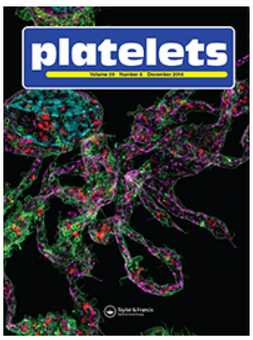

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SPECIAL REVIEW: GUS BORN

Of platelets and aggregometers: personal reminiscences of Gus Born (1921–2018)

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Abstract

This paper recounts the author's personal reminiscences of the late Gustav Born and details some of his major influences on the field of platelet biology and mechanisms of hemostasis. In particular, it focuses on his development of the 'Born aggregometer' and the differences that are seen in the aggregation response to certain stimuli when aggregation is recorded using other techniques such as the impedance method.

Keywords

Born optical aggregometer, electronic aggregometer, platelets, hemostasis

My first encounter with Gus Born

The late summer of 1966 found me travelling to London for a job interview. The advert in the national press had specified a vacancy for a technician to operate a computer in the laboratories of the Department of Pharmacology at the Royal College of Surgeons of England (RCS) in Lincolns Inn Fields, London. In those days, astonishingly half a century ago now, computers were large, high maintenance installations which could easily fill an average size room. Despite their feeble capabilities compared with (say) today's pocket calculators, these machines required constant supervision and attendance. Becoming a 'computer operator' seemed like an ideal career for a young man such as myself who had a genuine interest in science, although few qualifications of any significance.

However, my aspirations to join this new technocracy were quickly dashed. I was told by the laboratory manager, as I waited rather nervously in his office, that this particular post had just been filled. But, he added, they were still looking for a pharmacology technician to work in the lab and asked if I might be interested in that job instead.

I had, at that time, no idea what pharmacology was and indeed, no formal biological education at all. The subject had not featured in the curriculum of my schools, an omission that was all the more puzzling given the seismic changes in the discipline that were occurring at the time in the wake of the Watson-Crick paper on the structure of DNA and the ensuing molecular 'revolution'.

In spite of my ignorance, I accepted the suggestion and was shortly shown into a large lab. There, seated in front of a small device on one of the benches by a window, I saw a man in a white coat peering at a chart issuing from a recorder. He was of medium height, neatly but not fussily dressed with thick dark hair parted in the middle. He was wearing horn-rimmed spectacles and, when he spoke, I thought I detected a hint of an accent or inflection in his speech. Next to him stood a young assistant and from time to time, the older man would issue cryptic instructions such as 'Ten then five, Peter'. His assistant would then carefully insert a syringe into a glass tube in the machine and depress the plunger. Both of them would then stare intently at the chart for the next few minutes sometimes shaking their heads and sometimes nodding.

The elder man was introduced to me as Professor Gustav Born, the head of department. He indicated a seat beside him and, in a rather distracted manner, asked me a few questions about my educational background and interest in science while glancing, every couple of minutes, at the emerging chart.

After a few minutes, the lab manager appeared again and removed me to another office where I was introduced to Professor John Vane who, I was told, headed a separate group but jointly managed the department together with Professor Born. Here, I found myself the subject of rather more penetrating questions and, reviewing my performance later at home, my predominant feeling was disappointment at another opportunity missed. When a letter arrived from the Department offering me a job as a junior technician a couple of days later, I was pleased but also rather surprised. I accepted by return of post though not without some apprehension and the following day I went to the library to look up the meaning of the word 'pharmacology'. In later life, I learned that Gus was apt to prefer job candidates with a love of, and enthusiasm for, science and placed somewhat less weight on their academic record, all of which was lucky for me.

I discovered later that Gus Born and John Vane had been friends since their Oxford days where they had met in the (now legendary) pharmacology department run by the formidable JH Burn. Perhaps because of this, the two separate units in the RCS pharmacology department coexisted together happily and the whole department, with its flat management structure functioned amicably and efficiently (Figure 1). Working there was unlike any other job I had previously experienced and I found the environment very stimulating. Regularly passing through the department was a constant stream of academic visitors from other countries who brought with them fresh ideas and perspectives and generally enriched our intellectual (and social) life. A particularly important departmental ritual occurred daily at coffee and tea time: these refreshments were served on a trolley situated in between the two units and at these times all the staff gathered together, talked and swapped ideas. There was an expectant air of impending discovery in the labs which I have never encountered elsewhere.

