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In Memoriam: Wolfgang Kiowski, M.D. (1949–2012) - Pioneer in clinical endothelin research

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ABSTRACT

Wolfgang Kiowski, M.D. (1949–2012) was a German physician-scientist who made exemplary contributions to clinical research in human physiology, heart failure, arterial hypertension, and endothelin science. His academic career took him from Heinz Losse, M.D. at the University of Münster, Germany, to the University of Michigan, U.S.A., to work with Stevo Julius, M.D. In 1979, Kiowski was recruited to the University of Basel in Switzerland and ultimately moved to the Hospital of the University of Zürich in Switzerland. Twenty years ago, Kiowski published a landmark study pioneering the use of endothelin receptor antagonists (ERAs) in patients (*Lancet* 1995; 346: 732–736), which introduced a new therapeutic principle to human medicine. During his career, he published numerous studies in the area of pathophysiology, clinical pharmacology (particularly calcium channel blockers, ERAs, and PDE5 inhibitors), heart failure, cardiac transplantation, coronary artery disease, and many case reports from his clinical work. Kiowski was an active mentor and trained many young physicians and physician-scientists. He died unexpectedly in Zürich during the planning stages of the Thirteenth International Conference on Endothelin to be held in Tokyo in 2013. This article summarizes Kiowski's achievements, his role as a mentor and as the human being he was. He will be remembered as a role model of an outstanding, curious clinician who was highly successful as a physician, scientist, and teacher, and at the same time managed to enjoy many hobbies and life with his family. Referring to Wolfgang Kiowski, the article closes with a "It can be done!"—message to young physician-scientists by Dr. Stevo Julius.

> *"You are in this profession as a calling, not a business;*
> *as a calling which exacts from you at every turn self-sacrifice,*
> *devotion, love and tenderness to your fellow-men.*
> *Once you get down to a purely business level,*
> *your influence is gone and the true light of your life is dimmed.*
> *You must work in the missionary spirit, with a breadth of charity*
> *that raises you far above the petty jealousies of life."*
>
> SIR WILLIAM OSLER

Wolfgang Kiowski was born on April 27, 1949 in the city of Recklinghausen in postwar Germany, where he grew up. He graduated from Carl-Friedrich-Gauss Gymnasium in 1968. In the same year, Wolfgang matriculated at the University of Münster, Westfalen, where he obtained his M.D. in 1974 (Heagerty and Julius, 2013; Kjeldsen and Mancia, 2013). Wolfgang was awarded his doctorate (D.M. degree) "summa cum laude" in 1975 at the Institute of Biochemistry for this medical thesis, for which he received the faculty's prize for the best medical thesis of that year from the University of Münster. Meanwhile, Wolfgang had joined the medical policlinic of the Department of Medicine of the Münster University Hospital to work with Heinz Losse, M.D. (Fig. 1), who had worked under Franz Volhard in Frankfurt (Luft and Dietz, 1993). Prof. Losse was one of Germany's most respected hypertension researchers of the second half of the 20th century (Heintz and Losse, 1973; Losse, 1966; Rahn, 2006) (Fig. 2). Thus, Wolfgang continued a pedigree of some of Germany's foremost clinicians and biomedical scientists of the past 200 years, which goes back to Pflüger (Hierholzer and Ullrich, 1999), Naunyn, and Schmiedeberg (Starke, 1998) (Fig. 2); he was bound to become one himself.

In 1976, after his internship ("Medizinalassistent") at the Department of Medicine of the Münster University Hospital and the Chirurgische

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Fig. 1. Heinz Losse, M.D. (left), German hypertension researcher and Physician-in-Chief of the medical policlinic at the Department of Medicine of the University of Münster Hospital in Germany who became the first mentor of Wolfgang Kiowski, M.D. (middle, *ca.* 2005). Prof. Losse paved the way to start an academic career in clinical research which first took him to the University of Michigan in 1976 to work with Stevo Julius, M.D. (right).

