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INVITED ARTICLE: Celebrating the achievements of Professor Stan Heptinstall, Founder and Editor-in-Chief of *Platelets* (1990–2015)

Platelets: 25 years under the editorship of Stan Heptinstall

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Is there a more exciting cell lineage to investigate than the megakaryocyte/platelet axis? Some of us think not and have dedicated their life's work to unravelling the mysteries of platelet production and function. Likewise, platelet pathology offers a Pandora's box of both inherited and acquired diseases. What goes wrong? Why are platelet numbers sometimes so low or why do platelets fail to function? Red cells just go round and round in the circulation breathing quietly and enjoying a quiet life unless disorders such as malaria and sickle cell anaemia make things complicated. But the platelet dances and jigs its way around the body sticking to injured sites in the vessel wall, secreting its granule content or making metabolites that transform its surface into a stickiness that allows the formation of plugs that stop bleeding. So, until it tires, the platelet is energetic, it assures haemostasis; unless of course these events occur in places where they should not – such as in coronary arteries and cerebral vessels where accumulated platelet masses cause heart attacks and stroke. The need to know the fine details of how these processes has brought about as prompted much research and provided much knowledge that has to be shared. Platelet research has always featured in the best of the medical and fundamental journals and it has always had a prominent place in those dedicated to haematology. But something was missing; a specialist journal dedicated to platelets.

In 1990, this need was met when Professor Dimitri Mikhailidis (London, UK) persuaded Churchill Livingstone to publish a new journal, PLATELETS, entirely dedicated to their study and one that would bridge scientific and clinical interests. After some discussion it was unanimously decided to ask Professor Stan Heptinstall (Queens Medical Center, Nottingham, UK) (Figure 1) to be editor of this new journal, a task that Stan readily accepted. He enthusiastically put together a skilled international editorial team (Table I) and opened the journal to the publication of studies on all aspects of platelet biology, pathology and pharmacology regardless of the discipline. As well as original articles, PLATELETS was open to reviews written by well-known specialists with the view of providing up-to-date information and expert opinion on a wide variety of topics. Also encouraged was the publication of short communications, book and literature reviews and proceedings of symposia and workshops. To help him achieve his aims, Stan put together an impressive team of reviewers from around the world that responded positively to his



Figure 1. Stan Heptinstall: the retiring editor of PLATELETS.

appeals and, admittedly from time to time, his coaxing. That PLATELETS is successful has been totally due to Stan's drive, energy and expertise.

The first edition

The first volume of PLATELETS appeared in March 1990 and featured a similar cover as today. The items contained in this edition are shown in Table II. A major initial success for Stan was the publication of the text of the Marion Barnhart lecture given by Professor Marjorie Zucker at the XIIth Congress of the International Society on Thrombosis and Haemostasis in Tokyo in the summer of 1989. Marjorie Zucker was one of the all time greats in platelet research, making pioneering observations from 1947 until her sad death in 2006. She was particularly well known for her co-authorship with Professor Aaron Marcus of the book "The Physiology of Blood Platelets" published in 1965 and

Table I. Editorial staff for the first edition of PLATELETS in March 1990.

Editor-in-Chief

Dr S Heptinstall, Department of Medicine, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK

Principal Editors

J Dawes (Sydney, Australia), J L McGregor (Lyon, France), D Mikhailidis (London, UK), M A Packham (Toronto, Canada), F E Preston (Sheffield, UK), M C Scrutton (London, UK), R Takahashi (Tokyo, Japan), U Till (Erfurt, GDR)

Editors

B Ashby (Philadelphia, USA), C Chesterman (Randwick, Australia), K J Clemetson (Berne, Switzerland), R W Colman (Philadelphia, USA), P Dandona (London, UK), M Greaves (Sheffield, UK), R A Hutton (London, UK), J Y Jeremy (London, UK), W Lösche (Erfurt, GDR), S J Machin (London, UK), I Morita (Tokyo, Japan), Y Nozawa (Gifu, Japan), R Kinlough-Rathbone (Hamilton, Canada), P Spangenberg (Erfurt, GDR)

