Historical Perspective

The Prominent Pioneering 'Plateleteer': Reflections on and Personal Reminiscences of Gustav V. R. Born (1921–2018)

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Abstract

Among the pioneers in platelet research, Gustav Born was perhaps the most prominent representative, just a real "plateleteer". He achieved scientific fame for the invention and application of light transmission aggregometry. Importantly, he paved the way for contemporary antiplatelet therapy. Integrating his fundamental knowledge of platelet biology into the pathology of vascular disorders, Born provided seminal contributions to the understanding of atherogenesis and thrombogenesis. He also generated visions for pharmacological strategies that, nowadays, are translated into reality. Inside and outside of science, Born was a great man. He had a deeply held belief in humanity. In this article, his life, scientific career and achievements are appreciated together with personal reminiscences of this outstanding personality.

Keywords

- Gustav Born
- history of platelet research
- lifetime achievements
- platelet aggregometry
- atherosclerosis
- thrombosis

Gustav Victor Rudolf Born, DPhil, FRCP, HonFRCS, FRS, Emeritus Professor of Pharmacology at King's College London and Research Professor at The William Research Institute, St. Bartholomew's and The London School of Medicine and Dentistry, died on April 16, 2018 aged 96 (►Fig. 1). He was strongly associated with the Society of Thrombosis and Hemostasis Research (GTH), maintained close friendship with numerous members of our society, and provided postdoc training to several German fellows of my generation to whom he retained an intense and loyal relationship as a mentor and friend throughout his entire life.

Childhood in Göttingen

Gustav Born and his two elder sisters enjoyed a protected childhood in Göttingen. Their father, Max Born (Nobel laureate in 1954), hold the chair in Theoretical Physics and Mathematics. In the 1920s and early 1030s, the Göttingen University was the "Mecca" of quantum mechanics with Max Born as leading personality who gathered bright young scientists around him. Little Gustav, so his memories, used to sit under the grand piano when his father and Werner Heisenberg were playing Bach or Schubert sonatas four-handed after having completed their scientific work on matrix mechanics. Due to the hospitable atmosphere of his parental home, Gustav met world-famous scientists[a], rising shooting stars[b] and his father's doctoral students[c], most of whom later on became Nobel laureates.

Already at the age of 9, Gustav entered the Oberrealschule Göttingen. 'In my long life', Gustav told, 'I lost my temper only at two occasions. One of them was when a classmate beat my Jewish friend. This made me so angry that I threw the attacker through the window. Fortunately, the classroom was located on the ground floor'.[1]

[a] *Including Niels Bohr, Albert Einstein, James Franck, and Arnold Sommerfeld.*

[b] *Other than Werner Heisenberg there were Enrico Fermi, Gerhard Herzberg, Wolfgang Pauli, Léon Rosenfeld, Edward Teller, and Eugene Wigner.*

[c] *Among them were Max Delbrück, Siegfried Flügge, Friedrich Hund, Pascual Jordan, Maria Goeppert-Mayer, Lothar Nordheim, Robert Oppenheimer, and Victor Weisskopf.*

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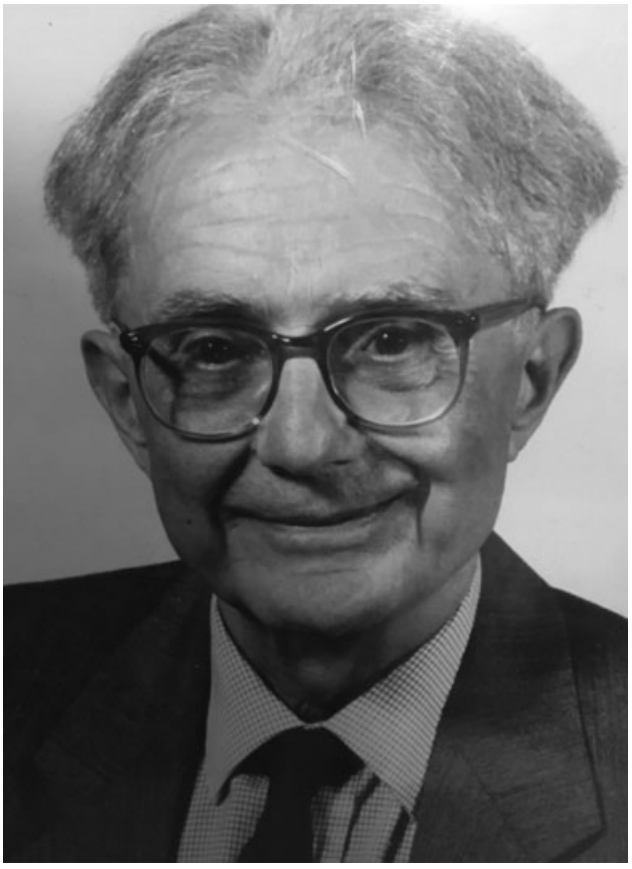

