The road less travelled...

Ashley Grossman

Oxford Centre for Diabetes, Endocrinology and Metabolism,
Churchill Hospital, University of Oxford, Oxford OX3 7LE, UK

(Correspondence should be addressed to A Grossman;
Email: ashley.grossman@ocdem.ox.ac.uk)

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‘Regrets, I’ve had a few, but then again, too few to mention’

In the autumn of 1969 I went for an interview at St Bartholomew’s Hospital Medical School, having recently graduated in Psychology and Social Anthropology from Bedford and Birkbeck Colleges at the University of London. Having been asked if any of my family had been doctors, my father (no), grandfather (no), anyone? (no), I was sent a short note rejecting my application. So fired was I by the perceived unfairness of this rejection that I applied to several other medical schools, having not previously been all that keen on studying Medicine anyway. University College Hospital Medical School (UCHMS) sent me a letter saying I was on their waiting list as they were awaiting the ‘A’ level results that year, but I phoned them and said I really couldn’t wait around for these results so could they kindly give me an immediate answer. To my surprise they said, yes, and so I ‘fell’ into medicine. Not that I had never thought about it. My grandparents had come to the UK from Poland, Russia and the Ukraine at the end of the 19th century, and I had thought about becoming a doctor at the age of 8, and of being the first person in my family to enter university. I had applied from school in North London to Cambridge to study Medicine, been accepted, and then switched at the last minute with an Open Exhibition to St Catharine’s in Natural Sciences. I then left after a few months as my father had died and I felt compelled to live in London, and then changed yet again to Psychology at the only colleges in London which had places mid-term. I was not very good at that age at taking decisions.

But after 3 months at UCHMS I realised that there was nothing else in life I would rather do than practise as a physician. After 2 years’ pre-clinical I then spent a glorious year under the great J Z Young, who ran the intercalated degrees in the Anatomy Department (quite a novel concept at the time), funded by an MRC bursary; ‘J Z’ had infinite patience with low-level pre-clinical students such as ourselves, and I still remember him going through an essay I wrote line-by-line. He was a great expert on the octopus, especially the octopus nervous system, and each year he would take a class load of his students to the marine laboratory in Naples to research the learning ability of the octopus – and to have fun. As we had a particularly large group of students that year, we drew straws to decide who had to stay behind; I drew the short straw that year, literally, and spent the vacation taking and developing photographs on glass slides of Golgi-stained rat brain nuclei. What I lost from the visit to Italy, I gained by the thrill of doing fundamental research, using a most aesthetically beautiful technique, and feeling I was the first person ever to see the visual pathways in the lateral geniculate nucleus. I was also sustained by my supervisor, Bob Lieberman. Bob was a wonderful role model for the love of research and pure boyish enthusiasm, and but for the fact that I had now finally decided that I wanted to be a ‘real doctor’ I would have stayed on at UCL for a PhD.

At this stage I had the fanciful idea of becoming a (neuro)psychiatrist; so, after house jobs at St Thomas and then as Registrar in Chest Medicine (in those days one could simply miss out grades of training if one was lucky!), I went to the National Hospital in Neurology and Neurosurgery in Queen Square to pick up some

neurology, but I decided that brain hard-wiring was more to my taste than psychiatric 'software'. I then had the quixotic idea that perhaps a little neuroendocrinology would help my neurology training. I had read some fascinating articles by Michael Besser and Lesley Rees, so I just rang up Barts and asked whether I could come along and work for a while, and oddly they just said yes – and with a salary! That was the beginning of the end of my career in neurology: when I subsequently applied for an MRC Training Fellowship, Mike Besser crossed off my career intention as 'Neurology' and wrote down 'Endocrinology', and for me the rest was history. I stayed at Barts for the next 33 years, rising to replace the outstanding previous lecturers such as Mike Thorner and John Wass, becoming a 'New Blood' MRC Senior Lecturer and then to a personal Chair. Whenever I was tempted to work elsewhere, I just looked at the wonderful variety of patients with neuroendocrine disease that Mike Besser had amassed, and it seemed that nowhere else at that time would have allowed me to study such a fascinating group of patients. It particularly allowed me over time to become fascinated by Cushing's syndrome, a lifelong interest, and work very fruitfully with John Newell-Price on adults, and later with Martin Savage and Helen Storr on paediatric Cushing's.

