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Elected FRS 1975

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With the death of Edward Charles Slater, Bill for insiders, biochemistry loses one of the key players in the field of bioenergetics in the second half of the twentieth century. Raised in Australia and trained as a chemist, he joined the lab of David Keilin FRS in Cambridge for his PhD where he discovered a new component of the mitochondrial respiratory chain, an Fe-S protein, long known as the Slater factor. After a brief post-doc period in the lab of Severo Ochoa in New York, where Slater started studies on oxidative phosphorylation that would remain his major interest, he returned to Keilin’s institute. In 1953 he formulated there his chemical hypothesis for the mechanism of oxidative phosphorylation that would dominate the field until displaced by the chemi-osmotic theory of Peter Mitchell FRS. In 1955 Slater moved to Amsterdam, The Netherlands, where he built up one of the largest and most successful biochemistry labs in Europe. He was not only an excellent biochemist, but also an outstanding mentor and a gifted administrator who turned Biochimica et Biophysica Acta (BBA) into the largest and one of the most influential biochemical journals of the 1960s and 1970s and who contributed to the governance of numerous organizations, such as the International Union of Biochemistry and Molecular Biology (IUBMB).

EARLY LIFE

Slater grew up in Melbourne, Australia, in a relatively well-to-do family. His father was a civil engineer for Victorian Railways, but also a fervent sea-sailor, a hobby that Slater would later also adopt. Slater describes his grandmother from his father’s side as ‘a very active and..."
intelligent woman, with strong views which she did not hesitate to express’ (41). Slater’s argumentative nature may have come from her.

As could be expected from a boy with Slater’s talents, he was a good pupil who passed through school with flying colours. It was a charismatic teacher, Tam Henderson, who succeeded in interesting Slater in chemistry. Henderson was also supervising the school magazine and he saw it as his duty to teach the student-editors how to write. Slater profited from these efforts and he attributed his ability to write comprehensible articles to Henderson’s instructions. Slater took pains to transmit the art of writing to his pupils. With admirable patience, he continued correcting our articles with a red pen in neat handwriting.

With his good school record, Slater succeeded in obtaining a fellowship for the University of Melbourne. He wanted to study chemical engineering, but as this was not possible in Melbourne, he settled for chemistry and engineering. Slater found the engineering course ‘rather a waste of time’ and he proved to have ‘no feeling for engineering design’ (41). Chemistry was different. Slater became enthusiastic about organic chemistry and he proudly mentions (41) that he ended as the best student of his year notwithstanding tough competition from other students who would go far in science. One of the practical chemical projects that Slater was given in his master studies was the determination of vitamin A in fish liver. Biochemistry did not yet exist as a separate field of science in the thirties and biomolecules were still part of organic chemistry. Vitamin A would be Slater’s entry into biochemical research and it would lead to his first scientific article (1).

Surprisingly, it was not possible to get a PhD in chemistry in Australia in 1939, when Slater completed his chemistry study. Before he could obtain a fellowship to go to Europe, World War II started. Chemists were still scarce and were not allowed to go into military service, but had to serve their country in other ways. This led to Slater’s appointment as biochemist in the Institute of Anatomy in Canberra with the instruction to determine vitamins in food, building on the experience he had gained with vitamin A. Slater started with vitamin B1 (thiamine) in wheat flour. By a curious coincidence, he used the thiochrome method for thiamine determination that had been developed by B. C. P. Jansen, the man that he would succeed as professor of biochemistry in Amsterdam 15 years later. Although Slater attracted several collaborators, there were no opportunities for more basic biochemical studies and the research remained very applied. Only an occasional publication is a reminder of Slater’s vitamin period.

Important for Slater’s later work was an intermezzo in 1942–1943, when he was stationed in the Chemical Defence Laboratories. Neither Japan nor the USA had signed the Geneva Convention prohibiting the use of chemical weapons. The possibility that Japan would use chemical weapons became real when, in early 1943, a Japanese shell was captured in which Slater’s team found mustard gas and lewisite. The British had discovered that the action of lewisite, an arsenic compound, could be counteracted by a dithiol, di-mercaptopropanol, that would become known as BAL, British anti-lewisite. Slater’s team synthesized BAL in Australia and this started Slater’s connection with BAL, the compound that would assume a prominent role in his later career.

When the risk of chemical warfare appeared to subside, Slater returned to Canberra, where he continued his nutritional research. Initially this consisted of determining vitamins in operational rations of the Army, ‘a silly job, totally useless’, as Slater says in his interview with Beechey (Beechey 1992). With gusto, however, he describes an experiment in which he was the guinea pig himself. Slater thought that the sulphonamides that were liberally
handed to soldiers to combat infections would interfere with thiamine utilization. To test this, he reluctantly ate soldiers’ rations with and without sulphonamides. The experiment was a success: the sulphonamides increased the excretion of thiamine substantially. This result was published in *Nature* after the war (2). Through experiments with rats, Kratzing and Slater (8) later showed that sulphonamides suppressed the function of the thyroid gland. The lower metabolism that resulted decreased the need for thiamine, with the consequence that more was excreted. ‘Although the results of these extensive and time-consuming experiments were of little or no importance,’ Slater writes (41), ‘I have never written a paper that gave me more satisfaction, since, within limits, it gave a completely rounded-off solution to the problem posed by the observation made with myself as the experimental animal.’

**The first period in Cambridge (1946–1949) and the Slater factor**

After the war, Slater managed to obtain a British Council Fellowship to go to England for his PhD. In that period, the University of Cambridge was the Mecca for biochemists, as Slater writes (41), and so he applied to David Keilin, director of the Molteno Institute of Parasitology and Biology. Keilin accepted him, but the British Council, seeing all their fellows flock to Cambridge, preferred Slater to go to Sheffield, where Sir Hans Krebs resided, the discoverer of the urea cycle and the citric acid cycle. When Slater, and his wife Marion, got on the boat in Australia he still expected to end up in Sheffield, but the British Council changed its mind and allowed him to go to Keilin after all. Careers are (co-)determined by chance and one may wonder, with Slater (41), what would have become of him had he gone to Krebs. Also a biochemist of world reputation, no doubt, but his fame would probably not have come from research on oxidative phosphorylation, because Krebs was more interested in intermediary metabolism and Slater did not easily switch his field of research.