Krankenanstalten Bergmannsheil in Gelsenkirchen, his mentor Prof. Losse secured him a position as a postdoctoral fellow at the University of Michigan in the United States to work with Stevo Julius, M.D., a renowned expert in the field of hypertension research (Fig. 1) (Heagerty and Julius, 2013; Kjeldsen and Mancia, 2013). During his time in Michigan, Wolfgang made seminal contributions, producing important papers on human physiology and blood pressure regulation (Julius et al., 1983; Kiowski and Julius, 1978; Kiowski et al., 1981), and contributing to the understanding of actions of antiadrenergic drugs (Simon et al., 1977, 1978). Wolfgang and his wife Monika spent three years in the United States where Wolfgang worked hard but also enjoyed life (Fig. 3).

In 1979, at the age of 30 and recruited by Fritz Bühler, M.D., Wolfgang returned to Europe to the University of Basel in Switzerland (Fig. 4), and joined the Department of Cardiology at the University Hospital where he worked as a clinical fellow under Felix Burkhart, M.D. At the same time, Wolfgang continued his research and developed his own scientific focus that would also become his clinical expertise, particularly the fields of arterial hypertension and heart failure. In 1984, he was appointed attending physician and head of the Hypertension Service of the University Hospital Basel, where he was also in charge of cardiac surgery and post-cardiac transplant patients. In 1985, Wolfgang passed the habilitation requirements at the University of Basel, qualifying him for faculty rank. His habilitation thesis discussed the role of sympathetic regulation in humans (Kiowski, 1985), work which he had begun a decade earlier in Dr. Julius' laboratory (Julius et al., 1983; Kiowski and Julius, 1978; Kiowski et al., 1981). During this time Wolfgang was hugely productive as a scientist. For his scientific achievements Wolfgang was awarded the Annual Scientific Prize of the *Swiss Heart Foundation* in 1992. In the following year he was recruited as senior physician to the University of Zurich's hospital division of cardiology (Fig. 4) to work under its division chief, Hans-Peter Kräyenbühl, M.D., where Wolfgang was in charge of the transplant and heart failure services. In 1994, he was appointed Professor of Medicine at the University of Basel, a position that he held until his untimely death.

Following Robert Furchgott's report of endothelial regulation of vasomotor tone (Furchgott and Zawadzki, 1980), Wolfgang became interested in the clinical aspects of this discovery. In the late 1980s, he developed a keen interest in the newly discovered vasoconstrictor peptide endothelin and its receptors, particularly in their antagonists as potential new therapeutics for the treatment of cardiovascular disease,

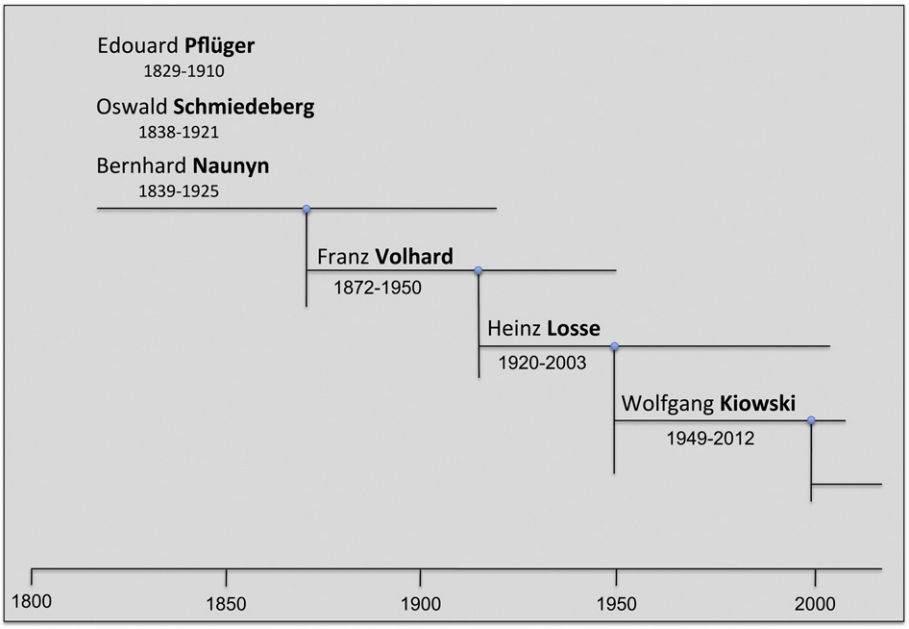

Fig. 2. Scientific pedigree of Wolfgang Kiowski, M.D., which includes some of the foremost German clinicians and biomedical scientists of the past two centuries.

