

# Andrew Szczeklik: a clinical scientist of the highest calibre

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Andrew Szczeklik has made so many outstanding contributions to medical science that it is difficult to know where to start. There will be many references in this series of vignettes to a wide range of Andrew's activities including his extraordinary contributions to medical education in Poland and his love for experimental medicine and translational research. His time as a Visiting Professor with John Martin in Sheffield (now at University College London) in the mid 1980s, and the times he spent at the Burroughs Wellcome laboratories with Sir John Vane, served to stimulate a research career focused on understanding the mechanism of aspirin in cardiovascular disease. Even early on in his medical career, Andrew displayed a remarkable thirst for new knowledge. This took him to the University of North Carolina, Chapel Hill, and the Karolinska Institute and University of Uppsala in Sweden, all of which fuelled his interests in inflammation and the chemical mediators responsible. With his interests in cardiovascular disease, platelet function, and thrombosis, he was soon to develop a deep interest in arachidonic acid metabolites especially prostanoids.

Perusal of his many peer-reviewed research publications and books illustrates how, throughout his illustrious career, he utilised knowledge from one medical speciality to add new light on another. His experience with prostacyclin for the treatment of pulmonary hypertension (1980), unstable angina (1980), and ischaemic ulcers (1985) are major contributions to medical science, but it is his fascination with asthma associated with aspirin intolerance (AIA) that has especially endured. Indeed, simply mentioning the term AIA produces immediate images of Andrew toiling away with his colleagues Richard Gryglewski, Marek Sanak, and Ewa Nizankowska-Mogilnicka to uncover the underlying mechanisms behind this unique subtype of asthma.

Over 60 publications on aspirin hypersensitivity spread over Andrew's entire career illustrates his total commitment to pursuing its mechanisms and treatment. Original research demonstrated distinct eicosanoid patterns at baseline and following aspirin challenge. He developed and refined oral aspirin and inhaled lysine

aspirin challenges as diagnostic tests. He uncovered both leukotriene D<sub>4</sub> synthase and human leukocyte antigen genetic associations with AIA. A great confirmatory step forward was the clear demonstration that patients with AIA responded well to treatment with zileuton, a 5-lipoxygenase inhibitor, and montelukast, a selective cysteinyl leukotriene receptor 1 antagonist. However, probably his greatest contribution was the discovery that AIA was linked to reduced prostaglandin E<sub>2</sub> production by asthmatic fibroblasts and epithelial cells and that this deficiency lay at the feet of a preponderance of cyclooxygenase 1 activity. To test such a hypothesis, he showed that patients with AIA could tolerate treatment with selective cyclooxygenase 2 inhibitors such as rofecoxib. Thus, the complete pathway was now exposed with aspirin, a nonselective cyclooxygenase inhibitor, inhibiting cyclooxygenase 1, reducing PGE<sub>2</sub> synthesis in the airways, thereby removing the "brake" on exuberant contractile cysteinyl leukotriene production by inflammatory cells in the asthmatic airways.

My small contribution to this story was in the form of a wonderful collaboration that Tony Sampson and I had with Andrew and K Frank Austen in Boston when uncovering increased cysteinyl leukotriene C<sub>4</sub> synthase activity in mast cells and eosinophils in the airways of AIA that was associated with increased airway and urinary leukotriene levels. However, since I also had a long-time interest in inflammatory mechanisms in asthma and the role of eicosanoid mediators, Andrew's and my paths frequently crossed since the mid 1980s especially in the field of prostanoid metabolism and the effects of the mast cell prostaglandin, PGD<sub>2</sub>, whose metabolism and effects I studied.

The description I offer of Andrew's pursuit of underlying disease pathophysiology applies just as much to his huge contributions to understanding inflammatory and thrombotic aspects of cardiovascular disease. For these lifelong studies, he also used combinations of epidemiology, experimental medicine, and clinical trials not only to expose novel disease pathways but to test their disease relevance functionally. It is this remarkable

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**FIGURE 22** From the left: Professor Szczeklik, Professor Ryszard Gryglewski, the wife of Professor Szczeklik – Maria, Sir John R. Vane

dexterity as a clinical scientist paying absolute attention to experimental and analytical detail that marked Andrew out as a very special clinical scientist and in no small part is this mix of talents that enabled him to make so many contributions for patient benefit.

Andrew and I have attended many scientific meetings together at which he was both scientifically stimulating and tremendously good company that was reflected in his great love of music, classical and contemporary literature, and history. It was a very special pleasure for Sven-Eric Dahlén and I to feature Andrew as a guest lecturer at our 1997 symposium “SRS-A to Leukotrienes: the Dawning of a New Treatment”, where he first laid out his ideas on the eicosanoid imbalance theory of AIA. It was also a huge pleasure for me to welcome and give the citation for Andrew as an Honorary Fellow of the Royal College of Physicians in 1998 as one of his very many awards. Andrew introduced me to Poland’s academic community in the most pleasant way by asking the Jagiellonian University to bestow upon me an honorary

doctorate and for the Polish Academy of Arts and Sciences to accept me as an Overseas Member.

How do I remember Andrew? – a true gentleman who was both brilliant and humble, a man who expressed so much humanity; he was a friend to so many, a man who must have fought so many battles quietly and without fuss to become a true leader not only of scientists but in setting an example to inspire so many. It has been an absolute pleasure to have known such a kind, charismatic, and productive person.