



Seven year units in science: general lessons from the personal experience of working on adrenal cortex innervation and cortisol secretion

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It seems to me that the learning and practice of science naturally falls into approximately seven year units; and indeed the same could be said about 'life'. (Note: My operational definition of 'seven' is 'more than five but less than ten'.) My academic life has certainly been consistent with this idea; and here I describe the first seven year unit of my work as an active scientist: this was the seven years I spent as a laboratory researcher focused primarily on the adrenal cortex. This unit was successful; in the sense that I solved, to my own satisfaction, the problem I was working-on. There may be some general interest and instruction to be derived from taking this specific example as a generalisable account of the different phases and aspects of an arc of science – how a line of research may be initiated, developed and brought to a conclusion. Furthermore, it is suggested that other scientists might (if it comes naturally to them) consider changing their focus and developing new interests every seven years or so.

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I once wrote an essay about how it seemed to me that the learning and practice of science naturally falls into approximately seven year units; and indeed the same could be said about 'life' (Charlton, 2006).

(My operational definition of 'seven', for the purposes of what follows, is in practise going to be 'more than five years, but less than ten'.)

Why this cycle should happen is a question I will leave aside; but I am far from the only person to notice it: the Jesuits ('give me a child until he is seven, and I will give you the man'), the Austrian spiritual philosopher Rudolf Steiner, and the great Hungarian physicist Leo Szilard are just three who proposed seven year units for life; plus there is the slang phrase of a 'seven year itch' (although more often cynically applied to marriages than to scholarship).

My academic life has certainly been consistent with this idea – and here I will describe the first seven year unit of my life as an active scientist: this was the seven years I spent as a laboratory researcher, working primarily on the adrenal cortex – its structure, control and function. This was a successful section of work in terms of fulfilling its aims; and I made a significant, albeit modest, contribution to understanding.

Of course, one person's experience of one particular line of research is probably of interest only to that one person! But there is a general interest in taking this specific example as a generalisable account of the different phases and aspects of an arc of science – how a line of research may be initiated, developed and brought to a conclusion. Also it illustrates both the validity and the fuzziness and overlapping nature of the seven year concept; such that although there is indeed a seven year unit here, it has a two year 'gap' and also overlaps-with and includes other significant but subordinate lines

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of work.

The phase began with three-plus years studying for my doctorate, and being given the basic problem by my supervisors. As so often, the project arose out of some anomalies in the existing understanding and an idea about how to solve them.

The standard accounts of the adrenal cortex in humans stated that its secretion of the main stress hormone, cortisol, was controlled by ACTH (Adreno-CorticoTrophic Hormone) which came from the anterior pituitary gland, and travelled to the adrenal through the systematic blood supply. Certainly, an ACTH-secreting tumour and injections of ACTH extracts would both increase cortisol levels; and absence of ACTH would lead to cortisol deficiency. But some detailed observations of ACTH and cortisol suggested that in ordinary and unstressed conditions, ACTH and cortisol levels were not closely correlated – that one might be high without the other being high, and vice versa.

Therefore some other factor seemed to be necessary to explain the moment-by-moment control of cortisol secretion – and the main candidate was that nerves to the adrenal cortex could modulate cortisol secretion by some mechanism: perhaps directly, by altering its sensitivity to ACTH or by altering the metabolism of the precursor molecule of ACTH. However, the ruling consensus was that there was no nerve supply to the cortisol-secreting endocrine cells of the adrenal cortex, but only to the adrenal medulla.

In sum, the problem I was given was a seeming contradiction in the literature of cortisol control, my job was to resolve it.

Like many doctoral students. I began by learning some lab techniques - specifically radioimmuno and immunoradiometric assays (RIAs and IRMAs) – which took several months to master; and also arranging to collect blood samples from normal control subjects (including myself – I was using about a pint of my own blood per month to develop the techniques) and from volunteer psychiatric patients.

(I also did measurements of neurotransmitters and their receptors on post-mortem brain tissue extracts, derived from a brain bank including people who had died – usually of natural causes – while suffering from depression.)

My thesis was mostly about looking for hormonal (and neurotransmitter) abnormalities in patients with endogenous depression (Charlton et al, 1987) – but ‘on the side’ I helped someone do 24-hour, every-hourly studies of ACTH and cortisol blood concentrations in normal subjects. This work was never published but the six subjects were enough to confirm, using more modern assays, the older studies that shown a lack of correlation between baseline ACTH and cortisol concentrations at many time-points.

At the time, I was interested by my work - but I was not obsessed by it; and indeed found many other things more interesting. Therefore, when my thesis was finished, I spent two years doing other things: a year researching an English Literature Masters thesis and a further year teaching Physiology (and researching the kidney). Throughout this two year ‘gap’, off-and-on, I mused-on and wrote-about the subject of my thesis (e.g. Charlton & Ferrier, 1989).

