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REVIEW

Of rodents, research and relationships: a pharmacological odyssey

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Abstract
This article is an autobiographical account of a research career in inflammatory diseases, mechanisms and pharmacotherapy, drug research and development, in academia and industry in various European countries spanning the last 55 years. The author describes how tenacity and independent thought, learned in formative years, and tempered later by the development of good relationships with colleagues have guided his career. This has spanned research, among other fields, on prostaglandins as pro-and anti-inflammatory mediators, oxidative stress and antioxidants, phospholipid mediators, cytokines, innate and adaptive immune responses and the establishment of various inflammatory and immunological models. The author has helped discover and develop novel therapeutic approaches to pain, arthritic, dermatological, respiratory, and autoimmune disorders and contributed to bringing eight drug candidates to clinical trials. He has helped establish new research labs in four different centres and been involved in teaching undergraduate and mature students in three different universities. With extensive experience in scientific publishing and several international awards, he emphasises that without good teamwork, little can be achieved in scientific research.

Keywords Autobiography · Pharmaceutical research · Immunopharmacology · Inflammation · Scientific writing

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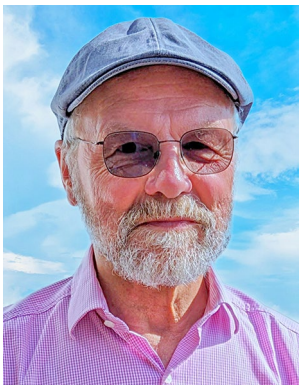
"No man is an island entire of itself" (John Donne, in a sermon 1624)



I have often been amused by the way in which films and other media in the past presented images of a crazy scientist alone in a laboratory making dramatic new discoveries. As we all know, scientific research doesn't work like that. Even more so today, advances are made most effectively by teams of scientists working together. My own experience has borne this out as I have worked together with a wide variety of capable and friendly colleagues with complementary expertise. For the team to be successful, though, it requires people who show a degree of independent thinking, who are prepared to buck the current dogma in order to make new discoveries. Presumably genetics plays a role but thinking out of the box can also be encouraged. In my case, I think my early days had a strong influence on my later attitudes.

Formative years

Born in London in 1951 in post-war England, my parents moved shortly afterwards to the West Country, where my father was a primary school teacher in the small market town of Axminster, Devon. Brought up in a conservative Christian environment in a small village in Cornwall, he was very intelligent and could tackle almost anything and do so almost perfectly and expected his children to follow the rules. Inevitably, I tried to find ways to get around them! As the smallest in the class at Woodroffe School in Lyme Regis and with a propensity to talk too much, I did not endear myself to my fellow pupils. What I did learn, though, was that I had to think for myself and not be put off by adversity. In this, my parents and parental grandfather, an ex-Royal Marine Sergeant-Major who had served in both World Wars, were great examples and sources of encouragement.

When Kim Rainsford, at the suggestion of Michael Whitehouse, asked me to write down my reflections on a career in inflammation and immunopharmacology, these two aspects of tenacity and independent mindedness occurred to me as characteristics I have tried to maintain, together with honesty. In addition, I have been privileged to work together with very capable scientists, many of whom over the years became good friends. This experience confirmed to me that, although maintaining critical thought, building good relationships with colleagues and teamwork represent the only effective long-term approach to science.

While I was at school, I planned to study medicine. For this, it was clear that I would need to do well in biology, chemistry and physics. Biology and chemistry I enjoyed, but physics took some mastering, as the elderly teacher was not good at explaining the subject. Like many boys my age, having come first in the initial class at grammar school, I thought I would not have to work too hard in future. So, I spent several years enjoying playing sport. Unfortunately, my somewhat intrusive personality meant that the maths teacher (also elderly) was not too excited about teaching me either. Consequently, I did very badly at the national GCE (General Certificate of Education) O-level exams, despite my father's attempts to get me to work harder. I did get a passable mark in English, which served me well later in my various scientific publication activities. However, I also failed to get the results I wanted in biology and chemistry at the end of my penultimate school year. I'm sure some other male readers shared a similar school experience. Somehow, girls at that age seemed to know that hard work is necessary. Having spent four of my six weeks summer holidays revising chemistry, I retook my chemistry and was able to continue for my last 9 months at school. Sadly, my plans to become a medical doctor had to be ditched along with my study of physics. Around the same time, I made the acquaintance of David Back who was a postgraduate student in pharmacology at Liverpool University. He convinced me that pharmacology was an interesting and challenging subject which I could study without needing physics. David, of course, went on to be a highly successful pharmacologist in his own right, in the field of endocrinology. At last (to my father's great relief), I realised I needed to work hard and managed to obtain decent results in my final exams in biology and chemistry. For most of the top universities, this of course was completely inadequate.

Once again, I met someone who, while being a very capable scientist, was also interested in each potential student and was not looking just for good exam results. This was Jack Botting, the senior lecturer responsible for student admissions at Chelsea College, London University. Jack, as I was later to discover, had taught many pharmacology students who went on to become successful researchers. Jack's approach was to hold an interview with each candidate. When I went up to London for this in early 1969, it became apparent to me that Jack was more interested in my

enthusiasm and reasons for studying pharmacology than he was about me achieving top marks and accepted me for the course. As others before and after me at Chelsea College (later absorbed into King's College) can testify, the subsequent four years were an excellent foundation for a career in pharmacological research. Jack always encouraged independent thinking and allowed me in more than one laboratory practical lesson to take a different course in the experiment to the one that was required. He also seemed rather laid back when I complained (to the dismay of my fellow students) in writing at the end of my final exam paper that his question in the exam was not entirely fair. The external examiner for our later oral examination was James Mitchell, Head of Pharmacology at Bristol University where I had applied to do my PhD. He challenged my impudence at questioning the exam question, but still welcomed me to his department! I remained in contact with Jack even after that and he was mourned by many when he died at 80 years of age in 2012. As John Hughes wrote in his obituary on Jack Botting on the British Pharmacological Society members website, "Chelsea had many fine and dedicated teachers, but Jack was exceptional in his eye for detail and in the pastoral care of his students" (https://www.bps.ac.uk/BPSMemberPortal/media/BPSWebsite/Documents/About/obituaries/Dr-Jack-Botting-obituary.pdf?ext=.pdf). Jack always began his lectures by introducing us to the history of the subject he was presenting which, as I describe later, was to be a great influence in some of my own later endeavours and teaching.

Perhaps an even more formative period that was to have a lasting effect on my career was the so-called sandwich or practical year, when third year students were given the opportunity to work for a year in a laboratory before returning for the final year of study. From 1971 to 72, I worked as a technician at the Royal College of Surgeons of England (RCS) in London. This again was thanks to Jack Botting who offered me the chance to take the position after a fellow student had turned it down because she was not keen to perform animal experiments. I gratefully accepted, not fully appreciating the enormity of the opportunity. The Head of Pharmacology at that time in the RCS was Gus Born, the platelet expert and the other leading professor was John Vane, in whose group I was placed. I worked for Sergio Ferreira in a lab in which Salvador Moncada, Rod Flower and Arnold Herman were all doing their PhDs. Priscilla Piper and Mick Bakhle were lecturers and Gerry Higgs was senior technician in the department which also had several guest researchers, including Ryszard Gryglewski from Poland. These names will be very familiar to those who have worked for any time in inflammation pharmacology. I arrived in the department just as a BBC TV crew was coming to the lab to make a brief documentary for TV on the recent discovery made by Vane and several other colleagues that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) work by inhibiting cyclo-oxygenase, which contributed to his award of the Nobel Prize in 1983. This discovery, John was graciously always at pains to point out, came following the many years of excellent research on salicylates carried out by Harry Collier.