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. Gus Born and his lifetime friend John Vane. Together they managed and inspired one of the most successful pharmacology labs of the day. This photo was taken in 1988 at a prostaglandin symposium in Düsseldorf.

I was assigned to John Vane's group but quickly learnt – largely from these coffee time discussions – something about aggregometry and platelets, and came to appreciate the contributions that Gus and his colleagues were making to understanding their biology. If things were slow in John's lab during the summer vacation, I would sometimes work with Gus's colleagues at 'the other end' of the department and so was exposed to a lot of their thinking about thrombosis and hemostasis.

Gus had headed up the department since 1960 having taken over from WDM Paton but in 1973 he left the department after being offered the Shield Chair of Pharmacology in Cambridge. At almost the same time, John Vane was tempted away from London by the offer of the R&D Directorship of the Wellcome Foundation, in those days a major pharmaceutical company. John took with him some members of his RCS group (including me) to form the nucleus of a new department of 'Prostaglandin Research' embedded in the pharmacology group at the Wellcome laboratories in Beckenham, Kent.

These changes at the top marked the end of a most productive and enjoyable era and it was only in retrospect that I realized what an astonishing privilege it was to have worked in the department during that period. It was undoubtedly one of the most innovative and influential departments of pharmacology in the UK, and well known around the world. It produced a string of major discoveries and many of its staff and students went on to win major international prizes (such as the Lasker Prize and the Nobel Prize) or to occupy high office in academia or industry.

During our time together, I had come to know Gus and learned from him that his fascination with platelets had begun while serving in the Royal Army Medical Corps, during a posting to Japan in the last phase of the Second World War. The crucial role of platelets in normal physiology and homeostasis was brought home to him vividly by the clinical examination of survivors of the atomic bomb blasts in Hiroshima and Nagasaki many of whom suffered from bleeding diatheses. I had also been introduced to other members of Gus's family including his wife Faith and, on one memorable Saturday morning, his father Max Born, the Nobel Laureate and pioneer of quantum mechanics. As a result of my exposure to Gus's influence and that of his colleagues during these years, I too became interested in the biology of platelets.

Aggregometers and aggregometry

It was during his postgraduate work in Oxford in the 1950s that Gus had first encountered the 'turbidometric' technique, which then was being used in his lab to measure the activity of ribonuclease in *Streptomyces* cultures. When faced with the challenge of quantitating platelet behavior, he adapted this idea for use in platelet-rich plasma (PRP). At first, separate readings of optical density were taken and plotted on a graph. Later, a continuous recording system was devised, such that the optical density data were logged using a chart recorder. The result was invention of the 'aggregometer'[1,2] and hence the technique of 'aggregometry' (a term Gus actually hated). It would be difficult to overestimate the impact of this device on platelet biology and on the diagnosis of hematological disorders. Virtually everything that we know about the aggregation of these enigmatic cells is derived to some extent or other, from the use of the device as attested by the huge number of papers published using the technique. 'Aggregometry' was soon adopted by many platelet labs around the world and, until it was produced commercially, Ziggy Sabikowski, the departmental electronics engineer at the RCS, struggled stoically to satisfy the burgeoning demand for these devices.

In addition to its use in clinical diagnosis and platelet biology *per se*, another often overlooked feature of the aggregometer was that it was probably the first example of a device that could measure the biological responses of a single human cell suspension in a relatively easy and straightforward manner. For all these reasons, Gus's original paper was quite rightly rated a 'Citation Classic' in 1977.

Later, when the technology became established and fully commercialized, variant forms of the aggregometer appeared such as the 'Lumi-aggregometer'[3] which enabled quantitation of released ATP as well as light transmission, thus providing another insight into the mechanism of the aggregation response. Eventually, the single cuvette of the original aggregometer was replaced by a multi well plate system enabling many samples to be read simultaneously and concentration-response curves to be constructed with speed and accuracy using a plate reader[4,5].

