

Introduction



A favourite Kewism; 'Write in haste and revise at leisure. Good writing is a craft, not an art.'

A clinician scientist often wears a variety of different hats, including those of researcher, administrator, mentor and teacher. While other prestigious awards may specifically honour research achievements, a festschrift acknowledges the many other facets of the career of an outstanding and influential scientist. Meaning 'celebratory writing' in German, a festschrift is a unique publication devoted to the lifelong accomplishments of an exceptional scholar, and traditionally includes a symposium, followed by the publication of a compendium of papers contributed by the honoree's mentees and colleagues.

The notion of a festschrift to celebrate Mike Kew's career was conceived 2 years ago by Chris Kassianides during a visit to Jay Hoofnagle at the National Institutes of Health in Bethesda. Jay's face lit up at the suggestion, and that was the signal to steam ahead. The concept was enthusiastically endorsed by others, and culminated in the Gastroenterology Foundation of South Africa symposium in Pretoria in August 2016 at the South African Gastroenterology Society congress to commemorate Mike's achievements and ultimately the publication of this festschrift. The symposium was dedicated to Mike's lifelong influence on hepatology, and some of his closest collaborators and most prominent colleagues highlighted the broad spectrum of his contributions to research on liver disease. Perhaps the most inspirational aspect was the admiration and esteem

the presenters demonstrated in describing his personal attributes. Mike brought to academia his insatiable sense of curiosity, his passion, his persistence, his determination and his dedication.

Mike Kew has had one of the most extraordinary careers in South African medicine, and is one of the best-known hepatologists of his era. The choice of a career that gives one an inner compass of purpose invariably has positive effects on one's life, and Mike is no exception. The sheer longevity and productivity of his academic career in medicine and hepatology, the magnitude of his impact and the quality of his science make Mike Kew the ideal recipient of a living celebration of his academic work.

It would be difficult for any prelude to a festschrift in honour of Mike Kew to completely cover the many notable achievements of his remarkable life and career. Mike had an enviable start to his academic career when he graduated *cum honoribus primus* and top of his class at the age of 21 at the University of the Witwatersrand. From that auspicious start, he conscientiously followed William Osler's dictum that the magic word for success in medicine is work, sustained hard work. Ever the consummate clinical and translational scientist, Mike spent over four decades at the forefront of research in hepatology. He made substantive contributions, in particular reshaping the understanding of hepatocellular carcinoma and hepatitis B virus infection in sub-Saharan Africa. Even when retirement beckoned, his enthusiasm remained undimmed, and the value of his wisdom and experience as a senior scholar was recognised and utilised by the Department of Medicine at the University of Cape Town.

One of Mike's most striking qualities was his skill and talent in directing and inspiring his many protégés. Albert Einstein opined that 'you should not use an old map to explore a new world' and this maxim underpinned his career. A good test of mentorship is the ability to inspire others, and the recognition that together, the landscape can be changed, and new knowledge brought into the world. He had an unparalleled intuition in recognising natural talent, which resulted in his recruiting and nurturing some of the best hepatologists in South Africa in the Department of Medicine at the University of the Witwatersrand, ensuring that each protégé followed a unique career pathway and that all became expert hepatologists.

There are a plethora of plaudits that describe Mike and the trajectory of his journey in South African medicine. During his career, he was the recipient of numerous national and international awards and honours, which are detailed in subsequent tributes. His contributions have left an enduring and indelible legacy. This festschrift acknowledges Mike's impact on hepatology, medicine and academia, and the profound influence he had on colleagues and coworkers. Few can equal the extent and depth of his accomplishments.

J E J Krige, S R Thomson, E Jonas, C Kassianides

Michael Charles Kew: A chronicle of his career

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Michael Charles Kew was born in 1939 in Johannesburg, South Africa. His parents, Max and Dorothy Kew, were South African citizens, his father a businessman. At an early age, Michael was recognised as a brilliant student. He graduated with first class honours from Jeppe High School at 15 years of age in 1955. From there, he enrolled at the University of the Witwatersrand (Wits) in 1956, the beginning of a more than 50-year career in association with the university. He received his MB BCh in 1961 (graduating *cum honoribus primus*), followed by an FCP (SA) in 1965, a medical doctorate (MD) in 1968, a PhD in 1974 and Doctor of Science (DSc) in 1982. His success in academic medicine was recognised with his induction as a member of the Royal College of Physicians of London (MRCP) in 1971, followed by his election as a fellow of the Royal College (FRCP) in 1979. This rapid acquisition of professional degrees and recognition is a testament to his academic and research performance at the Johannesburg Teaching Hospital Complex and University of the Witwatersrand. Here he began work as a physician in the Department of Medicine in 1967, later becoming a principal physician and senior lecturer (1971), a consultant hepatologist (1972), professor of medicine (1978) and senior physician and physician in charge of the Liver Unit (1972), as well as a member of the SA Medical Research Council (1997).