My work for the subsequent year included helping with animal experiments, such as the blood-bathed-organ technique developed by Vane to detect unstable muscle-contracting agents released into the blood of an anaesthetised dog (Vane 1997). On such days, I had to get in early and set up a bank of smooth muscle preparations from various animals in a cascade superfusion system and standardise them with reference compounds—good old bioassays! This completed by mid-afternoon, I had to be available till 6–8 p.m. when the dog experiment finished and then clear up the mess afterwards, including the ends of Havana cigars smoked by the Latin Americans in the lab. On more than one occasion, Salvador invited me to celebrate a successful day with a drink at "The George", our local pub around the corner. Sergio decided to follow up on John Vane's paper on NSAID inhibition of cyclo-oxygenase (COX) (Vane 1971), to demonstrate that the analgesic actions of these drugs were due to the inhibition of prostaglandins (PGs). Initially, he used Salvador and some friends as test subjects to induce forearm cantharidin blisters and added PGE_2 to the blister base, subsequently testing for pain induction with a syringe attached via a spring to a pen recorder for the "victim" to record nociceptive responses. Nothing happened because we now know that endogenous PGs were released by the cantharidin. Wondering whether PGE_2 caused pain at all, Sergio injected 50 µg PGE_2 into my forearm and asked me to record the response on the pen recorder. After a few minutes, my arm started to hurt, began to turn red and then blue and throbbed for 8 h after that! I am still proud to say that (though such experiments would be frowned on today) the nociceptive action of PGE_2 in humans was first demonstrated on my arm and I was able to use this for my BSc dissertation. Sergio's final study was to infuse nanogram quantities of mediators into the now accustomed subjects' forearms to show that PGE_2 sensitised nociceptors to pain production by histamine or bradykinin, but not the other way round. This confirmed that the analgesic actions of the NSAIDs were undoubtedly due to the inhibition of the sensitising effects of PGE_2 on nociceptive nerve endings. I was privileged to help write the paper, draw the figures and have my name added to the acknowledgements in the article published by Sergio in Nature New Biology (Ferreira 1972). A short time later, Tim Williams and John Morley at Imperial College London showed that PGE_2 acted in a similar sensitising fashion to enhance the plasma exudation occurring during inflammation (Williams and Morley 1973). These discoveries were to strongly influence international inflammatory and anti-inflammatory research for decades to come.

The two Latin Americans in the small lab we occupied, were joined later by a Brazilian technician and together with Arnold Herman made for a great atmosphere in the lab where we often worked till late. There was a continual feeling that we were pushing back the frontiers of knowledge. John Vane's occasional visits to the lab were also remarkable. He had a habit of arriving when things weren't quite working out, say "Try that" and we were usually put back on the right track. I cannot think of a better place to have started a career in science and I am indebted to the many excellent scientists with whom I was able to develop contacts, from which several friendships developed. Rod Flower and I have had opportunities to interact or collaborate throughout my career. There is no doubt that it is of crucial importance for young scientists to work hard and willingly in a team and to develop and maintain friendships for the future. To be able to call on Sir John Vane, Nobel Laureate as a reference in subsequent years certainly did not harm my chances!

After returning to Chelsea College for my final year, I obtained my BSc in Pharmacology and started work for a PhD in 1973 in the Department of Pharmacology, Bristol University, as approved by the department head, James (Jimmy) Mitchell. My supervisor was John Sneddon and I worked alongside the post-doc Ivor Williams who had done postgraduate research on PGs with John Vane while I was at the RCS. I was grateful to continue working on PGs again, albeit this time on their production by the uterus of the pregnant rat. Again, I was working with isolated organ baths and studied the potential regulation by foetal adrenals of PG release at parturition. The data generated were not spectacular, but at least provided me with a doctorate. I do remember though, that when performing thin-layer chromatography on the products of an incubation of rat uterus with labelled arachidonic acid, the peak that ran (I think) with PGD_2 seemed very broad. It is a shame we were not working with analytical chemists in Bristol, as Bengt Samuelsson in Stockholm discovered later that the peak also contained thromboxane B2, which had not then been discovered! While writing up some of the findings, I took a decision which I have adhered to ever since. In one set of experiments, I had used a constant number of animals per group and an animal in one of the groups died. It seemed to me much easier just to state that the same number of animals was present per group, but honesty demanded that in the table, one group should be indicated as involving one less observation. I added a note to explain that one animal died. I have always encouraged people working with me since then to be scrupulously honest in reporting experimental data. Such checking up on data presentation was a widespread and laudable process in Jimmy Mitchell's department. Each time a younger member of the department was to give a presentation to the British Pharmacological Society (BPS), a trial presentation had to be given to the whole department to ensure that the rules were adhered to. This had added importance because, in those days, presentations to the BPS, which I gave a couple of times while in Bristol (and many times since), were subject to approval for publication by all members of the society in the audience with a show of hands. Rejections or requests for rewrites did occur. As a consequence, I had seen even full professors a little nervous of giving presentations to the BPS! Things seem to have become more relaxed over the years.

One of the significant events of the 2.5 years I spent in Bristol, apart from meeting and marrying my wife Elaine, was that John Sneddon left in the middle of my research project and was succeeded as my supervisor by the endocrinologist Philip Brown to whom I had previously gone for advice. This gave me opportunity to do some lecturing, as I took over some of John Sneddon's work (Remarkably, I recently met at a society meeting, Steve Hill, past president of the British Pharmacological Society, who remembered my lectures in Bristol when he was a student. Pharmacology is a small world!) Philip was very helpful, particularly when I had to finish writing my thesis in a hurry and he read my handwritten text before it was typed (no computers in those days!). This was occasioned by the fact that the post-doc position in Ribeirao Preto I had been offered by Sergio Ferreira fell through (the government decided only to accept Brazilians for academic research). Sergio heard from a friend that a position was available in Rotterdam, The Netherlands and with Sergio's recommendation and a healthy report from my doctor in Bristol, as soon as I had handed in my typed and bound thesis, I left in April 1976 for a post-doc position with Ivan Bonta (whom I had never met) in the Department of Pharmacology at Erasmus University Rotterdam in The Netherlands. I was not to return to live in the UK for another 46 years!

Going Dutch

Ivan had been studying anti-inflammatory mediators in inflammatory models. He had previously investigated endogenous anti-inflammatory processes, including the phenomenon of counter irritation—the inhibitory effect of an irritant on an inflammatory response at a remote site. His group had also been using dietary essential fatty acid deficient (EFAD) rats to study the effects of a lack of PG precursor fatty acids. Following on from controversial studies in the USA in the late 1960s by Robert Zurier, showing that very large doses of PGE_2 could inhibit adjuvant arthritis in the rat via cyclic AMP, Ivan wanted to see whether this feedback effect of PGE_2 could be demonstrated pathophysiologically. I often thought about the irony that having helped demonstrate that acute inflammation and pain could be reduced by the inhibition of PGE_2 production, I was now trying to

demonstrate the anti-inflammatory effect of PGE_2. Needless to say, I had some lively but polite discussions at conferences with Gerry Higgs, but John Vane was always correct and respectful towards the Rotterdam group. Over the next 3 years, we sought to demonstrate this unexpected action of PGE_2, widely considered to be only a pro-inflammatory mediator, in a project funded by the Nederlandse Vereniging tot Reumatiekbestrijding (Netherlands Society to Combat Rheumatism). In this, we were ably supported by Ivan's technician, Martinus (Tiny) Adolfs, who later took a degree and headed a lab of his own.