But, like all techniques, optical aggregometry had some inherent drawbacks. The most obvious of these was that platelets *in vivo* do not function in citrated PRP but in whole blood at normal physiological calcium concentrations. This begged several questions: was there, for example, an effect of erythrocytes on platelet behavior? After all, there are almost 10–20 times as many erythrocytes in blood as platelets and they are about five times larger. Surely there must be some possibility of mechanical interaction at

least? Also, erythrocytes contain nucleotides which could leak into the blood and possibly influence the aggregation response. And what about leukocytes? Although less numerous than platelets, their capacity for making biologically active substances might surely influence aggregation events? There was another theoretical issue too: some clinical conditions (e.g. Bernard-Soulier syndrome) are characterized by abnormally large platelets. Might these not separate into the lower erythrocyte layer following the centrifugation step required for PRP preparation thereby removing from the sample the very cells that you want to study? Gus was well aware of these problems and highlighted them in several of his papers (e.g.[6,7]) but because whole blood was opaque, it was difficult to investigate these issues using the optical aggregometer.

Another, more subtle problem, only surfaced some years later when it was found that activated platelets generate potent, but extremely short-lived, aggregating substances such as thromboxane A_2[8]. Surely, if these were present in the blood sample, any trace would have disappeared during the sample preparation time required for optical aggregometry? This was characteristically some 20–30 min, including the centrifugation step required to separate the platelets from the other blood components, whereas the half-life of thromboxane A_2 was less than a minute.

Such problems became a real concern for us in the Vane laboratory at Wellcome when, in 1976, the group made a major breakthrough with the discovery of a novel prostaglandin, prostacyclin (PGI_2[9,10]:) generated by vascular and some other tissues. This proved to be an exceptionally potent inhibitor of platelet aggregation and vasodilator and, in collaboration with the Upjohn Company, PGI_2 was soon in development by Wellcome for clinical use. But how could we monitor in human blood the action of a substance with a half-life of only some 8 min at physiological pH? It seemed likely that any biological action of this evanescent prostaglandin in a blood sample could have waned – or vanished completely – by the time the PRP was ready for assay.

Gus's influence on my personal research had included an appreciation of the utility of the platelet as a biological model as well as a potential target of therapeutic interest and so the aggregometer was among our standard items of lab equipment. My group had already used platelets as model for studying another problem in prostaglandin biology, the origin of arachidonic acid used for the synthesis of prostaglandins and thromboxane synthesis [11] and, by chance, I had also been attracted to the problem of how to assess platelet aggregation in 'native' blood samples.

The event which triggered my interest was a lecture in which the speaker had discussed changes in ion fluxes in platelets during aggregation. It occurred to me afterwards that these could be reflected by some corresponding changes in electrical properties of the PRP and, if so, these might be detected equally as well in blood. Accordingly, and in the best traditions of the amateur 'tinkerer', I attached two bent paper clips to the leads of a multimeter, set the instrument to measure electrical resistance, adjusted the sensitivity range and immersed this makeshift electrode assembly into a cuvette of PRP. I then added some collagen to aggregate the platelets and saw, to my delight but also great surprise, a small deflection of the needle of the meter. In retrospect, it is astonishing that such a crude set-up could have measured anything of physiological significance (the deflection was $< 5\Omega$) and in fact, my attempts to reproduce this initially promising result, proved frustrating.

As luck would have it however, there was a well-equipped electronic workshop at the Wellcome Foundation and I was particularly friendly with David Cardinal, who headed up this unit. I explained what I was trying to achieve and left him to think it over. A couple of weeks later he phoned me to say that he had some exciting results. He had constructed a purpose-built circuit to measure, not electrical resistance as I had done, but electrical impedance, which had the advantage of not causing polarization at the electrodes. Using this prototype device which was now equipped with platinum electrodes, we watched a substantial deflection appear on the chart when we added ADP or collagen to PRP and, even more significantly, the same result was obtained when blood was used instead.

Thus was conceived what we called in our first paper, the 'Electronic Aggregometer'[12]. Using our device and the 'Born aggregometer' in parallel and comparing the traces we obtained, we convincingly showed that it shadowed the results seen in the latter device almost exactly. All the usual agonists (e.g. ADP, thrombin, collagen, prostaglandin endoperoxides) produced near identical effects in both, and the inhibitory responses to drugs such as indomethacin were also as expected. This was of course, very reassuring. Furthermore, the maximum aggregation recorded by this machine was found to be proportional to the log of the concentration of most agonists showing that the technique could also be used quantitatively.