My first area of clinical research involved the opioid peptides, or endorphins, and their involvement in the control of hormones. I recall Mike Besser saying that 'everyone knew' that morphine stimulated vasopressin release, so could I use a synthetic opioid peptide to demonstrate this in normal volunteers. All I would need to do was produce a constant diuresis by water-loading normal volunteers, i.e. medical students, and watch for the drug to stop the urine flow. Well, after four or five medical students failed to show any anti-diuresis I was getting rather fed up, when one morning a medical student arrived clearly in a pretty poor state with a bad hangover and looking much the worse for wear. Still, he needed the money, so we dutifully tried to water load him but he remained grossly dehydrated; but with the enkephalin analogue he started a water *diuresis*! Opioids clearly *inhibit* vasopressin release, and without this hungover student we would never have realised this. I subsequently went on to use the 'gold standard' test of vasopressin release, a hypertonic saline infusion, with Peter Baylis to prove this conclusively. If you ever want to know what it is like to feel thirsty, I advise you to try this investigation! Following on from this, I used naloxone as a probe for endogenous opioid tone in the human, showing a phasic and tonic control of the sympathetic nervous system and the pituitary–adrenal axis respectively, and

speculating that 'adrenaline junkies' were actually addicted to their endorphins rather than adrenaline. On a more pathological note, I was certain that I could show that the amenorrhoea of anorexia nervosa was due to excessive opioid inhibition, using hyperprolactinaemic amenorrhoea as the control: I was wrong, it was the hyperprolactinaemia that caused inhibition of GnRH release via hypothalamic endorphins. Yet again, it was through an error that serendipity revealed the truth; I learnt to (almost) always learn from my (frequent) mistakes.

So keen was I and ambitious that when the sequence of the hypothalamic ACTH-releasing hormone corticotrophin-releasing hormone (CRH) was discovered by Wylie Vale (who sadly died recently) I volunteered to be the first person in the world to have the synthetic peptide infused into me. Previously, TRH, GnRH and somatostatin had been given to volunteers by Mike Besser and Reg Hall, but CRH was a very large peptide with an unclear safety profile. I suspect the clear stimulation of ACTH and cortisol seen after the first infusion was partly related to my apprehension: learning point, always get a blinded control. We went on from that Lancet paper to get our hands on the next-described hypothalamic peptide, GHRH, and dashed to get out a paper on the use of GHRH to show that most children with growth hormone deficiency, in fact, had a hypothalamic defect. We managed to squeeze that into the same issue of the Lancet as a much fuller description by Michael Thorner and his colleagues in Charlottesville. Richard Ross then went on to show its therapeutic potential.

Clinical research was so easy in those days. A submission to the Ethics Committee took a few days or at most weeks, compared with the months or years needed nowadays. Blood samples were often 'routed' through the routine labs on the basis of 'knock-for-knock'. This system was based on the fact that university clinical academics were paid a full-time university salary and therefore saw patients for the NHS free of charge. In return, we were entitled to use some NHS facilities for research. The system worked well, there was zero bureaucracy, and everyone seemed to benefit, although at one point I was a little concerned that I was using up the entire NHS stock of naloxone for my studies! Of course, this is now a faraway land; everything is now monetarised, teams of accountants comb through every expense, and whole departments are in charge of watching these artificial money flows.

At the same time, I was carrying out our perfusion studies on the pituitary, using rat and human pituitaries in a tiny lab adjacent to our endocrine ward. We had to