Initially, a medical student doing a practical in the department, Leen van Vliet, extended the role of cyclic AMP in the anti-inflammatory effects of PGE_2, by demonstrating that the inhibitory effects of exogenous PGE_2 on adjuvant arthritis could be enhanced by co-administering the phosphodiesterase inhibitor, theophylline (Bonta et al. 1978). Tiny Adolfs and I then used a stainless-steel coaxial cannula, which Ivan had had made by the medical school workshop, pushed under the skin to perfuse the noninjected arthritic joint, to collect perfusion fluid at different times after initiating the arthritis. With the early arthritis response, PGE_2 levels in the perfusate rose and cyclic AMP fell, only for the latter to increase gradually, while PGE_2 continued to increase up to day 22 (Parnham et al. 1978). It, thus, appeared that in the later stages of the response, PGE_2 may have been associated with a cyclic AMP-mediated anti-inflammatory action. In parallel studies, using carrageenan-impregnated sponges implanted under the back skin of rats, we showed, in collaboration with Shmuel Shoshan in Jerusalem, that reduction of PG precursor fatty acids in EFAD rats, led to increased tissue proliferation and collagen synthesis in the granuloma formed around the sponge (Bonta et al. 1977; Parnham et al. 1977). We assumed that PGE_2, while promoting acute inflammation, might act as a feedback inhibitor during subacute or chronic inflammation to inhibit fibroblast activity. Consequently, following Ivan's suggestion, we cannulated the sponges, allowing PGE_2 to be injected into the inflammatory exudate in EFAD rats at different time points after implantation. This time, we used 50 ng/day of PGE_1 (considered more stable) which would reflect the physiological release of PGE in the absence of the synthetic precursor fatty acids. To our delight, PGE_1 given immediately after sponge implantation enhanced subsequent granuloma formation and given on days 4–7 it inhibited the granuloma tissue formation (Bonta and Parnham 1979). Since then, PGE has been shown to inhibit the functions of a variety of cells involved in inflammation, including lymphocytes, macrophages, fibroblasts and epithelial cells and the dual action of this arachidonic acid metabolite on inflammation has become textbook knowledge. In subsequent work, together with Laurie de Leve and Pramod Saxena in the same department, we studied effects of PGE on blood flow to granuloma tissue (Parnham et al. 1979a) and with Theo van der Kwast and Rob Benner in the Immunology department, on delayed-type hypersensitivity as well as the innate and adaptive immune response regulating pannus formation in arthritic rats (Parnham et al. 1979b; Parnham 1980; Parnham and Schoester 1980). It is interesting that biphasic effects of inflammatory mediators have been observed by others and this biphasic phenomenon in regulating inflammation was one I was to encounter later in my career with a widely used antibiotic drug, azithromycin.

It is worth noting that most of the work I was involved in at the RCS and Erasmus University involved in vivo and ex vivo studies on animals. This was well before the introduction in the 1980s of stricter regulations controlling animal experimentation in laboratories across Europe. But I am convinced that animal experiments remain a crucial approach to the study of pathophysiological processes and pharmacological effects of drugs. Although the studies I was involved in were carefully carried out, with suitable consideration for animal welfare, some anomalies did occur. For instance, in Rotterdam in the 1970s, the laboratory facilities were built with labs on the outside and animal houses on the other side of the corridor, on the inside of the building. Presumably, there was insufficient separation of air systems, as I developed an allergy to rats and mice—still an important issue in laboratory animal houses today. Later in Cologne, Germany, the animal house in the pharmacology building in which I worked was in the cellar, beneath the labs and offices and the animal rooms were fumigated in the late afternoon. As soon as I began coughing, I knew allergens were escaping and it was time to go home. Fortunately, over succeeding years, the standards of animal housing have improved considerably. Thus, twenty years on, in the new lab building at PLIVA in Zagreb, it took several years to set up and successfully gain approval for accredited toxicology labs.

Communicating science and editing

I also discovered in Rotterdam the importance of the communication of scientific findings in original publications, review articles and presentations to societies and conferences. This was a good training and served me well for the remainder of my career. Intriguingly, as of 2023, 45 years after a review article Ivan and I published in 1978 on Prostaglandins and chronic inflammation and long before the internet, digital publications, PubMed and open access, the paper has been cited a reasonable 166 times (Bonta and Parnham 1978). In contrast, in the 6 years since I was a co-author of a review article on Nrf2, published in an open access journal in 2017 when I was at Fraunhofer in Frankfurt, the article has received over 562 citations (Vomund et al. 2017). Such is the benefit of the digital era.

Ivan Bonta (and presumably the Dutch rheumatism grant-awarding society) had a very open approach to paying for attendance at conferences and I was able to participate in these in various places in Europe and to make my first trip to the US, to a conference in Washington DC. In the early 1970s, The Future Trends in Inflammation series of conferences organised by Derek Willoughby and Giampaolo Velo was the main forum for international communication of inflammation research findings and an ideal opportunity to meet new friends and colleagues. It set the standard for all subsequent conferences on inflammation. The series of conferences on Prostaglandins organised by Rodolfo Paoletti was also a forerunner for subsequent conferences on fatty acid metabolites. Held in Florence, Italy, they were always well attended and apart from the scientific programme and the beauty of Tuscany, I enjoyed meeting up with Ian Ahnfelt-Rønne from Copenhagen to eat dinner over a glass of red wine at Alfredo's restaurant overlooking the river Arno (a place I can still recommend, having been there several times since). I had first met Ian at a meeting organised in Rotterdam in 1977 by Ivan Bonta and Kay Brune from Erlangen, Germany. This meeting had long term repercussions as it led to the formation by Ivan and Kay of the European Workshop on Inflammation (EWI), an annual workshop held in different parts of Europe of which I was the founding secretary for many years. Later, we also set up for a time, half-day workshops at Frankfurt Airport, enabling European participants to fly in before lunch and return in the evening. The EWI proved popular and was a wonderful way of collaborating, networking, and building up good relationships. The workshops complemented for Central and Eastern Europe the work of the already existing British Inflammation Research Society (BIRAS) and the French Groupe de Recherche et d'Etude des Mediateurs de l'Inflammation (GREMI). However, the strength of inflammation research, as opposed to immunology research, in the UK and France was much greater than in other European countries, attracting members from across Europe and eventually made the EWI redundant. (Immunologists at the time considered inflammation a hybrid discipline and dominated by pharmacologists, not like "pure" immunology. Fortunately, times have changed) Nevertheless, during its existence, the EWI under Kay Brune's and later Giampaolo Velo's leadership built up excellent contacts with the Inflammation Research Association (IRA) in the US, which was then under the chairmanship of Alan Lewis. I well remember attending various IRA meetings in beautiful, difficult to reach natural settings in New England and always joined in with the karaoke evening which became a fixture (as was my singing of "The house of the rising sun" to kick the evening off!). This collaboration resulted in the subsequent formation by the EWI and the IRA of the International Association of Inflammation Societies (IAIS), which also still organises the biannual World Congress of Inflammation (WCI). Having been involved in these developments from the beginning, I had the privilege of working together with colleagues from Europe, Australia and both North and South America and to receive in 2015 a Lifetime Achievement Award from the IAIS, fittingly, together with my good friend Ian Ahnfelt-Rønne.

There is one anecdote on giving presentations to scientific conferences that I should mention. Michel Chignard was an eminent French researcher who was instrumental in helping to build up GREMI and was for a while its president. When we were still young, I gave a presentation at a conference we were both attending and fielded questions from the audience as usual. Chatting to Michel during the subsequent coffee break, he said to me, "You know Mike, I would never dare to ask you a question at a meeting, I'd be too scared of the answer." I never forgot that lesson. In my attempt to be convincing in my answers, I had obviously not been showing adequate respect for the questioner's point of view. I adapted my responses after that, as critical questions are essential to good science and should be responded to with consideration for the persons asking them. As the adage goes, "In science, there is no such thing as a stupid question."

