My Life as a Clinician-Scientist: Trying to Bridge the Perceived Gap Between Medicine and Science

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SOMETIMES, I THINK that trying to be an authentic clinician-scientist who straddles successfully the majestic fields of scientific research and clinical medicine is well-nigh impossible. The inherent danger of such an endeavor is that by trying to be good at both laboratory research and managing sick patients, one ends up by failing to do either well so that basic scientists are skeptical about your scientific knowledge and ability while your clinical colleagues do not regard you as a top-notch clinician, with both groups viewing you with not a little suspicion. No one can guarantee success in such a combined role but for sure I can think of three things that help a lot, indeed are critical: obtaining a first class training in both research work and clinical medicine, genuine enthusiasm, indeed passion, for both finding things out through research and looking after patients, and, crucially, good mentorship. While I am innately very self-critical (and with good reason!), overall I consider myself as having been quite fortunate in having experienced all three of these, and, of course, the last, indeed essential, ingredient to becoming a successful clinician-scientist is a smattering of good luck, which no-one can guarantee. But at least it is possible I believe to create a career background and attitude that is conducive to good choices, the avoidance of potential disasters (which unfortunately I have seen on occasion first hand) and consistent with the often quoted notion that “chance favors the prepared mind.” Avoidance of bad luck, if at all possible, may be just as, if not more, important as experiencing good luck. And it goes without saying that you really have to enjoy being this kind of person in such a dual role.

I should make clear at the outset that I am talking here primarily about laboratory-based “wet bench” research rather than pure clinical research. The latter is, of course, every bit as important, challenging, and rigorous as its laboratory counterpart and includes things such as carrying out clinical trials of novel diagnostics and treatments, many different types of investigations on living people, and retrospective and prospective epidemiological studies, including complex meta-analyses. I have colleagues who have been hugely successful at this type of research, but it is not the pathway that I chose almost 30 years ago. I think one should also be clear about motivation. I decided to be a clinician-scientist, because I

greatly enjoyed being in the laboratory but was not prepared to do that full-time at the expense of not seeing patients and ceasing to be a doctor. In other words, I wanted to be a part of both worlds. It was more a question of being self-aware, almost having one’s cake and eating it so to speak, rather than being an expression of some more noble sentiment. Increasingly, these days one hears about the critical role of the clinician-scientist in linking the science with the patient, taking discoveries “from the bench to the bedside,” in being the critical bridge between the two disciplines. That is absolutely true and for the past decade this has been my primary justification for what I and my colleagues do. Indeed, this is the key priority given by those in influential medical and scientific positions for promoting the training and importance of such “bridging” individuals, and quite rightly so. But at least in my case, and I strongly suspect in many others, the *initial* drive to wear both hats derived fundamentally from a genuine desire to live in the two worlds, because it is just more exciting and interesting than focusing on just one. So the bottom line is that you must really enjoy what you choose to do if you are to have a reasonable chance of making any kind of lasting contribution. If you choose such a path for purely career-oriented reasons, then it can all go very easily wrong.

So how did I get started in all this? The answer is rather late and largely by chance. At my well-known and enlightened Secondary (High) School in London (University College School), I was far better at languages than at science and maths, which were not my academic strengths though they were quite well taught, but I was greatly stimulated by and interested in popular science books, particularly those written by the science fiction writers Isaac Asimov and Arthur C. Clarke. I also wrote a few science fiction stories, one of which was actually published later in an American “fanzine.” Perhaps as a result of these influences I founded an Astronomical Society, an interest that has never waned. Completely disregarding the avuncular advice of my school teachers who felt I was far better suited to a career as an Oxbridge classicist rather than a scientist, I was loyal to an early passion for medicine and somehow got accepted as a medical student at the prestigious University College London (UCL). (Some of my schoolteachers thought I had taken

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leave of my senses to abandon languages and the classics and feared for my future).

This University ran an excellent medical course, at both the University and the affiliated University College Hospital (UCH) Medical School, and several UCL staff members were eminent scientists, including the Nobel Prize winners Andrew Huxley and Bernard Katz. Some of the lecturers, such as the renowned anatomist and scientist J. Z. Young, were superb but understandably we students tended to judge our lecturers more on the basis of their lecturing skills rather than on their scientific research. Nowadays, as we all know, if anything, the opposite tends to be the case at the higher levels of assessment. In reality, the ability to give good lectures and to do good research are independent just as, in my view, high intelligence, personal kindness, administrative ability, and personal appearance, all of which are totally independent variables. But we were well aware that we were privileged to be in contact with so many remarkable and scientifically accomplished individuals. At the time, I was naturally aware of UCL's academic prowess, but I did not foresee the extraordinary academic powerhouse that it was soon to become, facilitated in part by its incorporation of several other outstanding London Institutions. Whenever I now read about UCL's remarkable academic successes, I still get a brief *frisson* of vicarious pleasure, even though I haven't worked there for more than 30 years.