However, there were some interesting discrepancies between the recordings obtained with two techniques. As Gus had noted, one of the fascinating features of the aggregation response to some stimuli (such as ADP) was that it was preceded by a rapid isovolemic change in platelet shape which, by scattering light, caused a transient *increase* in the apparent optical density of PRP. In the case of ADP, this was succeeded by the 'first phase' and the 'second' phase of aggregation, a phenomenon first observed by Macmillan and Oliver[13], accompanied by the usual dramatic decrease in optical density.

Gus and his colleagues researched this 'shape change' in some detail[14,15] sometimes using a photocell detector set at right-angles to the incident light beam so as to provide more information about the 'shape change' phenomenon. The magnitude and velocity of the response were proportional to the log of the ADP concentration and conformed to Michaelis–Menton kinetics[15]. This, together with its speed, was interpreted (correctly) by Gus and his colleagues as evidence that ADP acted at discrete and specific membrane receptors.

These two phases of ADP-induced aggregation were clearly distinguishable in the electronic device as they were with the optical machine but obviously, no shape change information could be gleaned from the former. However, a comparison of the traces from the two devices revealed a hitherto hidden aspect of the aggregation response: in the optical aggregometer, administration of collagen, was generally followed by a 'latent' period and eventually a 'shape change' and then subsequently the full aggregation response. Simultaneous tracings using the electronic and optical devices in tandem revealed a 'first phase' of collagen-induced response, which occurred during the latent period seen with the optical device (Figure 2). In some cases, low doses of collagen failed to produce any change in light transmission in the optical device, and yet the electronic aggregometer clearly showed that some aggregation event was occurring (Figure 3). Furthermore, this phase was not susceptible to blockade by NSAIDs such as indomethacin. This finding was puzzling at the time, but was actually generally in accord with some previous work showing the release of adenine nucleotides and 5HT from platelets stimulated by collagen followed a similar pattern[16].

I discussed these observations with Gus when he visited with us on one occasion. He was intrigued by this observation and, as he pointed out, when aggregating agents are added to platelets in the optical device the photocell detector receives two types of information: an *increase* in light transmission as platelets form aggregates and a *decrease* in light transmission as the cells change shape. These signals are in opposite directions and so

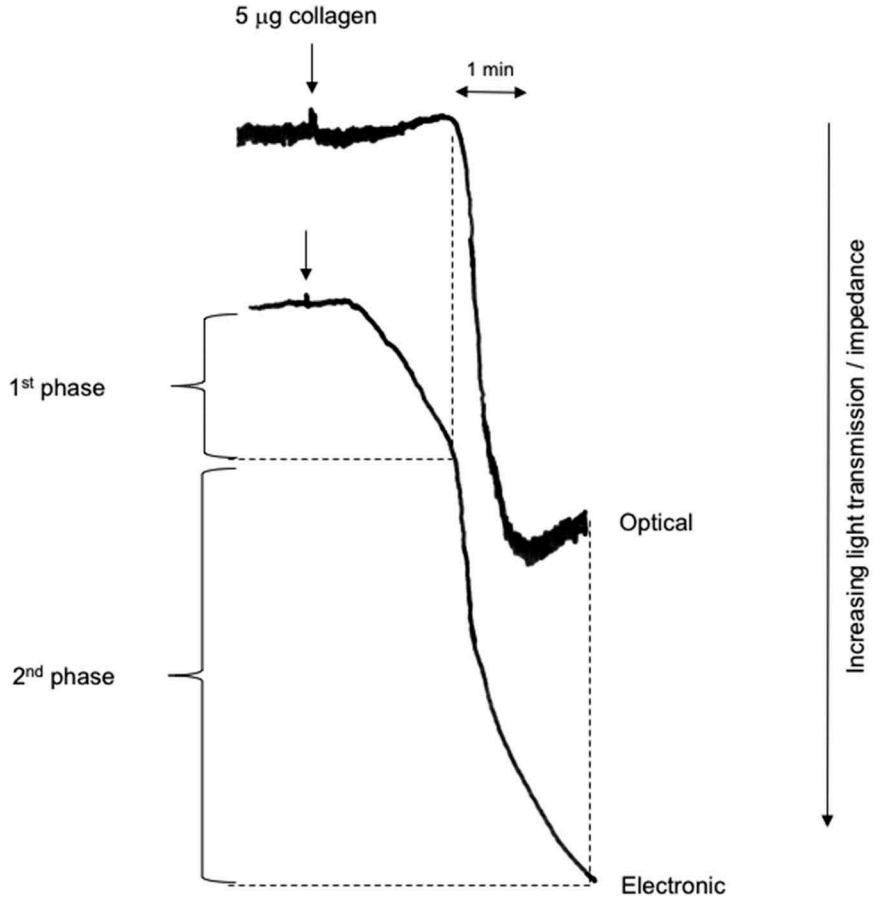

Figure 2. The 'biphasic' response of PRP (rabbit) to collagen. The two recordings were made simultaneously, in the optical and electronic machines, on matched samples. The 'first phase' of aggregation can only be detected with the electronic machine and corresponds to the 'latent' period in the optical device (rabbit PRP). Figure from Cardinal & Flower 1980 [12] redrawn and modified.

