IN MEMORIAM

Prof. Andrzej Szczeklik, 1938–2012: aspirin-induced asthma and much more

We were sad to learn that Andrzej Szczeklik died on February 3, 2012 after a short period of cardiac illness. We seek comfort in his many achievements that remain and which will continue to inspire and guide future generations of scientists and clinicians.

Among respiratory physicians and allergologists, Szczeklik will certainly be remembered as the world-leading authority on aspirin-induced asthma. At this juncture it is somewhat ironic that he, outside our field, is known because of a number of key basic and clinical findings relating to diagnosis and treatment of thrombosis and cardiovascular disease. In fact, the Polish Nobel Laureate in Literature, Czesław Miłosz, who wrote the foreword to Szczeklik's book *Catharsis* [1], described Szczeklik as a world famous cardiologist. That book, incidentally, showed yet another side of Szczeklik, the reflecting author providing a personal and very scholarly perspective on history, society and, above all, the moral and ethical issues that challenge us as human beings.

Szczeklik's career as a doctor scientist was formed by strong gene–environment interactions. He was born in Cracow, Poland, in 1938 as the son of the eminent Polish Professor of Internal Medicine, Edward Szczeklik. It may, thus, be more than coincidental that young Andrzej, mostly known as Andrew outside Poland, developed a deep commitment to the improvement of the health of his fellow humans. This heritage was most likely further inspired by the hardships of his countrymen that he observed growing up in the immediate post-war era. Szczeklik received his basic medical training in his home town of Cracow, followed by a 1-yr internship at Monmouth Medical Center, New Jersey, USA in the early 1960s. He once mentioned to one of us how the upbeat spirit in the USA during the early JFK years had inspired him.

Back in Poland in 1962, Szczeklik moved to the Academy of Medicine in Wrocław where he worked as an internist and obtained his PhD in 1966 with the Thesis *The activity of serum aminopeptidases in the diseases of liver and biliary tract*. In 1972 he returned to Cracow to become the chairman of the University's Department of Allergy and Clinical Immunology. This sparked a very creative phase that transformed the Department and has left everlasting imprints on the international scientific community. At the time of his death, his research team in Cracow, is by no doubt the internationally most recognised Polish centre within respiratory medicine and allergology.

His move back to his hometown Cracow thus initiated a scientifically very productive period in the early 1970s. This includes Szczeklik's most cited original paper where the mechanism involved in aspirin-intolerant asthma was demonstrated [2]. In this paper, published in the *British Medical Journal* in 1975, 11 patients with previously reported or documented intolerance to aspirin were challenged orally at

different occasions with rising doses of eight different analgesic drugs. Indomethacin, mefenamic acid, flufenamic acid and phenylbutazone triggered bronchoconstriction in therapeutic or lower doses, whereas even high doses of salicylamide, paracetamol, benzydamine and chloroquine were tolerated. The ability of the drugs to elicit adverse reactions correlated directly with their effectiveness to inhibit prostaglandin biosynthesis *in vitro*. These results unequivocally demonstrated that the intolerance reaction was related to inhibition of prostaglandin biosynthesis. Sadly enough, even today there are occasional deaths due to failure among health professionals to recognise that the intolerance is a class effect of all nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclo-oxygenase (COX) reaction.

Furthermore, this original study thus also showed that patients with NSAID intolerance generally tolerate salicylates and paracetamol (acetaminophen). This has recently been explained by the discovery that these two NSAIDs are only weak inhibitors of the COX-1 isoenzyme that is now recognised as the target of drugs that elicit the intolerance reaction. Accordingly, Szczeklik and his team have alone [3], or in collaboration with others [4], shown that aspirin/NSAID-intolerant asthmatics tolerate selective COX-2 inhibitors.