After completing the demanding and intensive preclinical course, I started the formal clinical training at UCH, which was famous for the quality of both its patient care and clinical research. I have described the student experience there in some detail elsewhere (Kennedy, 2007). I again went against the firm advice of my academic teachers by not taking up the opportunity of doing an intercalated BSc in a preclinical subject such as Physiology, Biochemistry, or Anatomy, a difficult and painful decision that I can still recall vividly. But my burning desire to get into the wards and see real patients narrowly exceeded my considerable enthusiasm to do what would have been the natural and sensible thing. But I was reassured by a leading and very sympathetic physiologist at UCL that some of the best PhD degrees by medical graduates are carried out by individuals with little or no previous scientific training so I should just get on with it and stop agonizing unnecessarily. He was right, of course, but I still regret that decision, as it was a lost opportunity and I believe that all doctors in training should be strongly encouraged, though not compelled, to do an undergraduate science degree during their medical course. It would have been very useful and a lot of fun.

It was while still a clinical student at UCH that I first became aware of what a clinician-scientist does, or at least tries to do. Interestingly, it was apparent to me which clinicians used a mainly scientific and evidence-based approach for patient diagnosis and management as opposed to a more anecdotal and personal experience-based approach favored by others. Of course, medicine is an art as well as a science so both approaches have their relative merits and in dealing with real people it is necessary to temper established knowledge with personal experience. Crudely speaking, in medicine the tendency is to say "I've seen this set of symptoms and signs before so therefore the diagnosis must be such and such," rather than the scientific approach that is more along the lines of "How can I use the knowledge

which I do know to predict and then hopefully answer what I don't know." Several of the physicians, often the ones I got on best with, had a distinct tendency to rush back to their respective research laboratories as soon as they had completed their ward rounds with their resident staff, and I recall the academic surgical unit being particularly strong in gastro-intestinal research in patients with stomach ulcers and gastric acid secretion, an area where UCH was a world leader at that time. Metabolic medicine and endocrinology were also strong research areas, and an academic physician who made a particularly strong impression on me was (Sir) Edward ("Bill") Pochin who looked after his thyroid cancer patients so well and who calculated their doses of radioactive iodine with such precision that he almost seemed to have magical powers. It was therefore a source of much pleasure to me that immediately after qualifying as a doctor in 1974 he chose me, after a surprisingly severe interview, as his last house physician. My work rota as a young resident required my working well in excess of 100 h per week, something that would be illegal now, but he was such a wise, caring, and intellectually powerful chief that I was able to take the physical and emotional strain without any undue damage. But at least I saw what an authentic clinician-scientist of the first rank could achieve, and he made many important contributions to our knowledge of both thyroid disease and radioactive drugs.

I had to wait 4 years until 1978 before venturing into an established laboratory and getting to grips with real science. After gaining intensive, if not exhausting, experience of general medicine at both UCH and the affiliated Whittington Hospital, where I had massive clinical responsibilities working ridiculously long hours and learning on the shop floor so to speak, I decided I was ready to start some proper scientific training. It was at this point that I had a piece of major luck. A wise and experienced neurologist and lifelong mentor called Gerald Stern advised me to do an MD project in a laboratory-based subject rather than pure clinically based research, as he thought that would be more suited to my personality. In contrast to the United States, where it is the standard medical degree, in the United Kingdom, an MD degree is a higher degree than the qualifying Bachelor of Medicine degree (MBBS in London University), and it is obtained by writing a thesis based on a period of research. It is generally regarded as equivalent in status to a PhD, though some clinical academics such as myself prefer to have the latter or (as in my case) both.

I then met with Patrick Wall, the eminent pain expert at UCL, whom I found both charming and helpful but he couldn't take me on as he already had a clinical research fellow in his lab and there was no space for more. So he advised me to contact another UCL researcher called Martin Raff, who was an eminent scientist previously trained as a clinical neurologist at the prestigious Massachusetts General Hospital in the United States. That turned out to be an extremely good suggestion. Martin's name will be well known to the readers of this journal, as his reputation and seminal accomplishments in Cell Biology, Immunology, and Neurobiology can be accurately described as legendary. An early discovery had been his demonstration that theta isoantigen was a marker of thymus-derived lymphocytes in mice. Even at that stage when he was barely 40 years old, he was a household name because of his groundbreaking work in Immunology, but a measure of my

ignorance at that time is that I had never heard of him though just about everyone else around me had in some way or another, including my then medical chief at the Whittington Hospital who urged me to take on this excellent opportunity to work in his lab. After Martin and I met for an informal interview at UCL and he took a chance on me by allowing me to work with him despite my complete lack of lab experience, I having been mesmerized by his account of the cellular neurobiological research that he and his colleagues were pioneering, my clinical colleagues seemed to treat me with a kind of vicarious regard for what I was about to start. Respect by association I guess.