Professor Kew's initial academic and research studies were on a broad spectrum of liver diseases including viral hepatitis, drug-induced liver disease, portal hypertension, haemosiderosis, heatstroke and hepatocellular carcinoma (HCC). These were the clinical conditions and challenges that he faced on the wards of the Johannesburg Teaching Hospital, and particularly at Baragwanath Hospital that serves the sprawling Soweto township. A very special and dramatic challenge was HCC, which in Johannesburg, unlike other places in the world, was an extremely aggressive, rapidly fatal cancer affecting young adults in their 20s and 30s, rather than the middle-aged or elderly, as seen in the rest of the world.

In 1970, Dr Kew was awarded a Wellcome Research Fellowship to work in the Liver Unit at the Royal Free Hospital, London, with the world-renowned Dame Sheila Sherlock. There he pursued investigational studies on portal hypertension, but also carried out a clinical study on the spectrum of HCC, co-authoring with Dame Sheila what is now recognised as a classic clinical description of this little-understood cancer.

Returning to South Africa, Dr Kew began what became a life-long commitment to the study of HCC. His initial studies were largely descriptive and clinical, but he rapidly initiated analyses of pathogenesis based upon epidemiology and application of the serology, virology and molecular assays for the newly discovered hepatitis B virus (HBV). He and others showed that chronic infection with HBV was closely linked to liver cancer, and probably nowhere more strikingly than in sub-Saharan Africa. In a series of epidemiological, clinical, histological, virological and molecular studies, Professor Kew mapped out the close association of HCC with chronic HBV infection, the integration of HBV DNA into the tumour cells, the contributing factors of age, sex, iron status and environmental factors in the progression and expression of HCC, thereby establishing himself as the foremost authority on this significant tumour.

I first met Professor Kew in 1978, at the 2nd International Symposium on Viral Hepatitis, held in San Francisco. I had just finished training in gastroenterology-hepatology with Leonard Seeff

(another South African) at the Washington DC VA Hospital, and started in the Liver Diseases Section of the National Institutes of Health. Mike gave the plenary overview presentation on hepatitis B and liver cancer. The talk was clear, concise and convincing, and given in that crisp, distinctive South African accent. It was immediately apparent to me and to all in the audience that this was someone who knew what he was talking about, a speaker who had seen and taken care of patients with liver cancer. It was immediately evident that he was a scholar, a careful thinker and, importantly, a clinical and basic scientist. Until that time, epidemiologists, pathologists, cell biologists and clinicians were the experts on HCC. Michael was all of these. He brought a freshness and excitement to the topic, proving a thoughtful and complete approach to understanding liver cancer and the role of hepatitis viruses, viral genes, host genes and environmental factors in its aetiology and pathogenesis. He also provided insights into what might ultimately be done for the prevention, early detection and treatment of HCC.

Following the meeting in 1978, Michael Kew was an invariable presence as a speaker at international symposia on viral hepatitis. In addition to contributing data from South Africa and the African continent, he succeeded in providing an overview and a balanced understanding of HCC, the most dreaded complication of viral hepatitis. He contributed to our knowledge of hepatitis B and liver cancer, documenting the abysmal results of conventional chemotherapy, and initiated trials of new therapies for chronic HBV infection, while documenting the changing epidemiology of hepatitis B and liver cancer.