Fig. 1 **Gustav Victor Rudolf Born** July 29, 1921–April 16, 2018 (courtesy of the Born family).

Both Born's parents were of Jewish background and had converted to the Lutheran faith. Gustav and his sisters were baptized. However, the Borns regarded 'religious professions and churches as a matter of no importance'.[1,2]

Escape to Great Britain

Life of the Born family changed dramatically when Hitler came to power. Gustav remembers that the ugly mood of anti-semitism had even reached the playground with some children not allowed to meet with him any longer. In April 1933, Max Born was one of six Jewish professors at the Göttingen University being suspended from office. It was Albert Einstein who told his friend and fellow scientist Max Born 'leave immediately while you are still able to travel'.[3] The Born family followed this advice and, by beginning of May 1933, headed across the border, first to Italy and then to England, where they arrived as 'part of what must have been the best-qualified refugee trail in history'.[3] Max Born, doyen of quantum mechanics, having trained so many scientists of whom eight should become Nobel laureates, was without employment. He accepted a temporary position from St. John's College at Cambridge University, and eventually, in October 1936, assumed the chair as Tait Professor of Natural Philosophy at the University of Edinburgh.

Gustav was educated at Perse School, Cambridge and, after the family's move to Scotland, at the Edinburgh Academy and University. Gustav remembers: 'The war was coming, and we were refugees. We were just being naturalized and become British. My father said to me: "Why don't you study medicine like your grandfather did? Then you don't have to kill people in the war and you are less likely to be killed yourself". Both these reasons were good reasons for studying medicine'.[4] And he continues: 'I couldn't follow my father into physics because I was too "unmathematical", but I was always interested in biological processes. And this was my main impulse to study medicine. I am very glad that I did for the two reasons that my father gave and also for having a very interesting life'.[4]

Hiroshima

After graduation from Edinburgh Medical School in early 1943 and internship at Western General Hospital, Gustav was called up into the British Army as a physician and almost immediately posted to the Far East. Prior to his military mission, he changed his name[d] into the nom de guerre George Vernon Buchanan.[1]

His subsequent horrific experience in the Far East should trigger off Gustav's life-long scientific interest. After the atomic bombing, the British invasion force for Japan was turned into an occupation force, and Gustav was a member of that. He arrived in Japan in late autumn 1945 and was sent to the main British hospital located quite near Hiroshima. Gustav remembers: 'The British Army in its best tradition looked after the local population, and amongst the patients were hundreds of Japanese who had survived the bomb blast but were bleeding unstoppably from all parts of the body. I knew that this was from thrombocytopenia. The radiation from the bomb had destroyed the haematopoietic cells in the bone marrow. All of this was a deep impression and one of the starting points of my later work'.[5] Having been in the Royal Army Medical Corps for nearly 4 years on active service until mid-1947, Born followed the family's tradition[e] and the scientific inspiration by his father and decided to become engaged in biomedical research.

Way into Science

After the war, the recently detected penicillin appeared to be a most attractive topic. Upon advice of his future academic mentor in Oxford, Born spent one year in pathology at the University College in London and also received a brief but intense preparatory training in biochemistry. In 1948, Gustav began postgraduate research at the William Dunn School

[d] *The reason behind this was that the Geneva Convention did not protect former fellow citizens from execution as traitors in case of captivity by countrymen.*

[e] *His great-grandfather Marcus Born had been a pioneer in what is called today public health; his grandfather Gustav Born senior was a professor of anatomy and had been an extraordinarily original embryologist. He discovered the endocrine function of the corpus luteum, which through progesterone was one of the starting points of the contraceptive pill.*

of Pathology with Sir Howard Florey (who developed penicillin for pharmaceutical use[f]) and gained his DPhil in 1951.