So by chance I ended up doing my first piece of real research in one of the world's leading laboratories, an experience that permanently defined the parameters of my subsequent career. The Department of Zoology at that time was headed by Avron Mitchison, also a renowned immunologist and the person who had originally recruited and mentored Martin. Av, as he was known to us, led the Imperial Cancer Research Fund (ICRF) Unit in the department, which comprised a host of talented basic immunologists, including Marc Feldmann, who went on to pioneer the use of TNF- α in rheumatoid arthritis and rose to great international prominence and recognition. The ICRF scientists were integrated seamlessly in the department with members of the MRC Neuroimmunology project, which was headed by Martin. For me as a visitor, it was a deeply stimulating experience to work side by side with scientists of such high caliber and Av made me feel extremely welcome. It was remarkable, but typical, that Martin and Av shared a very small and modest office completely devoid of any sign of opulence.

Martin was a kind, charismatic, and very creative person and supervisor who showed considerable patience and understanding when faced with my obvious laboratory inexperience. But I was quite a quick learner, perhaps through necessity, and I was taught well by his technicians and was fortunate to have "green fingers" in that I was good at culturing rodent neural tissues, a skill that was essential in that environment. I was also helped a good deal by Bob Lisak, a comparatively young but highly accomplished academic neurologist and clinical neuroimmunologist from the University of Pennsylvania who was on a 1 year sabbatical in Martin's lab. Bob was also a supportive mentor, and we worked closely together on my projects. We have remained good friends and colleagues ever since and he recently stepped down after a long and successful tenure as Chair of Neurology at Wayne State University. My first project was to try to confirm in rodent tissues a recently published report of antibodies that had been identified as being specific to oligodendrocytes (cells which produce myelin in the central nervous system [CNS]) in Multiple Sclerosis (MS) patients. That was obviously important because of the demyelination that occurs in MS but I was unable to confirm these findings despite trying extremely hard to do so using a wide variety of different procedures. After 4 months of this tedious work, Martin wisely suggested that I move on to a more interesting and ambitious project.

What Martin and his colleagues had achieved was to show that all the major neural cell types in the rodent nervous system could be identified in culture using cell-type specific markers (Raff *et al.*, 1979). For example, Galactocerebroside was a cell surface marker for oligodendrocytes, glial fibrillary acidic protein (GFAP) was confirmed as an

intracellular marker for astrocytes, neurons could be identified by their cell-surface expression of receptors for tetanus toxin, Schwann cells were identified by binding antibodies to Ran-1 antigen, and putative microglial cells were identified by the presence of cell-surface Fc receptors for IgG. Subsequently, he and colleagues showed that a glial progenitor cell existed that could develop *in vitro* into an astrocyte or an oligodendrocyte depending on the culture conditions (Raff *et al.*, 1983). With the increasing use of monoclonal antibodies, different subsets of various neural cells could be defined. My task was to determine whether these same markers could also be used to identify glial cells and neurons in the human nervous system. That was easier said but done, but it was accomplished after about a year of extremely intensive work, often working throughout the night and the next day, such was my excitement and enthusiasm to discover something important. It's surprising what one can do at the age of 27 years and in the peak of good health. The key to this was to use human fetal neural tissues, since they were far easier to grow in the tissue culture dish than adult tissues. After obtaining the required ethical clearances, I obtained multiple aborted human fetal tissues, mainly from a nearby tissue bank, and showed unambiguously that almost all of the markers that had been used in the rodent were also effective in humans (Kennedy *et al.*, 1980). There were a few differences—e.g. mouse anti-Ran-1 antibodies only labeled rat Schwann cells and not human cells, but the similarities were quite remarkable. I never failed to appreciate the remarkable beauty of both human and rodent oligodendrocytes and astrocytes when their stunningly intricate processes were revealed by the binding of antibodies coupled to red or green fluorochromes viewed with ultraviolet light in a fluorescence microscope.