Fig. 3. Photograph picturing Wolfgang and Monika Kiowski canoeing in Michigan in the 1970s. Photo courtesy of Stevo Julius, M.D., and used with his permission.

which had just been introduced at the *Second International Conference on Endothelin* in Tsukuba, Japan (reviewed in Barton and Yanagisawa, 2008).

Within only months after the endothelin ET_A and ET_B receptors were cloned in 1990 and 1991, respectively (reviewed in Barton and Yanagisawa, 2008), Roche researchers had synthesized a small molecule compound (RO-47 0203, later to be designated bosentan/Tracleer™) as an endothelin receptor antagonist (ERA) optimized from its less potent precursor RO-46 2005 (Clozel et al., 1993a, 1993b). The first batch of RO-47 0203 was synthesized and available already at the end of 1991 (Martine Clozel, M.D., personal communication 2014). In 1992, when Wolfgang was still at the University of Basel he was approached by Drs. Martine and Jean-Paul Clozel asking him to conduct a clinical proof-of-concept study in patients with heart failure, using the newly discovered orally active ERA. In 1994, bosentan as well as its acute effects in chronic experimental heart failure were published (Clozel et al., 1994; Teerlink et al., 1994). Meanwhile, Wolfgang had obtained results from his study in heart failure patients (obtained in collaboration with Osmund Bertel, M.D. at the Triemli City Hospital in Zürich) which he submitted in the Fall of 1994 as a conference abstract to be presented at the American College of Cardiology meeting in New Orleans, LA, in the Spring of 1995 (Kiowski et al., 1995a). The same year, the full article was published in the Lancet as the first ever study of clinical use of an ERA in patients (Kiowski et al., 1995b).

To our knowledge, these remain the only patient studies that were ever published using an orally active antagonist targeting G protein-coupled receptors within little more than three years after the cDNA and peptide sequences of these receptors had been identified, representing one of the fastest example of translational medicine in history (Barton and Yanagisawa, 2008). It is noteworthy that both events — the first ever study to use an orally active ERA in patients was performed at the Hospital of the University of Zurich, and the former Roche ERA brought into clinical application by the biopharmaceutical company Actelion newly founded in 1997 — originated from Switzerland, a country with a relatively small population but rather high scientific productivity (King, 2004).

Wolfgang did not slow down after publishing a landmark study 20 years ago (Kiowski et al., 1995b) but continued to explore the role of endothelin and cardiovascular disease in humans (Kiowski, 1991; Kiowski et al., 1991, 1994a, 1994b). He participated in several large-scale clinical trials investigating ERAs in heart failure (Packer et al., 2005; Spieker et al., 2000; Sutsch et al., 1997, 1998). Wolfgang published a total of 28 articles on endothelin, including review articles written with one of the authors about therapeutic principles of endothelin antagonism (Barton and Kiowski, 2001). In addition, as a general cardiologist with broad knowledge and interests, he published important studies in the area of pathophysiology (Brunner-La Rocca et al., 1999), clinical pharmacology (particularly ERAs and PDE5 inhibitors (Schalcher et al., 2002)), heart failure (Burkart and Kiowski, 1991), cardiac transplantation (Brunner-La Rocca et al., 1998), coronary artery disease (Kaiser et al., 2010), and case reports of patients from his clinical work (Scharf et al., 2001).

Aside from being a dedicated clinician-scientist, Wolfgang was also a clinical teacher who shared his knowledge and experience with his younger colleagues. During his cardiology fellowship in the Division of Cardiology of the Hospital of the University of Zürich, one of the authors (M.B.) first-hand enjoyed memorable clinical teaching and education in pathophysiology, as well as first-rate examples of physician–patient relationships that he remembers to this day. Occasionally, Wolfgang trusted him to take care of his private patients when he was busy doing coronary interventions in the cath lab or away at a conference. The words that Wolfgang's patients had for him were always of the highest praise and admiration. Wolfgang himself was modest in his clinical everyday work, and firstly and above all focused on his patients. Wolfgang was a true physician role model.