For his postdoc, Born joined the group of Hugh (Hermann Felix) Blaschko, a biochemical pharmacologist in Oxford, who shared the fate of being a Jewish scientist having escaped to the United Kingdom. As events would later prove, it was most important for Gustav's future work that Blaschko had his research focus on the biosynthesis, storage, and metabolism of catecholamines. Having demonstrated the association of adrenalin with adenosine triphosphate (ATP) in adrenalin granules,[6] Born had the idea that other endogenous amines might be stored similarly elsewhere in the body. Indeed, upon intense reading, he became aware that circulating 'pseudocells' (platelets) contain large amounts of the vasoconstrictive amine serotonin (5-hydroxytryptamine). Thus, along with his horrible impressions of radiation victims in Japan, the initial intention of his future research was to use platelets for pharmacological purposes.

Subsequently (1952–1953), Gustav was a staff scientist at the Toxicology Research Unit of the Medical Research Council, where he did his first independent research on various topics, including gastric histamine and acid secretion, foetal and newborn physiology, smooth muscle metabolism, and catecholamine pharmacology.

At his early stages, Born collaborated with John Robert Vane[g] whom he should meet again later in life at the Royal College of Surgeons and The William Harvey Research Institute (TWHI). In mid-1950s, according to the French saying 'on revient toujours à ses premières amours', Gustav was lured back by his fascination of platelet biology and pathology and began intensive studies of animal and human blood platelets. Working first on the biochemistry of their granules, he demonstrated that platelets contain ATP and actively accumulate serotonin and catecholamines.[7–11]

The Born Aggregometer

In 1962, Gustav published his landmark paper on 'Aggregation of blood platelets by ADP and its reversal'.[12] How did the invention of 'the Born aggregometer' come about?

Being asked that question in an interview by Rod Flower, Gustav laughed and replied: 'That's the only useful thing that came out of my DPhil in Oxford. There we had measured ribonuclease activity in *Streptomyces* culture filtrates turbidimetrically pushing light through suspension. Well, and then I thought that would be ideal for platelets'.[5] Using a rather simple device (►Fig. 2) in this method, a light beam is passed through anticoagulated platelet-rich plasma (PRP). When platelets are induced to aggregate, the optical density of PRP decreases and light transmission increases. Of note, using the same principle, John O'Brien almost concurrently published a two-part paper on platelet aggregation measurement.[13] When O'Brien subsequently claimed his primary inventorship, Born refused this allegation[14] by a specific comment[h].

Fig. 2 The first Born aggregometer. The instrument equipped with a stirring device and galvanometer was presented during a workshop at the Royal College of Surgeons in 1961. Of note, changes in the optical density had to be read and subsequently plotted manually (►Fig. 3). (taken from Born[14] and reproduced with permission of the Born family).

The technique which Gustav later on called 'a very banal idea and nothing to be proud of intellectually'[5] became enormously influential. It was the first example to do single-cell pharmacology in a pure human cellular population. Overall, Born's method permitted ex vivo/in vitro quantification and analysis of distinct agonists and inhibitors of platelet aggregation and thus paved the way to monitor the effect of antiplatelet agents.[15] To describe the assessment, implication and future impact of 'platelet aggregometry' (a term Gustav hated) in his own words, 'what we did with it was important but not the idea with the instrument'.[5]

It is noteworthy that, despite this self-critical assessment, more than 10 firms subsequently began to produce aggregometers. When facing thousands of optical aggregometers around the world, Born was often asked why he did not patent the device. As taught by Howard Florey, his Oxford Professor, Gustav was strictly against patenting anything of potential medical value for mankind.[16]

Nowadays, light transmission aggregometry (LTA) is the most common technique to assess platelet function in clinical and experimental settings (e.g. knockout models). Although considered the gold standard for the diagnostic

[f] *Recipient of the 1945 Nobel Prize in physiology or medicine that he shared with Sir Alexander Fleming and Ernst B. Chain.*

[g] *Recipient of the 1982 Nobel Prize in physiology or medicine along with Sune Bergström and Bengt Samuelsson for their discoveries concerning prostaglandins and related biological substances.*