Professor Kew was awarded a Fogarty Visiting Scientist position with Dr Robert Purcell in the Hepatitis Viruses section of the National Institutes of Health (NIH), and there he developed a working knowledge of the laboratory tools required to advance his research into the molecular virology of hepatitis B and liver cancer. I was at the NIH at the time, and asked Bob Purcell why we didn't see more of Mike Kew. Purcell answered that he was too busy, and added that Mike was the hardest-working, most dedicated Fogarty scholar who he had ever worked with. Following the 2-year sabbatical, Michael returned to Johannesburg, where he continued to make important contributions to our understanding of hepatitis B and HCC, using molecular tools to further elucidate the interaction of hepatitis B with the liver. He further explored co-factors that might alter viral carcinogenesis, defining the roles of genotypes and viral variants, the role of co-infection with hepatitis C and D viruses and viral host interactions. He also explored the potential role of chronic hepatitis B therapy as a means of decreasing the risk of HCC, and the changing epidemiology of hepatitis B and HCC in South Africa and worldwide.

I have personally benefitted greatly from my association with Professor Kew, and must pay tribute to his important role as a mentor of young physicians, attracting the best and brightest into the field of hepatology and viral hepatitis research. At the Liver Diseases Section of the NIH in the 1980s and 90s, Michael sent us three of his best trainees. All three were stars.

Geoff Dusheiko was the first hepatology fellow trained by Mike Kew. He came to our group a year after I joined the NIH. He got us started in hepatitis B immunology, and set up assays for HBV DNA

polymerase that were the bedrock of much that we did clinically on hepatitis B in ensuing years. Geoff returned to South Africa, where he worked with Michael Kew starting trials for the therapy of hepatitis B in South Africa, and 5 years later moved to London to become Professor of Medicine and chief of the Hepatology Section at the Royal Free Hospital.

Adrian di Bisceglie was our second Kew trainee. Adrian quickly showed his expertise, sound judgment and maturity, and was appointed a senior staff physician within 2 years of arriving, and subsequently was made chief of the Hepatitis Section. In the lab, he developed assays for HBV DNA in serum and liver, and helped us embark on studies for the therapy of chronic hepatitis B and what was then known as 'non-A, non-B' hepatitis using recombinant human interferon alpha. Adrian later went on to become Chief of Hepatology and Chairman of Medicine at St Louis University, and president of the American Association for the Study of Liver Diseases (AASLD).

The third Kew trainee was Chris Kassianides, who developed the duck HBV model in our lab and participated in our early trials of therapy for hepatitis B, C and D. Chris became a close friend, and a frequent visitor even after he left to finish specialty gastroenterology training and later returned to South Africa. Chris has become a

champion for advanced hepatology and gastroenterology training in South Africa and the African subcontinent and is founder and chairman of the Gastroenterology Foundation of South Africa. Chris conceptualised and organised a truly magnificent festschrift symposium in 2016 to honour Michael Kew, which led to the compilation of this festschrift.

I write of many things that occurred 20, 30 and even 40 years ago. I have achieved the age where I realise that one's contribution to biomedical science is not only in the number of papers you publish, or how often you are invited to speak, or what honorary degrees and awards you can claim. Perhaps more importantly, one's contribution is also measured in what you leave behind, those you have mentored, your trainees, your scientific children in whom you foster a love and commitment of science and medicine, and who then pass on this enthusiasm and commitment to future generations. Professor Kew has been successful in all of these respects, and a leading source in the growing light that has surrounded the darkness of viral hepatitis and the disease burden that it causes. I am proud to have been asked to contribute to this festschrift for this most deserving physician, scholar, researcher, teacher and mentor. Mike, congratulations on a sterling and successful career.

Professor Mike Kew and the Royal Free Hospital

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The Royal Free Hospital in London is one of the world's foremost landmarks in hepatology, being the hospital where Professor Dame Sheila Sherlock worked, providing key contributions to the discipline. Sheila Sherlock's legacy is a most impressive establishment, with possibly hundreds of clinical and research fellows having received training and inspiration from her, and subsequently from her closest disciples after her death in 2002. Many of these young trainees came to London from different parts of the world, and went back to their countries fundamentally primed to become leading hepatologists.

The original Royal Free Hospital was located in the centre of London, in Gray's Inn Road, and was then moved to the new establishment in Hampstead, North London, in 1974.

Professor Mike Kew joined the group led by Sheila Sherlock in 1969, and spent 1 year as specialist registrar at the Royal Free in Gray's Inn Road. London was probably the most exciting city in the world at the time. Everything seemed to happen there, with new trends originating from what was defined as 'swinging London'. In the imagination of somebody from South Africa, London was still the capital of the great British Empire, when in reality, the empire was over, and London was pursuing a different and far brighter future.