Academic medicine would not be possible without mentorship (Barton and Pollock, 2012), and Wolfgang was active as a mentor to his fellows. Wolfgang's team was always important to him. Wolfgang cared about the people who he was working with, recalls one of his former fellows, Hans-Peter Brunner-La Rocca, (Brunner-La Rocca, 2014) who now holds the Chair "Cardiology with a Focus on Clinical Heart Failure" at the Faculty of Health, Medicine and Life Sciences at the University of Maastricht where Dr. Brunner-La Rocca serves as Vice Chair of the Department of Cardiology and head of the Department of Clinical Heart Failure at Maastricht University Medical Center. Dr. Brunner remembers that Wolfgang's interest in the individual was

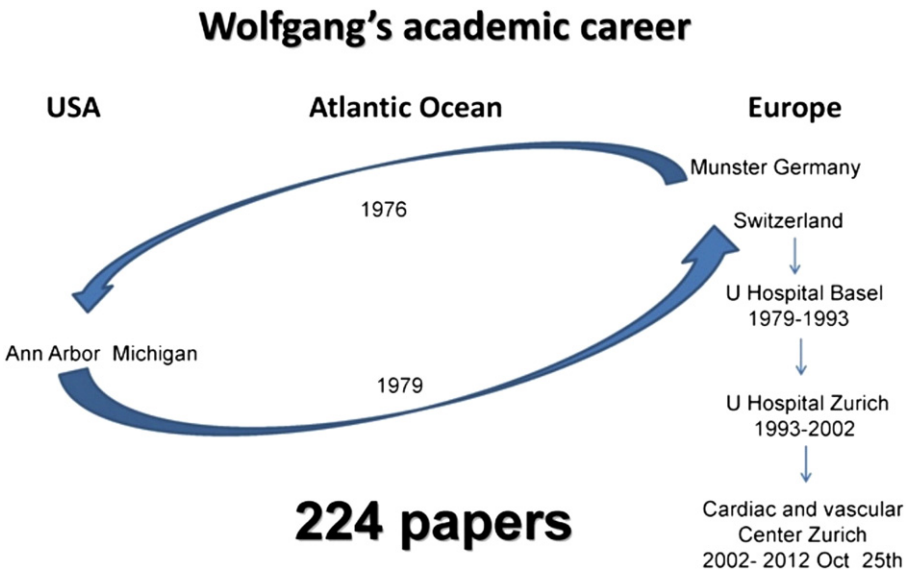

Fig. 4. Graphic summary of Wolfgang Kiowski's academic career as summarized by Dr. Stevo Julius for a lecture given at the 2013 meeting of the *European Society of Hypertension* in his memory. Figure courtesy of Stevo Julius, M.D., and used with his permission.

obvious from the very beginning when he started working in Zürich in 1994. He had initially planned to become a cardiologist working in a private practice and had basically no experience in research. He started working in Wolfgang's team on the heart failure service and cardiac transplant care. Twenty years later, Dr. Brunner is still enthusiastic about clinical research and his main clinical and research focus remains heart failure which, he thinks, says a lot. He remembers that Wolfgang was able to enthuse people says that in contrast to many so-called leaders in the field, he was genuinely interested in and cared for the individual. When Wolfgang realized Dr. Brunner's passion for computing and information technology, he made time available and allowed him to set up a central database using already existing, but unstructured data. Wolfgang also taught Dr. Brunner how to correctly analyze data from a scientific point of view. As a result, Dr. Brunner published his first article as first author in one of the top journals in the field (Brunner-La Rocca et al., 1996). Importantly, Wolfgang not only gave Dr. Brunner the opportunity to pursue a research fellowship at the University of Melbourne in Australia with one of his former colleagues from his Ann Arbor days, Murray Esler, M.D. (Brunner-La Rocca et al., 2001, 2002), but also guaranteed him a senior staff position upon his return to Switzerland, a promise which according to Dr. Brunner Wolfgang kept even against the strong opposition from within the division. Without Wolfgang, he would not be where and what he is today, says Dr. Brunner.

Wolfgang had the ability to motivate younger colleagues to enter cardiology and was even able to foresee the future development of cardiology. In the late 1990s, the internal medicine resident Christoph

Fig. 5. A composition of photographs of Wolfgang and Monika Kiowski pictured in front of the Taj Mahal in Agra, India, a few years before his untimely death (left) and during the research fellowship at University of Michigan in the 1970s (right). Photograph courtesy of Stevo Julius, M.D., and used with his permission.