[h] *'I am sorry that John O'Brien may have convinced himself that he invented the optical aggregometer, but the fact of matter is that it had been demonstrated to him by myself in my department some time before he published it without acknowledgement to me. This is confirmed by a letter from Sir John Vane who was present at the same time as my senior lecturer'.*

work-up of patients with suspected platelet function defects and therefore popular and widely used, the LTA method is lacking proper standardization (for review, see the work of Hayward and Moffat[17]). More recent activities by the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) have addressed this problem and published detailed recommendations in an expert consensus paper.[18]

Further Seminal Accomplishments

Light on platelets

During the 1960s, Born explored and elucidated several basic mechanisms of platelet aggregation using the aggregometer (►Fig. 2) that, in contrast to today's automated multi-channel systems, was rather a crude equipment (nothing more than a stirring device and a galvanometer to read the optical density that had to be plotted manually) (►Fig. 3). He postulated and confirmed the hypothesis that distinct nucleotides secreted by platelets, biogenic amines and chemically modified derivatives can induce, amplify, or even abrogate the aggregation response.[19–30] Specifically, Born and his collaborators discovered the first endogenous aggregation inhibitors, namely ATP and adenosine, initially looked at because of their close chemical relationship to proaggregatory ADP.[19,20] Moreover, Born devoted much effort to inhibitory mechanisms and promoted the concept that certain agents (including aspirin), which he had shown experimentally to prevent platelets from aggregating in vitro and in vivo, would be helpful as potential antithrombotic drugs in several clinical conditions.[15,31–33]

Atherogenesis and atherothrombosis

Integrating his fundamental knowledge of platelet biology into the pathology of vascular disorders, Born also directed his research activities to the development of atherosclerosis and thrombosis with a focus on pharmacological inhibition.[34] Specifically, he provided evidence that endogenous pressor agents such as adrenalin can accelerate atherogenesis, helping to explain why hypertension is a risk factor in coronary arterial disease.[35,36] Together with Michael Davies and Peter Richardson, Born also demonstrated that the vulnerability of coronary atherosclerotic plaques and their tendency to rupture very much depend upon their deformability and their macrophage and lipid content.[37,38] Moreover, he and his colleagues conducted the first systematic research on biomechanical factors (such as blood flow and resulting shear stress) in haemostasis and under pathological conditions promoting atherosclerotic plaque rupture.[39–42]

Gustav Born's ideas and experimental findings opened a new field of research and stimulated many investigators, including basic researchers and cardiologists. Overall, Born's impact on cardiology became so eminent and impressive that, by the mid of his time at King's College (1978–1986), he was even offered to transfer his position into a clinical professorship, as Gustav remembers.[1]

Platelet imaging and leukocyte biology

Quantifying platelet interactions with injured vessels required further methodological innovations, and Born was gifted to bring people from various disciplines together. He built up interdisciplinary research teams, conducting quantitative in vivo imaging studies of platelet adhesion, aggregation, and thrombus formation.[43] Born was also a pioneer in the use of intravital microscopy to explore the interaction of leukocytes with the vasculature in the microcirculation.[44–48] With his focus on neutrophils and their role in atherothrombosis, a today's 'hot topic', he was decades ahead of current research. Nowadays, Born's experiments are even more striking, when considering that, in the pre-digital era, the records had to be captured in pitch darkness on 16-mm cine film.