Editorial Advisory Board

R Apitz-Castro (Venezuela), M A Barradas (UK), J Belch (UK), D J Betteridge (UK), K R Bruckdorfer (UK), Wen-Chang Chang (Taiwan), G de Gaetano (Italy), L A Harker (USA), J Kambayashi (Japan), J G Kelton (Canada), S J Kirtland (UK), T Kunicki (USA), J F Martin (UK), T Matsuda (Japan), M Mori (Japan), G Scherthaner (Austria), P K Schick (USA), A I Shafer (USA), H Shio (Japan), J B Smith (USA), K Tanoue (Japan), L Viinikka (Finland)

which was at the time a much-cited source of information. Her review in PLATELETS was entitled "Platelet Physiology: A personal perspective" and is still available by consulting the journal online (Zucker, 1990). Marjorie was especially proud to be a woman in science and in this article she outlines her career and gives a personal perspective on platelet physiology and its history. A keen birdwatcher, Marjorie Zucker's career highlighted the value of combining an astute power of observation with a questioning mind. Also featured in this first edition was the proceedings of the 1989 Erfurt Platelet conference (Figure 2) and a feature of Stan's editorship was the place given to countries inexperienced in scientific publishing.

Publishing changes and the early years

Over the years, Platelets has undergone a number of changes of publisher. After an initial period with Churchill Livingstone the journal was progressively in the charge of Carfax, then Taylor and Francis, Informa, Informa Healthcare then back to Taylor and Francis from 1 January 2015. Happily, all of the publishers retained the spirit of the journal and Stan continued as editor throughout this period. In 1990, four editions were published and I highlight a publication from the late Fraser Mustard's group in Hamilton, Canada, on changes in phosphoinositides in rabbit platelets during clot formation, a manuscript that would not be out of place today (Vickers et al., 1990). There was also an interesting review on the VWF-GPIb interaction by Michael Berndt and his colleagues (Westmead, Australia) (Booth et al., 1990). The years 1991 and 1992 both featured four volumes. Of special note was a comprehensive review from David Cooper (London, UK) on the molecular genetics of platelet membrane proteins and their inherited disorders (Cooper, 1991) and another from Beng Chong (Sydney, Australia) on drug-induced thrombocytopenia (Chong, 1991). In 1993, PLATELETS featured six volumes together with a special supplement dedicated to coronary artery disease with Pier Mannucci (Milan, Italy) as guest editor. This special issue with 10 manuscripts featuring such recognized experts as Colin Prentice (Leeds, UK), Sergio Coccheri (Bologna, Italy) and Guiseppi G. Nenci (Perugia, Italy) showed just how

Table II. The content of the first edition of PLATELETS.

EDITORIALS

A New Journal called *Platelets*

Platelets—Issue Number 1

REVIEWS

Platelet Physiology: A Personal Perspective. *Marjorie B. Zucker*
Prostaglandin Regulation of Cyclic AMP Metabolism in Human Platelets. *B. Ashby*

ORIGINAL ARTICLES

Platelet Size and Adenine Nucleotides in Patients Undergoing Bone Marrow Ablation: A Useful Model for Studying Platelet Ageing. *B. J. Boughton, A. Macwhannell, A. Simpson, R. Hawker*

Platelet Aggregation in Primary Raynaud's Phenomenon and the Effect of Enalapril Administration. *A. Dowie, J. L. Francis, O. S. Roath, V. F. Challenor, D. G. Waller*

Detection of a Protein in Human Platelet Membranes which Binds Low-density Lipoproteins. *D. G. Hassall, K. Desai, J. S. Owen, K. R. Bruckdorfer*

Effect of Aspirin and Dipyridamole on Sequential Graft Platelet Accumulation after Implantation of Small Diameter PTFE Prosthesis. *A. G. Nordestgaard, C. S. Marcus, S. E. Wilson*

ABSTRACTS

Abstracts of Papers Presented at the 3rd Erfurt Workshop on Platelets, held in June 1989 at the Medical Academy of Erfurt, GDR

BIBLIOGRAPHY

Recent Literature on Platelets, supplied by the British Library Information Service



Figure 2. Stan Heptinstall: Start of the journey – discussion with Dr Uwe Till (a principal editor) at the Erfurt Platelet Conference in 1989.

PLATELETS was marking its place in the field. The place given to cardiovascular research continued to be emphasized and I note an excellent review from Karsten Schrör (Dusseldorf, Germany) on early studies on clopidogrel and ticlopidine (Schrör, 1993). A major contributor to PLATELETS over the years has been James G. White (Minneapolis, USA) with many beautiful electron microscopy images of platelets often published in association with his colleague Ginès Escolar (Barcelona, Spain). Overall, I have noted 49 citations in PLATELETS by White JG, a number that must be applauded. In 1993, he contributed a review manuscript on membrane glycoprotein movements during the platelet response to activation (White & Escolar, 1993). Another excellent review that year came from Johan Heemskerk (Maastricht, Holland) and Stewart Sage (Cambridge, UK) on calcium signaling (Heemskerk & Sage, 1994). Apart from the review

manuscripts, a feature of PLATELETS continued to be the high proportion of papers being published from Eastern Europe and from the Far East and the place given to promising young scientists and clinicians.