Scharf, M.D., asked Wolfgang about career opportunities in invasive cardiology. Wolfgang responded: "*If I were to be young again I would choose electrophysiology and get into how to ablate atrial fibrillation*". This was long before ablation of atrial fibrillation became a clinical treatment option, and only initial first results had been published at the time (Haissaguerre et al., 1998). Wolfgang motivated his young colleague to obtain licensure in the U.S. and to move to the University of Michigan, the same institution where he had trained 25 years earlier. After completing a clinical cardiology fellowship and research with Fred Morady, M.D. (Oral et al., 2002; Scharf et al., 2009), Dr. Scharf returned to Zürich to introduced the new technique in Switzerland and joined his mentor at the Zürich Cardiovascular Center (HGZ Zürich).

Another of Wolfgang's successful mentees is Erwin Oechslin, M.D., now Professor of Cardiology at the University of Toronto in Canada, where Dr. Oechslin heads the world's largest program of adult patients with congenital heart disease and where he continued to do research together with Wolfgang (Oechslin et al., 2005).

At scientific meetings, Wolfgang was known to strongly present his views and argue convincingly with his peers about issues that did matter to him. For several decades Wolfgang was active in medical societies, such as the *European Society of Hypertension* and the *Swiss Society of Cardiology*, and he was elected Fellow of *the European Society of Cardiology* and Fellow of the *American College of Cardiology*. For many years Wolfgang was on the editorial board of medical journals, including the *European Heart Journal*, and also served on the scientific advisory boards of the *International Conferences on Endothelin* (including ET-6 held in 1999 in Montréal, Canada).

The last decade of his life Wolfgang spent at the HGZ Zürich after he left the University Hospital (Fig. 4). Wolfgang until the time of his death remained one of Switzerland's most respected experts in heart failure, invasive and general cardiology. Wolfgang had many hobbies, including windsurfing, and he can serve as a prime example of someone who is successful as a physician, scientist, and father who enjoyed life with his family and his wife Monika (Fig. 5). Wolfgang Kiowski — according to Dr. Julius in a message to young colleagues given at the 2013 ESH meeting — was a great example who demonstrated that this can be done and that you do not need to be obsessed with work and that you can enjoy life in academic medicine (Fig. 6).

We mentioned earlier the reminiscences of one author of this article on Wolfgang. For the other author (E.L.S.), who met Wolfgang mainly at scientific meetings, and was invited to his home and enjoyed the company of him and his wife Monika, Wolfgang was a superb physician-scientist with a deep understanding of cardiovascular physiology and pathophysiology. His varied interests, his humor, and his empathy as well as his rigorous intellect were compelling. It was a real pleasure to exchange about any subject with him, scientific or other, and a pleasure to see him with Monika, since they evidently enjoyed each other so much (Fig. 5).

Wolfgang was an avid photographer. He did not let go of this passion until the last day of his life: in the morning cycling to work, Wolfgang took a picture of the Zurich skyline overlooking Lake Zürich just after sunrise (Fig. 7). After his last clinical assignment at the HGZ Zürich on that day, he took his bike to cycle back home when he stopped to take his last picture, now the mountain skyline facing Lake Zürich in the last sunlight shortly before sunset (Fig. 7). Only minutes after taking this picture he suffered a massive myocardial infarction which was too extensive to allow recovery (Heagerty and Julius, 2013; Kjeldsen and Mancia, 2013). On November 25, 2012, Wolfgang Kiowski died of heart failure, a clinical syndrome that was the center of his clinical and scientific interest for his entire professional life.

Wolfgang's first academic teacher and mentor Prof. Losse has been described by Karl-Heinz Rahn, M.D. (his successor at the University of

