes and thrombocytes subjected to high flow forces. Biorheology 1981;18:415–444. doi:10.3233/BIR-1981-183-609
12. Born GVR, Richardson PD. Activation time of blood platelets. J Membr Biol 1980;57:87–90. doi:10.1007/BF01868994
13. Sumen C, Mempel TR, Mazo IB, Andrian UHV. Intravital microscopy: visualizing immunity in context. Immunity 2004;21:315–329.
14. Atherton A, Born GVR. Relationship between the velocity of rolling granulocytes and that of the blood flow in venules. J Physiol 1973b;233:157–165. doi:10.1113/jphysiol.1973.sp010303
15. Atherton A, Born GV. Proceedings: effects of neuraminidase and N-acetyl neuraminic acid on the adhesion of circulating granulocytes and platelets in venules. J Physiol 1973a;234:66P–67P.
16. Atherton A, Born GV. Quantitative investigations of the adhesiveness of circulating polymorphonuclear leucocytes to blood vessel walls. J Physiol 1972;222:447–474. doi:10.1113/jphysiol.1972.sp009808
17. Riffo-Vasquez Y, Man F, Page CP. Doxofylline, a novofylline inhibits lung inflammation induced by lipopolysaccharide in the mouse. Pulm Pharmacol Ther 2014;27:170–178. doi:10.1016/j.pupt.2014.01.001
18. Pan, D., Amison, R.T., Riffo-Vasquez, Y., Spina, D., Cleary, S.J., Wakelam, M.J., Page, C.P., Pitchford, S.C., Welch, H.C. P-Rex and Vav Rac-GEFs in platelets control leukocyte recruitment to sites of inflammation. Blood 2015;125:1146–1159. doi:10.1182/blood-2014-07-591040
19. Kornerup KN, Salmon GP, Pitchford SC, Liu WL, Page CP. Circulating platelet-neutrophil complexes are important for subsequent neutrophil activation and migration. J Appl Physiol 2010;109:758–767. doi:10.1152/japplphysiol.01086.2009
20. Kanabar, V., Tedaldi, L., Jiang, J., Nie, X., Panina, I., Descroix, K., Man, F., Pitchford, S.C., Page, C.P., Wagner, G.K. Base-modified UDP-sugars reduce cell surface levels of P-selectin glycoprotein 1 (PSGL-1) on IL-1β-stimulated human monocytes. Glycobiology 2016;26:1059–1071. doi:10.1093/glycob/cww053
21. Etulain J, Schattner M. Glycobiology of platelet-endothelial cell interactions. Glycobiology 2014;24:1252–1259. doi:10.1093/glycob/cwu056
22. Petri B, Phillipson M, Kubes P. The physiology of leukocyte recruitment: an in vivo perspective. J Immunol 2008;180:6439–6446. doi:10.4049/jimmunol.180.10.6439
23. Page CP, Paul W, Morley J. An in vivo model for studying platelet aggregation and disaggregation. Thromb Haemost 1982;47:210–213. doi:10.1055/s-0038-1657169
24. Beijer L, Botting J, Crook P, Oyekan AO, Page CP, Rylander R. The involvement of platelet activating factor in endotoxin-induced pulmonary platelet recruitment in the guinea-pig. Br J Pharmacol 1987;92:803–808.