Shortly after the formation of the EWI, Kay Brune, who was Editor-in-Chief of the journal Agents and Actions (published at the time by Birkhäuser Verlag, now Springer/Nature), asked me to become an Associate Editor of the journal, read widely by inflammation researchers. Subsequently, in 1992, I took over as Editor-in-Chief, establishing the journal as the official publication organ of the IAIS and the European Histamine Society and changed the name to Inflammation Research to adapt to the major emphasis of the articles we were publishing. Ian Ahnfelt-Rønne, among others, joined me as Associate Editor on this project, as did Gerd Geisslinger who had been a postgraduate student in Kay's department in Erlangen. But more of Gerd later. My goal was to establish this journal as a leading publication organ for inflammation researchers and after nearly 30 years with the journal, we achieved what was then an appreciable citation impact factor of 2.0 and I gladly handed over to John Di Battista, who had also been a conscientious Associate Editor, representing the Canadian Inflammation Society. John has built up the journal admirably since then. I should also mention in this context, another good friend, Mike Bray, who I met first while he was a postgrad with John Morley in London in the 1970s. We have worked together for the EWI and jointly edited several books. I well remember travelling by train in May 1991 with Mike and Kim Rainsford from a joint EWI/NSAID Side-Effects meeting in Verona to Basel and holding a stimulating discussion for several hours on faith, science and various other topics of existential importance. I am also grateful to Mike for recommending me for the position I later took at PLIVA in Zagreb, which gave a distinct boost to my career. As I said before, friends we make

in science are ultimately more important than our scientific achievements.

While in Rotterdam, I also made friends with Wim van den Berg in Nijmegen, later publishing articles with his group, and two other Dutch colleagues with whom I was to build longstanding collaborations. The first was Jacques Bruinvels, a CNS pharmacologist and professor in Ivan Bonta 's department. He shared my interest in the history of pharmacology which had been awakened by Jack Botting. Jacques who, at the time, was editor of European Journal of Pharmacology and consequently had good contacts at Elsevier, approached the publisher with our idea of producing a volume on the history of pharmacology, drawing on the experiences and memories of scientists who had been involved in the original discoveries. On gaining the publisher's approval, Jacques and I spent the next few years putting together and editing chapters by many eminent scientific pioneers who shared their experiences in a three-volume publication on Discoveries in Pharmacology (Parnham and Bruinvels 1983; Parnham and Bruinvels 1984; Parnham and Bruinvels 1986). The fascination of this work has been that we were able to obtain as authors, the contributions of scientists who had been involved either directly or in collaboration with the people who made the early discoveries. In many cases, discoveries were made unexpectedly, after overcoming a whole number of hurdles or simply by hard work. In any case, the tenacity and often independent thinking of the scientists involved were crucial. From comments I have received, these books appear to have proven valuable to many teachers of pharmacology. Jacques was a little disappointed that Elsevier wanted a high-quality hardback version, which became expensive and was not at a price students could buy. Jacques' vision, however, has been realised recently, as with support from Clive Page at King's College London, we were able to persuade Elsevier to reprint many of the original chapters together with commentaries by today's experts (Parnham Michael et al. 2022, 2023, 2024). It is worth mentioning that the third volume contains the reprint of Harry Collier's fascinating chapter on "The Aspirin Story", which he finished writing just before he died.

The other longstanding friend I made during my time in Rotterdam is Frans Nijkamp. We often met each other at scientific meetings in The Netherlands and 20 years later, as we were waiting to fly back to our respective homes from a European pharmacological meeting in Milano, we agreed to produce a textbook on immunopharmacology. Principles of Immunopharmacology has now gone through four editions, the fourth edition running to nearly 1000 pages, appeared in 2019 with Adriano Rossi from Edinburgh as a co-editor (Parnham et al. 2019). This was a major challenge as Springer Verlag and Nature Publishing had merged in the middle of our work, changing our contacts at the publisher regularly and moving the printing to India. Gone were the "good old days" when manuscript submission and proof correcting was all done by hand with texts sent by mail or courier! Now we were receiving emails from India at totally inappropriate times and places, such as the weekend or on holiday, requiring us to forget relaxation and correct printing errors in rapid time. This messed up a holiday in The Netherlands with friends which neither they nor my wife Elaine were very happy about! During this holiday, Frans and I, with our wives, met for a meal in Utrecht to celebrate the longevity and success of the book and decided that at our age, the effort was a little too much. The textbook has been widely used and we are hoping that Adriano and the publisher may be able to sustain the continued appearance of new editions.

As the Principles of Immunopharmacology textbook was in the final phase of compilation, I was also asked by SpringerNature if I would edit an Encyclopedia of Inflammation, as part of the publishers' encyclopedia series. This was intended to be a printed and online reference work, which could subsequently be updated by authors of contributions. On accepting the challenge, little did I know what I would be facing. The field of inflammation has become so vast that the term can almost be used synonymously with pathology and the field of immunopharmacology is now equally diverse. Unfortunately, as many scientific editors and authors have discovered, while the scope and task of publishing in this field has expanded, publishers have cut back on internal costs and placed increasing burdens on the scientific contributors. An encyclopedia with the selected scope required a huge number of individual entries each written by a specialist in the relevant subject and each of these had to be invited individually! Over a period of several years, I sought the assistance of many different associate editors, some who started the work and eventually had to give up due to other responsibilities. The planned scope had to be cut back, also due to the continuing changes in strategy and personnel within the publisher, leading to a name change to Compendium of Inflammatory Diseases. After 14 years on the project, we finally managed to publish the book, which ran to two volumes and 1400 pages (Parnham 2016a). I decided my job was more than done!

While discussing publications, I should also mention the longest running publication for which I have been Editor-in-Chief since 1996. Together with Agents and Actions/Inflammation Research, Principles of Immunopharmacology and the Compendium of Inflammatory Disease, the book series Progress in Inflammation Research (PIR; https://www.springer.com/series/4983/editors) arose from my collaboration with Birkhäuser Verlag in Basel. Now running to more than 90 chronologically numbered volumes, the series has been a great success and I am grateful to the various series co-editors and volume editors who have been involved over the years. As Birkhäuser was a medium-sized Swiss

publisher, the early years of the publication involved regular cordial contacts with members of the publishing house. In later years, I worked closely with Detlef Klüber and his colleagues and we were able to influence how the series developed. As many have experienced, once a large multinational publisher like Springer/Nature runs the show, the input from individual editors becomes less, but contacts with staff at the publishing house remain close and productive. I assume the PIR series is now known to many researchers in inflammopharmacology, as we have sought to keep the themes that are addressed in line with the latest developments in the field of inflammation.

The time spent working in The Netherlands was brief, only just over 4 years, but proved to be one of the most productive periods of my career. It also established my value as a language editor from a native English-speaking country, able to check manuscripts for publication and doctoral theses for submission, written by my non-native English-speaking colleagues. In this respect, my ability (thanks to my father's genes and insistence) to express myself well in written and spoken English has been much appreciated and made use of by many of my colleagues, even up to the present day. As Stefan Szelenyi from Degussa, Germany, like Ivan Bonta a native Hungarian, said of me tongue-in-cheek, "You're an above average scientist, but your ability to take the results of a few experiments and turn them into several publications and presentations is what makes you invaluable!" I suppose the evidence of over 200 publications in PubMed and a Google Scholar H-index of 51 supports Stefan's conclusion!

A career in industry

I had very much hoped to be able to stay in Rotterdam and the availability of a vacancy for a professorship in the Department of Pharmacology seemed to offer the ideal opportunity. However, this was the end of the 1970s and budgets were tight all over Europe. As a result, academic tenured vacancies in Benelux countries were frozen and I was forced to look for an alternative. This came at Kim Rainsford's recommendation, via Ivan Bonta who was contacted by Eugen Etschenberg, a German who had worked with Janssen in Belgum and had many contacts in the Low Countries. He had recently been appointed Head of Research at A. Nattermann & Cie, a traditional phytopharmaceutical company in Köln, Germany where Eugen planned to modernise the research efforts. With two small children in tow and Elaine's support, I took the attractive opportunity to set up a new lab on in vitro inflammation models in the Pharmacology Department at the company and in May 1980 we set off for Köln.