David Keilin FRS was a parasitologist who had become famous by his discovery of the cytochromes in the respiratory chain, and he proved an ideal mentor for Slater (41): ‘Keilin was certainly the liveliest mind I have ever known. He had a tremendously wide knowledge of the whole of biology. For me, with a chemical background, this opened completely new worlds.’ Keilin also took time to teach Slater biochemistry. He told him to attend the standard lectures in biochemistry, and he would intercept Slater on his way home in the evening to discuss ongoing experiments; for Slater these were highlights in his Cambridge period. Slater had taught himself some biochemistry in Australia, but, as he says in the Beechey interview (1992), ‘in teaching myself, I had either been a very bad teacher, or a very bad pupil’.

Given Slater’s limited knowledge of biochemistry, Keilin gave him a research project close to his own work, to keep an eye on him. This project derived from an observation of Hopkins and Morgan, who had found that the oxidation of succinate by succinate dehydrogenase was inhibited by GSSG (oxidized glutathione). For these experiments, they had used the Keilin and Hartree heart-muscle preparation, now known to consist of fragments of the mitochondrial inner membrane. Slater found that GSH (glutathione) inhibited the oxidation of succinate even better and that BAL, the dithiol that Slater had used in Australia, inhibited best. This led Slater to his first discovery, as BAL did not inhibit succinate dehydrogenase itself, but the oxidation of succinate by the respiratory chain. This block occurred at an unknown component of the respiratory chain, the BAL-labile factor, long known as the ‘Slater factor’.
After the initial publication of the Slater factor (3), Slater spent the next 2 years on a thorough study of the oxidation of succinate and NADH by the respiratory chain and on additional experiments to solidify his discovery of a new component of the chain and to rule out any possibility that his BAL-labile factor was an artefact. This work was published in a series of articles in the *Biochemical Journal* (4–7, 9) and these made Slater a recognized respiratory chain expert. Slater’s respiratory chain in that period still lacked several components. The omission that he regretted most was cytochrome $c_1$, because he initially did not believe the evidence presented for its existence (41). Slater would return several times to the Slater factor in his later career (28), but it was Rieske who discovered that the factor was an Fe-S protein (33).

By present-day standards the experimental facilities in Keilin’s lab were still primitive. There was a microspectroscope and a Hilger spectrophotometer, but no cold room and no cooled centrifuge. In isolating the Keilin and Hartree heart-muscle preparation, Slater had to add ice to the centrifuge tubes to avoid overheating.

After 3 years of hard work, Slater obtained his PhD. His plan was then to return to Australia, as he was still on leave of absence from the Institute of Anatomy in Canberra. All Slater’s attempts to find a suitable job in Australia in the period 1946 to 1949 failed, however. This would happen again in the fifties after he had gained an international reputation. One can only guess why. No doubt his wish to continue in basic research conflicted with the wish of his Australian bosses to expand the applied work on nutrition. Probably character was also a (Slater) factor. He had a strong personality with outspoken opinions and he was argumentative. Not somebody to play second fiddle. Once, he was even told that the staff doubted whether he would fit into the new department (41). Slater was obviously a captain looking for his own ship, and he would find that in Amsterdam.

**New York**

In 1949 Slater went to New York on a Rockefeller fellowship to study oxidative phosphorylation in the laboratory of Severo Ochoa, chairman of the Pharmacology department of New York University. The department included a large number of talented staff members, mostly involved in the investigation of metabolic pathways. Oxidative phosphorylation had been discovered earlier by Vladimir Engelhardt in Russia (30), and subsequently Lehninger had shown that the process can be catalysed by isolated mitochondria. When he was still in England, Ochoa had studied oxidative phosphorylation in a rat-heart homogenate and Slater built on these experiments. The results were modest, but the environment was stimulating and Slater learned a lot in the year of his fellowship (41). He also used the period in New York to visit a large number of American labs and present his Cambridge work. This contributed to his reputation and to a network of biochemical colleagues that would become useful in his later career.

**The second period in Cambridge (1950–1955)**

When Australia did not come forward with a job, Keilin found a fellowship for Slater from the Agricultural Research Council (ARC) that allowed Slater to return to Keilin’s lab in an independent position. Remarkably, the ARC fellowship did not specify research on plants and
Slater could investigate what he wanted. What followed was probably the most productive period in Slater’s scientific life. An important factor was the quality of the Molteno staff, allowing Slater to start productive collaborative projects with scientists such as Tsou, Bonner, Tissieres and Lewis. Keilin supported Slater by providing him with collaborators: graduate student Francis Holton, a technician, and a guest, Ken Cleland.

Several of the projects of this period are noteworthy. With Walter Bonner, Slater published a detailed analysis of the inhibition of succinate dehydrogenase by fluorophosphates (10). This became a citation classic (38), in part because of the introduction of an improved method to measure the activity of the enzyme. Indeed, Slater had a special talent for improving methods. Enzyme kinetics would retain Slater’s interest in the remainder of his career. He would always check whether the equations of his students were balanced and even his medical graduate students were instructed to learn about the Gibb’s energy of enzymatic reactions (29).

With Cleland, Slater developed a procedure to isolate stable heart-muscle mitochondria. Key was the addition of EDTA to the isolation medium. This binds the Ca$^{2+}$ that the mitochondria will otherwise suck up (11). The stable mitochondria allowed Slater and Holton to obtain accurate measurements of the P:0 ratio of the oxidation of 2-oxoglutarate by heart mitochondria (13). The value found, 3, differed from that reported by other investigators. Slater’s values were lower because he averaged all determinations, whereas the competition believed that the highest values were the correct ones, a procedure that Slater considered unscientific. In fact, the most recent data support Slater’s value.

With Stan Lewis, Slater studied the mitochondria of the blowfly (14), because other investigators had reported that these mitochondria were unable to catalyse oxidative phosphorylation. This was an implausible finding that most people would have ignored, but a fairly representative start for a Slater project, as Slater liked to check implausible results; ‘policing bioenergetics’ would become a hobby. Of course, Slater and Lewis found oxidative phosphorylation in their flies, but the follow-up experiments inspired Slater to formulate his mechanism of oxidative phosphorylation that would become known as the chemical hypothesis, summarized in the following reactions:

$$\text{AH}_2 + \text{B} + \text{C} \leftrightarrow \text{A} \sim \text{C} + \text{BH}_2$$

$$\text{A} \sim \text{C} + \text{Pi} + \text{ADP} \leftrightarrow \text{A} + \text{C} + \text{ATP}$$

$\text{AH}_2$ and $\text{B}$ are adjacent components of the respiratory chain; $\text{C}$ is required for the redox reaction and remains covalently linked to $\text{A}$ in an energy-rich compound that can be used for the synthesis of ATP. The postulated $\text{A} \sim \text{C}$ would be hydrolysed by dinitrophenol, used by Slater to uncouple the respiratory chain from the associated phosphorylation. The *Nature* letter (12) with the chemical hypothesis would become Slater’s best known paper and the hypothesis would drive much of his later research.