25. Smyth, E., Solomon, A., Birrell, M.A., Smallwood, M.J., Winyard, P.G., Tetley, T.D., Emerson, M. Influence of inflammation and nitric oxide upon platelet aggregation following deposition of diesel exhaust particles in the airways. Br J Pharmacol 2017;174:2130–2139. doi:10.1111/bph.13831
26. Solomon, A., Smyth, E., Mitha, N., Pitchford, S., Vydyanath, A., Luther, P.K., Thorley, A.J., Tetley, T.D., Emerson, M. Induction of platelet aggregation after a direct physical interaction with diesel exhaust particles. J Thromb Haemost 2013;11:325–334. doi:10.1111/jth.12087

27. Holbrook L, Moore C, Sanz-Rosa D, Solomon A, Emerson M. A NOD/SCID mouse model for the assessment of human platelet aggregation in vivo. J Thromb Haemost 2012;10:490–492. doi:10.1111/j.1538-7836.2011.04595.x
28. Moore C, Tymvios C, Emerson M. Functional regulation of vascular and platelet activity during thrombosis by nitric oxide and endothelial nitric oxide synthase. Thromb Haemost 2010;104:342–349. doi:10.1160/TH09-10-0715
29. Moore C, Sanz-Rosa D, Emerson M. Distinct role and location of the endothelial isoform of nitric oxide synthase in regulating platelet aggregation in males and females in vivo. Eur J Pharmacol 2011;651:152–158. doi:10.1016/j.ejphar.2010.11.011
30. Oyekan AO, Botting JH. A minimally invasive technique for the study of intravascular platelet aggregation in anesthetized rats. J Pharmacol Methods 1986;15:271–277. doi:10.1016/0160-5402(86)90057-4
31. Smyth, E., Solomon, A., Vydyanath, A., Luther, P.K., Pitchford, S., Tetley, T.D., Emerson, M. Induction and enhancement of platelet aggregation *in vitro* and *in vivo* by model polystyrene nanoparticles. Nanotoxicology 2015;9:356–364. doi:10.3109/17435390.2014.894150
32. Jones H, Paul W, Page CP. A new model for the continuous monitoring of polymorphonuclear leukocyte trapping in the pulmonary vasculature of the rabbit. J Pharmacol Toxicol Methods 2002;48:21–29. doi:10.1016/S1056-8719(03)00005-4
33. Page CP. The involvement of platelets in non-thrombotic processes. Trends Pharmacol Sci 1988;9:66–71.
34. Pitchford, S.C., Momi, S., Giannini, S., Casali, L., Spina, D., Page, C.P., Gresele, P. Platelet P-selectin is required for pulmonary eosinophil and lymphocyte recruitment in a murine model of allergic inflammation. Blood 2005;105:2074–2081. doi:10.1182/blood-2004-06-2282
35. Pitchford, S.C., Momi, S., Baglioni, S., Casali, L., Giannini, S., Rossi, R.,Page, C.P., Gresele, P. Allergen induces the migration of platelets to lung tissue in allergic asthma. Am J Respir Crit Care Med 2008;177:604–612. doi:10.1164/rccm.200702-214OC
36. Pitchford, S.C., Yano, H., Lever, R., Riffo-Vasquez, Y., Ciferri, S., Rose, M.J., Giannini, S., Momi, S., Spina, D., O'connor, B. and Gresele, P. Platelets are essential for leukocyte recruitment in allergic inflammation. J Allergy Clin Immunol 2003;112:109–118.
37. Coyle AJ, Page CP, Atkinson L, Flanagan R, Metzger WJ. The requirement for platelets in allergen-induced late asthmatic airway obstruction: eosinophil infiltration and heightened airway responsiveness in allergic rabbits. Am J Respir Crit Care Med 1990;142:587–593.
38. Keir SD, Spina D, Page CP. Bradykinin and capsaicin induced airways obstruction in the guinea pig are platelet dependent. Pulm Pharmacol Ther 2015;33:25–31. doi:10.1016/j.pupt.2015.05.004
39. Amison, R.T., O'Shaughnessy, B.G., Arnold, S., Cleary, S.J., Nandi, M., Pitchford, S.C., Bragonzi, A., Page, C.P. Platelet depletion impairs host defence to pulmonary infection with *Pseudomonas aeruginosa* in mice. Am J Respir Cell Mol Biol Rcmb 2018;2017–0083OC.
40. Gresele P, Page CP, Fuster V, Vermylen P (editors). Platelets in thrombotic and non-thrombotic disorders: pathophysiology, pharmacology and therapeutics. Cambridge: Cambridge University Press; 2002.
