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EDITORIAL

Editorial Special Section: "Commemorating Leading Inflammo-Pharmacologists"

Commemorating the life at 90 years and work of Professor Michael Wellesley Whitehouse, BA, MSc, D Phil, F.R.I.C., FRSB (UK) KSJ

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This Special Editorial Section of the Journal is dedicated to the lifetime contributions by an outstanding multidisciplinary scientist, academic scholar, colleague, and friend to many throughout the world. To describe Michael's field of specialization in a single term, would be a gross understatement of his training, skills and scholarship.

Throughout about 70 years of academic life, Michael has accrued a great thirst for knowledge whether scientific, scholastic or cultural. He is anything but selective or exclusive in his approach to acquiring knowledge or focus as an academic. I have had the great pleasure of knowing Michael both as a research and scholastic colleague as well as being close friend for the best part of half a century! From the beginning of our working relationship, I have found that Michael has that special kind of quality in a natural 'meeting of the minds'. Many occasions when we have worked together on research projects or writing manuscripts, I have thought that we sense the others' intuition and thoughts. This is a very special quality for which I am immensely grateful. It is not to say we have been uncritical of one another's ideas, but we have a special way of inter-weaving our ideas and working together for what many would say is 'for the common good'. I find that many of Michael's colleagues from different disciplines, lives and backgrounds also have great respect for him, his ideas and thoughts. Basically, Michael gets on very well with all and manages to bring out the best in so many of his lifetime of contacts. Some of the contributions from colleagues and friends shown at the end of this article attest to these views and show how much he has given to many of those with whom he has had contacts through his life.

Michael was born 90 years ago in Hendon (formerly an ancient parish of Middlesex, now part of Greater London) and grew up in Sheffield (South Yorkshire) and later in Wigan (Lancashire) where he went to Wigan Grammar School, Then, he went to Alsop High School in Liverpool and Highgate School (North London). The period of his school and later higher education at Oxford must have been very trying as this was during the 1930s recession and then World War II with the bombing in and around the areas where he lived with his parents. He moved around quite extensively during his secondary education with his father who was a leading secondary school modern languages teacher. I sometimes wonder if Michael's undoubted skills in writing and English expression came from his father.

Tribute to Professor Michael Wellesley Whitehouse.

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Certainly, he had a very high standard of education in wartime and immediate post-war conditions, which must have been very challenging. In 1948, he won a scholarship to Keble College, Oxford University where he read Chemistry and Biochemistry, graduating with a 1st Class honours degree with distinction in biochemistry. Keble College must have been a stimulating environment, not only for learning the sciences, but also cultural as the first Oxford College of "the modern era" founded in memory of John Keble who was a key member of the "Oxford Movement" that sought to recover some Catholic heritage of the Church of England. It was well supported in its foundation by being endowed by the Gibbs Banking Company who made money from a monopoly on imports of bird droppings from the Galapagos Islands as a source of fertiliser in Victorian times. The college has particularly attractive chromatic brickwork described as Butterfield Architecture.

While at Oxford, Michael undertook studies to be admitted as an Associate Member, followed later in 1962 as a Fellow, of the Royal Institute of Chemistry (London) which qualified him as a professional chemist. This has enabled him to analyse biological and medical problems through the eyes of a chemist so giving him privileged insight into the molecular aspects of diseases, development of therapeutic agents and as well as the potential properties of biological agents. Michael can be regarded as one of the unique class of "biological chemists" (following the approach of the classical journal [Journal of Biological Chemistry] and the textbook of the same title by Lubert Stryer). His post-doctoral experience (1955–9, supported by the English Speaking Union) ranged from biochemistry at the University of Pennsylvania, and University of Stockholm (1960; as Geigy Travelling Fellow of the Empire Rheumatism Council, now the British Society of Rheumatology), where he had a particularly productive period working with Dr. Harry Bostrom at the latter university. His early period involved work with the famous biochemist, Dr. Paul Kent, as Drs. Lash, Zilliken, Denko, Kritchevsky, Dean, Skidmore among others working on the chemistry, biochemistry of liver and mitochondrial metabolism of lipids (including those in bile), cholesterol, polysaccharides, sialic acids, glycoproteins, and effects of anti-inflammatory drugs on intermediary and polysaccharide metabolism. He undertook research while a Lecturer in the Biochemistry Department (headed by Prof Hans Krebs) at the University of Oxford (1960–1966), as well as being the Staines Medical Research Fellow of Exeter College, and Tutor in Physiology and Biochemistry at Keble College and St Peter's Hall, Oxford. Several of his outstanding publications of the time appeared in Nature, leading biochemical, medicinal chemistry and pharmacological journals. It was this and later work on the diverse molecular aspects of drugs used to control inflammation and immunity to which I was particularly attracted. Michael and I first met and started to work together when he was a Visiting Research Fellow (1966–1967) and had a Commonwealth Travelling Bursary funded by the Royal Society) and later Senior Research Fellow (1973–1981) at the prestigious, John Curtin School of Medical Research (JCSMR) at the Australian National University in the Australian national capital of Canberra, during the 1970s when I was a Lecturer/Senior Lecturer in Biochemistry at the University of Tasmania Medical School, Hobart, Tasmania, as well as being a Visiting Fellow in the JCSMR. This was among the many productive periods of our collaboration which has extended now for over half a century.