**Amsterdam, 1955–1985**

In the mid fifties Slater had become one of the most visible and productive scientists in the bioenergetics field and with his obvious drive and ambition he looked like an ideal chairman for a biochemistry department. No offer came forth from Britain or Australia, but in Amsterdam a committee was formed to find a successor for B. C. P. Jansen, professor of physiological chemistry (the old name for biochemistry). One of the members
of the committee was Professor Bruno Mendel, molecular pharmacologist, originally from Canada, who had a large Anglo-Saxon network. He approached his British friends, including Keilin, who warmly recommended Slater. The committee was duly impressed with Slater’s credentials and placed him as number one on the nomination list. Slater had never been in The Netherlands, but reacted enthusiastically. As he writes (41):

We approached the idea very positively, Marion [his wife] even more so than I. The title of Professor, the novelty of an Australian being appointed in continental Europe, the idea of living in Europe, which had fascinated us on our visits (although these had not included Holland), the challenge of learning a new language, but above all, the chance it gave to build up my own school of research, which I had hoped to do in Canberra, were all in favour of acceptance.

When the medical faculty in Amsterdam also accepted all Slater’s requests for a generous budget for the lab, Slater decided to make the jump over the North Sea.

The task in Amsterdam was not simple. Although Jansen had done ground-breaking work on vitamins, the research had stalled in recent years. A large part of the laboratory was occupied by the Institute for Nutrition Research that Jansen had set up to supplement the meagre university funds. No modern biochemistry in sight. The department was housed in the quaintest of buildings, a former leper hospital (figure 1). The practical courses were given across the street in a seventeenth-century warehouse, which also housed the excellent animal facilities. There was sufficient space, however, and the ramshackle housing had a certain charm. It was not ideal. I still remember how unpleasant it was to cross the street with a bucket of experimental animals, or to climb the ultra-steep worn-out staircases with racks of tubes. Many an experiment ended in a pool of broken tubes.

Slater tackled the problems with characteristic energy and ingenuity. The Institute for Nutritional Research was handed over to the University of Wageningen, while Slater managed to retain eight of the well-trained technicians. He rapidly learned some Dutch, at least sufficient to talk to the technical staff, who spoke not a word of English in that period. Initially, Slater had to run the department with the staff he had inherited from Jansen, but soon he succeeded in attracting new people that allowed him to continue his own research lines in Amsterdam. He imported his technician from Cambridge. Post-doc Paul Greengard, the future Nobel laureate, also joined from Cambridge, and Slater obtained another post-doc from Mendel, Dave Myers. Soon, colleagues from Slater’s large network flocked to Amsterdam for a sabbatical and within a year Slater attracted the first graduate students.

When I started working as a graduate student under Slater’s supervision in 1958, the lab was already in full swing. The atmosphere was excited; this was the place where discoveries would be made. The charisma and the quality of Slater as a lab boss obviously offered that perspective. Everybody worked hard and there was effective collaboration within the lab. For Slater, collaboration was self-evident. Only results counted. He had no understanding for internal competition and as a consequence there was hardly any. As Slater once wrote (37), he firmly believed in the teacher–apprentice model for training students to become researchers in biochemistry. Students should work in small interactive groups on a topic selected by their supervisor. This allowed for effective supervision and it created an environment in which the brighter students would inspire the mediocre ones. Although this resulted in students only trained in a narrow field of biochemistry, that did not worry Slater (37): ‘Once they have learned to master a narrow field and to extend the existing boundaries of knowledge, they will
be able to do the same in completely different fields.’ Indeed, Slater’s students successfully went from oxidative phosphorylation into all branches of biochemistry.

In the hectic early days in Amsterdam in 1955 Slater also had to learn Dutch. One year after his arrival he was already fluent enough to teach medical students in Dutch. His Dutch would never become perfect, however. For instance, he would mix up the Dutch words *schoorsteen*, which means chimney, with *gootsteen*, which means sink. We always relished the moment when Slater decided that an experiment was no good and that the results should be thrown down the chimney, rather than the sink.

In the first 10 years of Slater’s stay in Amsterdam, the university expanded: the number of students increased and so did the number of staff positions. Slater managed to profit disproportionately from the largesse. In 1959 he accepted a second appointment in the science faculty. This provided access to chemistry students, another source of graduate students, besides medical students. Eventually, the Amsterdam biochemistry department would grow out into a super-department, serving four (sub) faculties—medicine, chemistry, biology and dentistry—housed in three different locations in the city, but all under the co-ordinating chairmanship of Slater supported by seven (associate) professors, mostly recruited from the ranks of his pupils. As biochemistry was expanding in the 1960s and 1970s, other Slater pupils
Biographical Memoirs

were exported to chairs in many other Dutch universities. The Amsterdam lab became the start for many outstanding careers all over the world.

In 1967 a large part of the biochemistry department moved to a new institute, the B. C. P. Jansen Institute. Slater was deeply involved in the planning of the construction and layout of the building. This was a job Slater liked. He already had experience with building in Canberra, where he had contributed to the plans for the expansion of the Institute of Anatomy, and later with the building of his house in Cambridge, where he would never live because of his departure to Amsterdam. After Slater retired, the B. C. P. Jansen Institute was rechristened the E. C. Slater Institute, but this did not last to the present day, as the institute eventually merged with the Swammerdam Institute for Life Sciences.

Besides the large B. C. P. Jansen Institute, located at the chemistry faculty, the department had two annexes: the section for medical enzymology and molecular biology within the grounds of the medical faculty and a section for molecular biology within the biology faculty. These annexes were an integral part, however, of the biochemistry department led by Slater. The advantage of this structure was that all tasks were shared and that substitute teachers were always available if illness struck. Another advantage was that the staff, appointed in the medical or the dentistry faculties, had direct access to the undergraduate students and prospective graduate students from the science faculty. More than any other Dutch lab, Slater continued to host a large cast of foreign visitors as well, attracted by his world reputation as an outstanding investigator and organizer.