The fact that I continued to think about and work on the subject reassured me that I was genuinely self-motivated, and that my adrenal research was not simply a means to an end. So, when I took up a lectureship in Anatomy I returned to working on adrenal control for a further three-and-a-half years – but this time I focused on the adrenal itself rather than the brain and pituitary end of things. I decided to see for myself whether there really were any visualise-able and apparently actively-secreting nerves in the substance of the adrenal cortex.

However, this move out of neuroscience meant that funding dried-up. Having been generously funded for neuroscience research; I wrote five grant applications for adrenal research during 1989-1990, all of which were rejected outright.

My choice was between continuing to follow my spontaneous interest and researching the adrenal without a grant; or else to do some other kind of research which might stand a better chance of getting grant funding. In other words; I had to decide whether to follow my interest, or follow the money!

I made the scientifically-correct decision – and decided to follow my interests. (And indeed I have never written a grant application since.) This decision was possible because I was supported by a few hundred pounds a year available from the department to buy basic reagents, some second-hand apparatus which they also provided, allocations of time from departmental technicians – for example, doing tissue preparations, and collaboration with two undergraduate project students.

My starting point was to write a review and hypothesis paper for a respected specialist journal on the subject of adrenal cortex innervation (Charlton, 1990). I concluded that there ‘must be’ such innervation in humans. The first problem was therefore to get hold of some human adrenal gland tissue. A difficult problem; because the adrenal gland ‘auto-destructs’ and putrefies almost immediately after death; and even before death when there has been a severe illness, pain or stress.

But I had an idea. Due to my experience as a junior doctor and via the synchronicity of having done renal (kidney) research as a physiologist, I had connections with a urological surgeon who could provide snap-frozen human adrenal gland tissue which he removed as a by-product during nephrectomy procedures. Later I teamed-up with a pathologist who was able to get a small number of post-mortem adrenals in suitable condition from that small minority of people who died ‘instantaneously’ and without terminal stress (for example, in road traffic accidents), and whose autopsies were done very soon after death.

Visualising the innervation involved my retraining in a new set of techniques of microscopic anatomy, including the detection of nerves by a variety of chemical and immunochemical staining methods.

Over the next few years, with various collaborators, I discovered dense, three-dimensional networks of (apparently) locally-active general innervation in the glandular tissues of the human adrenal cortex; and both acetylcholine-containing (cholinergic) and noradrenaline containing (noradrenergic) nerves in the cortex (McNicol et al, 1994). In the end, I concluded that the cholinergic nerves were merely passing-through the cortex on the way to causing adrenaline release in the adrenal medulla; but the noradrenergic nerves seem to be releasing into the substance of the cortex of the gland, where they might plausibly be controlling fine, moment-by-moment cortisol release – with ACTH operating only as a coarse control of large scale hormone release, for example in emergency stresses (Gilchrist et al, 1993).

Therefore, I had (to my own satisfaction) found the elusive adrenal cortex innervation, and identified it as noradrenergic in nature (Charlton, 1995).

Job done.

Such was the story of the span of my research into adrenal cortex innervation. Since then, these results have been broadly confirmed in the work of others (so far as I can tell), and note of this work was made in the 1995 edition of the textbook-of-record Gray’s Anatomy. However, as I left this field, I also had several unanswered questions which had emerged concerning the structure and evolution of the human adrenal gland – and I could have continued to work in this field; except that my major interests had by this time moved-on. So why did I draw a line under this seven year unit?

From around 1990, I began to get interested in epidemiology and questions of the methods of large statistical studies in medicine – and in 1993 I took up a lectureship in this field and remained actively publishing in it until the late 1990s; but although indeed lasting the usual seven-or-so years, that was not my next major research arc.

What happened was that in the early summer of 1994, in a kind of ‘conversion experience’ which led to my first ‘full-on’ immersion in science, I discovered and read-into the emerging field of Evolutionary

Psychiatry. Natural selection had always been of interest, and now I thought I saw a way of becoming a purely theoretical scientist by combining this with my training in medical science, psychiatry and biology. The specific trigger was firstly seeing an interview with Margie Profet in the popular magazine *Omni*; rapidly followed-up by reading *The Red Queen* by Matt Ridley.

Because, although I had worked in laboratories for seven years and published observational and experimental research – I never much enjoyed the actual ‘hands-on’ bit; it was something I did purely as a means to an end (and because nobody else would do it!); and the ‘end’ in view was thinking and writing theory. Thus, my last act of the adrenal research arc (published a little after the seven year arc was completed) was to write-up a concluding hypothesis paper (i.e. Charlton, 1995; which partly led to my later editing of the theoretical journal in which this was published).