In between the two periods (1967–1973) in Canberra, Michael was Associate Professor of Medicinal Chemistry, Ohio State University, Columbus and Full Professor in Medicine/Rheumatology at the University of California at Los Angeles (UCLA) where he worked with the late Carl Pearson, Frances Beck (see later contribution) and others on some of the key immunological aspects of chronic inflammatory diseases especially the roles of adjuvants and lymphocytes.

Since we first started to collaborate in 1975, we have had a very productive and stimulating friendship. Sometimes this was accompanied with intense discussions and critical encounters, but these had very positive outcomes. A few occasions this led to an agreement to disagree, but from my side an immense respect and deep appreciation of Michael's breath of knowledge and his intellect. We collaborated in our research not only on a broad range of projects focussing on exploring and modifying the actions of salicylates, and other NSAIDs and analgesics in attempts to make these drugs safer, especially to the gastro-intestinal tract, as well as to be more effective therapeutically.

We tried hard over the years to encourage clinical exploitation of these key findings and observations. Most notable was with leading pharmaceutical companies, some of the principal scientists, medical directors and clinicians, as well as with management and laboratory staff. Many of these associations were very useful insights into industrial approaches and the requirements and difficulties in meeting the diverse regulatory and clinical requirements for getting drugs into clinical use, as well as that strange entity known as the market. We did achieve some success, but it has to be said there were many disappointments (to put it mildly). Overall, our experiences in working with the pharma industry could be summarized (in hindsight) as being profoundly negative even though in many cases we had very strong support from rank and file, researchers and clinicians. Often, we hit a log-jam with mostly middle-order managers and marketers with deeply entrenches views, many of which were based on arcane concepts and ideas. A key point was, however, that in many cases our discoveries and developments were made on their own company products, especially

on aspirin and other salicylates. We and our own scientific advisors and colleagues genuinely believed these would benefit both, the company and us. With one or two exceptions these proved not to be the case as senior management (often who had little understanding of the clinical benefits or knowledge of the fields in which the discoveries were made or their benefits to patients) often actively blocked or connived to derail exploitation and development of the innovative forms of the drugs either because (a) it would be a counter-development to the company's existing products or product range, (b) the risk commercially could not be redirected from disadvantages to advantages. Most managers in the pharmacy industry are inherently risk-averse and have one eye on the shareholders (who in most cases are non-scientists, non-physicians and don't even have the vaguest understanding of the drugs in development) or the complexity of the deep-seated politics in big pharma, or (c) the attitudes, poor scientific quality and background as well as attitudes, intrinsic risk-adverse negativity of national and multinational (especially in the European Union and its member states) of the regulatory agencies that govern approval of new products. While very occasionally encounters or interactions with a few members of these agencies have been positive, they are governed by negative pressures from political and bureaucratic masters. Thus, the whole process of taking a promising (often very promising) new discovery or development through company and drug-regulatory processes is rather like seeing horses jumping over and falling at a grand national steeplechase (especially like that of the annual event in Aintree, UK).

We did go through many exhaustive processes including getting university committee or administrative approvals, patent applications, many of which were very challenging and intellectually unique exercises in themselves (writing a patent specification is in my view a somewhat arcane art–science form, wrapped in its own legalese, but which can be very rewarding, especially when the patent is finally approved and in some cases an elaborate document and certificate is produced by the Patent Office or agency concerned. Working with patents attorneys can be both an intellectually challenging and a satisfactory experience that proves you have to know your invention, competitive other discoveries and developments.

Finally, there is the ever-expanding involvement of university administrators and deans. In a number of cases we had some encouragement and support from these senior officers. However, a few of the middle order management seem to see us a 'cash cows' with rapacious appetites for money and royalties to be siphoned off into their coffers and without recognition of the hard work done by those who have been the creators, fund-raisers and who have done everything to create novel drugs. As Michael and I know only too well, the foot soldiers never receive any gratitude—maybe the odd award and promotion but not without dripping envy and jealousy. We have the T-shirts but they are all blank.