For a brief period, this well-functioning superstructure was reeling when, between 1968 and 1971, the call for democratization, initiated in Paris, reached the Dutch universities. Scared politicians responded with a new law that eliminated the position of the professor-director of laboratories. In essence, this robbed Slater of his formal function as boss. He was extremely annoyed that the Dutch government would treat his guaranteed rights in such a negligent fashion. He always stuck to the rules himself—a real boy-scout people sometimes said—and a government practising such ugly antics was foreign to him. He even applied for a job in Australia, but, fortunately for Amsterdam, he was not appointed.

In the end, the damage was limited. An elected laboratory council was put in place and this council had to elect a chairman, of course Slater. He had already involved his senior staff in decision-making and now representatives of the technical staff and the students were added, allowing them to learn from master Slater how to run a big laboratory. While laboratory organizations collapsed left and right in the University of Amsterdam under the pressure of the democratization, the superstructure built by Slater remained intact, thanks to his authority and organizational talents.

Democratization made the university more informal and, as a young professor, I became Piet for my students, rather than Professor Borst. Not Slater. He stuck to (Anglo-Saxon? Australian?) formality and remained Professor Slater, including for the close colleagues who became full professor in his department. Only when I became a ForMemRS—an honour that Slater particularly cherished—did he decide that I should call him Bill.

Although Slater retained close ties with his Australian and English roots, he completely settled in The Netherlands and contributed in many ways to the organization of Dutch science. As a member of the Board of the Dutch Research Councils he helped allocate money to the best, although he did not like the bureaucracy and administrative burden involved. In 1964 Slater was elected into the Royal Netherlands Academy of Arts and Sciences as a member of the chemistry division. He was extremely pleased with his election, as he considered it proof
that his move to The Netherlands had become a success and that he now really belonged to the Dutch scientific community. From the start, Slater was very active in the Academy. He even convinced his colleagues to start a new section for biochemistry and biophysics, because he expected that this would promote the development of these new disciplines. Indeed, when Slater joined he was the only biochemist in the entire Academy.

Another important function that the Academy entrusted to Slater in 1964 was the secretariat of the new Dr H. P. Heineken Prize for Biochemistry and Biophysics. Slater drew up the rules for the selection of the prize recipients and for the modus operandi of the jury and he remained a member of the jury until 1976. He enjoyed the social side of the prize activities, the jury meetings, the award ceremony, the dinners, and he was sorry that he had to give up his jury membership in 1976 when he was proposed for the prize, especially since he did not get it.

Slater remained a faithful member of the Academy and he visited almost all monthly meetings. As he writes (41): ‘I found the Academy a refuge of eliteship from the over-democratised outside world.’ With typical Slater irony, he adds (41): ‘I recall the surprise of my colleagues in the USSR when I told them that, in contrast to the privileges of an Academy member in that country (car, dascha, extra salary, etc.), my only privilege as an Academy member in the Netherlands was being given the key to the bicycle shed.’ Slater was not a man claiming privileges. ‘Public money should be spent on research, not on taxis’, he used to say. Slater never owned a car and he cherished his Dutch bike. Anybody who saw Slater cycle through Amsterdam would not easily guess that this typical Dutchman was born in Australia, retained his Australian nationality and cherished his roots (25).

**Research in Amsterdam**

In Amsterdam, Slater continued his experiments on the mechanism of oxidative phosphorylation. Initially, he had no equipment for sophisticated experiments and he therefore turned to the mitochondrial ATPase activity, which was easy to determine. Lardy had established the link of this ATPase to oxidative phosphorylation by showing that it is stimulated by dinitrophenol. The first experiments in Amsterdam suggested that there were three separate ATPases in the mitochondrial inner membrane, but this conclusion proved untenable (15). The experiments made Slater realize, however, that the ATPase activity was not affected by inhibitors of the respiratory chain and that his chemical hypothesis for oxidative phosphorylation had to be modified by introducing an additional intermediate:

\[
AH_2 + B + I \leftrightarrow A \sim I + BH_2
\]

\[
A \sim I + X \leftrightarrow A + X \sim I
\]

\[
X \sim I + ADP + P_i \leftrightarrow X + I + ATP
\]

Now X \sim I was the intermediate sensitive to uncouplers of oxidative phosphorylation. The hunt for A \sim I and X \sim I would remain a central theme in Slater’s research as these intermediates were, of course, the essence of the chemical hypothesis. Initially, post-doc Jack Purvis (1958) found indications for the existence of A \sim I in the form of NAD \sim I. Later work by Karel van Dam (1964) showed, however, that the putative NAD \sim I was the result of an experimental artefact. By that time, Slater was already in discussion with Peter Mitchell (see below).
Several early Slater students studied the phosphorylation coupled to individual steps in the respiratory chain—solid research with useful results, but without real discoveries. Coen Hemker (1962), in work that did not receive the attention it deserved, according to Slater (41), studied the effect of lipid solubility and pK on the uncoupling activity of a homologous series of 2,6-dinitro-4-alkylphenols. He concluded that the uncoupling activity was determined by the amount of phenol dissolved in the mitochondrial membrane, suggesting that uncoupling was due to the ability of the phenols to shuttle protons through the membrane, a conclusion compatible with the chemi-osmotic hypothesis of Mitchell, although that was not Slater’s conclusion at the time.

Slater’s enzymological interest was reflected in the work of a number of students. Koen Minnaert (1961) studied the kinetics of cytochrome c oxidase and Bob van Gelder (1966) found that this enzyme contained two haem molecules and two copper centres. Van Gelder also introduced EPR spectrometry in the Slater lab.

Another enzyme studied by subsequent students in the lab was glyceraldehyde-phosphate dehydrogenase (27). This enzyme catalyses substrate-bound phosphorylation and it uses undisputed chemical intermediates, making the enzyme a suitable model system for oxidative phosphorylation in Slater’s philosophy. The most important result of the studies of this tetrameric enzyme was the discovery of negative cooperativity of the binding of NAD$^+$ to the enzyme by Jan de Vijlder (18), who was also the first student to use the stopped-flow apparatus. This had been built for Slater by Professor Van der Tweel, the biophysicist of the medical faculty, and it became known in the lab as the ‘advantage wheel’. This term originated in a letter from Britton Chance, who dictated his letters and did not bother to correct them. ‘Van der Tweel’ was typed by an ingenious secretary as ‘advantage wheel’, to the joy of Slater who ran through the lab to show Chance’s letter to all his collaborators.