Quite apart from the research expectations, moving to industry had some attractive side-effects, like help with moving, buying a new car and renting a house. In addition, my superiors, Hans Winkelmann, Erich Graf and Eugen Etschenberg (and later Günther Lambrecht) were very capable and easy to work with. I even had a Dutch colleague, Gerrit Prop and with him and his wife To, who lived close to us, we maintained some continuity with our previous domicile, not least being able to sustain our Dutch communication. I was rather surprised when, after about 18 months in the company, Hans Winkelmann left to return to veterinary practice and I was asked to become Acting Head of Pharmacology with 60 staff. This was decidedly challenging and I initially made several mistakes, but learned quickly through on-the-job training. When Günther Lambrecht came from Goethe University Frankfurt in 1982 to take over as Head of Pharmacology, I stepped down again but a new opportunity also opened for me. I had never given up my hope of a professorship, but in Germany, this meant first completing 5 years of independent research and a further thesis for "Habilitation", the qualification needed to become a "Privat-Dozent" with approval to teach university students. Günther opened the way for me to complete my Habilitation with a thesis on the oxidative burst of macrophages and I was appointed Privat-Dozent in the Department of Pharmacology for Life Scientists at Goethe University Frankfurt in 1990. I finally received the coveted title of "Außerplanmäßiger (Adjunct) Professor" of Pharmacology and Toxicology in 1998, 29 years after starting my academic career at Chelsea College. While my responsibilities for teaching immunopharmacology to pharmacy students ceased in 2016, the establishment of a joint Master of Pharma Business Administration (MPBA) course by Goethe Business School with the Faculty of Pharmacy gave me the opportunity to establish a module on Drug Discovery and Development, mostly for mid-level managers in the pharmaceutical and allied industries. The course has been very successful with students attending for 2 days/week even from outside Germany. Drawing on expertise from teachers with both academic and industry backgrounds, the specialist MPBA has certainly filled a need within the broader chemical, pharmaceutical, biotech and diagnostics industries.

The family-owned company of A. Nattermann & Cie GmbH had made its reputation by isolating pharmaceuticals from plants, with an emphasis on "Essential Phospholipids", a preparation of phosphatidylcholine with a high proportion of unsaturated fatty acid constituents. Obviously, no longer having academic freedom, we were expected to work with this product and Gerrit Prop (who worked on cardiovascular effects), together with Sigurd Leyck (who ran an in vivo inflammation lab) and I undertook several projects, including demonstrating that given orally, the product reduced gastric injury caused by NSAIDs(Leyck et al. 1985). These novel findings on a well-tried plant-derived pharmaceutical product appealed to our medical marketing division and I

was asked to help prepare several marketing brochures and present lectures on the benefits of Essential Phospholipids, which gave me opportunity to represent the company at meetings in Bombay (now Mumbai) and Cairo, where I got to visit the pyramids of Gizeh. Later, working together with Armin Wendel—head of the phospholipid group—on the use of polyunsaturated phosphatidylcholine in liposomal and cosmetic products, I was asked to give presentations to several conferences in Germany (Parnham et al. 1996).

With considerable foresight, Eugen Etschenberg (who sadly died in December 2023, as I was writing this article) also facilitated the development of plant cell culture labs to isolate secondary ingredients for pharmacological testing. The resulting unit became one of the largest plant cell culture centres of its kind in the world at a time when interest in natural, particularly plant-derived products was increasing dramatically. The greatest achievement of the plant cell group was to tweek *Coleus blumei* cell cultures so that they produced 20% of their weight as rosmarinic acid (Ulbrich 1985). We showed that it was antioxidant and anti-inflammatory and together with Werner Englberger (who later joined Nattermann) and Ulrich Hadding at the University of Mainz, we found that it was an inhibitor of complement C3 convertase, preventing complement activation and the generation, among others, of chemotactic factor C5a (Englberger et al. 1988). Sadly, when we were taken over by Rhône−Poulenc a few years later, the French management decided, against the trend, that phytopharmaceuticals were not their speciality and shut this exceptional unit down. This was the first of several occasions that would arise during my career when a nonspecialist and in several cases, nonscientific management would take decisions that annulled many years of highly promising research work. The axing of plant cell culture was taken as international moves were afoot to encourage acquisitions and mergers of pharmaceutical companies to enhance dividends. The result was the replacement of research cognizant members of upper managements with economically orientated CEOs to optimize short-term profits and the closing of huge numbers of research divisions across the globe with the loss of capable scientists. The effects on new drug discovery were catastrophic, as I discuss later. For me, the term "shareholder value" was to become almost a swear word.

Undoubtedly, Eugen Etschenberg's most significant initiative at Nattermann was to start working with an organoselenium compound (PZ 51) he had come across while at Janssen in Belgium, through collaboration with academic researchers on oxygen free radicals in Liege. Etschenberg came to Köln with several related compounds "in his pocket" and wanted to investigate the possibility that the selenium they contained, bound within a benzene ring, could be released in a nontoxic form to be incorporated into the selenoenzyme glutathione peroxidase (GpX), which catalytically degrades organic and inorganic peroxides. We started work on this project across various disciplines in the Nattermann Research Labs, looking for optimal structures and investigating potential mechanisms of action. In this, right from the start, we collaborated with Helmut Sies in Düsseldorf, an expert on reactive oxygen species (ROS) and later with Albrecht Wendel at the University of Tübingen, an expert on GpX which he had characterised with Leopold Flohe. Helmut's group demonstrated that PZ 51 had antioxidant activity in vitro and required glutathione (GSH). In my lab, we used mice fed a selenium deficient diet to investigate the activities of PZ 51 and found that PZ 51 given orally to such mice only started to increase GpX activity in zymosan-elicited peritoneal macrophages when the animals had been on the deficient diet for 19 weeks and their GpX activity was almost negligible. The compound was able to inhibit ROS generation by the macrophages (Parnham and Kindt 1984). This suggested that PZ 51, rather than releasing selenium for incorporation into GPx, was itself acting like the enzyme. The finding encouraged Helmut to go back to his earlier data and to show that PZ 51 catalytically degraded hydroperoxides in a GSH dependent manner, similar to the action of the endogenous enzyme and potential mechanisms of PZ 51 were proposed by our chemists, involving diselenide and selenosulphide intermediates (Müller et al. 1984; Fischer and Dereu 1987). The fact that selenium was not released from PZ 51 was demonstrated subsequently by Albrecht Wendel (Wendel et al. 1984). These findings were published in a series of articles in Biochemical Pharmacology in 1984. On application to the WHO, the name benselen was proposed as an INN and changed by the authority to nebselen. Since the German word for fog is Nebel, we didn't want a nebulous compound and proposed the name ebselen which was accepted. The discovery of the action of ebselen offered the possibility to develop an enzyme-like compound which broke down reactive hydroperoxides without the toxic side effects of inorganic selenium. The therapeutic applications seemed broad and potentially highly profitable.