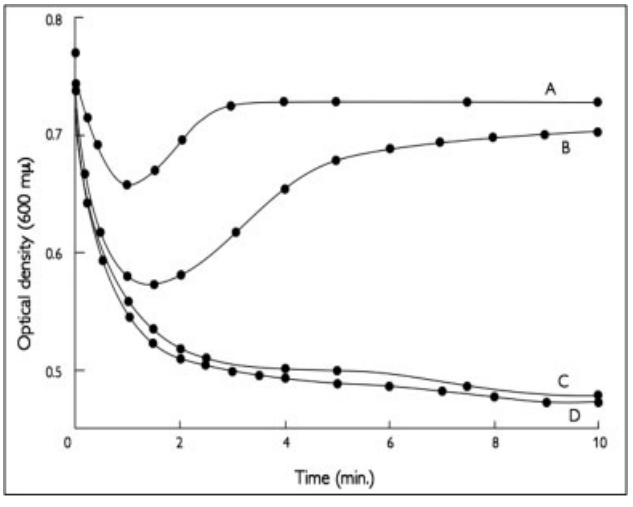

Fig. 3 **The first optical record of ADP-induced aggregation.** Depicted is the increase in transmitted light, illustrated here as downward defection, upon addition of different concentrations of ADP at time 0: (**A**) 2.5×10^{-7} M; (**B**) 5×10^{-7} M; (**C**) 10^{-6} M; (**D**) 2.5×10^{-6} M. (taken from Born[14] and reproduced with permission of the Born family).

Academic Career and Honours

Gustav Born entered academia upon his appointment as a Lecturer at St. Peter's College Oxford (1953–1960). Throughout his subsequent, very distinguished career, he held three prestigious chairs in pharmacology: Vandervell Professor of Pharmacology at the Royal College of Surgeons (1960–1973), Sheild Professor of Pharmacology at the University of Cambridge (1973–1978), where he was a Fellow of Gonville and Caius College, and Professor of Pharmacology at King's College, University of London (1978–1986). Becoming professor emeritus at King's (1986), he continued working in (and was a cofounder of) TWHI at St. Bartholomew's and The London School of Medicine and Dentistry since 1989. In his pathopharmacology laboratory at TWHI, he pursued his research interest in atherogenesis and was still active and publishing until his late 80s.

Professor Born was elected a Fellow of the Royal Society (1972) for his work on platelets and subsequently awarded the Royal Medal. He was an Honorary Fellow of the Royal College of Surgeons, of the Royal College of Physicians, of

King's College London, and of St. Peter's College Oxford. He was an Honorary Life Member of the New York Academy of Sciences and a member of the Leopoldina. Born served as President of ISTH (1979) and was the Founding President of the British Society for Haemostasis and Thrombosis (1980). In 2009, he was awarded the Wellcome Gold Medal of the British Pharmacological Society. Among the many distinctions and honors that he received from numerous academic or scientific institutions around the world, Professor Born was awarded the Paul Morawitz Prize (1980), the Alexander von Humboldt Award (1994), and the Ernst Jung Gold Medal in medicine (2001). In 2010, the Centre for Vascular Research at the University of Edinburgh and a professorship were named after him.

Professor Born received 10 honorary MD or DSci degrees from nine universities, including Münster (1980); Leuven (1981); Edinburgh (1982); Sorbonne (DSci 1987; MD 1999); Brown, Providence, Rhode Island (1987); Ludwig Maximilian University, Munich (1989); Loyola, Chicago (1995); Bordeaux (1999) and Düsseldorf (2001) (►Fig. 4). His CV identifies 28 named lectures and some 350 publications.

Personal Reminiscences

The numerous prestigious awards reflect Born's lifetime achievements, but which are the characteristics that made Gustav an excellent person and outstanding man? Perhaps, some personal impressions and experiences can be helpful to describe his particular nature.

I first met Professor Born at the London ISTH Congress in 1979, which he chaired as congress president. At that time, I just had completed my postdoc and was ready to give my first talk at an ISTH conference. So, I was extremely excited. Surprisingly, after the session, Born, small in stature but great in science, talked to me asking additional specific questions to our experimental findings. Of course, I was even more excited than prior to my oral presentation. Over the years, I have forgotten his questions and suggestions, but I still remember lively is his friendly, open-minded, warm kind and the absolutely unpretentious way in which he talked to a greenhorn in science.

Fig. 4 **Gustav Born following the presentation of the honorary MD from the Düsseldorf Faculty of the Heinrich Heine University in 2001**. Depicted are (L to R): Professor Dieter Häussinger, Dean; Professor Gustav Born; Dr. Manfred Osten, Secretary General, Alexander von Humboldt Foundation; Professor Emmeran Gams, Vice Rector; Helmut Sies, Chair of Biochemistry and Molecular Biology. (courtesy of Press Center of the Heinrich Heine University Düsseldorf).