A productive line of research, started by graduate student Cees Veeger, was the study of flavoproteins, first succinate dehydrogenase, later NADH dehydrogenase. With Vincent Massey, the enterprising Veeger managed to completely elucidate the mechanism of action of NADH dehydrogenase (Veeger and Massey 1962). In the end, this project moved with Veeger to the University of Wageningen, when he was appointed to their biochemistry chair.

A new line of research sprang from a collaboration with the professor of paediatrics in Amsterdam, van Crevel, who had (co-)discovered the first glycogen storage disease and who was interested in inborn errors in carbohydrate metabolism in general. Slater set up a collaborative project on G-6-PD deficiency and glycogen storage diseases, and he facilitated this with the creation of a new and separate annex of the Slater lab located elsewhere in the city, within the grounds of the academic hospital, the section for medical enzymology (and, added later, molecular biology). To Slater’s satisfaction, the head of the new section, Wim Hülsmann, found that the original patients, in which van Crevel had discovered the glycogen storage diseases, had a defect in the enzyme phosphorylase, required for glycogen degradation (Hülsmann et al. 1961).

Another new line of research was the study of mitochondrial protein synthesis. This was a controversial topic at the time when Slater started because prominent investigators promulgated that all protein synthesis in mitochondrial preparations was due to bacterial contamination, given its inhibition by chloramphenicol and other inhibitors of bacterial protein synthesis (Kroon 1965). The issue was settled by graduate student Ab Kroon, who demonstrated active protein synthesis in steriley-prepared rat-liver mitochondria (Kroon et al. 1967). Another new side-line was the study of tumour mitochondria, inspired by Warburg’s
theory that cancer is caused by defective mitochondria. When, as a student, I showed that the mitochondria of the highly aggressive Ehrlich ascites tumour were completely normal in every aspect that could be measured in the Slater lab, this side-line came to a natural end.

The enormous diversity of the research repertoire that would eventually characterize the Slater lab mainly came from former students who became staff members in the department in Amsterdam. Joseph Tager and I started work on lysosomal storage diseases. My early studies on glutamate oxidation by mitochondria (16, 39) evolved into wide-ranging studies by Tager and Fred Meijer on intermediary metabolism and control theory. On my return to the Slater lab after a postdoctoral period in New York, I started working on mitochondrial nucleic acids. This led to a study of the mtDNA (kDNA) of trypanosomatids and eventually to studies of antigenic variation in African trypanosomes and the discovery of the glycosome. Slater remained interested, but was not directly involved anymore. However, the burgeoning DNA research brought some of the most famous future alumni to the Slater lab, Richard Flavell FRS, Sir Alec Jeffreys FRS, Jan Hoeijmakers and Titia de Lange, to mention a few.

SLATER VERSUS MITCHELL

In 1961 Mitchell proposed his chemi-osmotic hypothesis to explain the mechanism of oxidative phosphorylation. This hypothesis postulated that electron transport through the respiratory chain generated a proton gradient that drove ATP synthesis. Mitchell only required an intact membrane; he had no need for the energy-rich intermediates of Slater. Although Slater emphasizes (Beechey 1992; (41)) that his initial reception of the Mitchell hypothesis was positive, this is not what I remember of the first lecture by Mitchell in Amsterdam in 1962, in which he presented an early version of his hypothesis. Slater was not amused by this direct attack on his pet chemical theory of oxidative phosphorylation, and he bombarded Mitchell for an hour with critical questions and comments. Not unreasonable, of course, because Mitchell’s concept was brilliant, but the fit with the known facts was still far from perfect.

The subsequent competition between the chemi-osmotic hypothesis and Slater’s chemical hypothesis would dominate bioenergetics in the 1960s. Eventually, Mitchell would prevail and receive the Nobel prize. It took Slater a long time to be converted. In 1967 he wrote in a review that the current version of the Mitchell hypothesis was ‘untenable’ (17). It would last until 1977, when Slater conceded in a review with others (23) that the Mitchell hypothesis was the best working hypothesis to explain the mechanism of oxidative phosphorylation, but he would never become a wholehearted proponent. When retired, Slater published a detailed review of the existing knowledge with his remaining doubts and a new ‘collision hypothesis’ for the interaction between respiratory chain and the ATPase complex (35).

I think that the clash between Slater and Mitchell was not only a matter of biochemical theories, but also of personalities. Mitchell was a Dionysian scientist, with brilliant insights, but not always precise with facts. Slater was the Apollonian type, meticulous, critical, analytical and systematic. His reviews were models of clarity and precision and he had little affinity for the romantic way of doing research. Representative is Slater’s reaction to a biography of Mitchell, entitled: Wandering in the gardens of the mind: Peter Mitchell and the making of Glynn (Glynn was the private lab that Mitchell had installed in a castle he bought). Slater wrote in his review for Nature (46): ‘In Mitchell’s garden of the mind, ideas seem to have deeper roots than facts.’
Nevertheless, the Slater–Mitchell controversy was productive. Although both were strong personalities and argumentative, they were not vindictive and they maintained an intensive and friendly correspondence during the entire controversy. The persistence of Slater in pointing out loopholes and inconsistencies in the early versions of the chemi-osmotic theory (17) probably led Mitchell to a more complete theory. That the contacts remained cordial is illustrated by visits of Slater’s associate, Karel van Dam, to Glynn for collaborative experiments in which van Dam and Mitchell sorted out differences in experimental results and interpretations. Slater’s lab also contributed other experiments to help plug the holes in the chemi-osmotic hypothesis. Graduate student Jan Berden and guest Mårten Wikström clarified part of the controversial role of co-enzyme Q (ubiquinone) in the respiratory chain (Wikström and Berden 1972), but, in the end, it was Mitchell who solved the problem with his ingenious Q-cycle (31). After Mitchell’s early death, Slater wrote a scientifically detailed obituary for the Royal Society (40), praising Mitchell’s genius. That masterful analysis of the complex development of Mitchell’s ideas illustrates the power of Slater’s mind, even when he was well into his seventies.