The period 1990–1999 began with a stimulating review from Catherine Hayward (Montreal, Canada) on multimerin, a newly discovered alpha-granule protein (Hayward & Kelton, 1995) and a review from a tissue factor pioneer, Bjarne Osterud (Tromsø, Norway) (Osterud, 1995). Original articles during this period often featured platelet receptors and included an interesting study of thrombin binding to platelets from the late Graham Jamieson's group (Bethesda, USA) (Greco et al., 1995). Jos Vermynen (Leuven, Belgium) and his collaborators showed how plasmin-modified platelet function (Blockmans et al., 1996). Significant review articles were those on thrombin receptors by Wadi Bahou and Valentina Schmidt (Stoney Brook, USA) and from Christian Gachet and his group at the time led by Jean-Pierre Cazenave (Strasbourg, France) (Bahou & Schmidt, 1996; Gachet et al., 1996). This same year also featured one of 17 publications in PLATELETS from my group, an immunological study of GPIIb-IIIa and its association with CD9 performed by Jeanny Laroche-Traineau (Bordeaux, France) (Laroche-Traineau et al., 1996). Another loyal contributor to PLATELETS has been Alan Michelson (Boston, USA) who in 1997 provided a review on the applications of flow cytometry (Michelson, 1997). This review was quickly followed by an assessment of the importance of reticulated platelets by Paul Harrison and his colleagues (Oxford/Birmingham, UK) (Harrison et al., 1997); Paul has 16 citations in the journal.

It was the choice of review articles that continued to mark the journal at the time and expert reviews on the molecular genetics of Glanzmann thrombasthenia by Debbie French (New York, USA) and of Hermansky-Pudlak and Chediak Higashi syndromes by Richard Spritz (Madison, USA) were particularly comprehensive (French, 1998; Spritz, 1998). Original manuscripts with a clinical bias were not forgotten, as illustrated by a research article by Armin Reininger (Munich, Germany) that highlighted the usefulness of studying platelet spreading in peripheral occlusive arterial disease (Reininger et al., 1998); while Martine Jandrot-Perrus (Paris, France) and her group characterized platelet aggregation by the GPVI agonist, convulxin (Jandrot-Perrus et al., 1998). Christel Poujol and Paquita Nurden (Bordeaux, France) showed the fine ultrastructure of platelet aggregates, including platelet-to-platelet bridges formed in the PFA-100 apparatus (Poujol et al., 1998).

From 2000 to 2015

By the year 2000 PLATELETS consisted annually of 8 volumes and continued to contain a wide variety of research articles as well as invited reviews. A manuscript from Yukio Ozaki's (Yamanashi, Japan) group on tyrosine kinase signaling initiated by VWF binding to GPIb showed the advances in our understanding of platelet physiology (Sato et al., 2000). Invited reviews featured an assessment of structural determinants on GPIb for VWF binding from Hans Deckmyn and his colleagues (Kortrijk, Belgium) (Cauwenberghs et al., 2000). Jan-Willem Akkerman and his group (Utrecht, Holland) highlighted platelet α IIB β 3 signaling (Litjens et al., 2000); while an excellent review from Australia on calpain regulation of α IIB β 3 signaling was provided by Shaun Jackson and his colleagues (Melbourne, Australia) (Schoenwaelder et al., 2000). The willingness of PLATELETS to publish articles whose interest extended outside the haemostasis field was illustrated by the excellent publication on CD40L by Artur-Aron Weber and his group (Düsseldorf, Germany) (Herrmann et al., 2001). Pharmacodynamic studies were

