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Retrospective and perspective on the occasion of receiving the SSIBs Distinguished Research Award

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ABSTRACT

Upon receiving this honor from the Society for the Study of Ingestive Behavior, I was asked to reflect on my life and science. The outcome is below.
Last night I asked 2 of my kids who live in the Bay Area what I should do with this piece that I've been asked to write — I had already droned through 8 single spaced pages, and they had turned into an extraordinary and very happy memory lane for me, with vivid images of the people who were in the lab, their contributions to the direction(s) the lab took and their quirks. It was clear that this was going to stretch out to be a book (I'd only arrived at the early 80s in the lab in 8 pages), probably of vital interest only to me. They suggested that I cut the piece into 3 parts – each easy and breezy – that told of my beginnings, with the science as it was, the functional lab and what I thought was novel about it, with the science as it was then, and other parts of academia, as they were for me. 'The big picture, Mom.' Here's my attempt.

1. How come a scientist?

When I was 14 years old, someone in my family – of 2 parents and 2 siblings – asked me what I was going to be when I grew up. I think I'd never considered the possibility that I'd be something else than what I was, and really thought about the question in a somewhat panicked way. My blurted answer was that I was going to be a scientist. It was the only option I saw, because I most definitely did not want to compete with my sister, the artist, or my brother, the musician — they were 7 and 5.5 years older than I and each had a hefty, and admired, head start. I stuck to that through an organic chemistry major at college (one of 10 chemistry majors in a class of 400) and became completely fascinated with the structure of the cholesterol molecule (ring structure called cyclopentanoperhydrophenanthrene, magic when said out loud in the meter of 'this is the forest primeval' — the mother structure of the steroid hormones).

After college, I was urged to go to graduate school in biochemistry at Columbia College of Physicians & Surgeons (P&S) by members of a steroid hormone lab where I'd worked in the summer of my junior year. Again, I thought 'why not?' and spent a year at P&S in 1956–57. I remember a lecture in which the recently-described structure of DNA [1] was cleverly illustrated using a necklace of 'popit' beads to demonstrate unwinding of the double helix. The excitement of that recent insight riveted me. In all though, P&S was horrid for me, because it was the year of Sputnik, and the Government had recognized that we needed to increase our scientific prowess to compete in the Cold War with the Russians — much funding became available for graduate school fellowships, and many (but not I) appropriately took advantage of them. Most of the students were men; many had seen the new funding as a means for further education and good jobs, but not as a means to pursue what their tummies told them they needed for an exciting and fulfilling life-adventure. I was, and am, a romantic and I was very off-put by the matter-of-fact approach many seemed to have toward the new vistas of knowledge that would open to them during this schooling. Moreover, there were 4 women in the program, 3 of them dressed in drab, looking dorky (as librarians used to dress) who seemed to want to fade into the woodwork and make themselves invisible in this time when women were not welcomed with open arms into the workforce. I quit at the end of the year.

A few years later, after a job as a technician running a calcium metabolism lab in New York City, I decided that I really did want to get more learning, but that the only place for me was the (then) Rockefeller Institute. Fantastic, free and highly original science was being done there, and I thought it would be enormous fun to be part of that venture. To be admitted, I had to have an interview with the head of the institute – I'd bought a new suit at a fancy department store for it – but the moment I walked in, the President glanced at my left hand, asked, 'what is that ring on your finger?', and when I said that I was engaged to be married, he said 'I knew it was a waste of time to interview a woman' — and that was the end of the interview. It was not a grand time to be a woman and potentially a mother who wanted to learn and practice the best science.

Peter and I married and went to Boston for a year of fellowship for him, and a year of finding my scientific level of thrall, for me — physiology was it, the level of science that absolutely inflamed me then and will keep me enthralled for the rest of time. No more reactions in test tubes, or tissues in dishes. I was entirely at home

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with the rat and finding out what's going on at the whole animal level — particularly so when things turn out not to be as they were thought to be. It was a fantastic year that finished (simultaneously) with the last corticosterone measurements that completed the 'reset' studies [2], and the birth of our first child. The 'reset' studies used intravenous corticosterone injections and showed that stress-induced corticosterone secretion is under feedback control, although the 'setpoint' for corticosterone increases under conditions of stress, compared to basal values. I adore the ambiguity and challenge of physiology that's best summed up for me by a quote that Gene Yates used from a poem by Robert Frost: "we dance in a circle and suppose, but the secret sits in the middle and knows". I was, and am still, hooked.

A few years later, I went back to school, then with children who were 3 and 1.5 years old, and worked toward a PhD in physiology at Stanford studying the regulation of the hypothalamo-pituitary-adrenal (HPA) axis, again with Gene Yates. During those studies, we found that dexamethasone feedback was saturable, and that certain 'steroid insensitive' stressors could overcome the maximal feedback signal [3], and we also found that rapid steroid feedback was a physiologically meaningful process [4]. It was not comprehensible to me that, when I entered Gene's lab in 1963, the physiological import of glucocorticoid feedback was questioned by some, as was the physiological relevance of the HPA 'reset' with stress that we'd found in Boston. I believed the data from the Boston year entirely and was proud that I'd done the corticosterone analyses for them. Believing data, provided that the methods were reliable, became the way I worked, even when the results did not conform to the (then) current notions of how things were. Pursuing the findings from Stanford occupied the eventual lab at UCSF for many years.