However, the old Royal Free in Gray's Inn Road was an outdated structure, totally insufficient to satisfy the blossoming rapid expansion of the more and more specialised branches of medicine. The building was like an old veteran of many battles, full of glory and medals, but close to ruin. Hepatology, one of the newcomers in the race to medical specialisation, was mostly relegated to an interconnected series of huts on the roof of the old hospital building (Fig. 1). I can imagine young Dr Kew, used to the warmth, spaces and colours of Africa, encountering the grey and humid London atmosphere, and moving from one hut to another between ward rounds and academic meetings.

In the memory of the few people I was able to contact and ask about the days of Mike Kew in London, and most notably one of my predecessors, Professor Neil MacIntyre, Mike was regarded as a shy

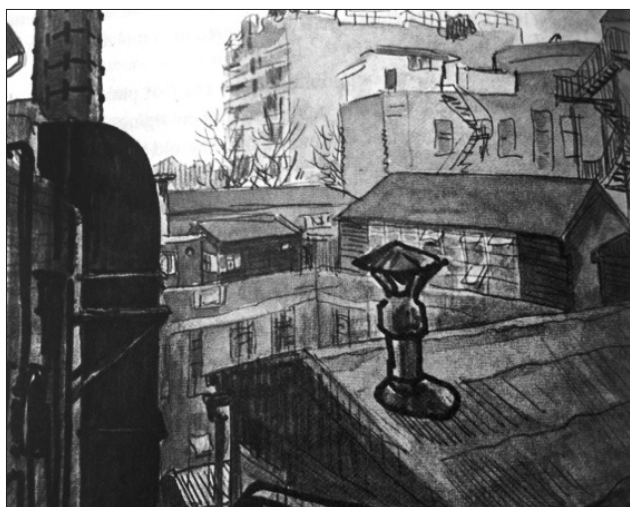


Fig. 1. The huts on the roof at the old Royal Free Hospital in Gray's Inn Road, London.

but extremely knowledgeable doctor, and, apparently, a formidable tennis player. This may have contributed to his making a favourable impression on Dame Sheila, who loved tennis and did not allow anybody to beat her. In this regard, it would be interesting to know Mike's point of view!

The intense activity of Mike Kew at the Royal Free was largely concentrated on renal impairment in patients with cirrhosis of the liver. In 1971, Mike published his first landmark paper on this topic in *The Lancet*.^[1] By employing the innovative ¹³³Xe washout technique, Mike and colleagues clearly demonstrated for the first time that a decrease in creatinine clearance is invariably associated with significant cortical hypoperfusion, likely attributable to active vasoconstriction of the cortical vessels. In a paper published in 1972,^[2] Mike and coworkers showed that an identical situation occurs in non-cirrhotic portal hypertension, and established the concept that vasoconstriction of the renal cortex occurs as a consequence of portal hypertension independently of the progressive failure of liver function typical of advanced cirrhosis. Working along these lines, these authors provided the first characterisation of portal hypertension in primary biliary cirrhosis.^[3] Another key intuition in this pioneering area of hepatology was the relationship between the circulatory derangement typical of decompensated cirrhosis and renal function.^[4] In this paper, the authors showed that the administration of octopressin, a vasopressin analogue, was able to improve renal function only in those patients in whom the drug increased a very low mean arterial pressure, thus establishing the relationship between effective blood volume and glomerular filtration rate in cirrhosis. Taken together, these acquisitions represent the very fundamental basis of our current understanding of renal function in cirrhosis, the hepatorenal syndrome and the relative therapeutic approaches. I vividly remember quoting Mike Kew's paper in my MD thesis, and I was deeply honoured to meet him for the first time in Cape Town.

This intense and innovative research activity had distracted Mike Kew from his original and everlasting love: hepatocellular carcinoma (HCC). Indeed, he published only one paper on this topic with Sheila Sherlock, dedicated to the diagnosis of this malignancy.^[5] I can imagine that Mike was probably the hepatologist with the greatest experience in HCC at the Royal Free, as a result of the far higher incidence of this cancer in Africa, and the still poor recognition of the association between chronic liver disease and HCC in Europe and the USA.

I feel honoured to celebrate in this article the association between the Royal Free Hospital and one of its most renowned fellows in hepatology. Mike's lifetime achievements are a great source of motivation for me and for the young research fellows that I am honoured to mentor and host, thus maintaining Sheila Sherlock's legacy.

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