illustrated by the review from Robert Storey (Nottingham, UK) describing the mode of action of clopidogrel (Storey, 2001). As well as being editor-in-chief, Stan Heptinstall was also a regular contributor (equalling James G. White with 49 citations in all) often with articles characterizing the effect of ADP on platelets and its pharmacological inhibition (see Storey et al., 2002). Another original contribution from Nottingham detailed P-selectin and CD40L expression in platelet-leukocyte conjugates (Zhao et al., 2003). Rare was an edition of PLATELETS published without a contribution from James G. White whose electron micrographs continued to fill the pages of the journal often describing unique and rare disorders of platelet secretion (White, 2013; White & Ahlstrand, 2013). Meanwhile, advances in our understanding of platelet signaling pathways were illustrated by a study from Satya Kunapuli and his colleagues (Philadelphia, USA) showing how p160ROCK (Rho-kinase) exerted dynamic regulation of microtubule coils in ADP-induced platelet shape change (Paul et al., 2003). My group combined with that of Bernhard Nieswandt (Würzburg, Germany) to characterize the morphological changes in platelets and megakaryocytes that accompanied the transient thrombocytopenia induced following the infusion of monoclonal antibodies to GPIb in mice (Poujol et al., 2003). An interesting article from Niamh Moran (Dublin, Ireland) and her colleagues described the importance of the GFFKR sequence in the α IIB cytoplasmic tail (Reilly et al., 2004). Wolfgang Lösche's group (Erfurt, Germany) examined the release of microvesicles (microparticles) from platelets while Dimitri Mikhailidis and his colleagues (London, UK) provided more on the effects of clopidogrel and aspirin in peripheral arterial disease (Lösche et al., 2004; Jagroop et al., 2004). Both Wolfgang Lösche and Dimitri Mikhailidis have been major contributors to PLATELETS with 26 and 40 citations, respectively. An excellent article from Steve Watson and his colleagues (Oxford/Birmingham, UK), one of 13 high quality manuscripts published in PLATELETS by this group, defined the role of integrins in collagen-induced platelet aggregation (Jarvis et al., 2004). Publications from Russia and India on von Willebrand factor-mediated platelet activation, and the Bernard-Soulier syndrome, respectively, confirmed the broadening international status of the journal (Naimushin & Mazurov, 2004; Ghosh et al., 2005). The platelet–thrombin interaction continued to receive much attention as shown by papers on GPIb-dependent tyrosine phosphorylation by Maribel Diaz-Ricart (Barcelona, Spain) and the excellent review by Roger Lundblad and Gil White (Chapel-Hill, USA).

George Dale and his co-workers (Oklahoma, USA) proposed that the procoagulant “coated” platelet subpopulation was enriched in patients with Alzheimer's disease and that this subpopulation was enriched in derivatized amyloid precursor protein (Prodan et al., 2006). Continuing on a clinical theme, Carlo Balduino (Pavia, Italy) and his Italian coworkers proposed that VWD2B should always be considered when diagnosing inherited thrombocytopenia while Changgeng Ruan (Suzhou, China) reported a patient with macrothrombocytopenia and platelets with giant granules (Loffredo et al., 2006; Wu et al., 2006). Koneti Rao (Philadelphia, USA) and his colleagues described abnormal splice variants of phospholipase C-beta2 in platelets (Sun et al., 2007). Steve Watson's group continued their productivity in PLATELETS by publishing reference curves for platelet aggregation and secretion as an aid to the diagnosis of platelet-based bleeding disorders (Dawood et al., 2007). In an interesting comparison, Paul Gurbel and his colleagues (Baltimore, USA) described the analysis of platelet function in the VerifyNow apparatus and the detection of high residual reactivity in some patients treated with aspirin in cardiovascular disease (Dichiara et al., 2007).