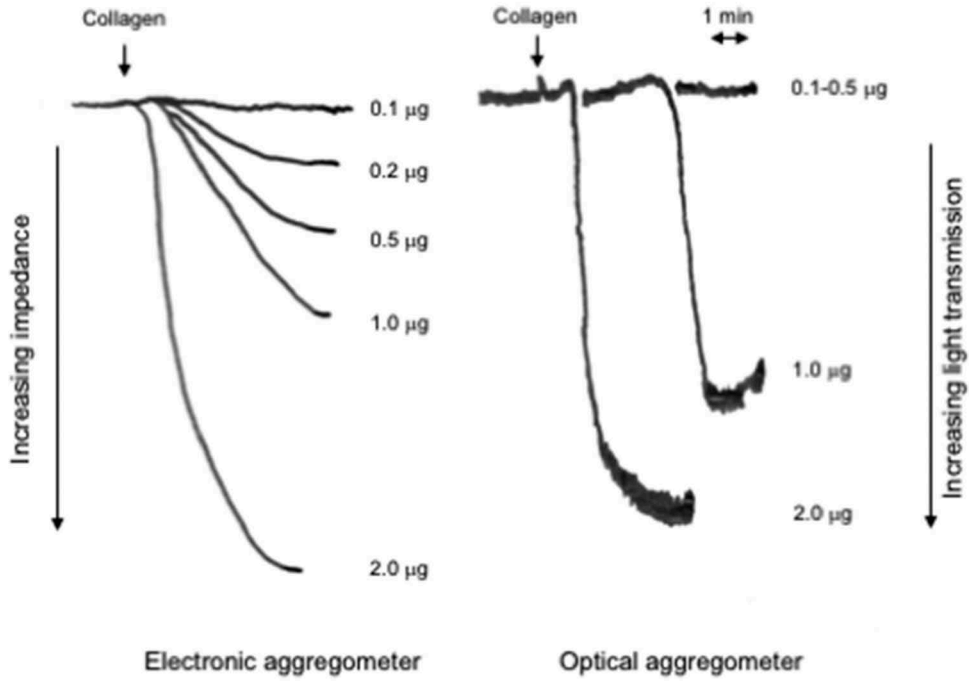

Figure 3. Sometimes it is possible to detect an effect of collagen using the electronic aggregometer even when there is no apparent response visible in the optical device. This concentration response study in rabbit PRP shows this clearly. Aggregation is taking place in the cuvette in response to 0.1–0.5 µg collagen as detected by changes in impedance even when there is no sign of aggregation in the optical device. The two recordings were made simultaneously, in the optical and electronic machines, on matched samples. Figure from Cardinal & Flower 1980 [12] redrawn and modified.

the photocell records the net transmission and hence some information may be lost. Because the electronic machine works in a different way, all it sees is the aggregation event.

But what was actually going on when the electronic device recorded an 'aggregation' response? Early in our experimental work with this new technique, we had abandoned the 'ionic' theory as an explanation for the phenomenon. Using electron microscopy, we had instead discovered that when the electrodes were dipped into platelet containing medium, a monolayer of these cells formed on the metal quickly reaching an equilibrium state. When subsequent stimuli were added, the platelets in suspension aggregated onto that monolayer causing the changes in impedance we observed. Electron micrographs of samples at the peak of the aggregation response, showed a dense mass of platelets with associated leukocytes and even some erythrocytes adhering to the electrodes, and so it would be more correct to refer to the output of the device as an 'adhesion-aggregation' response. It appeared then that collagen promoted a two-phase response but that only the latter was visible in the optical machine, the former appearing as a 'latent' period of the collagen response.