The next entrepreneurial venture which Michael and I have been involved in over the years is the communication of our science as well as ideas and criticisms, and that of our highly valued colleagues. This has taken the form of the development of a journal devoted to the broad subject area which up to the late 1980s had been somewhat neglected or left to other journals with less specialized expertise, focus or scope. Enter 'Inflammopharmacology', a journal dedicated to the pharmacology of inflammatory diseases and their associated aches and pains, their clinical treatment and pharmacotherapy. The history of the development and achievements of this journal since its inception in 1991 has been told elsewhere (Rainsford 2016). Since its inception, the journal has benefited over the years from many ideas, commentaries, publications and concepts initiated and developed by Michael. Among the many significant concepts begun by Michael was that of 'Conditional Pharmacology' which he pioneered (Whitehouse 1987, 1991) and developed with the late Professor Barrie Vernon-Roberts (University of Adelaide, Australia) (Whitehouse and Vernon Roberts 1991) and Dr. Michael Powanda (M/C Biomedical Consultants LLC, Mill Valley, CA, USA) (Powanda 1995).

In essence, this concept states that (a) inflammatory processes may alter the basis for the actions of drugs that have been designed to act on these processes by means of altering the receptors, enzyme activities, drug metabolism or other physio-pathological mechanisms that are affected by these agents, and (b) that through these actions, the alteration of these inflammatory processes they may in turn affect those mechanisms (e.g. drug metabolic enzymes) that influence their mode of action.

This elegant, if little appreciated, concept may be summarized as the vicious cycle of drug actions and influences of their consequences; elements of this vicious cycle may have positive therapeutic consequences and possibly negative or positive toxicological impact.

Another part of our collaboration has been in the contribution to the ethos and development of the International Conference series which initially began (in collaboration with the late Professor Giampaolo Velo, Verona, Italy) as the "Side Effects of Anti-inflammatory/Analgesic Drugs" conferences and then progressed to the "International Conference on Inflammopharmacology with the symposium on Side Effects of Anti-inflammatory Drugs" and also Safety and Efficacy of Non-Prescription (OTC) Analgesics and NSAIDs which was held in collaboration with Dr. Michael Powanda. These were followed with the conference series on "Inflammopharmacology", held in collaboration with Dr. Brian Callingham (University of Cambridge and Queens' College, Cambridge) (Rainsford 2016). Not only did

Michael make presentations of major significance to these conferences, but also challenged many of the arguments and data that were presented and contributed to the ideas and planning of these conferences.

It is interesting to reflect back to the earliest conference that we organized in 1975 which was held on "Aspirin and Related Drugs. Their Actions and Uses" (Rainsford et al. 1977). Here we presented concepts of how aspirin and related drugs produced their anti-inflammatory actions as well as causing side-effects. Notably, presented data on salicylates that were derived from natural products and how these might produce anti-inflammatory effects and have differing actions (or inactions) on platelet aggregation. Strikingly, these observations are relevant today and may still be worth consideration in the pharmacotherapy of inflammatory conditions.

From these early observations on salicylates derived from natural products, Michael and his colleagues have continued to have interests in natural products as anti-inflammatory and analgesic activities. Among the most notable of these has been the ethanolic extract of the celery seed derived from Amritsar (India) which has proven clinical activity as well as gastro-intestinal protection (Rainsford et al. 2015). The latter extends to an important and unique action found in a phthalate component of celery seed oil which has since been found to have anti-helicobacter activity (Zhou et al. 2009). Our interests and research work in this and many other natural products, as well as development of derivatives thereof would not have been possible without the initial and continued interest by Michael.

Like so many research collaborations, the unique and highly significant results come from a meeting of minds, personal relationships and long-standing friendship. We owe an immense debt of gratitude to Michael for all these especial qualities.

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Mini Symposium 'Commemorating Life and Works of Leading Australian Scientists in the Fields of Inflammation and Pharmacotherapy of Inflammatory Diseases'

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The reviews are based on a small symposium held in Adelaide on July 5, 2019. The symposium was organized by Professor Kim Rainsford, Sheffield Hallam University, Sheffield and University of Adelaide and Professor David Haynes, University of Adelaide.

As outlined during this symposium, Professor Michael Whitehouse has freely given his time and valuable research advice to all presenters at the symposium. As outlined below, Professor Whitehouse has published over a wide range of research areas. Not surprisingly, he has a considerable publication record. Reference to Google Scholar indicates that he has published 422 papers with 9324 citations. His h-index, a measure of interest in his publications is 53.

Studying Chemistry and Biochemistry at Oxford started Professor Whitehouse off on a line of research that led through various aspects of molecular medicine; including chemistry of animal polysaccharides, sterol metabolism and ischemic heart disease, cartilage degradation and osteoarthritis, toxicity of adrenocorticoid hormones, non-steroidal anti-inflammatory drugs and natural products. Professor Whitehouse has conducted many studies on the evaluation of the anti-inflammatory activity of compounds in experimental animals and is an expert on the details of these often-difficult studies. In research management, Professor Whitehouse was very much involved in the establishment of committees for the ethical examination of animal-based research.