As is most often the case when scientific discoveries are made, the seminal study of the nature of the intolerance reaction to NSAIDs occurred in a very creative environment with a mix of persons with complementary competence. Thus, the pharmacologist Ryszard Gryglewski from Cracow had trained with Sir John Vane in London, UK, and been part of the team that in the beginning of the 1970s discovered that the common mode of action of anti-inflammatory NSAIDs was to inhibit prostaglandin formation. This was one of the reasons why Sir John was, in 1982, awarded the Nobel Prize in Physiology or Medicine for discoveries on prostaglandins and other compounds, together with Sune Bergström and Bengt Samuelsson from Karolinska Institutet (Stockholm, Sweden). Szczeklik had since long been intrigued by the clinical features of aspirin intolerance, which were incidentally first described in the Polish city of Poznań a few years after aspirin had been introduced as an analgesic [5]. Together with Gryglewski, it was now possible to design the pivotal study to test the hypothesis that the clinical reactions were related to the anti-inflammatory properties of the drugs. The pharmacologic effects of the drugs on prostaglandin biosynthesis *in vitro* were assessed by a bioassay on the rat stomach strip. At that time this was the state-of-the-art method for measurement of prostaglandins. Immunoassays had not been invented. The prostaglandins were generated by incubating bovine seminal vesicle microsomes with arachidonic acid, also the best available method. The clinical response was evaluated in challenge protocols that Szczeklik had developed.

It should be recognised that this first demonstration of the relationship between prostaglandin biosynthesis and clinical reaction to NSAIDs truly was translational medicine before the term had been thought of. It consisted of a demanding clinical provocation study where 11 subjects were challenged each with different NSAIDs on up to eight different occasions. The safe completion of this task required considerable skill in performing these potentially very dangerous challenges. Likewise, significant “fingerspitzengefühl” was required to perform the pharmacologic assays on the smooth muscle preparation of material from the incubations of seminal vesicles.

Together with Gryglewski, Szczeklik went on and also contributed to studies associated with the other main reason for Sir John being awarded a Nobel Prize, namely the discovery of prostacyclin as an anti-platelet vasodilator. Thus, together with Gryglewski, he performed the first intravenous injections of prostacyclin (PGI₂) in humans and reported in the *Lancet* [6] on the beneficial effect of PGI₂ on the peripheral circulation in subjects with severe arteriosclerosis. Altogether, many of the some 650 publications that Szczeklik authored concerned effects of eicosanoids and other messenger molecules, such as nitric oxide on haemostasis and cardiovascular responses, aiming to gain a better understanding of cardiac and vascular diseases.

Over the past 35 yrs Szczeklik and his team have performed a step-wise dissection of the key mechanisms in aspirin/NSAID-intolerant asthma. This has taught us most of what we know about this enigmatic syndrome. So far the best explanation of the pathophysiology in aspirin-intolerant asthma, namely that the patients for some reason are particularly dependent upon the ability of prostaglandin E₂ (PGE₂) to stabilise mast cells, draws support for example from the observation that inhalation of PGE₂ blocks the aspirin-induced bronchoconstriction in aspirin-intolerant asthma [7]. Although we still do not understand why this “PGE₂-dependence” develops in these particular patients, it is clear that inhibition of PGE₂ formation with NSAIDs has detrimental effects in these patients and is associated with mast cell activation [8].

Aspirin-intolerant asthma is arguably the most well-defined phenotype of asthma. With an adult onset and a preponderance among females, subjects characteristically suffer from chronic rhino-sinusitis and nonallergic asthma where ingestion of aspirin and other NSAIDs will induce bronchoconstriction. The natural history and much of the clinical features of aspirin-intolerant asthma have been established by a pan-European project that Szczeklik initiated in the 1990s. Together with, in particular, his long-time close collaborator Ewa Nizankowska-Mogilnicka, Szczeklik had the vision to create a database of aspirin-intolerant asthmatics from all over Europe and take advantage of the emerging computer technology. There were, however, many steps between the vision and the completion of the project. For example, the personal computers were at that time still at a rather primitive stage and there were many hurdles on the road to completion. The team struggled on and at the end, data from 500 patients were collected. This study of the AIANE (Aspirin Induced Asthma Network in Europe) consortium is the largest collection of subjects with aspirin-intolerant asthma ever systematically characterised. Despite origins from 16 centres in 10 European countries, the clinical picture of aspirin-intolerant asthma was remarkably homogeneous [9]. The AIANE study

required provocation-verified diagnosis of the intolerance. It turned out that 15% of the patients in the study were unaware of intolerance to aspirin and learnt about it only after having had the provocation tests. The presence of this undiagnosed risk group is, however, familiar to clinicians that have experience with aspirin-intolerant asthma.