As described in the review article Helmut and I published in 2013 on the research and development of the compound, the initial results stimulated an explosion of activity within Nattermann to characterise and develop ebselen and among researchers who requested samples to test (Parnham and Sies 2013). It possessed clear anti-inflammatory activities in several in vivo models involving release of reactive oxygen species. I became international project leader and later Director of General Biology. Under Erich Graf as Head of Research, we started collaboration with Daiichi in Japan and Ciba-Geigy in the United States and this continued following the acquisition of Nattermann by Rhône-Poulenc. For 5 years, I had the challenging and exciting privilege of coordinating the project, as a Brit working in Germany, with French, US and Japanese

colleagues and meeting every quarter-year in Germany, the US or Japan. I learned to value the precision and commitment of the Japanese, the urgency of the Americans, the thoroughness of the Germans and the temperament of the French. Sadly, when Ciba-Geigy withdrew from the project, the French were discouraged, but the Japanese continued to pursue the project and called on my advice on several occasions, even years after I had left Rhône-Poulenc. My Japanese counterpart, Hiroyuki Masayasu stayed with the project through clinical development for acute treatment of stroke, only for the compound to fall at the last hurdle of the Japanese authorities because the primary outcomes in stroke patients on placebo were too high and the difference from the ebselen-treated patients too small. The negative outcome was probably also due in part to the difficulty in being able to treat patients as soon after the stroke as possible. We in the original Köln-Düsseldorf-Tübingen team received the Claudius-Galenus-Prize Germany (now Galenus-von Pergamon prize) and collaborated across various continents with academic and commercial partners, including previous colleagues such as Wim van den Berg, as well as Joe Lunec and Helen Griffiths in Leicester—who demonstrated efficacy in inflammatory models (Schalkwijk et al. 1986; Griffiths et al. 1992).

This, however, was not the end of ebselen. It has been resuscitated by several groups, shown in Oxford by Grant Churchill and colleagues to act like lithium in treating bipolar syndrome, inhibiting IMPase in the brain (Singh et al. 2013), is undergoing (as SPI-1005) phase 3 clinical trials for Menieres Disease and for traumatic ear injury with Sound Pharmaceuticals in the United States and is widely used as an experimental tool in many parts of the globe (Kil et al. 2022). The compound has been shown not only to degrade hydroperoxides, but to act as a thioredoxin reductase substrate, to inhibit lipoxygenases, NO synthetases, NADPH oxidase synthetase, and most recently to inhibit the main protease of SARS-CoV2 (Sies and Parnham 2020). However, it reacts with any free thiol groups, so making sure it arrives unbound at the required site of action is the challenge. I'm still hoping for the day when ebselen is finally approved as a new therapeutic agent. To date there are 1305 publications on ebselen in PubMed. It was with ebselen I learned how to develop a drug in an international collaboration, to appreciate the excitement of working in interdisciplinary teams across the world and to build further lasting friendships. Twenty years after Rhône-Poulenc shut down research in Köln for strategic reasons, Erich Graf, Helmut Sies, Albrecht Wendel and our wives met for several enjoyable weekends in the Bavarian countryside. Erich was a great leader, encouraging and showing respect and consideration for all the ambitious scientists he brought together and while concentrating on the task and the people, rather than on his own career (which was furthered by top managers for his leadership skills), he built us into an exceptional team. It was a privilege to have worked with him.

The decision by Rhône-Poulenc in 1990 to close the research labs in Köln came as a shock and ironically, followed closely on our celebratory trip to Berlin to receive the Galenus Prize for ebselen. Fortunately, most of the employees found other employment, but the process was not pleasant, as many other industry researchers have experienced. Fortunately, the redundancy process in Germany is carefully regulated to cushion the blow for employees, and I am always disturbed by the apparently heartless process in the United States of issuing pink slips with barely any warning. I decided to take the opportunity to change direction, enabling me to get more involved in our church community and set up my own consultancy. Despite warnings from friends about the difficult first 2 years when starting a new business, the challenge of maintaining enthusiasm and focus as the finances took a nose-dive was very demanding. After 3 years, though, I was regularly consulting for several large pharmaceutical companies, had one full time and 3 part-time employees and a good turnover. Early in the consultancy, I had been advised to attend conferences to keep up to date. But how could this be paid for? I hit on the idea of providing customized conference reports, tailored to the needs of individual clients for a fee. I only needed 4−5 client requests to cover my costs. This remained an important part of my business, long before large publishers came up with a similar idea. Nevertheless, in both research and business, it is a consistent fact that there's nothing as constant as change! This time it wasn't financiers or customers that instigated the change. The German government at the time (1993) kindly decided to introduce a new health reform law. As a result, the country that had been called "the pharmacy of the world" experienced an exodus of pharmaceutical activities, cessation of research in medium-sized companies and a total change in the pharmaceutical landscape in Germany. I changed the emphasis of the business, but the loss of research and development centres considerably reduced the size of my market. With the university education of our children to pay for, I was very grateful for the offer I received in late summer 1997.

After the first isolation of the broad-spectrum macrolide antibiotic, erythromycin, in the early postwar years and its marketing in 1952 by Eli Lilly, it soon became apparent that this class of naturally occurring compounds presented a distinct advance over penicillins and sulphonamides. As usual, other companies scrambled to copy this success. But copying a heterocyclic chemical synthesised by natural organisms was a tall order. Clarithromycin (Taiisho) and roxithromycin (Hoechst Marion Roussel) were among the first of the second-generation macrolide antibiotics, together with what was to turn out to be the subsequent market leader, azithromycin. This blockbuster drug originated from an

unusual source. PLIVA was a well-established manufacturer of nutritional, chemical, pharmaceutical and veterinary products, mainly generics, based in Zagreb, at that time in Yugoslavia. A research group, mainly of chemists who collaborated with other researchers at Zagreb University, was occupied with approaches to synthesis of known drugs. In 1980, three of the chemists, Gabrijela Kobrehel, Gorjana Radobolja-Lazarevski, and Zrinka Tamburašev, under Research Director, Slobodan Đokić came up with a new approach to the modification of erythromycin, by inserting a nitrogen into the macrolide ring, generating azithromycin. Patented a year later, the team beat Pfizer to the patent by 2 weeks and Pfizer then came to PLIVA management requesting a licence. Both companies subsequently marketed the antibiotic, Pfizer's Zithromax becoming the world leader, making large profits for Pfizer and appreciable royalties for PLIVA. With unexpectedly improved pharmacokinetics and marked accumulation in leukocytes, the drug attracted attention beyond that of microbiologists. By this time, Zagreb had become capital of newly independent Croatia (in 1991) and went through a brutal war of independence. The new management of PLIVA decided to post a sign for the newly re-formed country and invested royalties from azithromycin into preparations for a new modern research centre. Obviously, this would need staffing and thanks to Mike Bray's recommendation, as mentioned earlier, I received a phone call from an executive search company, asking if I was interested in a position as Director of Pharmacology & Toxicology in the revamped research division. The position was made attractive by a broad package of incentives and offered me an exciting chance to get back into research, quite apart from the added incentive of long warm summers, beautiful countryside and a short drive of a couple of hours to the Adriatic Coast. The fact that the War of Independence only finished 2 years previously obviously meant that there was much to do to get the country up and running again. I flew from Frankfurt to Zagreb on 15th February 1998, leaving my wife and children to wind up our home (and my extensive files, books and record collection) in Bonn.

On arrival, I met Wolfgang Schönfeld, who had arrived one month previously from Bayer to set up Microbiology and Vesna Erakovic, an MD who had just completed her PhD at Rijeka University and was to be my deputy. With limited facilities and plans for the new building only reaching fruition 5 years later, we had to make the best of what was available, including a temporary container housing an animal room! There were, though, some capable researchers, many of whom (mainly women) had had no pay increase for over a decade because of the war. Vesna and I converted a small storeroom into an office for two, which we occupied for 2 years and set about deciding what to do. Wolfgang initiated a promising search for novel macrolide antibiotics, working with the growing team of chemists, including some of the original azithromycin team now led by Suleyman Alihodzic, while Vesna and I decided to follow up on the recent findings that azithromycin was highly accumulated in leucocytes, also modulating several of their functions. The studies of Marie-Therese Labro in Paris, who had shown a variety of effects of macrolides on neutrophils in vitro, were an important basis for our studies and we invited her to come and give us a guest lecture (Labro 2004). We also drew on the extensive research carried out on erythromycin in Japan, particularly the work of Shoji Kudoh who had shown that erythromycin is highly effective at inhibiting lung neutrophilia in patients with fatal diffuse panbronchiolitis, even curing many of the patients (Kudoh 2004). We decided that with its improved pharmacodynamic and pharmacokinetic properties, azithromycin could be a potential new anti-inflammatory agent and under Suley Alihodzic's leadership, further new derivatives were synthesized.