To Professor Whitehouse, the world is chemical in nature and cannot be understood without knowledge of the chemical properties of compounds under study. His initial studies in pathology were on mucins in the gastrointestinal tract and, because of his interest in the relevant chemistry, was a co-author of a book on the constituent amino-sugars (Kent, Whitehouse 1955). This book is still being referenced.

Professor Whitehouse has conducted much research in Australia, starting in the Department of Experimental Pathology, John Curtin School of Medical Research, the Australian National University, Canberra, with the initial assistance of Professor Sir Howard Florey in 1966–1967 and again 1973–1981. In the intervening period (1968–73),

Professor Whitehouse was Professor of Medicine and Acting Professor of Pharmacology at University of California, Los Angeles (UCLA). From 1981 to 1994, Professor Whitehouse was a senior researcher successively at three South Australian institutions, Flinders University of South Australia, the Department of Pathology and Institute of Medical & Veterinary Science, University of Adelaide, and the University of South Australia. He has also worked for several years with Professor Michael Roberts, School of Pharmacy, University of Queensland. Currently, he is an Honorary Research Professor in Experimental Medicine at Griffith University in Queensland.

While at UCLA, Professor Whitehouse was a consultant to Riker Laboratories with a particular interest in the anti-inflammatory drugs used in the treatment of rheumatoid arthritis. At the time, Riker Laboratories were developing an unusual anti-rheumatic drug and because of his expertise in chemistry, Professor Whitehouse rapidly and correctly identified the drug as reacting with sulfydryl (thiol) groups.

Professor Whitehouse has published many papers on the anti-inflammatory and anti-cancer activity of metals, including complexes of zinc, copper, silver, platinum, and gold. He has also shown that colloidal gold has anti-inflammatory activity. This work was published from the 1970s onwards but is still being referenced, an indication of the novelty and value of Professor Whitehouse's research approach. Professor Whitehouse's two papers on colloidal gold are of note. Metallic gold is generally considered to be inert. However, Professor Whitehouse showed that colloidal gold is not inert but has anti-inflammatory activity (Brown et al. 2007, 2008).

Consistent with these findings, gold pellets also have anti-inflammatory activity and have continued use and investigational studies as local injections for anti-inflammatory action in hip dysplasia in dogs (Jaeger et al. 2016). This activity is due to dissolution of gold from the surface of the pellets which may be increased with greater pharmacological effect due to the greater surface/mass ratio of colloidal gold than gold pellets.

Other notable and widely cited work of Professor Whitehouse includes his finding that thiocyanate, SCN-, a normal body constituent, has pro-inflammatory activity in rats (Whitehouse and Jones 2009) but, on the other hand, may decrease neutrophil-induced tissue damage (van Dahlen et al. 1997). Professor Whitehouse was responsible for the introduction of the term, 'Conditional Pharmacology' which is defined as the modification of the pharmacological actions of a drug changing pathophysiological conditions or the addition of a compound which is not a drug. Professor Whitehouse et al. (2013) first discussed this concept on how thiocyanate modifies the activity of silver and the anti-rheumatic gold complexes. Further work on conditional pharmacology, particularly with thiocyanate, is warranted from the work of Professor Whitehouse.

Another example of early work of Professor Whitehouse was his studies of emu oil which is reviewed elsewhere (Whitehouse et al. 1998) which has been widely applied to the skin by Australian aboriginals. The anti-inflammatory activity of topical emu oil was quickly realized by Professor Whitehouse (1998) Unfortunately, Professor Whitehouse could not continue this work due to patenting questions and consequent lack of support by funding organisations. However, his work has been confirmed by several other groups and is a further example of research studies initiated by the work of Professor Whitehouse.

Professor Whitehouse is now 90 but is still an active researcher putting forward novel ideas in pharmacology and toxicology, particularly with his wife, Desley.

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The evolution of conditional pharmacology

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The concept of conditional pharmacology and toxicology originates in the studies of drug-disease interactions in inflammation done by Dr. Whitehouse and his colleagues (Whitehouse 1985, 1991; Whitehouse and Vernon-Roberts 1991). The concept originally focused on how expression of anti-inflammatory activity may require pre-existent inflammatory mediators/hormones. A few years later I commented on how broad the implications of conditional pharmacology might be, even extending the concept to preclinical toxicology studies (Powanda 1995).

As I stated then and now recapitulate, "Conditional pharmacology/toxicology involves employing the physiological or metabolic activity, the genetic and/or molecular structure of the host, of the disease process and/or of the parasite to activate and target the drug or biologic, as well as to regulate and delimit its activity. This definition emphasizes the multifactorial aspects of the approach and sets the stage for a listing of some existing as well as proposed examples of use of the concept in the treatment of inflammatory diseases and in the treatment of neoplastic and infectious diseases. This concept is also an underlying assumption, and expected consequence, of successful gene therapy."