This was an important advance and as a result of this Martin suggested I switch from an MD to a PhD degree, which I did with the help of a sympathetic senior member of the Zoology staff, but also at considerable personal expense as I was then forced to pay massive annual fees as an internal student amounting to about a third of my net salary. Though these were partially remitted due to my impecunious state, it was literally a painful price to pay. But I am glad these laboratory findings have proved useful to others and they have been employed to increase our understanding of cell-specific responses to infection, immune-mediated challenge, and other CNS disorders. Later during those productive 2 years, I spent 6 weeks in Bob Lisak's Neurology Department in the hospital of the University of Pennsylvania, my first ever visit to America, and I formed a strong emotional bond and affinity with that country that has lasted until now. It was an excellent and friendly Department, full of very smart clinician-scientists, and I saw again how clinicians could combine top-quality research work with sound clinical practice. I also met and collaborated with Don Gilden, already a leading neurovirologist, who was to become one of my closest scientific colleagues and friends in the United States. We were able to show in a very short time, for example, that JC virus (the cause of the demyelinating disease Progressive Multifocal Leukoencephalopathy-PML) grows *in vitro* in multiple marker-identified cell types (Wroblewska *et al.*, 1982).

A key difference between US and UK clinical academics is that the former are usually allowed about 9 months per year for doing research and 2–3 months per year of intensive

clinical responsibility as the attending consultant on wards. That allows a real and sustained focus on laboratory work for most of the year, and no wonder that they are so often spectacularly successful. By contrast, in the United Kingdom, protected time for research is seldom as generous as that; for example, I have no contractual option but to carry out outpatient and inpatient clinical work for 16–20 h every week of the year unless I am away on leave. That is a profound difference and I sometimes wonder how we manage to get anything useful done at all. But that's the way it is. Notwithstanding this, in retrospect I consider those 2 years in Martin's lab as being the happiest I can ever recall. Furthermore, at no point during that period was I ever bored, and for that I shall always remain truly grateful. This is particularly significant, as I have a low boredom threshold. I also realized that the daily life of a full-time scientist was more enjoyable and easier overall than that of a full-time clinician, but I retained the hope, or at least expectation, that it might also be possible 1 day to work in both worlds. I had also met my future wife Catherine 2 years before starting at UCL so this research period was also good news for what was a flourishing relationship. Those London summers were balmy, bright, and often idyllic, and life was an agreeable contrast to the relentless pressures and stress of practicing acute general medicine in the wards.

Having obtained the PhD degree, I realized that I was still just a tyro at research so I decided to do a postdoctoral placement in Neurovirology in Glasgow University in Scotland. Some of my senior medical mentors thought that was a bit over the top for a clinician in training. This was preceded by a useful 6 month period of Clinical Neurology at the Southern General Hospital with Iain Simpson who was my wise and genial predecessor as Chair of the University Department of Neurology there (though, of course, this possibility never even entered my head at the time). My interest in Virology had been kindled by a chance visit by Moira Brown of the MRC Institute of Virology during my time at UCL, so it was logical that I came to work in her Glasgow lab together with Geoffrey Clements in the summer of 1981. Glasgow is a very underrated city and still suffers somewhat from its perceived history of gangs and violence and past legacy of urban poverty. In reality, it is an excellent city in which to live culturally rich and vibrant, pretty friendly, and with great restaurants, affordable high-quality housing and schools, and a truly outstanding University. The only problem is the weather, which is frequently overcast and wet, but I guess you can't have everything.

We used the recently developed human cell-type specific markers together with antibodies to herpes simplex virus (HSV)-1 antigens to define in some detail the different neural cell susceptibilities to acute viral infection. Culturing human fetal neural tissues was a challenge and often frustrating because of the high incidence of fungal contamination, but persistence was eventually rewarded. I found the virological techniques pretty demanding, if not somewhat tedious, and it was a very different type of approach compared with what I had been used to. Here, I was setting up aesthetically elegant systems only to try to damage them with viruses rather than trying to learn more about their cellular properties. The behavior of a large number of temperature-sensitive HSV-1 mutants (as opposed to deletion mutants with smaller changes to their genomes) was characterized in considerable detail and we had soon amassed a large amount

of data (Kennedy *et al.*, 1983a). I also studied the by then well established mouse model of HSV-1 latency after footpad inoculation, and was able to demonstrate convincingly that the latent virus was located in neurons since the first cells to express HSV-1 antigens on viral reactivation in culture were also labeled with a neuronal marker (Kennedy *et al.*, 1983b). That also made biological sense. Anyway, these results seemed to be appreciated by the distinguished Director of the Institute John Subak-Sharpe, who became a long-term friend and mentor, especially in matters of science, life, and University politics. I was able to submit these data successfully as an MD research degree and then moved on to obtain a rigorous training in Neurology at the world famous National Hospital in Queen Square in London at the very end of that year.