When I met him subsequently at small conferences, my impression of our first conversation was entirely confirmed. Every discussion about platelets 'and beyond' (such as history, literature, the fine arts, or social problems) was highly stimulating. When he made experimental suggestions, he was bubbling over with inspiring ideas to explore a biological process and to dive into a certain phenomenon or objective. Each time, it was fascinating listening to him.

I also remember one of the platelet Ascheberg meetings close to Münster in the mid-1980s. When we had breakfast together, Gustav stared at the table, carefully inspected the opulent dishes of the lipid-rich Westphalian cuisine, paused, and then looked at me, announcing his brand-new discovery: 'Rüdi, now I know where the atherosclerosis comes from'.

Three of my fellow residents who had spent their postdoc with Professor Born identically remembered that one of the first questions that he had typically asked upon their arrival was 'Do you need additional money for living?' Born never forgot his own personal history and took always care of the distress of his students. On top of all that, they esteemed Professor Born to be one of the nicest personalities you could ever meet—warm, generous, convivial and kind.

Over the years, I specifically valued Gustav's noblesse de coeur and his liberal spirit. I also got to know additional features of his personality and talents outside the world of science. For example, Gustav was a highly talented flautist with a keen interest in music. He also had a pronounced literary ardour, was extremely wide read and an elegant writer throughout. Even in his mid-80s, he wrote a children's book for one of his granddaughters to provide answers to the mysteries and puzzles of life[i]. And Gustav was a marvellous raconteur and had a brilliant combination of elegance, charm, humour and subtlety. Due to his integrated understanding of cardiovascular biology and pathology, Gustav could easily use his talents when communicating current research findings to a large lay audience or, apart from that, when talking about the history of the Born family and his father's work in several guest lectures that he delivered in Göttingen and Düsseldorf. He was also highly familiar to utilize the media in the pre-mobile and pre-video clip era. Thus, he acted on several TV productions.

A most individual habit of Gustav was what his British colleagues called 'Born's love affair with the telephone'. I assume that this is the only behavior that Gustav has been feared for. But he really became famous for it. His colleagues gradually grew accustomed to receiving calls at odd hours from around the world, and his students and technicians often took lengthy phoned instructions for the current

[i] *GVR Born, L Karnath. Wohin geht die Sonne, wenn ich schlafe? Nymphenburger Verl, München 2006 (ISBN 3-485-01075-8).*

experiments. It is reported that, sometimes, his call would be followed immediately by the appearance of Gustav himself, who had made the call from the telephone box just around the corner. Most of his staff and colleagues at home identified Gustav's trait as that of a virtuous and a little absent-minded scientist, others found him endearingly eccentric in such situations, but everybody valued him for his generosity and noblesse, his smartness and charm, and his kindness and liberal spirit. In fact, Gustav was a kind of legend in his own lifetime: a personality entwined with numerous anecdotes most of which may be true. At least, Gustav himself confirmed some of them.[1]

Born's Legacy

During his Alexander von Humboldt Visiting Professorship at the Düsseldorf University, Gustav Born delivered a remarkable lecture. His central message to all of us was: 'Keep being curious, follow your research persistently, and keep your interest very much in the forefront of your mind! Whatever has grabbed you, keep an enquiring mind and, importantly, choose who you work with very carefully!'

Are there other messages that we can take from Born? One certainly is his enthusiasm and persistence in research, another one his generosity, kindness and tolerance in his dealings with students and colleagues, all of which may have contributed to his success, recognition, and appreciation. However, there is another message from Gustav Born to future generations and us.

The Born family received two advices from Albert Einstein: the first that they followed to leave Germany soon in 1933, the second that they did not follow to never enter German soil again. Gustav's parents returned to their former homeland after war. A major motivation to do so was their wish to contribute to the democratic and moral rehabilitation of Germany.[2] Indeed, Max Born was very active to overcome the hate and isolation that had been brought to Germany and its scientists.

Throughout his life, Gustav Born acted in the same way from his new homeland, and he was very energetic and persistent due to his deeply held belief in humanity. His ability of a perfect networker and brilliant communicator made him a very effective builder of bridges in the United Kingdom, across the Channel and the Atlantic Ocean. Being a cosmopolitan and a real philanthropist, he contributed essentially to reconciliation. Gustav Born will remain an outstanding and eminent role model for everyone who had the privilege to become in touch with him both inside and outside of science.

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