Almost three decades later, there are a number of drugs and biologics whose actions depend on the presence of a receptor or an overactive gene. In breast cancer, a gene called HER2 makes too many copies of itself in about 20% of people with breast cancer. Trastuzumab (Herceptin), an antibody, is the standard treatment for this type of breast cancer apparently acting by sticking to certain areas on cancer cells, stopping them from growing, as well as signalling the body's immune system to attack cancer cells (Romão et al. 2017).

About 2 out of 3 breast cancers are hormone receptor-positive. Their cells have receptors (proteins) for the hormones estrogen (ER-positive cancers) and/or progesterone (PR-positive cancers) which help the cancer cells grow and spread. Tamoxifen blocks estrogen receptors on breast cancer cells. It stops estrogen from connecting to the cancer cells and telling them to grow and divide. While tamoxifen acts like an anti-estrogen in breast cells, it acts like an estrogen in other tissues, like the uterus and the bones. Because of this, it is called a selective estrogen receptor modulator (SERM). It can be used to treat women with breast cancer who have or have not gone through menopause (Kahlenberg and Fox 2011).

In the case of rheumatoid arthritis, there are a series of biologics that work by interfering with the activity of tumor necrosis factor. This is a key immune system cytokine. These drugs include: adalimumab, etanercept, infliximab and golimumab. Another cytokine target is interleukin-1 (IL-1); Anakinra blocks the action of interleukin-1. Tocilizumab is a biologic that works by blocking the cytokine interleukin 6 (IL-6). In contrast, Abatacept is a selective T cell co-stimulation modulator, while Rituximab, a CD20-directed cytolytic antibody, appears to help control RA by destroying another category of immune system cells called B cells.

In November 2012, the U.S. Food and Drug Administration (FDA) approved tofacitinib citrate, a drug "to treat adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate." Tofacitinib is a Janus-associated kinase (JAK) inhibitor. It works by blocking a cellular signalling pathway inside cells. It can be taken orally.

The above drugs/biologics all depend on some factor/factors related to the disease being present in the extra or intracellular milieu, as 'conditional pharmacology' would predict. Despite this array of drugs and biologics for breast cancer and rheumatoid arthritis, it is clear that these agents may be ineffective or less effective in some cases (5–7). Also, none of these is a cure. Plus, virtually all these agents display toxicities (8). It remains to be seen whether other disease related factors can be identified and targeted so as to increase efficacy and decrease toxicity of cancer and arthritis treatments.

In the case of drugs, safety and efficacy may be related to drug–drug interactions, either metabolism mediated drug interactions or transporter mediated drug interactions. In concert with metabolizing enzymes, transporters can govern a drug's disposition and pharmacological action. The US Food and Drug Administration has recently published a final guidance document to assist investigators in determining whether drugs are affected by metabolism and or transporter interactions (9).

The continuing hope inherent in the concept of 'conditional pharmacology' is that the discovery of new, even more highly specific disease related targets may help in the development of drugs and biologics that are both more efficacious and, if possible, less toxic.

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A personal appreciation of Professor Michael W. Whitehouse

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Early in the decade of 1970 at the University of California, Los Angeles (UCLA), one found Professor Michael W. Whitehouse investigating mediators of inflammation and their pathological importance in rheumatoid arthritis at a time when the new field of Immunology was at its rudimentary beginning. In addition, he was a research consultant to the late Dr. Louis Levy at Riker Laboratories (now 3 M) in Northridge, California where questions concerning effectiveness of anti-inflammatory compounds were also being addressed. At Riker, where compounds were both manufactured and evaluated, the question asked was: "Are these compounds effective in reducing the inflammatory response?". However, most testing was done using healthy animals. Several years later, I was honoured to join Professor Whitehouse at UCLA where the question was turned around: "Does the physiological state (healthy/unhealthy {disease}) of the subject alter the ultimate efficacy of the drug being administered". At the time, it was an interesting exercise in experimental research, but eventually, over time, it became clear that the answer would be a resounding "YES!" and is the central theme of today's concept of 'Conditional Pharmacology' applied in nutrition, drug development, ageing studies and particularly in cancer research as well as in other disciplines. Thus, Professor Whitehouse had at that time laid the groundwork for both of our individual careers in academic research even though our respective careers would soon diverge. Two years later, Professor Whitehouse relocated to Australia where he would continue to investigate this subject in search of better treatments for arthritis for the rest of his academic career. However, before leaving, he was instrumental in providing arrangements with the late Dr. Carl Pearson that would allow me to continue our research at UCLA for the interim between his exit and the appointment of a new investigator to his former position. This provided for me an unprecedented opportunity to be an independent investigator responsible for the design and execution of experiments leading to several publication years before I was able to obtain advanced degrees. It was the grand initiation into an interesting, enjoyable and successful career in academic research.