I was quite lucky to get onto "the house," as being a neurological Registrar was then called at the National Hospital, as it was extremely competitive, but the University neurologists there were supportive of the kind of doctor I was striving to become. The departmental Chair, however, the formidable and very powerful Roger Gilliatt, warned me that there were no jobs available in academic neurology though that shouldn't deter me from trying. In reality, he and some of the other clinician-scientists there, notably Ian McDonald and John Newsom Davis both of whom I greatly admired, were extremely encouraging, and this continued to be the case for all three until their untimely deaths. Many of the consultants knew about my academic leanings and a few referred to me as a "boffin," which irritated me. The National Hospital for Neurology and Neurosurgery, as it is now called, is one of the most famous Neurology Institutions in the world (and probably the one with the greatest reputation). Not only did it contain, as it still does now, some of the UK's finest clinical neurologists but it is also now a world leading Center for outstanding Neuroscience research as a part of UCL. I was also impressed by the world-class-associated departments at the hospital such as Neuroradiology, Neuropsychology, Chemical Pathology, Neuroimmunology, Neuropathology, Neuro-otology, and Clinical Neurophysiology.

Apart from learning to be a competent clinical neurologist, I managed to be associated with Mark Noble's Neurobiology lab there. Mark was (and is) a very talented, rigorous, and original scientist and we knew each other from our time in Martin Raff's group about 3 years earlier. Here, I embarked on the ambitious project of trying to identify the human equivalent of the O2A bipotential glial progenitor cell that he and Martin had recently described in the rodent nervous system (Raff *et al.*, 1983). I again used the human tissue culture techniques that I had previously developed and managed after many gruelling weekends and evening hours to show that such a counterpart cell did exist (Kennedy and Fok-Seang, 1986), another discovery that I think has been useful to others who developed this kind of human progenitor work much further and to a greater extent than I had done. Mark, Bryn Watkins, and I also collaborated with the academic Neurosurgeon David Thomas in showing that the morphological classification of brain tumors does not correlate with their antigenic expression of the corresponding cell types (Kennedy *et al.*, 1987), a finding that seemed similar to heresy at the time but now seems hardly controversial. In retrospect, I now appreciate that this was the first time that I had truly functioned as a clinician-scientist doing clinical training during the day and

research in the evenings and weekends, and I loved it. The fact that I was single with no family responsibilities of any kind was also an essential element to the success of that period, one that was generously appreciated by most, but not all, of my clinical consultants.

After 3 years of intensive clinical training at the National Hospital, I was invited by Guy McKhann, who was then the Chair of the Neurology department at Johns Hopkins University and Hospital in Baltimore, to spend a year there working as a visiting Assistant Professor in Richard T. Johnson's Neurovirology Division. Dick Johnson is widely regarded as the father of Neurovirology, an assessment with which I entirely concur because of his multiple scientific contributions over many years and his exemplary leadership and encouragement of future leaders. He has always been a role model to me. Guy was a superb and supportive Chair and we had already met during my second year in the Raff lab when he was on a sabbatical. I recall that I had taught him how to culture rat oligodendrocytes and he was a fine student! The decision to leave London and work at Johns Hopkins was an excellent one, and my wife and I set off just over a year after getting married. I have always found going to America a kind of adventure, due in part to the inherent openness of my US colleagues and their refreshing "can do" mindset, which I find so stimulating. Few things are so conducive to success as sustained enthusiasm.

At that time (1985), the Neurovirology Division contained a wealth of research talent to the extent that it was a veritable cornucopia. The key person for me was my supervisor Opendra ("Bill") Narayan, who was making major discoveries in the visna-maedi slow virus infection of sheep. Though until then this disease had been an interesting experimental system in which to study key mechanisms of viral immunopathogenesis, visna had suddenly acquired great significance because of its close homology to HIV, which had literally burst on the medical scene only a few years earlier (at that time, it was known as HTLV-III). I worked very hard at the bench but was very fortunate to be able to jump onto a highly productive research bandwagon that had by then acquired considerable momentum. There was a lot of mutual interaction and cooperation between the different research leaders and I learned a great deal.

We were able to demonstrate the properties of a unique lentivirus-induced interferon in producing an ongoing inflammatory response in the presence of restricted viral replication (Kennedy *et al.*, 1985), and working with Howard Gendelman, who has gone on to become a major international figure in HIV pathogenesis, the pattern of increasing viral replication during monocyte maturation to macrophages was defined (Gendelman *et al.*, 1986). Other prominent individuals whom I remember well were Diane Griffin, Janice Clements, and Justin McArthur, all of whom went on to become renowned academic figures and occupy very senior positions in their respective areas at Johns Hopkins University. Collaboration with other departments was common, and working with colleagues in the Wilmer Eye Institute we were able to show using molecular techniques that cytomegalovirus (CMV) was present in the retinitis lesions in AIDS patients with severe visual impairment (Kennedy *et al.*, 1986), a good example of how basic science methodology can be used to address an important clinical problem with clear therapeutic implications. Bill Narayan died tragically

before his time but for many years we kept in touch and he was unquestionably the most productive and creative viral pathogenesis scientist that I have ever known. I also agreed with his opinion privately expressed to me that I had made one mistake there, which was not to spend a second year working with him. He was right, but that came about because of a job offer back in Glasgow that I just couldn't refuse.