(A primary interest in theory is very rare among biologists, who are mostly averse to thinking hard and for long periods; they much prefer doing stuff, observing, measuring and experimenting – or at least being awarded large grants, buying expensive machines and paying big teams of other-people to do the needful observations, measurements and experiments. I have always supposed that anyone who thought consecutively and in a focused fashion for, say, fifteen minutes had actually done more than 95% of biologists ever would – and anyone who thought for a few days solidly, on the same subject, during a forty year research career, was among a tiny intellectual ultra-elite.)

Anyway, my next approximately seven year unit was from 1994-2001 when I focused on theoretical work concerning the evolutionary psychology of Psychiatry. The unit after that (2001-7) was complex systems theory and its applications; and the one after that (2008-15) was intelligence (IQ), personality and creativity.

(Cutting across these last two, from 2003-2010, was another seven-ish year stint editing the theoretical journal *Medical Hypotheses* – but that was not an arc of personally-motivated scholarship.)

How, then, would I evaluate this ‘adrenal’ period during 1984-93? In terms of scientific quality it was moderately good – useful but not major, solid but not spectacular. In terms of my own attitude and performance, also moderately good. The work was honest, truthful and genuine – however I did not work as hard or as intensely as I would do in later units. I did not, for example, rise early in the morning because I was so eager to begin learning more about the subject, nor did I take scientific books and papers to read in the bath, nor go on long walks while wracking my brains over theoretical problems – all of which I did in later phases.

On the other hand, I was sufficiently engaged that I had a ‘peak experience’ when I made one of the discoveries (Charlton, 2000 – Appendix 2 ‘A personal example’).

Furthermore, I was sufficiently serious about this research to pursue it through my own labours and without grant support; furthermore, I did not – as so many people do – simply stick with or build-on the techniques I happened to have learned during the doctorate; but in following ‘my problem’ I went to the effort of learning several new lab skills and methods (despite that my interest-in and aptitude-at this ‘hands-on’ side of things was no more than ‘enough’).

One advantage I had in those days, was that publication and dissemination of results was not an issue; at least up until the early 1990s. Whenever I had discovered enough to be worth communicating, I could easily publish in one of the relevant non-commercial specialist or ‘scientific society’ journals, either for anatomy or endocrinology. Once published, the research would be read and noticed by the necessary people; supplemented by posting a free ‘offprint’ copy of the paper to any specific individuals I wanted to be sure had noticed it.

‘Peer review’, although rapidly becoming a problem, was at that time still light and respectful – for example the *Journal of Anatomy* only used a single reviewer as a ‘coarse filter’, when members of the Anatomical Society submitted papers. I was also the recipient of considerable kindness and some favours from people in the field: a US scientist sent me, a stranger, some rare and vital noradrenaline-

detecting antibody that he had made – free of charge. The atmosphere in my (somewhat unfashionable) branch of science was therefore genuinely ‘collegial’.

In conclusion, this was a very decent first seven years in science, and one that I can look back on with some satisfaction – aware that it was the tail end of a golden age of real science done by self-motivated and self-regulated individuals (not professionalised, managed and peer-review-regulated teams); an era which modern researchers ought to regard with nostalgia tinged with sadness.

Although I rather ‘wasted’ two years in the middle doing mostly other things, I was also fortunate in that luck was mostly on my side; and the seven years was therefore split between two major phases. Firstly I was given a problem and an approach, learned the field and methods; then made discoveries and published work that confirmed the validity of the problem and clarified what was happening. Then (after a pause) I refined and focused the problem; devised a method of how to address it within time, resource and ability constraints; then successfully followed-through to arrive at a plausible answer and to publish it.

For someone like myself, these seven year spans of work are not just how things happen-to-happen, but also normative units of how best I personally should organise my intellectual life. Because after seven years I do tend to get an ‘itch’: I start getting bored, I feel a need to seek challenges, and I crave the excitement of a new quest. By changing my scholarly focus several times, I have maintained a high level of personal motivation, and avoided most of the pitfalls of ‘careerism’.

This is captured by the ninth of Leo Szilard’s ‘Ten Commandments’ which reads: “Do your work for six years; but in the seventh, go into solitude or among strangers, so that the memory of your friends does not hinder you from being what you have become.” (Cooper, 2014).

As Szilard implies, as often as not it is the expectations and worries of our friends (and colleagues, and employers) that stop us from following our highest scientific and scholarly instincts. So far as career success goes, they are right to advise us to stick to what we know – but ultimately they are wrong, and we ought to try, at least, to accomplish what our hearts are telling us to do.

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