Slater would search in vain for his chemical high-energy intermediates, but eventually Harris, Rosing, Berden and Slater would find tightly-bound ATP and ADP in the highly purified F1-complex (19). Slater immediately realized that the high-energy intermediate might be a high-energy state of this complex (41). If the operation of the respiratory chain would cause the dissociation of the ATP tightly bound to the ATPase complex from the protein, this would be the final step in oxidative phosphorylation. Although Slater reported this idea in his plenary lecture at the International Congress of Biochemistry in the summer of 1973, others would be first when it came to providing the details. Harvey Penefsky demonstrated that purified F1-ATPase, associated with stripped mitochondrial membrane, spontaneously synthesized ATP from ADP and Pi, whereas Paul Boyer formulated the most complete version of a theory in which the operation of the respiratory chain results in a change in the 3-D structure of the F1-ATPase, allowing release of ATP.

Slater found it satisfying that an energy-rich intermediate did exist after all in oxidative phosphorylation, albeit as the energy-rich form of F1-ATPase. Mitchell had also been wrong in one aspect of his theory: the synthesis of ATP is not directly driven by the proton gradient generated by the respiratory chain, but indirectly via a conformational change in the ATPase. The Nobel prize for the conformational hypothesis of ATP synthesis went to Boyer, however.

It remains surprising that Slater did not go after the structure of the F1-ATPase after the work of Rosing and Berden. With Kemp and Berden he had also determined the stoichiometry of adenine nucleotide binding to the ATPase, using the 8-azido-ADP and -ATP, made by Kemp (Wagenvoord et al. 1977). The value obtained, 6, has stood the test of time. Although Slater was not a structural biologist, he could have started a collaboration with the excellent crystallographic group in Groningen, only 2 hours from Amsterdam. With Slater’s experience in purifying and testing the enzyme, and young stars like Wim Hol in Groningen, he might have successfully competed with Andrew Lesley FRS and John Walker FRS, who solved the elegant F1-ATPase structure. Why Slater did not go for the ATPase structure, I never asked. He may have been already too much entangled in organizational work, or he may have wanted to leave more space to his pupils/colleagues in the lab.

Slater did start a completely new project, however, in 1973, inspired by the oil crisis. The goal was to couple photosystem II with a bacterial hydrogenase to produce hydrogen as a clean source of energy. A consortium was formed, initially led by Slater, in which several Dutch labs
participated (21). In Slater’s lab, Siem Albracht became the driving force. Although the project did not solve the energy crisis, it did result in interesting basic findings, e.g. the discovery that carbon monoxide and cyanide act as ligands of nickel and iron in all hydrogenases (Happe et al. 1977; Pierik et al. 1998). The project is still alive today, and even in Amsterdam, but not in the Department of Biochemistry any more.

Slater as a mentor and a colleague

Eventually, Slater would become the most influential biochemical scientist in The Netherlands and the dominant force in shaping Dutch biochemistry in the second half of the twentieth century. This was not only due to his exceptional talents as a scientist and organizer, but also to his ability to attract the best students, post-docs and colleagues on sabbatical and to inspire and educate them. The main tool that Slater used to direct the research in his department was the Saturday-morning research meeting. There, we presented our ongoing experiments and Slater would scrutinize them for errors in design, lack of the proper controls or alternative interpretations. In these meetings, we learned from master Slater how to do research, how to analyse the results, how to accept criticism in a constructive fashion and to maintain the highest standards of integrity, like Slater did himself.

Slater also taught us the importance of financial control. Public money should be spent frugally. Research is expensive and must be planned and executed carefully. Slater’s bookkeeping became legendary in the university. Every year his own records of the lab income and expenses did not completely match the bookkeeping of the university, and always Slater was right. At the lab’s Christmas parties, Slater would give us a detailed overview of the money we had spent and what we had produced for society in return, in terms of research output and teaching.

Slater was argumentative and had strong opinions. His exceptional knowledge of the literature and sharp intellect made him a formidable debater and his persistence in scientific discussions was legendary. Symposium sessions would be stretched when Slater would take on worthy opponents in bioenergetics, such as Britton Chance or Peter Mitchell. When Slater criticized experiments, he was civil, but blunt, and he had little patience with scientists who could not deal with critique or, worse, who took criticism of their experiments personally. Slater disliked stupidity, laziness, ignorance (when opponents should have known) or behaviour that he considered unethical. Emotional as Slater was about science, he could then get angry and become red as a beet. This ‘traffic light’ effect was well known to insiders, but it would never last long.

Although Slater was a workaholic, he also liked sports. He was a serious opponent on the tennis court and he used to go skiing in Switzerland, where he had a second house (figure 2). As a child, he had sailed with his father and later he would make long trips on the seas around The Netherlands in his own boat with students/post-docs as crew. As I am invariably seasick on boats, I never had the pleasure of that experience in the 25 years that I spent in Slater’s department. Slater was a very sociable man, notwithstanding his dominant personality and emotional nature, and a fair and congenial boss. He readily acknowledged his mistakes, even though they were rare. He was also generous. Graduate students who developed their own line of research received his full support and advice, but he would take his name off their papers. The reference list of this obituary testifies to that. For his students, Slater was the ideal role model with his high standards, his devotion to well-planned research, his fantastic knowledge...
of the literature saving his students from duplicating what had been done elsewhere and his superb way of organizing and running a department.

His systematic and well-planned mode of research also had a down-side: he would hesitate to venture on uncharted roads or ventilate speculative hypotheses. Of course, one can sometimes find treasures by digging deeper and deeper at the same location, but sometimes the treasures are elsewhere. Slater spent an unusual amount of time checking results that he did not trust. His aim was not only to find the correct answer, but also to understand how the erroneous conclusion had been reached in the first place by the other lab. This was undoubtedly useful and important police work that helped to sanitize bioenergetics, but all these efforts to correct the record may have replaced more innovative new projects.

EMBO, EMBL AND IUBMB

From his base in Amsterdam, Slater increasingly contributed to the organization of biochemistry in the world. He was secretary of the Committee on Biochemical Nomenclature...
of IUPAC (1959–1964) and he contributed in many ways to the running of EMBO (European Molecular Biology Organization) and the EMBL (European Molecular Biology Laboratory). He chaired the EMBO Fund Committee (1974–1978); he was the president of the EMBL Council; he was the chairman of the Search Committee that selected Lennart Philipson as the new director-general of EMBL to succeed John Kendrew; and he was the (almost eternal) auditor of EMBO.