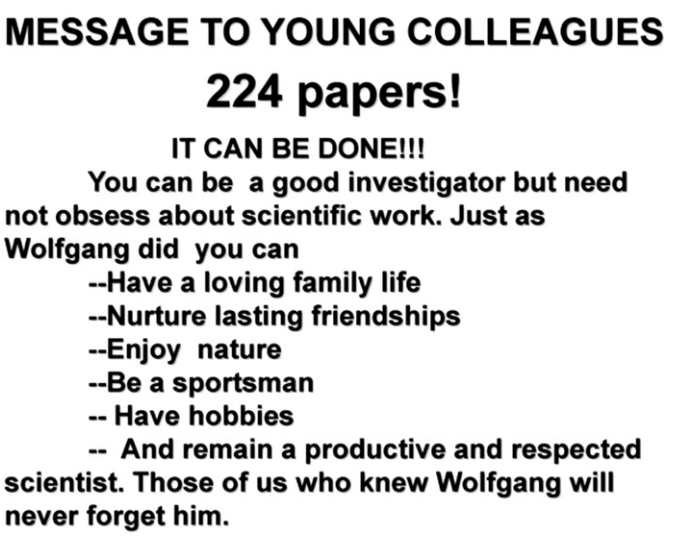

Fig. 6. The final slide of the lecture delivered by Stevo Julius, M.D. in memory of Wolfgang Kiowski at the 2013 *European Society of Hypertension* (ESH) meeting in Milan, Italy. The slide summarizes personality, abilities and achievements of Wolfgang Kiowski and at the same time represents a motivating message from Stevo Julius to all young colleagues and embarking on a career in cardiovascular medicine and science. Figure courtesy of Stevo Julius, M.D., and used with his permission.

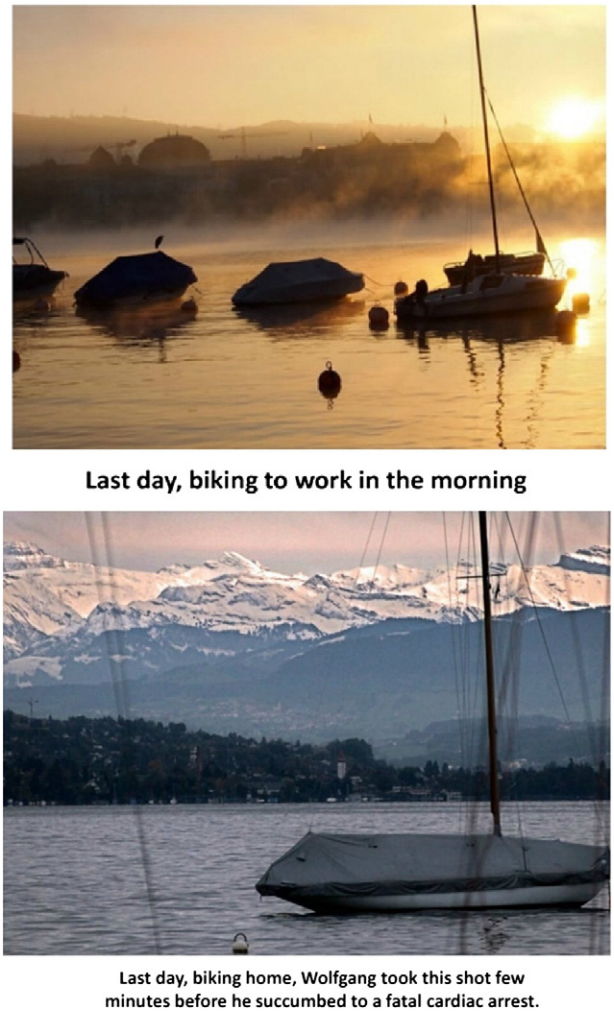

Fig. 7. Two examples of Wolfgang Kiowski's skills as a photographer, both taken on the last day of his life before he succumbed to a fatal cardiac arrest due to myocardial infarction. These photographs were shown by Stevo Julius, M.D. (who also provided the subtitles of the slides), during a lecture given in memory of Wolfgang Kiowski at the *European Society of Hypertension* (ESH) meeting in 2013 Milan, Italy. Photographs courtesy of Stevo Julius, M.D., and used with his permission.

Münster) as "*caring physician, highly motivated scientist and clinical teacher able to create enthusiasm among his students*" (Rahn, 2006). The same is to be said about Prof. Losse's student Wolfgang Kioswki. What he did for his patients, for his trainees, for cardiovascular medicine and clinical endothelin research will not be forgotten. Wolfgang's professional ethos is reflected in the words of Sir William Osler that we quoted at the beginning of this article as well as in Osler's words quoted below, an ethos that young physicians and trainees working with Wolfgang Kiowski could experience in everyday clinical work.

> *"Hard though the conditions may be, approached in the right spirit – the spirit which has animated us from the days of Hippocrates – the practice of medicine affords scope for the exercise of the best faculties of the mind and heart*
>
> SIR WILLIAM OSLER

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