The MRC had recently created the "New Blood" lecturer scheme to support University recruitment, and I was fortunate enough to have been appointed to a Senior Lectureship (roughly equivalent to an early Associate Professorship in the United States) in Neurology and Virology at Glasgow University as a part of this new initiative, the position having been created by John Subak-Sharpe and Bryan Jennett, the distinguished academic neurosurgeon who was the Dean of the medical school at the time. I returned to Glasgow to take up this position, the first of its kind in the United Kingdom, with (in theory) half of the time to be spent as a consultant neurologist at the Institute of Neurological Sciences within the Southern General hospital and half working as a laboratory-based neurovirologist in the MRC Institute of Virology with a distance of about 3 miles between them.

It was similar to returning to my roots, and the position worked pretty well except when on a few occasions my major virology experiments were fatally interrupted by the absolute necessity of rushing back to the hospital wards to care for an acutely ill patient. Patients' needs always take precedence over scientific experiments if you are a clinician-scientist, and making just one clinical mistake is and always has been totally unacceptable. It was, surprisingly perhaps, easier than I had thought to satisfy both my clinical and scientific colleagues though I still had to work at it, but most colleagues were supportive. I noticed that one's entire persona seemed to change depending on whether I was in the labs or the wards, even extending to the relative formality of how one dressed, maybe that's why I now always wear a tie even when "dressing down"! The research went fairly well though it was difficult to take on "blue sky" work under those circumstances with available and shared laboratory resources being very dependent on adequate grant funding, but it was a stimulating and agreeable existence. Then, it all had to stop 18 months later, because a Chair position had appeared on the horizon and, wisely or otherwise, I ran toward it with a measure of controlled enthusiasm.

Those few summer months in 1987 should have been exciting, but they turned out to be a bit of a nightmare with what was a painful embarrassment of choices. To cut a very long and complicated story short, I was appointed to the Burton Chair of Neurology at Glasgow University at the early age of 36 years, having also been offered simultaneously senior positions at both Kings College Hospital in London and Oxford University (with a College fellowship), both of which I declined. In the process, I learned a good deal about the politics of University recruitment and also made a few people in London very disgruntled and incredulous that I could choose Glasgow over London and Oxford. In reality, this acutely painful decision was made almost entirely on the basis of where I thought the best science could be done over the next decade, and Glasgow University, particularly the Virology department and Veterinary School, already had everything I needed to be able to carry on the work successfully, even though we frankly would

have much preferred to live in the south of England. I was amazed to see just how long some people were angry with me for making what was actually quite a brave choice, one that was based on a realistic assessment of my abilities, or, more accurately, my scientific limitations. But that's people for you. I recall the then Principal of Glasgow University, the eminent geologist Sir Alwyn Williams, reassuring me earlier on that I shouldn't worry too much about all the fuss as academic memories tend to be rather short and the best way for that to happen is just to be successful. I think that's mainly, but not entirely, correct and over the next few years, he helped me enormously in making this new and demanding role as successful as possible.

Combining medical practice in the wards and in the clinic as well as carrying out laboratory research, writing grant applications, and administering a Neurology department proved to be a major challenge and I had little protected research time. However, similar to most other senior academics faced with such wide responsibilities, I managed to recruit several scientists at differing levels who helped me maintain a degree of research productivity. My biggest problem, indeed mistake, at that time was that I invariably said yes instead of no to various requests, a bad habit that I eventually got out of, but I guess I didn't want to upset the colleagues who had supported me. Some of the recruits to the department were pretty successful at laboratory research but others were less so, and as a very young Professor and Chair I had to learn fast on the job and try to relegate any mistakes to experience.

One thing that always attracted me in people was enthusiasm, which I have invariably found to be infectious. It was vital to quickly expand and equip the research precinct and attract more scientists. In this context, I believe there are two particular attributes that a clinician can bring to clinical science projects: One is the capacity to see the whole disease picture and perceive which clinical questions can best be addressed by scientists, and the other is the practical ability to obtain diseased human tissues because of closer contacts with clinical colleagues. Over the next 10 years, there was a marked expansion in the number of, and equipment in, the few pre-existing laboratories, a 10-fold increase in grant acquisition, and a significant increase in the number of technicians, research assistants, graduate students, and postdoctoral scientists. Some of these were outstanding and none shone more than Chris Hunter, an outstanding post doc who carried out seminal studies in experimental animal trypanosomiasis (Hunter *et al.*, 1992a, 1992b) and who went on to a stellar career in parasite immunology, currently occupying the Chair of Pathobiology in the Veterinary School in the University of Pennsylvania. The most outstanding young clinical academic that I recruited was Hugh Willison, who quickly rose through the ranks of Glasgow academia to become a full Professor and is now the United Kingdom's foremost authority on inflammatory neuropathies as well as a superb clinical colleague.