Slater liked the scientific excitement and camaraderie of scientific meetings and until 1994 he was one of the few biochemists in the world who could claim to have attended every single International Congress of Biochemistry organized by the IUB(MB) (43, 48). Hence, it is not surprising that a person of Slater’s scientific stature and managerial qualities would be recruited by the IUBMB for help. In 1964 he became a council member; for 8 years (1971–1979) he acted as treasurer of IUB; in 1985 he became president-elect; and from 1988 to 1991 he served as president. He became treasurer for a second time from 1999 to 2000 (42).

One famous incident should be recalled here. This concerned the sensitive relations of IUB with the ‘two Chinas’, Taiwan and mainland China. When Taiwan joined the IUB in 1961, China withdrew, accusing the IUB council members of being ‘lackeys to American imperialism’. In the mid seventies, Slater applied for a visa to China without success, but finally managed to get there in 1979 by making use of an exchange programme between the Dutch and Chinese academies. A period of intense shuttle diplomacy followed, requiring 10 visits to China and Taiwan, which finally led to the return of China to the IUB. The compromise crafted by Slater and IUB General Secretary Whelan became a model for other international scientific unions to deal with China and Taiwan (26). The Chinese were obviously impressed by Slater’s ingenuity and tenacity. They invited him to become a member of an international advisory panel for the Chinese University Development Project of the World Bank. This involved ‘extensive, not always comfortable, visits to universities all over China’, as Slater writes in his memoirs (41). No doubt, these visits contributed to the revival of Chinese biochemistry.

**Slater as Mr BBA**

The early history of *Biochimica et Biophysica Acta* (*BBA*) was described by Slater himself with characteristic precision and in exquisite detail in a monograph (34) and here I summarize only some of the highlights of Slater’s essential role in the success of the journal. The initiative for *BBA* was taken by the Dutch biochemist Westenbrink and the Danish biophysicist Linderström-Lang, directly after World War II in 1946. It was Westenbrink, however, who became the central figure in pushing the new journal, recruiting reputable editorial board members and authors, and keeping it alive in the early tough years when *BBA* was a money-loser for Elsevier, its publisher. It would take 7 years before Elsevier had recouped its losses and even in 1953 Elsevier tried to sell *BBA*, without success. Westenbrink also kept *BBA* going by doing an incredible amount of administrative work for the journal, dealing directly with all authors who submitted papers.

The fate of *BBA* changed when it started publishing Preliminary Notes and Short Communications in 1951. Slater (34) has been unable to trace the origin of this innovation, whether it came from Westenbrink, the publisher, or one of the other editors, but it was an instant success. At the time, no other journal published such titbits and there was clearly a
latent demand, especially for rapidly publishing new findings in the increasingly competitive field of biochemistry. Although *Nature* and *Science* published letters, these journals had limited space for biochemical papers, as they covered all science. They also did not yet have the reputation they enjoy today. In fact, the Preliminary Notes of *BBA* became such a success that Westenbrink was overwhelmed by submissions.

In looking for help, Slater was an obvious choice for Westenbrink. After his appointment in Amsterdam, Slater had contacted Westenbrink as the leading Dutch biochemist in the country. They got along well; Westenbrink even lent equipment to Slater. Initially, Slater was reluctant to accept a major side-job in 1956, only one year after starting in Amsterdam. As ‘always when he was undecided about an important scientific or academic matter’ (34), he consulted his teacher, Keilin, for advice. To his surprise, Keilin was positive: ‘an editorial function was an intellectual stimulus and would give scientific contacts of value to the editor’s scientific development.’ Keilin, knowing Slater’s talents, obviously thought that this was the appropriate side-job for his pupil, and this advice started Slater’s long and intensive involvement with *BBA*.

From 1957 onwards, Slater was managing editor of the Preliminary Notes and Short Communications section of *BBA* and he contributed to the success of the new section. It is therefore not surprising that Elsevier asked Slater to become managing editor for the whole of *BBA* after the early death of Westenbrink. This was the perfect job for Slater. Running a rapidly growing journal required enormous energy, deep knowledge of biochemistry and biophysics, a vision on the future of the field and the tact and tenacity to deal with Elsevier—not only interested in scientific quality, but also in profit. To spread the burden, Slater asked two prominent Dutch biochemists to join him as associate managing editors, Laurens van Deenen and Max Gruber. The size of *BBA* doubled every 4 years in the first 20 years of its existence and its growth was much larger than that of all other biochemical journals (34). By dividing *BBA* in more and more subsections—starting with biophysical subjects, enzymological subjects, nucleic acids and related subjects, lipids and related subjects—Elsevier managed to keep the journal comparatively accessible to insiders, notwithstanding phenomenal growth. Although Slater admits that this contributed to the success of *BBA* (34), he was not enthusiastic about this subdivision, because he believed in the unity of biochemistry.

In the 1960s *BBA* managed to combine growth with quality. Biochemistry and biophysics grew like weeds and for many labs *BBA* was the first choice for publishing results. That held primarily for enzymology and bioenergetics and for the biomembranes and lipids, the fields in which Slater and van Deenen had a world reputation. There was hardly any competition between journals. Investigators published in a serious journal, in which other investigators in their field of interest also published their articles. Careers were not made or broken by citation scores. Editorial boards watched over the quality of the published articles, but the hunt for the most interesting discoveries did not yet exist.

Of course, the ‘Growth Explosion of *BBA* in the 1960s’ (34) became an increasing concern for Slater and the editorial board, as was the rising cost of *BBA* to subscribers, which led to a stream of complaints from colleagues. A memorandum of the managing editors in 1965 compares the price of *BBA* to that of other commercial journals and concludes that it is about average. How much profit efficient Elsevier made with *BBA*, Slater did not find out (34).

The editorial board did not use the opportunity provided by the sectionalization to go for increasing quality, instead of size. This was probably not only due to the drive of Elsevier for expansion and profit. Slater was just not the person to start selecting the ‘sexy’ articles.
He was convinced that all good solid biochemistry reporting new results should be published. The arrival of newcomers, such as the *Journal of Molecular Biology (JMB)*, that tried to pick the currants from the cake, introduced a style that was not Slater’s. Already in 1967, however, there were extensive editorial board discussions about the unfortunate loss of the best papers to the *JMB* and the *PNAS*. In fact, Slater concludes that the section on nucleic acids (later renamed Gene Structure and Expression) had ‘badly missed the boat’ (34). Why that had occurred is not analysed by Slater. Adding additional managing editors with a strong reputation in this field, such as Charles Weissmann and Richard Flavell, did not help to regain the ground lost. It is probably typical of Slater that he did not change course and started to aggressively solicit the best and most interesting papers. This made *BBA* vulnerable when, in the 1970s, competition between journals escalated and journals such as *Cell*, *Nature* and *Science* started to take the cream off the publishing milk.