bring the animals up in the patients' lifts, and cough whenever the covered cages let out a little squeak. This relatively crude technique allowed for a surprisingly sophisticated study of the hypothalamic regulation of the pituitary, and we were able to prove Macleod's theory that dopamine was actually a hypothalamic regulator and that bromocriptine acted directly on human lactotrophs. One has to imagine what an almost miraculous breakthrough it was to find that dopamine agonists could actually cause prolactinomas to get smaller, simple tablets drugs shrinking true tumours: indeed, the blind could start to see. With the ideas and help of Phil Lowry and Glenda Gillies, I was able to study human corticotroph tumours and show the importance of two releasing factors, one then unknown (now realised to be CRH) and vasopressin. Even today, the importance of vasopressin as a synergising factor for ACTH release is under-recognised. However, inevitably my interest tracked up the portal blood vessels and a very talented visiting fellow, Ana-Maria Lengyel from Brazil, was able to adapt a system (originally devised by Morton Jones) for studying hypothalamic hormone secretion. It was all a bit Heath Robinson but worked surprisingly well. We were able to study the neuroamine and neurotransmitter regulation of hypothalamic function, could see how immune-related peptides such as the interleukins could activate the hypothalamic ACTH-releasing peptides and the thus the hypothalamo-pituitary-adrenal (HPA) axis, and could model how the immune system could 'talk to' the neuroendocrine system in acute illness. We went on to investigate the modulation of hypothalamic function by gaseous neurotransmitters such as nitric oxide (NO) and carbon monoxide. My co-worker at this time, Pierluigi Navarra from Rome, expanded this work when back in Rome and got his group the sobriquet 'The Gas Board'. At a subsequent 6-month sabbatical in Seattle with Bob Steiner we (my good friend in Washington state was Winfried Rossmanith, a gynaecologist who preferred research...) were able to show GnRH neurons surrounded by a network of NO neurons, which we imagined sending out little puffs of NO to modulate GnRH release. In addition, we speculated that the carbon monoxide regulation of vasopressin could be dysregulated in disorders of haem synthesis such as acute porphyria variegata, and thus explain the intermittent SIADH and hypertension characteristic of this condition.

My sabbatical in Seattle also allowed me to get some hands-on experience of what was then the burgeoning new science of molecular biology. While never very adroit at experimental procedures (I was quite good at giving mouth-to-mouth to expiring female rats,

though), the period away from home was ideal to think about the new molecular science. My family came with me, and we rented a lovely little house overlooking Puget Sound on one side, and the Cascade mountains on the other: one of the happiest times of my life was cycling in a T-shirt and shorts to the Medical Centre every morning, no bleep, no mobile phones then, and the pungent smell of *Starbucks* as I entered the hospital. Bob Steiner was an enthusiastic scientist and a keen kayak expert and hiker. If we looked out of the lab window and we could see 'The Mountain' (Mt. Rainier) through the mist and rain, everyone stopped what they were doing and went out hiking.

Returning to Barts I was extraordinarily fortunate to come across Marta Korbonits, a young researcher who had no plans to stay in the UK until her husband decided he was leaving the BBC World Service and was not going back to Hungary. Marta had started some clinical studies with Peter Trainer, and then over the years we developed a laboratory with a particular interest in the molecular pathogenesis of pituitary tumours, originally stimulated by my enthusiastic and very bright Brazilian research fellow, Patricia Dahia. I gradually moved from my initial interest in hypothalamic function to molecular oncology, which has become my major interest to the current day. Marta originally saw the importance of ghrelin when it was first identified (we still seem to pronounce it differently to the rest of the world!), and then with the discovery of the importance of AIP she has become an international authority in this area. I am proud to have been in at the early stages of her career, and maybe having played a small part in developing her interest.

The ability to learn from each and every patient should never be underestimated. A delightful paediatrician, David Grant, passed to my care a family of young adults in which two of three siblings were glucocorticoid deficient without any evidence of mineralocorticoid deficiency. The parents were normal, and clearly we were looking at an autosomal recessive condition. I recall flying home from a meeting in Germany and opening *Science* to see that Roger Cone had sequenced the ACTH receptor, now known as MCR-2. I rushed round to Adrian Clark on my return, and we realised that a mutation of this receptor could be a possible cause of the condition; the receptor was sequenced, the mutation confirmed, and a quick phone call to The Lancet established publication. Even one important patient can teach one a huge amount.