In fact, the necessity of aspirin provocations for the diagnosis of the intolerance was also highlighted when Szczeklik first visited Japan. His hosts said that they rarely saw these patients, but when they started to do provocations after his visit, the prevalence of aspirin-intolerant asthma turned out to be as frequent in Japan as at other centres with experience of the syndrome. In fact, subsequently, several important contributions to our knowledge about the syndrome have in fact been made by colleagues in Japan [10], as well as in other Asian countries [11].

Szczeklik was, however, disappointed with the ways the European Commission support research. The AIANE project was clearly very successful but only received a relatively small concerted action grant from the beginning. Most of the work had to be supported by the participating centres themselves. In several discussions he expressed his opinion that the lack of a renewal process for successful European Commission projects was a major mistake and a waste of invested public money.

Realising the importance of long-term interactions and exchange of ideas, Szczeklik has almost every year during the past decade arranged a very friendly gathering in Cracow of clinical and basic scientists with an interest in aspirin-intolerant asthma, and aspirin-exacerbated respiratory disease (AERD). The name AERD has recently been introduced to also include patients that don't have asthma but get nasal reactions to NSAIDs. This annual meeting of the HANNA (European Network on Hypersensitivities to aspirin and other NSAIDs) group was initially partly funded as one work package of the European Union supported GA²LEN network of excellence for asthma and allergy, but with time Szczeklik covered most of the costs himself. The meetings were very interactive and always managed to gather participants who had new findings and ideas to share. We will certainly miss Andrew at future meetings, but are convinced they will continue in his spirit and, piece by piece, the mysteries of the aspirin-intolerant asthma puzzle will be put in place.

Although Szczeklik was a dedicated clinician and teacher, and much driven by a relentless compassion for science, he did not step back when leadership was required. During the time of the marshal laws in Poland, when life was difficult, Szczeklik actively defended academic and societal freedom. Szczeklik was a member of the scientific advisory academy of the Vatican at the time of Pope John Paul II, who also came from Cracow. Together with other Polish intellectuals, such as Wislawa Szymborska, the Nobel Laureate in literature from Cracow, who predeceased him by 2 days, they certainly contributed to the build-up of confidence in the future that resulted in the Solidarity movement and the fall of the regime of General Jaruzelski in 1989. The same year Szczeklik became chairman of the Dept of Medicine at the Jagiellonian University School of Medicine in Cracow. During 1990–1993 he was elected the Rector (President) of the Copernicus Academy of Medicine in Cracow, and then Vice-Rector of the

FIGURE 1. Andrzej Szczeklik, 1938–2012.

Jagiellonian University for Medical College (1993–1996). As Rector he managed to reunite the Faculty of Medicine and return it to the Jagiellonian University after many years of separation. From 2006 until present he held the position of Vice-President in the Polish Academy of Sciences and Arts.

Andrzej Szczeklik was always in the forefront of the international scientific community, due to his prolific reading as well as regular exchange of ideas with colleagues all over the world. He trained abroad on many occasions, including stints at the Karolinska Institutet in Stockholm and the University of Uppsala, Sweden, as well as at the University of North Carolina, Chapel Hill, NC, USA. He was visiting professor at the Faculty of Medicine at the University of Sheffield, Sheffield, UK, King's College School of Medicine, London and Hochgebirgsklinik, Davos-Wolfgang, Switzerland. Although Szczeklik had formally retired from his clinical duties a few years ago, he continued to be a very active and passionate leader of the research team in Cracow.

We met Andrew the last time during the European Respiratory Society (ERS) meeting in Amsterdam 2011. With his characteristic unassuming presentation style, but with much vigour, he gave an excellent early morning seminar on aspirin-intolerant asthma. Despite the early hour, the audience listened and learned. It is with deep regret we realise he will not be at the next

ERS meeting but his legacy will still be with us. The necessary introduction for all newcomers in the field is quite simple, download Szczeklik's papers and start reading!