In Australia, Professor Whitehouse continues to define the mechanisms by which adverse physiological conditions would affect drug efficacy using unique animal models that were developed during his time at UCLA. For his extensive research into the treatment of arthritis and inflammation, he was elected to Life Membership of the Australasian Society and the Australian Rheumatism Association of Clinical and Experimental Pharmacologist and Toxicologists. Although unaware of each other's work, Professor Whitehouse's research into the effect of zinc on the inflammatory response in a compromised system paralleled our similar studies at Wayne State University School of Medicine, Detroit, Michigan under the direction of Dr. Ananda Prasad. There, we demonstrated that multiple molecular mechanisms involved in the production and expression of inflammatory cytokines as well as the regulation of target receptors were altered in the physiological zinc deficient state whether zinc deficiency was nutritionally, experimentally or disease induced or genetically inherited. Later, in collaboration with the University of Queensland, Professor Whitehouse founded and managed research at Pharma Quest, a Consultancy to promote research on natural medicines. Near the same time, my work at the Barbara Ann Karmanos Cancer Institute in Detroit, Michigan with Drs. Ramzi Mohammad and Ayad Al-Katib, was centered in evaluating the efficacy of anti-cancer compounds also isolated from natural sources. That cancer cells respond to specific drugs quite differently from that of normal cells is possibly the most complex form of the 'Conditional Pharmacology' concept embraced at UCLA 45 years earlier and now requires investigative research be executed at the molecular level. The search for compounds that modulate specific intracellular molecules aberrantly expressed in cancer cells but not in normal cells is at the core of cancer research pharmacology.

Before Professor Whitehouse became semi-retired from active research, our paths would cross once again. It was a privilege to share results of our respective research careers with each other and with his colleagues at the University of Queensland in 2002. Conversations concerning all manner of things discussed within the "Whitehouse Research Family" at UCLA years ago were easily continued as if it were

but yesterday. Old acquaintances were remembered (Drs. Peter Fowler, J. P. Famaey, Carson Dick, Kim Rainsford to name a few) and new ones established. Sprinkled between seminars, conferences, presentations and experiments were short trips to explore nearby surrounding Australia with his dear wife and colleague, Desley Butters. Recently, he was awarded Chevalier of the Hospitalier of St. John's of Jerusalem, one of many accolades he has received throughout his lifetime. On behalf of the many, many individuals who have benefited from Professor Whitehouse's support and friendship we say "Congratulations on your many contributions to science, medicine and humanity, the honours are well deserved." To Professor Whitehouse, the true honour for each of us, however, is to have been and continue to be your colleague and friend.

Some biographical reflections

Prof. M. W. Whitehouse

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Michael was born in Middlesex, North London, in 1930, both his parents being schoolteachers. He was raised first in Sheffield (Yorkshire), Wigan (Lancashire) and finally in Liverpool (Merseyside) from where he was twice evacuated to Wales, before heading south, first to Highgate School (North London) and then Oxford University.

After studying Chemistry and Biochemistry at Oxford he went off on a line of research that led through various aspects of molecular medicine; including chemistry of animal polysaccharides, sterol metabolism and ischaemic heart disease, cartilage degradation and osteoarthritis, toxicity of the adrenocorticoid hormones and non-steroidal anti-inflammatory drugs, including complexes of the coinage 'noble metals' Cu, Ag & Au used as 'novel' drugs to control inflammation. Resulting from a long-standing interest in immunological adjuvants as aetiologic agents in (poly)-arthritis, he undertook a search for environmental arthritogens (oils, bacteria) and for natural anti-inflammatories. These included those sourced from Aboriginal (Australia), Maori (New Zealand), Melanesian and Ayurvedic (India) traditions of healing. Recently he has returned to nutritional medicine, believing that low cost 'Preventative Medicine' is the most needed item for helping people world-wide to increase their wellbeing—without recourse to the expensive and/or labile (i.e. those needing refrigeration) medications promoted by the Western pharmaceutical industry.

For personal support he successively taught organic chemistry, biochemistry, endocrinology, molecular pharmacology, immunology, molecular pathology and toxicology in six medical schools (Oxford, Pennsylvania, Ohio State, California Los Angeles, Adelaide, Flinders South Australia), and worked in six hospitals (Serafima, Stockholm, University of California at Los Angeles, Royal North Shore, Sydney, Royal Newcastle, NSW, Christchurch, NZ, and Princess Alexandra, Brisbane). He reckons his best teaching (and stimulating learning) experiences were located outside the norm: particularly in the South Australian College of Natural Therapies (Adelaide, Australia) and the Canberra College of Advanced Education—all with eager mature students but regrettably little in the way of relevant textbooks.