My initial research focus continued to be in Neurovirology, specifically both HSV-1 and Varicella-Zoster virus (VZV) infections of the nervous system both *in vitro* and in patients' neural tissues, working closely with Geoffrey Clements at the Institute of Virology with which I continued to be closely affiliated (Clements and Kennedy, 1989). My other previous colleague was Moira Brown, who was actually transferred to my own department in 1995 to pioneer the use of an HSV-1 mutant as a therapeutic tool for treating malignant human

gliomas (brain tumors) and started a company there to take the work forward. Most significantly, I started several research collaborations with scientists at the illustrious University Veterinary School, an association that has lasted until the present time, indeed so strong that in 2008 I moved all my research to three laboratories there, mainly because it was no longer feasible to study our particular pathogens in the midst of a patient environment in the hospital where I am permanently based. In 1988, I was very fortunate to meet Max Murray who was Head of the Veterinary Medicine department; we started collaborative work on the mouse model of trypanosomiasis that had been developed by Frank Jennings and mirrored the key brain pathology seen in human African trypanosomiasis (sleeping sickness). Max and I started a trypanosomiasis neuropathogenesis research group that has flourished until the present time, and we have remained close friends and colleagues. I have been very fortunate to have had Max as a mentor for my entire senior career. With gifted scientist Jean Rodgers and expert animal technician Barbara Bradley, as well as a succession of research assistants, the group has published several discoveries in this model that have much relevance to the human disease (Kennedy, 2004, 2007; Rodgers *et al.*, 2009, 2011).

Most recently, we have developed an oral form of the highly toxic intravenous melarsoprol for late-stage sleeping sickness (Rodgers *et al.*, 2011). This drug is a melarsoprol-cyclodextrin inclusion complex ("complexed melarsoprol") that has already been approved as an orphan drug by both the European Medical Agency (EMA) and the US FDA for the treatment of human African trypanosome infections, and it will, we hope, soon be trialed in human patients in the African field. That would happen if it worked to be a very good example of the "bench to bedside" ideal. I also collaborated closely with Ian Griffiths of the Veterinary Surgery department who was a peripheral nerve and demyelinating disease specialist and who proved to be a delightful and highly productive colleague (Schneider *et al.*, 1992). His particular interest was in the "rumpshaker" mutant demyelinating animal model (Mitchell *et al.*, 1992). When interviewed by the Riley committee, which at one stage was attempting to close down the Glasgow Veterinary school, it was put across to me that I was sounding as if my research would hardly exist in the absence of the Glasgow Veterinary School. My answer to this question was a simple "Yes that's correct." That still remains the case.

One hears a lot these days about the so-called "work/life balance." During the first few years of my position, I certainly didn't manage to get this right and worked ridiculously long hours to get through the administrative and clinical workload at the expense of spending time with my wife and two young children and being as productive as I should have been in research. I suspect I am one of the few University employees who has received a friendly but firm letter from their Principal telling them to cut down their working hours because of fears about the physical consequences, and it's surprisingly easy to become too thin from missing regular meals. The problem was mitigated by my listening to and acting on such well-meaning advice, saying No to unreasonable demands more frequently, and spending a year (1993–4) on sabbatical in the United States.

As a young scholar-in-residence at the International Fogarty Center at the National Institutes of Health (NIH) in Bethesda, Maryland, where I had a spacious office in the

historic Stonehouse building, I was able to focus full-time on laboratory research. This was carried out in Stephen Strauss's medical virology lab in NIAID for the first 6 months and then in Eugene Major's molecular neurovirology lab in NINDS during the second 6 month period. The main effort was in VZV research where all of us collaborated to demonstrate downregulation of GFAP in human astrocytes after exposure to a vaccine strain of VZV (Kennedy *et al.*, 1994), and it was a pleasure to be able to do virtually all the lab work myself. I was involved in a number of other projects and, most significantly, met up with a fellow scholar called Susan Leeman who was, and indeed still is, a famous and highly productive pharmacologist at Boston University who had previously determined the amino-acid sequence of the neuropeptides Substance P (SP) and neurokinin. We set up a collaboration to test an antagonist to SP in our trypanosomiasis mouse model, and after 3 years of work we were able to report the amelioration of an experimental post-treatment reactive encephalopathy after treatment of an SP antagonist, a result that directly implicated SP as one of the key determinants of the observed neuroinflammation (Kennedy *et al.*, 1997).