41. Born GVR. Update on platelets: a personal story (April 2003). Platelets 2003;14:333–334. doi:10.1080/0953710031000151996
42. Kiernan FJ, Kluger J, Regnier JC, Rutkowski M, Fieldman A. Epoprostenol sodium (prostacyclin) infusion in acute myocardial infarction. Br Heart J 1986;56:428–432. doi:10.1136/hrt.56.5.428
43. Pozo RD, Hernandez Gonzalez I, Escribano-Subias P. The prostacyclin pathway in pulmonary arterial hypertension: a clinical review. Expert Rev Respir Med 2017;11:491–503. doi:10.1080/17476348.2017.1317599
44. Bousser, M.-G., Amarenco, P., Chamorro, A., Fisher, M., Ford, I., Fox, K.M., Hennerici, M.G., Mattle, H.P., Rothwell, P.M., de Cordoüe, A. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. Lancet (London, UK) 2011;377:2013–2022. doi:10.1016/S0140-6736(11)60600-4
45. Born GVR, Richardson PD. A classic collaboration: Michael Davies on plaque vulnerability. Atherosclerosis 2012;220:593–597. doi:10.1016/j.atherosclerosis.2011.11.022
46. Burleigh MC, Briggs AD, Lendon CL, Davies MJ, Born GV, Richardson PD. Collagen types I and III, collagen content, GAGs and mechanical strength of human atherosclerotic plaque caps: span-wise variations. Atherosclerosis 1992;96:71–81. doi:10.1016/0021-9150(92)90039-J
47. Lendon CL, Davies MJ, Born GV, Richardson PD. Atherosclerotic plaque caps are locally weakened when macrophages density is increased. Atherosclerosis 1991;87:87–90. doi:10.1016/0021-9150(91)90235-U
48. Lendon CL, Davies MJ, Richardson PD, Born GVR. Testing of small connective tissue specimens for the determination of the mechanical behaviour of atherosclerotic plaques. J Biomed Eng 1993;15:27–33.
49. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet (London, England) 1989;2:941–944.
50. Görög P, Born GV. Increased uptake of circulating low-density lipoproteins and fibrinogen by arterial walls after removal of sialic acids from their endothelial surface. Br J Exp Pathol 1982;63:447–451.
51. Thorngren M, Shafi S, Born GV. Delay in primary haemostasis produced by a fish diet without change in local thromboxane A2. Br J Haematol 1984;58:567–578.
52. Born GVR. Obesity in North America. Lancet 1985;326:1313. doi:10.1016/S0140-6736(85)91604-6
53. Medina RA, Cardona-Sanclemente LE, Born GV, Brown MJ. Effect of deoxycorticosterone acetate on blood pressure in relation to accumulation of low-density lipoprotein and fibrinogen by aorta and other tissues of normotensive Wistar rats. J Hypertens 1997;15:531–536. doi:10.1097/00004872-199715050-00009
54. Shafi S, Palinski W, Born GVR. Comparison of uptake and degradation of low density lipoproteins by arteries and veins of rabbits. Atherosclerosis 1987;66:131–138. doi:10.1016/0021-9150(87)90188-2
55. Shafi S, Cusack NJ, Born GV. Increased uptake of methylated low-density lipoprotein induced by noradrenaline in carotid arteries of anaesthetized rabbits. Proc R Soc London Ser B, Biol Sci 1989;235:289–298. doi:10.1098/rspb.1989.0001
56. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. Eur Heart J 2015;36:ehv349. doi:10.1093/eurheartj/ehv349
57. Stefanadis C, Antoniou C, Tsiachris D, Pietri P. Coronary atherosclerotic vulnerable plaque: current perspectives. J Am Heart Assoc 2017;6:e005543. doi:10.1161/JAHA.117.005543
58. Kelly-Arnold A, Maldonado N, Laudier D, Aikawa E, Cardoso L, Weinbaum S. Revised microcalcification hypothesis for fibrous cap rupture in human coronary arteries. Proc Natl Acad Sci U S A 2013;110:10741–10746. doi:10.1073/pnas.1308814110
59. Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., Fonseca, F., Nicolau, J., Koenig, W., Anker, S.D., et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–1131. doi:10.1056/NEJMoa1707914