One of the highlights of his early career was having the Australian pathologist Howard Florey OM, Nobel Laureate, President of the Royal Society UK and Professor of Pathology at Oxford as his 'technical assistant' (!) while doing research for the D.Phil degree at Oxford. This happened because Florey was rather fearful that cortisone, the new wonder drug for arthritis and septic shock, would damage the production of protective gastrointestinal mucins, just as it could severely damage the production of other carbohydrate polymers present in cartilage, skin, the vasculature, etc. Cortisone then being in extremely short supply in the UK (1954), the Medical Research Council would only provide small quantities to qualified investigators who would personally administer the drug, either to patients or for animal studies. So Florey began the experimental work by injecting duodenal-cannulated rabbits and Michael then measured intestinal mucin production (using the incorporation of ^{35}S-sulphate as a new tool to monitor mucin biodynamics). Outcomes from this early experience were learning to use radiotracers for metabolic studies and that toxicology was a most important aspect of therapeutics. Furthermore, personal status should be no hindrance to scientific collaboration. Subsequently, when the opportunity came to take sabbatical leave from Oxford (1966) to be a Visiting Fellow at the Australian National University, Canberra, Florey kindly facilitated this visit.

Another instructive experience was learning that if you saw a need for, or discovered a new research tool, you were then either ignored for an unwarranted period or almost immediately overwhelmed by other editors and authors who felt challenged to out-publish you. When Paul Kent and Michael wrote a book on the amino sugars in 1954, the first since PA Levene's monograph on hexosamine and muco-proteins published in 1925, very soon thereafter a four volume compendium on glycosaminoglycan was produced by E. Balasz for Academic Press. Subsequently Bob Scherrer (then at the 3 M Research Minneapolis) and Michael prepared and edited a two volume treatise on Anti-Inflammatory Agents in 1974 (Academic Press NY). This was a monumental effort bringing together an immense literature on the medicinal chemistry of non-steroidal and steroidal anti-inflammatory drugs. This book is remarkable in that its contents are still current today. In 1967, Peter Ghosh and Michael serendipitously discovered the fluorigenic reagent, NBD chloride for detecting and labelling amino acids and peptides. It is still in use today,

having been exploited and cited in over 2000 publications. Later, a look-alike NBD fluoride was patented, duly promoted and became undoubtedly profitable.

Another highlight was collecting and collating the supportive data for seven labour-intensive publications that gave him particular satisfaction. These were:

1964. Uncoupling of oxidative phosphorylation by salicylate analogues: relationship of structure to activity. Biochem Pharmacol 13:319–336.
1969. Passive transfer of adjuvant-induced arthritis and allergic encephalomyelitis in rats using thoracic duct lymphocytes. Nature 224:1322.
1974. Freund's Adjuvant: relationship of arthritogenicity and adjuvanticity in rats to vehicle composition. Immunology 27:311–330.
1982. Rat polyarthritis: induction with adjuvants composed of various mycobacteria (and oils) from the environment. J Rheumatol 9:494–501.
2009. Pro-inflammatory activity in rats of thiocyanate, a metabolite of the hydrocyanic acid inhaled from tobacco smoke. Inflamm Res 58:696–704.
2010. Questioning the safe use of vaccines containing squalene. Immunol Cell Biol 88:497–499.
2015. Silver pharmacology: past, present and questions for the future. Progr Drug Res 70:237–273.

The passage of time is still affording judgement and (re) appraisal of these publications.

Michael particularly appreciated being awarded research scholarships/fellowships throughout his career, particularly from the Medical Research Council UK, the English-Speaking Union, the Royal Society UK, Empire Rheumatism Council (now Arthritis UK) London, Exeter College Oxford, the Australian National University (ANU) Canberra, the National Academy of Sciences and National Institute of Health, Washington DC and the 3D Centre, University of Queensland. Currently he is Honorary Professor of Experimental Medicine at Griffith University, Gold Coast, Queensland, Australia, still particularly interested in alternative/neglected anti-inflammatories.

None of this would have been possible without the moral support of various heads of departments, colleagues and the able assistance of many storekeepers and animal attendants.