Vesna built up a very effective and hard-working team of biologists to tackle the project, including Ines Glojnaric, who was later to become Head of Pharmacology, and Martina Bosnar, who was later to carry out crucial in vivo studies on the mechanism of the immunomodulatory effects of macrolide antibiotics, particularly on murine lung neutrophilia. Ognjen Culic, in the first few years, helped bring many of the diverse findings on macrolides in the literature together and was the initial author of the first review article, published in 2001 on anti-inflammatory effects of macrolide antibiotics, which has been cited 482 times to date and gained me an invitation to give a lecture in the United States on the subject (Culic et al. 2001). My host was Bruce Rubin, with whom I have collaborated on several projects since. Another article which has been highly cited was our collaborative clinical trial with clinicians at Zagreb University. Treating human volunteers with a standard daily oral antibiotic dose of 500 mg azithromycin for 3 days (intended as a preliminary study to the later trial in COPD patients) we surprisingly found that azithromycin enhanced release of lysosomal enzymes and the oxidative burst in circulating neutrophils within the first few hours and subsequently, over the next few days and weeks, inhibited this release, together with circulating levels of cytokines (Čulić et al. 2002). Azithromycin could still be detected in neutrophils 4 weeks later. Based on these data, we proposed that the macrolide was acting in a biphasic manner to initially stimulate the antibacterial defence reaction and subsequently reduce bystander inflammation. This was particularly attractive to PLIVA Medical Marketing and I was once again requested to help prepare a marketing brochure on azithromycin.

Our follow-up trial in COPD patients showed that in ongoing chronic lung inflammation, the initial stimulatory actions of azithromycin are blunted, but some of the later inhibitory actions are sustained (Parnham et al. 2005). This, incidentally, was the first study to look at the

immunomodulatory effects of azithromycin in COPD and led to a burst of international clinical trials. In one of these, the group of Hodges and Reynolds in Adelaide found that azithromycin enhances the depressed phagocytosis of alveolar macrophages in COPD, suggesting that the drug alters the phenotype of the macrophages from inflammatory M1 to pro-resolving M2 (Hodge et al. 2008). This action was subsequently confirmed in *Pseudomonas aeruginosa*-infected mice by Feola in the United States (Feola et al. 2010). Over a period of several years, our biology group in Zagreb under Vesna Erakovic Haber's direction, showed that inhibition by azithromycin of murine endotoxin (LPS)-induced lung neutrophilia was mediated by actions on macrophages, that azithromycin directed interferon-γ differentiated, LPS-activated human blood monocytes towards an M2-like phenotype and the differentiation by GM-CSF/IL-4 of human blood monocytes to a regulatory dendritic cell phenotype (Bosnar et al. 2009; Polančec et al. 2012; Vrančić et al. 2012). We also confirmed the anti-inflammatory/immunomodulatory effects of azithromycin in a variety of animal models, including skin, as well as working on projects in wound-healing and antifungal candidates.

We moved into the new building in 2003 and with new organisation, Vesna took over Biology Research, while I became Senior Advisor, including working on nonclinical development of biosimilar drugs with the generics division. This led subsequently to the first marketing of biosimilar erythropoietin and filgrastim (later acquired by Hospira and Pfizer). I had devised the nonclinical development strategy, gaining me the honour of representing the European Generics Association in regulatory approval discussions with the EMEA, now the European Medicines Agency (Parnham et al. 2007). In 2005, PLIVA New Drug Research was acquired by GlaxoSmithKline and the Generics division eventually landed in the hands of TEVA. Under GSK, we concentrated on developing the nonantibiotic azithromycin derivative we had developed for COPD while still under PLIVA ownership. Our biologists also identified valosin-containing protein (VCP) as a potential low affinity target of azithromycin (Nujić et al. 2012). Ginny Norris at GSK in the UK was tasked with planning the clinical trials of the novel nonantibiotic macrolide, but under new top management, the project was axed. I was to work with Ginny under more encouraging circumstances more than a decade later. Although our lead compound was shelved, azithromycin has continued to be used off-label for its immunomodulatory properties in inflammatory lung disease, particularly COPD. It is now recognised by the GOLD guidelines as an effective secondary treatment for acute exacerbations of COPD (AECOPD) but has never received regulatory approval for this purpose (https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-POCKET-GUIDE-FINAL-pgsized-wms.pdf).

Repurposing and retirement

With a reduction of the research team in Zagreb in 2008, once again as 18 years previously, I became superfluous to requirements and spent the next 3 years consulting and looking for another job! This, sadly, has been the experience of many highly capable and effective industry researchers over the years, who have had to succumb to the vicissitudes of economically minded management board members, regarding researchers as easily expendable "cost factors"! This was not always so, as when I first entered industry in 1980, it was common for scientists to spend their whole careers working within the same pharmaceutical companies. At that time, it was also usual for the CEO to have been a chemist, pharmacist or medically qualified person, well able to understand the long-term nature of drug research. Alas, succumbing to shareholder pressure for enhanced dividends, it soon became preferable to place the company into the hands of an economist or marketing trained leader. The result was a prolonged period of mergers and acquisitions, with large multinationals gobbling up other companies to enhance sales and profits, with no thought for the long-term effects of the dismantling of successful research divisions. As John L. LaMattina, former President of Pfizer Global R&D has stated, "although mergers and acquisitions in the pharmaceutical industry might have had a reasonable short-term business rationale, their impact on the R&D of the organizations involved has been devastating" (LaMattina 2011). Sadly, the lost expertise could not be restored and has been replaced by open research, with large companies often seeking to capitalise on the research efforts of low-paid and overworked academics and small biotech researchers to boost their pipelines.

Ultimately, after 3 years of looking for a new position and living off savings and the occasional income from consulting in Zagreb, at 60 years old I was offered a new position by Gerd Geisslinger. This was to help establish a new project group for the Fraunhofer Institute for Molecular Biology and Ecology (IME), in association with Gerd's Institute of Clinical Pharmacology and the interdisciplinary Centre for Drug Research, Development and Safety (ZAFES) at Goethe University Frankfurt—where I had continued to teach. Programme funding was obtained from the Landesoffensive zur Entwicklung Wissenschaftlich-Okonomischer Exzellenz (LOEWE, State Offensive for the Development of Scientific and Economic Excellence) of the State of Hessen. This led to a wide variety of fruitful collaborative projects with colleagues in different University Departments within the ZAFES centre. These included in Clinical Pharmacology with Gerd Geisslinger on pain and analgesia, Irmgard Tegeder on autoimmunity

and Jörn Lötsch on epigenetic effects of drugs; in Pharmaceutical Chemistry with Dieter Steinhilber on lipid mediators; in Pharmaceutical Technology with Matthias Wacker on drug delivery; in Biochemistry I with Andreas Wegert and Andreas von Knethen on cytokines, macrophages and sepsis; and in Biochemistry I with Ivan Dikic on cell signalling pathways. In addition, within the Fraunhofer Society, there were close connections between the constituent groups of IME, headed by Rainer Fischer in Aachen and subsequently with Armin Braun at the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM) in Hannover. Inevitably, this was an exciting and horizon-extending experience, expanding my understanding of a wide spectrum of research approaches and techniques, quite apart from widening my circle of friends and acquaintances.