Further collaborative work followed later, also in Glasgow, using SP receptor knockout mice that, after infection with trypanosomes, demonstrated an unexpected phenotype with a dissociation between the clinical and neuroinflammatory response, both of which we could quantitate using grading scales that we had developed. We showed that the phenotype was mediated by alternative tachykinin usage (Kennedy *et al.*, 2003). It is very sad to mention that Steve Strauss, a brilliant, charming, and erudite man, died tragically young when barely 60 years old about 10 years ago. My friendship with Gene Major has continued unabated until the present time. A further recent loss, quite terrible in its effect on his family, friend, and colleagues, was that of the brilliant and kind statistician George Gettinby of Stathclyde University, who had helped us so much with the sometimes complex statistical analyses required in our animal model system. If ever I needed to be reminded of the sheer fragility of life, then it was George's untimely death last year.

After a year of pure research activity, and the luxury of actually seeing and talking with my young son and daughter, it was somewhat difficult to readjust to the life of a clinician-scientist again after I returned to Glasgow. But we managed to recruit some more scientific staff and with a little difficulty managed to keep the grant income at a viable level. I continued to focus on VZV latency in human ganglia and with the aid of Esther Grinfeld, a rigorous and talented scientist whom I had recruited, we showed unambiguously that latent VZV resided predominantly in neurons (Kennedy *et al.*, 1998), thereby ending a vigorous debate that had raged for a decade. Esther was my right-hand person in the neurovirology lab for about 14 years and we published several solid papers together, particularly focusing on VZV gene expression in ganglia (Kennedy *et al.*, 2000; Cohrs *et al.*, 2003), working out at the rate of about one per year (which soon add up!). This work involved close collaboration with Don Gilden and Randall Cohrs, our masterly VZV colleagues from the University of Colorado. The work on trypanosomiasis also continued and indeed has now become my more dominant research interest, indeed passion, interspersed with many annual visits to the African field where I saw the tragic cases of sleeping sickness at first hand. For the first decade, these were carried out in rural Kenya with our fine

colleague and friend Joseph Ndung'u who has made so many important contributions to the field of neglected tropical diseases. My visits to the African field since 2002 have been mainly with my good colleague Jeremy Sternberg of Aberdeen University, and we focus now on Ugandan cases of sleeping sickness (MacLean *et al.*, 2010, 2012). I also wrote a popular science book on sleeping sickness (Kennedy, 2007) based on these experiences, which seems to have been well received, and I developed a genuine liking, indeed passion, for increasing the public understanding of science. These days, I think it is even more important than earlier to communicate scientific ideas and discoveries to the nonspecialist public, and indeed this is becoming increasingly recognized as of crucial importance by higher educational institutions and the research funding agencies worldwide.

If I were advising a young doctor on the merits and perils of becoming a clinician-scientist, the first thing I would do is try and judge his or her level of enthusiasm for doing science and medicine for the rest of their lives. Without that innate desire, indeed passion, it probably isn't worth pursuing this path. Then I would advise them to spend about 3 years in a leading basic science laboratory with a wise and sympathetic supervisor, preferably after completing some general medical training but probably before their specialist clinical residency. It is also very important to work on a scientific problem that is likely to be significant. It would be advantageous to do this doctoral work with the support, if possible, of a prestigious research training fellowship such as from the MRC or the Wellcome Trust. Then, it's important to do post-doctoral work and to realize that obtaining a PhD or a research MD degree doesn't make you a scientist. I see it more similar to having passed one's driving test in that the real learning develops after that. And it is vital these days to have a good understanding of molecular biological techniques and when and how they should be used.

It is critical to obtain a first-rate clinical training, one that preferably allows you to keep in touch with a relevant research laboratory. It should be appreciated, however, that certainly in the United Kingdom the prospects for a clinical academic career have improved considerably over the past decade because of structured new training pathways that allow an integrated clinical and research training over several years. Both the academic foundation programs and the academic clinical fellowship schemes now provide a better prospect of a successful future career as a clinician-scientist than was possible when I was a young trainee. Already I can see a real difference and an expansion of interest in clinical academia and also the numbers of committed and talented young clinician-scientists, which augers well for the future. After all this training, I think it should be pretty clear whether an academic medical career is really the best option. If so, then an academic position such as a lectureship in the United Kingdom or an assistant professorship in the United States can be sought to have a chance of becoming a successful and, importantly, an authentic clinician-scientist. Thereafter, it will be essential to recruit committed basic scientists to your research team to be continuously productive, and, critically, to collaborate with other clinical and basic scientists in cognate areas. I also don't think it is a crime to be unorthodox in one's approach to training. I well recall Professor Roger Gilliatt telling me with a twinkle in his eye at an interview for the National Hospital that he couldn't fail to notice that I was doing my neurological training backward! And, finally, don't forget to say No.

Disclosure Statement

No competing financial interests exist.

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Received for publication February 24, 2015; accepted February 24, 2015.