Looking back at these turbulent years of *BBA*, it remains remarkable that Slater successfully managed the increasingly complex journal in the same period that he built up his super-department, combined with the large number of other side-jobs described above. It illustrates his enormous talents, his persuasiveness, his administrative skills, his grasp of the whole of biochemistry and biophysics, and his ability to work efficiently for very long hours. To cope with the increasing volume of submissions, Slater recruited pupils and colleagues as associate managing editors and I served in that function for some time. The editorial board meetings were lengthy affairs. Slater would see to it that all relevant numerical information was presented in detail, numbers of submission for each section, numbers of rejections, revisions and acceptances, and especially the time lines. Slater would put enormous pressure on his staff and associate editors to keep the time between submission and the final decision to a minimum. He continued the demanding side-job of running *BBA* until 1982 and he remained honorary executive editor and did editorial work until well into his eighties.

**Retirement**

Slater’s retirement from the university in 1985 did not end his involvement with science and teaching. He moved to Lymington in southern England, became an honorary professor at the University of Southampton, where he contributed to the teaching of biochemistry and to the difficult task of distributing scarce money. Slater was uniquely qualified for this task, as an outsider, a meticulous administrator and a tactful but forceful committee chairman. The University of Southampton thanked him for his important contributions with an honorary doctorate. He also received an honorary doctorate from the University of Bari, Italy, in recognition of his contributions to the highly successful Bari–Amsterdam Symposia on Bioenergetics, the first truly European biochemical symposia. Slater received many other honours during his professional life, such as the honorary membership of the British Biochemical Society and four other biochemical societies. He was, of course, a Fellow of the Royal Society and a member of the Royal Netherlands Academy of Arts and Sciences, but also a foreign member of the Academies of Science of Argentina, Australia, Belgium and Sweden. In The Netherlands, he received the Royal Dutch Shell Prize and Queen Beatrix made him Knight in the Order of the Netherlands Lion, one of the highest distinctions bestowed on scientists in The Netherlands (figure 3).
Slater was blessed with excellent health and he retained this well into his nineties. He skied from his home in Switzerland until 80; he sailed single-handedly on the North Sea until 90 (figure 4) and he continued writing lucid and interesting overviews of the history of the
development of biochemistry (33, 45, 47). He wrote detailed, precise and warm obituaries for former colleagues (32, 40, 49); and he kept up a lively correspondence with colleagues and former pupils. His final years were difficult, also because he lost his only daughter to cancer. His wife Marion, who survives him at the age of 100, lost hearing and vision. He is mourned by his three grandchildren, his son-in-law and a wide circle of former colleagues and pupils as a warm friend and an unforgettable mentor.

**BIOGRAPHICAL SOURCES**

Slater has meticulously recorded his life in science in an autobiographic review, ‘An Australian Biochemist in Four Countries’ (41) and in other articles on specific topics (20, 22, 24, 33, 34, 36, 44, 45, 47). I have previously written about Slater and his contributions to biochemistry (Borst and van den Bergh 1977; Borst 2007) and I quote here (modified) text from these papers and from other Slater obituaries I recently wrote. Van Helvoort (2003) has produced an historic overview of Dutch biochemistry—unfortunately not very precise, to Slater’s irritation—but containing extensive and striking quotations from Slater’s correspondence. Slater in action can be seen in a long interview with Brian Beechey in 1992, entitled *A life of research in mitochondrial energy metabolism*, recorded on DVD, obtainable from the UK Biochemical Society Archive. Here, I present only some of the highlights of Slater’s long and productive life. A more complete overview of Slater’s life and publications can be found in (41).

**HONOURS AND AWARDS**

1956 Medal of the University of Brussels (Belgium)  
1961 Koninklijke Shell Prize  
1964 Member of the Royal Netherlands Academy of Sciences  
1965 Gold Medal of the University of Bari (Italy)  
1965 Elected Member of EMBO  
1966 Half-century Medal of the Société de Chimie Biologique (Netherlands)  
1969 Pierre Bruylants Chari in Chemistry, University of Louvain (Belgium)  
1969 Medal of the University of Helsinki (Finland)  
1970 Member of the Hollandsche Maatschappij van Wetenschappen (Netherlands)  
1971 Honorary Member of the American Society of Biological Chemists  
1973 Correspondant étranger de l’Académie Royal de Médecine de Belgique  
1973 Corresponding Member Academia Nacional de Ciencias Exactas, Físicas y Naturales, Argentina  
1973 Honorary Member of the Japanese Biochemical Society  
1974 Keilin Lecturer, Biochemical Society  
1974 Corresponding Member of the Sociedad Argentina de Biología  
1975 Fellow of the Royal Society  
1975 Foreign Member of the Royal Swedish Academy of Sciences  
1975 Honorary Doctor of the University of Bari (Italy)  
1984 Knight in the Order of the Netherlands Lion  
1987 Honorary Member of the British Biochemical Society  
1995 Honorary Doctor of the University of Southampton (UK)
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AUTHOR PROFILE

Piet Borst

Piet Borst MD PhD CBE ForMemRS was persuaded by Slater to interrupt his medical studies for a project on tumour mitochondria, which led to the formulation of the malate-aspartate shuttle, also known as the Borst cycle. After finishing his medical studies, Borst joined the lab of Severo Ochoa in New York, where Slater had also spent a post-doc year. After 2 years Slater recruited Borst as associate-professor in his Amsterdam biochemistry department, where Borst collaborated closely with Slater in running the department and where he set up molecular biology. In 1983 Borst became director of The Netherlands Cancer Institute in Amsterdam, but retained an honorary professorship in Slater’s biochemistry department. Borst is known for contributing to the discovery of circular mitochondrial DNAs; the glycosome (an organelle of trypanosomatids containing the glycolytic system); Base J, a new base in the DNA of trypanosomatids; the mechanism of antigenic variation in African trypanosomes; and the role of ABC-transporters in drug resistance and in protecting mammals from toxins. Borst also contributed to the scientific advisory boards of institutes in Europe, the UK and the USA, and he served as president of the jury of the Jeantet Prize.

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