Masaaki Moroi (Fukuoka, Japan) and colleagues chose PLATELETS to define the collagen-type specificity of GPVI as a receptor for platelet adhesion while Alastair Poole's group (Bristol, UK) highlighted critical roles for the actin cytoskeleton in regulating another platelet collagen receptor, the integrin $\alpha 2\beta 1$ (Jung et al., 2008; Pula & Pöole, 2008). Continuing on this theme, Willem Ouwehand and the Bloodomics consortium (Cambridge, UK) analyzed variation in the platelet transcriptome associated with *GP6* haplotype (Burns et al., 2008). This manuscript showed how platelet research was about to enter a new cycle. Holm Holmsen (Bergen, Norway) a regular contributor to the journal with 16 citations provided a review on phospholipase D in platelets and other blood cells (Vorland et al., 2008). Cardiovascular disease continued to feature prominently with, for example, a manuscript on platelet-leukocyte conjugates in atrial fibrillation from Chiara Cerletti and her colleagues (Campobasso, Italy) while Robert Storey, Stan Heptinstall and their colleagues in Nottingham continued to lead the debate on the mode of action and the comparative efficacy of pharmacological inhibitors blocking the ADP pathways of platelet aggregation (Storey et al., 2008; 2009). Rapid screening of residual platelet activity in cardiovascular disease was the object of many papers in the journal. A new Methods section was introduced in the journal in 2009. Ulrich Walter and his group (Würzburg, Germany) reported a procedure whereby prostacyclin receptor stimulation facilitates detection of P2Y₁₂ receptor inhibition in the PFA-100 system (Kobsar et al., 2010). Lucia Stefanini and Wolfgang Bergmeier (Philadelphia, USA) (2010) provided an excellent and far-sighted review on the role of CaLDAG-GEFI in platelet activation. Pathology continued to feature prominently and Bernd Jilma and his colleagues (Vienna, Austria) (2010) described an unexpected role for granulocyte colony-stimulating factor in enhancing shear-dependent platelet activation. With a clinical orientation, Bernard Payrastre and his colleagues (Toulouse, France) reviewed platelet changes during pregnancy (Valera et al., 2010). A new feature, the Spotlight article began with reviews of the role of the P2Y₁₂ receptor in platelet activation and of nitric oxide from Satya Kunapuli (Philadelphia, USA) and Khalid Naseem (Hull, UK) (Kim & Kunapuli, 2012; Naseem & Roberts, 2012). These were followed by excellent reviews on CLEC-2 and on semaphorins in platelets from Yukio Ozaki's group (Yamanashi, Japan) and from Skip Brass and his colleagues (Philadelphia, USA) (Suzuki-Inoue et al., 2012; Wannemacher et al., 2012). Meanwhile, the series of articles by James G. White (Minneapolis, USA) continued with the discovery of the York syndrome and further cases of the Medich giant platelet syndrome (White et al., 2013; Gunning et al., 2013). The Spotlight Articles were a success and Hervé Falet (Boston, UK) contributed a thought-provoking review on the many faces of platelet filamin (Falet, 2013). Kent Gartner and his colleagues (Memphis, USA) re-examined the role of GPIb in thrombus formation and Paul Harrison's group (Oxford/Birmingham, UK) continued their support for the journal by critically assessing how the therapeutic use of autologous platelet-rich plasma facilitates the repair of tissue injury, a procedure increasingly used in sports medicine (Alsousou et al., 2013). On-treatment platelet reactivity in patients receiving clopidogrel was re-examined by Kurt Huber and his colleagues (Freynhofer et al., 2014). The clinical evolution of the journal was nicely highlighted by a multi-centric study provided by Pall Onundarson (Reykjavik, Iceland) on the complementary effect of fibrinogen and rFVIIa on clotting in the Bernard-Soulier syndrome (Palsson et al., 2014). Meinfred



Figure 3. Stan and Lillian Heptinstall at an informal lunch in Boston in 2009. An editor's work is never done!.

Gawaz and his colleagues (Tübingen, Germany) looked at platelet-bound stromal cell-derived factor-1 in patients with congestive heart failure (Jorbenadze et al., 2014). A fascinating multi-center study brought together by Robert Storey and featuring authors from the UK, Denmark, France, Sweden, and the USA was the finding of lower mortality following adverse pulmonary events and sepsis with ticagrelor compared with clopidogrel in the PLATO study (Storey et al., 2014). This manuscript started a new trend by being available on open access.

Conclusions

It is a tremendous achievement for Stan Heptinstall to have been founder editor of PLATELETS and to have continued this role over 25 years. His hard work and enthusiasm for the project have ensured the continuation and success of the journal. Often with the help of his senior colleagues, including Sue Fox and Jane May he has been unflinching in his desire to make PLATELETS a recognized authority journal in the field. In this he has succeeded and in doing so he has helped many young researchers begin their research career as well as enhancing science in Eastern Europe and other parts of the world where publishing research was still in the learning process. The support from his wife Lillian has also been key; in fact for 25 years she has been married to both Stan and the journal (Figure 3). In my review of PLATELETS, I have tried to show its popularity by citing a wide range of senior authors and the topics of their papers. The list could have been much larger, but space restrictions impose a limit. I apologize to those whose work is not cited. Now life for Stan has changed, no more the early morning connection to the Internet and to the journal office. Instead Stan will give all of his time to his political career, to his work as Councillor for Bramcote and as Mayor of the Borough of Broxtowe in Nottingham, and to his eight grandchildren. In 1997, Stan received the MBE from the Queen for his work in local government. Not only do the people of Bramcote and Broxtowe owe him a debt, the scientific community does as well. Stan is a distinguished and popular member of the platelet and haemostasis field. Thank you Stan and well done.

Declaration of interest

Alan Nurden has no conflicts of interest with regard to this article.