Further work by us showed that the electronic machine could be used with blood/PRP samples containing any common anticoagulant and indeed sometimes proved more sensitive than its' optical counterpart. We also demonstrated later that the technique could be adapted for use with tiny (100µl), or diluted samples of blood and that it was even capable of selectively measuring leukcoyte aggregation in response to agents such as the chemotactic tripeptide f-Met-Leu-Phe[17].

When human clinical trials of prostacyclin were initiated at the Wellcome Foundation, we were able to use the device to monitor the effects of intravenous prostacyclin in human subjects literally at the bedside. Following the infusion, small anticoagulated blood samples were taken at various time points and added directly to the cuvette in the electronic device. Within few minutes, the sample was ready to test with a standard concentration of ADP (or other agent) and the resulting traces confirmed that this new prostaglandin was a very potent aggregation inhibitor indeed[18,19].

Gus had never patented his aggregometer. He explained to me that this was due to the influence of his Oxford mentor, Howard Florey who, when asked why he had not patented his process for purifying penicillin, had apparently responded 'Can you patent sunlight?' Florey evidently believed that advances in medical science should be made freely available to all. It was a noble sentiment which Gus had also embraced but, working for a company as I was at that time, the same considerations could not be applied to our invention and Wellcome eventually sold the rights to the *Chrono Log Corporation* a well-known US manufacturer of optical aggregometers. During my talk at Gus's ninetieth birthday *festschrift*, I showed a slide of the *Chrono-Log* web page advertising both his optical machine and its great grandchild, the electronic machine, side by side.

It is almost 40 years since we published our initial description of this device and since then it has been extensively tested in laboratories around the world as well as in hospital hematology units (cf [20–22]). It functions well with all the conventional anticoagulants and in all species so far tested (e.g. [23]). In the main, it has proved to be a very useful addition to the study of platelet biology and has been favorably compared with other devices for this purpose. It has also been combined with other techniques such as luminescent detectors of ATP release e.g. [23] and re-engineered into a multi-plate device[24,25]. In the clinic, it has been used successfully in many clinical trials (e.g. [26–29]) to diagnose many platelet related disorders (e.g.[30] although some laboratories prefer the optical device for some purposes (e.g. [31].

The prediction that erythrocytes would influence platelet aggregation proved to be correct and this technique is certainly hematocrit-sensitive[32]. In addition, the interaction between leukocytes and platelets was indeed a significant factor for several reasons, including that fact that these cells can generate prostacyclin[33] and also because of the potential interaction between platelet P selectin and the leukocyte P selectin glycoprotein ligand, PSGL-1[34].

The impedance technique now occupies a useful niche among the ever-expanding armoury of devices for assessing platelet behavior and I hope that Gus was proud since it was his influence that set me off down this particular research avenue.

William harvey years

'The phone rang' Gus said to me one day over lunch, 'and it was John (Vane). He said 'why not come and join me here. Let's start again and have some fun!'

The year was 1990 and Gus, by now almost 70 years of age. He had left Cambridge in 1978 and had moved to take the pharmacology chair at Kings College in London, from where he subsequently retired in 1986. John Vane had also retired from the Wellcome Foundation about the same time and, not wanting to stop work at that time, had been offered a small lab on the Charterhouse Square campus of (what was then) St Bartholomew's Hospital Medical School. John had ambitions to grow this operation into something larger and more influential and to get things going, he invited some of his old scientific friends and colleagues to join him. I had received a similar call myself and was preparing to leave the department at Bath that I had been heading up for the previous 5 years, to join him in what promised to be a very exciting new initiative.

Within a couple of years John, together with Gus, Erik Änggård (a colleague originally from the Karolinska Institute in Stockholm), Derek Willoughby (the Professor of Experimental Pathology at Bart's), David Tomlinson (the incumbent Professor of Pharmacology at the medical school) and (later) Iain MacIntyre (Hammersmith Hospital) and I had formed an independent registered medical charity we called *The William Harvey Research Institute*. The name had been picked by John in honor of the eponymous ground-breaking physician/anatomist who had worked at Barts at one point during his career. Shortly afterwards, we also created a trading company, *William Harvey Research Ltd*, which organized conferences, undertook contract research and consultancy work and which generated an income stream for the Institute.