The return to an academic setting was refreshing and challenging, quite apart from the return to the familiar environment of Germany. With the sizeable grant from the State of Hessen to build up a new research group, we set up novel test systems for drug discovery. We were working in the areas of lipid mediators, pain and analgesics, anti-inflammatory and immunomodulatory drugs with the intention of facilitating collaboration with industry, and the research was increasingly directed towards repurposing of known drugs. Initially, as Head of Preclinical Research and later of Translational Drug Discovery, I had the privilege of coordinating the work of a productive group of scientists and some excellent technicians. An advantage we had was the proximity in the medical school to research orientated clinicians and we were able to collaborate with rheumatologists, dermatologists and other groups in European centres, as well as with university pharmaceutical chemists and pharmaceutical technologists. We also collaborated with colleagues across the Fraunhofer network of institutes across Germany. We were able to establish discovery approaches to anti-inflammatory drugs, analgesics, inhibitors of multiple sclerosis, Alzheimer's disease, sepsis and drug delivery with publications in high quality journals, with beneficial effects on our citation indices. One of the interesting projects we ran for 3 years was a collaboration with Ulrich Dirnagl at the Charite in Berlin and Anton Bespalov and Christoph Emmerich at PAASP in Heidelberg to establish Guidelines on Target Assessment for Innovative Therapies (GOT-IT). The final GOT-IT guidelines were published in Nature Reviews in Drug Discovery (Emmerich et al. 2021). Collaborations with academic groups also opened possibilities to establish spin-offs, including the successful discovery by Frank Behrens, Harald Burkhardt and Rikard Holmdahl, Karolinska Institute, Stockholm of a novel approach to induce tolerance to autoantigens in rheumatoid arthritis which led to the formation of the biotech company aidCURE AG. With time, the research centre grew and after I officially retired at the end of 2019, it became the Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP) with six different centres across Germany. Some of the projects we established are still running and I continued to provide limited advice and input to a couple of these for several years after leaving. These include a project run by Susanne Schiffmann, as part of the European Innovative Medicines Initiative (IMI) financed project imSAVAR (Immune Safety Avatar) to develop a platform for the integrated nonclinical assessments of safety and efficacy of immunomodulatory therapies, which I helped establish. This led to the recent publication of methods to assess in vitro the potential hepatotoxicity of immunomodulators such as recombinant interleukin-2 (Roser et al. 2023). We also achieved the successful spin-off of a protein engineering project to develop an agonist at PD1 immune checkpoint receptors for the treatment of autoimmune diseases. This arose from the study led by Andreas von Knethen that during sepsis in mice, expression of the PD1 ligand, PDL1, on the surface of hepatocytes is strongly depressed by reactive oxygen species and that replacement therapy with an exogenous PDL1-IgG fusion protein inhibits liver injury in mice in vivo (von Knethen et al. 2019). The company Phialogics AG, founded by Andreas Ernst, Andreas von Knethen, Andreas Weigert and I from Goethe University Frankfurt and ITMP, together with Pascal Oromi from Marseille, continues to grow from laboratories at BioLabs in Heidelberg and headquarters in Basel.

For most researchers, apart from emeritus professors given the chance to continue working in a lab, retirement represents an abrupt transition from high activity to life at a more sedate pace. Two months before I left Fraunhofer, Clive Page, whom I had not seen for years, phoned me. He was Chairman of the Board of EpiEndo Pharmaceuticals, a Reykjavik, Iceland based company formed only five years previously, that was investigating the effects of azithromycin-derived compounds which enhance the airway epithelial barrier, as potential treatments for COPD. This seemed like a dream come true. Having spent a decade looking for compounds derived from azithromycin for treatment of inflammatory lung diseases, only to submit to GSK's guillotine, here I was 11–12 years later being offered the opportunity to act as scientific advisor to a company that was doing just this. I could barely contain my excitement. During the last few years, the enthusiasm has not diminished as we have taken the lead compound through preclinical and nonclinical development into the clinic and are now carrying out clinical trials on COPD patients. I doubt whether many, if any scientists have had the opportunity to return to a project similar to one that was terminated and to contribute to its clinical development. Inevitably, this has also led to new working relationships and friendships. I am grateful to Clive, Fredrik Lehmann, Maria Bech, Finnur Einarsson and Jennifer Kricker for allowing an old man to join them in the

hope of realising past dreams and even act as interim Chief Scientific Officer for a year.

Within a few months of my retirement, the SARS-CoV2 pandemic hit and focussed researchers worldwide on the search to understand the disease and look for potential therapies. Living in Germany, we were close observers of the development by BioNTech with Pfizer of the mRNA vaccine against the virus and of another vaccine by Oxford Biomedical (where my son Ian was working) for AstraZeneca. Many old drugs were repurposed in the hope that they would be effective, including two I had worked on, azithromycin for its effects on lung inflammation and ebselen, the latter because of its inhibition of the SARS-CoV2 protease. As Helmut Sies and I pointed out, the interaction of ebselen with thiol groups in vivo may reduce its accessibility to the virus (Sies and Parnham 2020). The renewed interest in azithromycin, which has been shown to exert some antiviral action on the CoV2 virus, has certainly helped to draw attention to the work at EpiEndo, and so the odyssey continues.

Faith or fate

After all I've written above, you may find it hard to believe, but I strongly dislike moving house! Packing away all the possessions, arranging the paperwork for removers, cancelling services, finding a new home and having to set up new services, finances etc. all over again. Add to this the dimension of moving to yet another country and learning another language and tax laws, the task can be quite daunting. Why have we done it then? Having written a draft of this article, I was unexpectedly asked to say something of the faith by which I live. The fact of the matter is, I'm sure that without faith in a loving God who cares for me and died for me, I doubt whether I could have easily coped with so many challenges. I learned in my youth to trust in the goodness of the God of my grandparents and parents who had themselves, despite sadness and disappointments, repeatedly found Jesus to be faithful. Like the many Christian friends of varying nationalities and backgrounds we made over the years, Elaine and I have also proved that God cares for us. Otherwise, it would be an exceptional series of coincidences that a young man who was mediocre at school ended up at one of the best universities for studying pharmacology and worked in a lab run by a future Nobel Prize winner. Then, suddenly blocked from a planned job move to Brazil, we went to live in the Netherlands where I learned so much that would guide my future career. Was it just fate that we moved to Germany where I worked on an exciting new compound which is still studied globally and is now close to being a marketed drug and where I was able to gain a professorship and learned the hard way how to run a business? Facing difficult circumstances, a door opened for us to move to a country just coming out of a war where we carried out research which 20 years later, I have been able to work on again and help bring another new drug into the clinic. These remarkable experiences were all subsumed under a biblical promise that Elaine and I read and claimed, early on in our odyssey, before we left Bristol in 1976, "I am sending an angel ahead of you to guard you along the way and bring you to the place I have prepared" (Exodus 23:20, New International Version). This promise has been a source of continual encouragement and has been fulfilled many times over. That is not coincidence, but faith in action. On the way, we have shared lives with Christians in churches of different denominations across Europe in each of which I have been a lay preacher and where we found friendship and support. When looking for a job for 3 years in Croatia, I used these experiences to write a book on the challenges and benefits of Christian unity in diversity, later translated into German (Parnham 2012, 2016b). We have learned a great deal and I have been able to pass on several of these lessons of life to my colleagues of differing ethnic backgrounds at work. As one of the senior managers I worked under wrote when I asked him for a reference, "having Mike on board with his experience and wisdom was very important. He was a manager, but at the same time also a dedicated mentor, who always found time to teach, advise or just serve as the 'voice of wisdom'. I have no doubt that Mike had an important, formal or informal impact on the development of a number of people within the organization." These practical lessons from experience may be open to several interpretations. I myself do not ascribe them to fate, serendipity or simply to autodidactism, but to knowing the "only wise" God I have learned, over 73 years, to love and trust.

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Reviews and chapters

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Declarations

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