This approach would most likely be appealing to Szczeklik who was very keen on using modern technology to improve science, clinical care and teaching. Together with Piotr Gajewski he has, since 2005, edited a textbook on internal medicine that is very user-friendly and continuously updated with the most recent evidence. It has become the main source of current knowledge in internal medicine for physicians and medical students in Poland, and there is a mini-version available for download to smartphones.

Andrzej Szczeklik was truly an extraordinary man who will be remembered for substantial life achievements. Our thoughts now go to his wife Maria and his three grown-up children, Michał, Ania and Wojciech, as well as the grandchildren who share our loss.

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We deeply regret to inform you of the death of Andrzej Szczeklik on February 3, 2012. Born in 1938 in Cracow, Poland, Andrzej Szczeklik, MD, PhD, was a professor and long-term Chairman of the Dept of Medicine, Jagiellonian University Medical College in Cracow. He received his graduate degree from the Medical University of Cracow and, after completing his 1-yr internship in the USA, he worked for 7 yrs at the Academy of Medicine in Wrocław, Poland. There, in 1966 he obtained his PhD. From 1972 he was the Chairman of the University Dept of Allergy and Clinical Immunology and in 1989 became Chairman of the Dept of Medicine, Jagiellonian University School of Medicine in Cracow. His training abroad also encompassed 3 months at the Karolinska Institutet in Stockholm, Sweden and University of Uppsala, Sweden and 5 months research fellowship at the University of North Carolina, Chapel Hill, NC, USA. In 1985–1989, Prof. Szczeklik was a visiting professor to the Faculty of Medicine of the University of Sheffield, Sheffield, UK, King's College School of Medicine, London, UK and Hochgebirgsklinik, Davos-Wolfgang, Switzerland. In 1990–1993 he was elected the Rector (President) of

the Copernicus Academy of Medicine in Cracow, and then Vice-Rector of the Jagiellonian University for Medical College (1993–1996). Prof. Szczekliks main research interest included cardiopulmonary disease, aspirin-induced asthma, and chemical mediators in diseases of circulatory and respiratory systems with special reference to eicosanoids.

Prof. Szczeklik was lecturing extensively in major European, American and Japanese Universities. He was an author or co-author of more than 650 papers published, mostly, in the leading biomedical journals, including *Nature*, *Lancet*, *NEJM*, *JCI*, *BMJ*, *Blood*, *Circulation*, *JACI*, *etc*. He was also author, co-author and co-editor of several international and Polish books; organiser or co-organiser of 14 international symposia, and a member of numerous scientific societies, such as the American Academy of Allergy Asthma and Immunology (AAAAI), European Academy of Allergy and Clinical Immunology (EAACI), European Respiratory Society (ERS), International Society on Thrombosis and Haemostasis (ISTH), Polish Academy of Sciences, Pontifical Academy of Sciences in Vatican and Royal College of Physicians in London (honorary member).

In 1995 Prof. Szczeklik was awarded “Gloria Medicinae”, a medal of the Polish Society of Medicine, and in 1997 the first prize of the *Lancet* for the paper reporting on genetic polymorphism of leukotriene C₄ synthase. In 1998 he received the scientific prize of the Royal College of Physicians and was elected to the College. In the same year he received the first award of The Polish Science Foundation for his studies on the mechanism of action of aspirin. In 1999 the University School of Medicine in Wrocław bestowed upon him the doctorate *honoris causa*. In 2000 he was awarded “The Robert A. Cook Memorial Lectureship” by the American Academy of Allergy Asthma and Immunology. From 2001 to 2009 he received doctorate *honoris causa* from four other University Schools of Medicine: in Warsaw, Katowice, Lodz and Cracow. From 2006 until now he was Vice-President of the Polish Academy of Sciences and Arts.

To the public at large he was also known as a writer and essayist. His books *Catharsis* [1] and *Kore* [2] were nominated to the Polish literary prize Nike and were translated into English, French, German, Hungarian, Lithuanian, Russian and Spanish.

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