Throughout this time, and then my 2 post-docs (with our 2 kids in Sweden, and another who was added at UCSF) it would have been entirely impossible to keep going without Peter's unequivocal support. He kept pushing me, and eventually he convinced me that I should be an academic rather than the super-technician that I knew would be easier for us all — being a lab member, rather than head, was a situation that I wanted as I thought I'd be able to do science without the additional pressures of time and energy finding funding for the venture. When they were each old enough to be witting, the 3 children joined with Peter in being enormously supportive and great sources of joy and laughter. I'm very lucky, and I am whoever I have become, because of them all.

It was a huge deal having two very different, but equally challenging, lives to waver between — work and home. Frequently, they got mixed up, until I finally realized that priorities had to be flexible and adjusted to the moment at hand. When there was sickness at home work went by the wayside – unless I could convince the kids that they weren't too sick for school – and when a grant application was due that took me away from my usual 'being there' at home — I just hunkered down with a typewriter and said 'yes' or 'no' as seemed appropriate to the input from kid's voices. The eventual understanding, that pragmatic flexibility was essential to the specific moments, relieved a huge amount of guilt — but it took a long time to come.

At work, I needed to know what I could do after my post doc, and was offered by 3 different people, 'bench space and supplies – we like your work Mary, but you don't want to take bread out of a man's mouth', and was scolded by a fellow post-doc for working with a baby at home – it still was not a good time for women academics, whether or not they were mothers with families. During those years, I had the enormous pleasure of collaborating with Mortyn Jones [5] and Takenori Sato [6] on the physiological feedback of corticosterone on ACTH secretion. Peter had my back unwaveringly, and constantly saw (pushed) me through it. Through a variety of maneuvers, I became co-PI on a funded NIH grant, and through subsequent game-playing, became a faculty member at UCSF.

2. The lab

It is the people in it who make a lab, and none of what I am about to describe could have been achieved without the splendid input, imagination, insights and energies of the graduate students, post-docs and technicians who populated the lab for all of the years. Listening to the advice of my biological children, I will not detail their individual contributions — although it's they who determined the successes that we've had. There are several themes that came out of our collective work that I am extremely proud of, and, am pleased to believe has pushed our understanding of the 'secret in the middle'.

2.1. Dogs

In the 70s, it seemed as though the HPA axis might be responding to stressors in an unregulated fashion. Our studies in dogs, showed us that ACTH and corticosteroid responses to stimuli were proportional to the strength of the stimulus, and that the ensuing glucocorticoid response reliably reduced the responses as a function of the amount of glucocorticoids secreted. This was very useful information because, at the time, people wondered whether the HPA axis responded in an all-or-none, open-loop manner, with maximal responses to each stressor that only varied with respect to stimulus duration (reviewed in [7]). Not so uncontrolled after all.

2.2. Stress-induced facilitation of the HPA axis

Logically (we thought) we tested whether stressors that stimulated corticosteroid secretion, would inhibit the subsequent HPA responses to new stressors [8]. Appallingly (to me), they did not! This started another long run by the lab to understand how the glucocorticoid feedback signal was ignored by the HPA axis under conditions of prior stress, when it was so closely listened to if either ACTH or an equivalent amount of corticosterone was injected. It was partly this diminished response to a 'feedback' signal that made the HPA axis appear to function in an open-loop fashion. The 'real' experiments were so often performed after a set-up operation, or a prolonged fast, both of which constituted prior 'stressors' [9]. Although we never uncovered the basis for the answer to this problem (we were still pretty stuck at the hypothalamus and pituitary; [10], but see [11]), I believe it has been beautifully solved by others [12–16]. These groups have unequivocally demonstrated that whereas glucocorticoids not only inhibit the HPA axis at the hypothalamic/pituitary level, they also stimulate corticotropin-releasing factor (CRF) synthesis and secretion from the amygdala. In turn, the emotional brain, through secretion of CRF, greatly amplifies the stress (fear) signal to the hypothalamus and orchestrates appropriate behavioral responses.

2.3. Fast feedback

We continued to do experiments that demonstrated 'fast' feedback of secreted corticosteroids which occurred within minutes of a stressor that damped the magnitude and duration of the ACTH, and subsequent corticosteroid response [17–21]. These results lay fallow and were not picked up by others for nearly 4 decades, because, at the same time, nuclear hormone receptors and the wonderful things they do to regulate transcription and translation of RNA and protein were discovered. Our results did not fit into the common high enthusiasm and wisdom about how steroids work in the cell, and they languished. It is clear now that the steroid hormones have many temporal windows in which they achieve their effects, and, I think there's good evidence that many of the key actions of hormones on brain and behavior are initiated by their rapid, membrane-associated actions [22].