The medical school was moving many of their pre-clinical teaching departments from the Charterhouse site to another campus at Mile End in anticipation of a merger with Queen Mary, University of London and The Royal London Hospital Medical School at Whitechapel. This freed up a lot of laboratory space which we gratefully filled. My new department (*Biochemical Pharmacology*) was situated on the same floor as Gus's new labs, which he dubbed the *Department of Pathophysiology*. Since his office was just a couple of doors away from mine, we had plenty of opportunities to chat and discuss science. The photograph (see Figure 4) I took of him in his office dates from that period.

Glaxo had generously provided a start-up grant to John when he first moved to Charterhouse Square and other, equally significant funding, followed as the Institute gained momentum. My lab was supported at the beginning by Lilly and subsequently by the Wellcome Trust, but in those early days, a substantial grant from Ono Pharmaceuticals in Japan, proved to be a major stimulus enabling us all able to take on additional staff and refurbish more laboratories.

Gus had brought invited some of his colleagues from Kings College to join him and, together with some new PhD students, he embarked upon a new phase of his career. His main collaborators during these years included Peter Görög, Eduardo Cardona-

Figure 4. Gus in his office at The William Harvey Research Institute *circa* 1995.

Sanclemente, Shahida Shafi and Rudy Medina together with PhD students including Claire Ludlam and Hayley Farmer, but he also continued to collaborate with old friends such as Peter Richardson. His research program focused mainly on lipoproteins and their role in atherogenesis, the effect of catecholamines and angiotensin II on the uptake by vessel walls of atherogenic proteins and lipids and the nature of the plaque itself. This period was a productive time for Gus and, before he finally 'retired' aged almost 80 years old, he and his group published more than 65 papers.

Inevitably, over the passage of time, grants expired, students graduated, staff left, Gus stopped coming to the Institute every day and his department eventually closed. Even then, he was always happy to come and lecture if asked to do so. One of these talks, which made a big impact on the students (as well as many academic staff who attended), was his fascinating – and very dramatic – account of his life and that of his family. Visitors to Gus's office often marveled at the historical photographs hanging on the wall. One of these showed the participants at the famous 1927 Solvay conference (considered to mark a milestone in physics), which his father had attended and which included many of the giants of the discipline including Einstein, Heisenberg, Bohr, Dirac, Schrödinger, Pauli, Planck and even Marie Curie. As Gus always remarked (quoting his father), only a few of the people in that photograph actually *failed* to win a Nobel Prize. Through his father, Gus was personally acquainted with many of these founders of modern physics and listening to him talk about intellectual life in Göttingen in his father's day was to get a tantalizing glimpse into a quite extraordinary period in the history of science.

During the next few years, I remained in contact with the Gus and Faith and sometimes visited them at their cottage in the Cotswolds or their flat in Highgate. In addition to his almost fanatical devotion to the telephone (I grew accustomed to calls early in the morning or late at night), Gus also wrote frequently sending me comments and papers that he had written and requesting me, in turn, to keep him updated with my research which, by now, had diverged quite considerably from platelets and hemostasis.

A highlight of these latter years was the *festschrift* held in honor of Gus's ninetieth birthday in July 2011. At this happy event, Gus was reunited with many old colleagues, students and coworkers. He gave a fine talk at the end of the symposium which brought a wonderful perspective on his life and work. Figure 5 is a photograph taken at this event.

Gus was not just a scientist, but also a man of science. He believed passionately in curiosity-driven research, the importance of learning and – no doubt recalling his families flight from Göttingen during Hitler's rise to power and his father's subsequent status as a refugee academic in the UK – the necessity of preserving intellectual freedom, particularly in countries where academics were persecuted for their beliefs. This was a topic that was close to his heart and he campaigned and wrote about these subjects often[35].

His death in April 2018 was a great loss not only to his friends and family but also to the wider scientific community. His legacy will endure in his papers and his ideas and of course, in the work of his former students, many of whom are now high ranking academics in their own right. Although he made many contributions to biology and medicine, Gus will be remembered most vividly for his pioneering research into platelet function and the invention of the aggregometer. When, in my later university career, I discovered how difficult it was to keep actively working

Figure 5. The author together with Gus at the podium on the occasion of his 90th birthday *festschrift*, July 2011 at the William Harvey Research Institute.

at the bench when increasingly burdened with administrative duties – and how few senior academic staff actually succeeded in doing this – my first memory of him sitting by his aggregometer provided an inspirational example of what could be achieved.

Disclosure Statement

The author reports no competing declarations of interest.

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