Which brings me to one of the most important facets of my career, which has been to work with, supervise, learn from and encourage so many younger scientists

from all over the world. It has been an enormous privilege to work with such lovely and talented people from every part of the globe, and to see them return to their home countries and flourish. I recall working with Prof. Ivan Doniach at Barts, 'Do' being a dedicated pathologist and a very kind and humble human being. He first described the pathology of coeliac disease, pointed out the need to suppress TSH in thyroid cancer, and made many other seminal discoveries; but if you asked him what he considered most important in his career, he proudly named all of his trainees who had become professors in their own right. He faced his death from pancreatic cancer with calm equanimity. In academic research one becomes part of a super-family spanning the whole world, every region and every ethnicity. Those of us who have been allowed to spend time as both physicians and helping, in any tiny way, to move forward our discipline are really lucky souls.

My first Greek research fellow was Stylianos, Tsagarakis, and 'Stelios' and his family have remained great friends ever since. Then Gregory Kaltsas joined us from Athens and identified the fact that we had a large number of patients at Barts with neuroendocrine tumours, an area barely studied by endocrinologists. He wrote a magnificent review which stimulated my interest in this area and which remains to this day. Greg was among the most dedicated people I have worked with, and our 'Greek connection' has flourished with other fellows such as Kristallenia Alexandraki.

The more I travel the world, the more I realise that all our problems are related, all doctors face the same challenges, and our patients are all so very similar. If you have Cushing's syndrome in Birmingham, Buenos Aires, Beijing or Beirut, the challenges, the problems, the uncertainties, are the same. It has been a great privilege to work in academic endocrinology, and never have I regretted that strange decision, based on irritation, to make a career in medicine. My more recent career in endocrine oncology has been more challenging, the patients more sick, and the outcome less secure, but the work more pressing.

International links have also allowed me to see a great deal of our beautiful planet, and make some many friends from all over the world. I have had a special interest in the Middle and Near East, travelling to Libya, Algeria, Egypt, Turkey, Israel, Jordan, Lebanon, Kuwait, the UAE, Saudi Arabia and Iran. With the Lesley Turnberg Fund we have sent endocrinologists to Israel and Palestinians to London. I was most proud when President of the ENEA held the biennial meeting in Athens one year, with many Turkish attendees, and then next in Antalya, Turkey, with many Greek participants;

at both, we had a great turnout from many parts of the Middle East and Central Asia. For the past 10 years I have also been able to travel once or twice a year to Tashkent, Uzbekistan, to help develop a pituitary service in the region. Michel Powell from the National Hospital in Queen Square has performed more than 100 operations in Tashkent, and trained many local neurosurgeons in transsphenoidal surgery. Medicine transcends all political, ethnic and religious barriers.

Naples returned to play a part in my life when my long-term colleague John Wass said he was taking early retirement from running the Endocrine Department in Oxford. I intimated to him while looking at a Madonna in a large rococo church in Naples that maybe I could take over; 12 months later I was here in Oxford. We are now building on the base of pituitary expertise to provide a major centre for all forms of endocrine oncology.

Now, as President of the Society for Endocrinology, I see my major ambition to put British endocrinology in general, and the Society for Endocrinology in particular, more firmly at centre-stage in world endocrinology, to help enthuse and support more clinical and basic science trainees, and to reach out more to engage the general public. I still have some more things to do. Only one of my six daughters is a doctor, but I think that is probably enough. My family has certainly always been my support, and I have been grounded by watching my daughters grow and thrive. You can never make up time lost when they are growing, and truly no one ever has written on their grave 'he wished he had spent more time at the office'.

Recently, I discovered the original letter from Barts rejecting me as a medical student. It was signed by the then Dean, with whom I later collaborated to carry out many clinical studies. I never showed him this letter, but I suppose it emphasises the contingency of our lives. Medicine has become heavily bureaucratic, junior doctors face an unending series of paperwork or electronic interrogation almost unequalled in any other profession. Morris Brown struggled valiantly to get our juniors a better deal, but I feel it is an unequal struggle. We have failed our trainees, and sometimes I am very uncertain about our medical future. But whenever I get too pessimistic, I just have to stride onto the ward and see the enthusiastic, intelligent, and talented young doctors, and I become less grumpy and more optimistic. For all the uncertainties past and present, I am sure that the road I travelled was the right one, and our youth will guarantee our future.

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