After-thoughts

- Nowadays, free thinkers and bench workers are being stifled with demands for frequent reports, changes in thinking and inability to discuss ideas outside the immediate group, etc. Gone are the days where a disparate group of researchers could sit drinking tea or having a beer together, discussing what they were doing and especially in sharing ideas.
- Its almost impossible to believe that the head of a pharmaceutical company would give one a cheque to assist travel expense and say, "Come back in 12 months and tell me what you've found out." The 'bean counters' and ethics committees would be unable to relate to such a happening. Yet, this is precisely what Lou Sarett of Merck USA did in 1966. After 10 months Michael hadn't found the golden elixir but had shown that methyl glyoxal (pyruvaldehyde) and cortisol aldehyde were potential endogenous metabolites that might behave as pseudo-NSAIDs in regulating lymphoid and epithelial cells (J Pharm Pharmacol 1967; 19:590–595).
- In 1992 while working in Adelaide he was asked by Peter Ghosh (then in Sydney) to help investigate the therapeutic potential of emu oil. Since European settlement in Australia, stories abound about the successful treatment of muscular ailments with emu oil as practised by the First Peoples of Australia. The West Australian Aboriginal community at Wiluna, with enlightened support from friends in Perth WA commissioned this work. So began an adventure learning about the life cycle and productivity of emus. [A case of pharming for farmaceuticals?] A provisional patent (PP) was lodged from Western Australia to protect their intellectual property. However, for some inexplicable reason the Australian Patents Office released the PP. An Aboriginal community in Queensland then claimed priority for the intellectual property but had never demonstrated its validity. The end result was that the good work and knowledge obtained was unable to be further financed.
- He was rather surprised on returning to Australia in 1973 to find that few, if any, universities had established animal ethics committees. In the UK and USA he had always worked within the guidelines of such committees. So with the help of two veterinarians, he set down some guidelines for working with animals in Australia, responding to a request from the National Health and Medical Research Council (NH&MRC). These guidelines, largely based on those in the UK, were written in a user-friendly style—unlike the very restrictive guidelines issued today.
- Later on, he was even more surprised when the Australian Government, having set up a Department of Productivity and Innovation, then awarded support for development of non-gastrotoxic aspirin formulations in collaboration with Kim Rainsford; only to have it rejected by the ANU on the grounds that they might be providing scarce facilities to promote a commercial enterprise!! [Good sense eventually prevailed: but it was an uncomfortable experience being branded a pariah by the 'pathology establishment' and initially denied approved government support.]
- Commercial collaborations within Australian university laboratories during the early 1970s were not gener-

ally encouraged. Yet, within 12 months of his leaving ANU the medical school was actively promoting such activities. Such a contrast to today when universities are encouraged to undertake research work for pharmaceutical and other organisation with shared patent rights and a business office to supervise negotiations.

- While at UCLA the then Californian governor (R Reagan) ordered the university's closure in response to a vigorous student protest about extending the Vietnamese war into Cambodia. This lock-out also affected the university's peripheral research and medical research on campus. No provision had been made for the welfare of animals under treatment. It was enforced by the presence of armed police, who had no interest in conducting further dialogues. So Michael used to crawl through the bushes to gain entry to the laboratory by the fire escape in order to feed, care for and treat his animals. This all had to be done by daylight, as anyone moving around at night was asking for serious trouble (police policy then being shoot first, ask questions later). This injustice/melodrama was further extended to the teaching staff who were then denied their incremental pay-rise that year—these extra funds being distributed to others who were no more deserving. In fact, the floor cleaner got a double bonus! The medical school teaching staff voluntarily repeated interrupted courses as students reappeared, being brave enough to try to continue 'as normal'. Michael taught his contribution to the pharmacology and toxicology course three times over and had accordingly to conduct three sets of examinations. This determination to continue the education of medical students was never recognised by the State authorities. In fact, for supporting student rights to object, many teaching staff were 'punished' by being denied agreed prospects of promotion or tenure, as the University of California's five-year plan was then junked/torn up by the State legislature. This was yet another re-enactment of the serious divide between politicians and educators. Consider the fate of Socrates 399 BCE "refusing to recognize the gods recognized by the state" and of "corrupting the youth." (http://www.eyewitnesstohistory.com)
- An ill-mix of politics and science had got him into trouble previously in Czechoslovakia in the 1960s. While attending the International Congress of Rheumatology in Prague he found his way to the home of a Dr. X, a geneticist who had taught at the famed Charles University but who, unbeknownst to Michael, was apparently under house arrest. [His crime: pointing out that T.D Lysenko (a Russian)'s neo-genetics, as approved by Stalin, was false and that G. Mendel (a Slovak)'s theory should still be taught. For this, he was stripped of Czech citizenship, declared an enemy of the State, and therefore ineligible for a job and receipt of food rations.] Michael's visit was on behalf of a supporter in London who was trying to find Dr. X a job in the UK; but meanwhile asked him to check on his welfare and give him $US50. The State police apparently knew of this visit and subsequently followed Michael around because his visitor's visa was peremptorily terminated. The president of the Congress and Professor of Balneology in Prague, Franz Lenoch, spoke to Michael, insisting the conversation be in Latin; a somewhat arduous task for Michael not having used this classical language for 17 years. Very fortunately Milan Adam, a medical physiologist, took care of him as, no longer having a valid visa, he had to leave the country the next day. Milan made sure he was delivered to the airport where he had a body search and was stripped of all cash on his person, quite a memorable visit! Michael was able to add 'persona non grata in the CSSR' to his CV! As it so happened when he next applied for a Czech visa to attend a pharmacology congress, he had no trouble; the visa having been completed in the Czech language.

Publications—M. W. Whitehouse

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