Professor Andrzej Szczeklik (1938–2012): a European intellectual defining aspirin-asthma and much more

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After a short period of cardiac illness, the heart of Andrzej Szczeklik ceased to beat on the morning of Friday, 3 February 2012. This ended the life on Earth of an extraordinary man, but his legacy will prevail. Driven by a relentless curiosity and a compassion for science, his life achievements are manifold and substantial in diverse areas. Among respiratory physicians and allergologists, he will be remembered as the world-leading authority on aspirin-asthma. At this juncture, it is particularly ironic that Andrzej Szczeklik should be recognized among cardiologists due to his publication of a number of key basic and clinical findings relating to diagnosis and treatment of thrombosis and cardiovascular disease. Current and future generations of Polish medical students and specialists will remember him as Editor of the very modern textbook of internal medicine, which is continuously updated with the most current scientific evidence. For some laymen, his name will be associated with the authorship of two fascinating books integrating profound knowledge on humanities, art and science into thoughtful perspectives on history, society, and above all, the life of human beings. We understand that for many people in Poland, Szczeklik will also be remembered for his contributions to academic and societal freedom at times when many black shadows made life difficult.

Born in Krakow in 1938 as the son of the eminent Polish Professor of Internal Medicine, Edward Szczeklik, it may 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. He received his basic medical training in his home town, Krakow, followed by a 1-year internship at Monmouth Medical Center, New Jersey, in the United States in the early 1960s. Back in Poland in 1963, he moved to the Academy of Medicine in Wrocław where he obtained his PhD in 1966 ("The activity of serum aminopeptidases in the diseases of liver and biliary tract") and continued to work as an internist. In 1972, he moved back to Krakow to become the chairman of the University's Department of Allergy and Clinical Immunology, and in 1989, he became chairman of the Department of Medicine at the Jagiellonian University Medical College in Krakow. Andrzej Szczeklik was always in the forefront of the international scientific community, much due to his prolific reading as well as regular exchange of ideas with colleagues all over the world. He also trained abroad on many occasions, including monthly stints at the Karolinska Institutet in Stockholm and University of Uppsala, Sweden, as well as at the University of North Carolina, Chapel Hill, United States. In the years 1985–1989, Andrew Szczeklik was a visiting professor at the Faculty of Medicine at the University of Sheffield, UK, King's College School of Medicine, London, UK and Hochgebirgsklinik Davos-Wolfgang, Switzerland. During 1990–1993, he was elected the Rector (President) of the Copernicus Academy of Medicine in Krakow, and then Vice-Rector of the Jagiellonian University for Medical College (1993–1996). Although he had formally been retired from his clinical duties for a few years, he continued to be a very active and passionate leader of the research team in Krakow that arguably is the internationally most recognized Polish centre within Respiratory Medicine and Allergology. From 2006 until present, he held the position of Vice-President in the Polish Academy of Sciences and Arts. During the time of Pope John Paul II, also from Krakow, Szczeklik was a member of the scientific advisory committee of the Vatican.

The movement back to his hometown Krakow initiated a scientifically very productive period in the early 1970s when, in particular, the seminal demonstration of the mechanism involved in aspirin-intolerant asthma was made.[1] This is Szczeklik's most cited original paper. In this paper, published in the *British Journal of Medicine* in 1975, eleven patients with previously reported or documented intolerance to aspirin were challenged orally at different occasions with rising doses of eight different analgesic drugs.

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FIGURE 19 Professor Szczeklik in his office, 2nd Department of Internal Medicine, Jagiellonian University Medical College, Krakow, 1995

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 propensity of the drugs to elicit adverse reactions correlated directly with their ability 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. Such unfortunate subjects may have been given ibuprofen as an alternative when they have reported intolerance to aspirin. Furthermore, this original study also showed that patients with NSAID intolerance generally tolerate salicylates and paracetamol (acetaminophen). This has much later been explained by the discovery that these two NSAIDs are only weak inhibitors of the COX-1 isoenzyme, which is now recognised as the target of drugs that elicit the intolerance reaction. Accordingly, Szczeklik and his team have alone[2] or in collaboration with others[3] shown that aspirin/NSAID-intolerant asthmatics tolerate selective COX-2 inhibitors.

It should be appreciated that this first demonstration of the relation between prostaglandin biosynthesis and clinical reaction truly was translational medicine before the term was coined. That seminal study, as often is the case, occurred in a very creative environment. And so, the group included a pharmacologist, Ryszard Grygewski, also from Krakow. Gryglewski had trained with Sir John Vane in London and had been a member of the team which 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 awarded the Nobel Prize in Physiology or Medicine in 1982 for the discoveries on prostaglandins and other compounds, together with Sune Bergström and Bengt Samuelsson from the Karolinska Institutet. Szczeklik had long been intrigued by the clinical features of aspirin intolerance, which were incidentally first described in the Polish city of Poznan a few years after aspirin had been introduced as an analgesic.[4] 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 bioassay on the rat stomach strip. This was at that time the state-of-the-art method for measurement of prostaglandins. 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 which

Szczeklik developed. Moreover, it should be recognised that this was a demanding provocation study where eleven subjects were challenged each with different NSAIDs on up to eight occasions.

Szczeklik has 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 antiplatelet vasodilator. Thus, together with Gryglewski he performed the first intravenous injections of prostacyclin (PGI_2) in humans and reported in *The Lancet*[5] and other journals on the beneficial effect of PGI_2 on the peripheral circulation in arteriosclerosis. Altogether, many out of 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.

Szczeklik and his team have over the past 35 years performed a step-wise dissection of the key mechanisms in aspirin/NSAID-intolerant asthma that have 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 PGE_2 to stabilise mast cells, rests considerably on the observation that inhalation of PGE_2 blocks the aspirin-induced bronchoconstriction in aspirin-intolerant asthma.[6] Although we still do not understand why this "PGE_2-dependence" develops in this particular group of patients, it is clear that inhibition of PGE_2 formation with NSAIDs has detrimental effects and is associated with mast cell activation.[7]

Aspirin-intolerant asthma is arguably the most well-defined phenotype of asthma. With an adult onset and a preponderance among women, 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, Professor Ewa Niżankowska-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 very primitive stage and there were many hurdles on the road to completion. The team struggled on and in the end data from 500 patients were collected. This is the largest collection of subjects with aspirin-intolerant asthma ever systematically characterised. Despite origins from 16 centres in ten European countries, the clinical picture of aspirin-intolerant asthma was remarkably homogenous.[8] As inclusion in the study required provocation verified diagnosis, one recurrent impression acknowledged by most that have worked with aspirin-intolerant asthma was in fact verified in the study. Thus, surprisingly, 15% of the patients in the study were unaware of intolerance to aspirin and learnt about it only after having provocation tests performed. In fact, this happened also when Szczeklik visited Japan. On his first visit, 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 around other centres with the experience of the syndrome. After that many important contributions to our knowledge about the syndrome have been made by colleagues in Japan, as well as in other Asian countries.

Following the AIANE experience, Szczeklik has almost every year during the past decade arranged a very friendly gathering in Krakow of clinical and basic scientists with an interest in aspirin-intolerant asthma. This HANNA (European Network on Hypersensitivities to aspirin and other NSAIDs) meeting was initially partly funded by 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 bring in participants that had new findings and ideas to share. We will now certainly miss Andrew much at future meetings, but we are convinced that they will continue in his spirit, and piece by piece the mysteries of aspirin-intolerant asthma will be unraveled.

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