The History of Neuroscience in Autobiography
Volume 13

Edited by Thomas D. Albright and Larry R. Squire
Published by Society for Neuroscience
ISBN: 978-0-916110-12-3

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pp. 0–53

https://doi.org/10.1523/hon.013001

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Elected Fellow, British Academy Medical Science (2007)
Yngve Zotterman Prize, Stockholm Physiological Society (2007)
Elected Fellow, American Association for the Advancement of Science (2009)
Joseph Erlanger Lecture, American Physiological Society (2010)
Member (Chevalier) French Order of Merit (2011)
Founder's Award, American Academy of Pain Medicine (2013)
NIH Director's Lecture, (2016)
Reeve-Irvine Medal and Prize for Spinal Cord Injury and Pain Research (2017)
Thomas Willis Lecture, Oxford, UK (2017)
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Fellow, American Society of Regional Anesthesia and Pain Medicine (2023)
Elected, Council Member of the Neuroscience Section of the AAAS (2024)
Mentor of the Year Award, NIH HEAL PURPOSE Initiative (2024)
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Allan Basbaum's research takes a multidisciplinary approach to study peripheral (sensory neuron) and central nervous system (spinal cord) mechanisms that process pain and itch messages, including the neurochemical and neuroimmune mechanisms that generate and control chronic pain after tissue or nerve injury. Recently, using calcium imaging, his laboratory developed methods to monitor spinal cord neurons, long term in the awake, behaving animal. The laboratory also turned its attention to cortical mechanisms of pain processing, including the action of existing and novel general anesthetics. In collaboration with UCSF colleagues who use in silico screening, his laboratory discovered several novel analgesics with excellent therapeutic windows.

Allan Irwin Basbaum

The Origin of Serendipity

While on sabbatical in France in 1985, in the middle of a research study, I was commenting on a really interesting and unexpected finding of a technician in the Parisian laboratory of Jean-Marie Besson, a giant in the pain research field. As I grew up in Montreal, and am a Francophile, I have a reasonable command of the French language. I told the technician that her discovery was really interesting, thanks in part to *serendipité*, namely serendipity. I assumed that serendipity was a cognate, readily understood in many languages, but all that I received was a blank stare. The technician who made the discovery had no idea what serendipité meant; no surprise, as it is not a French word. I looked up the origin of the word and learned that it derives from Farsi, was coined in 1754 by Horace Walpole, and is based on the Persian story of *The Three Princes of Serendip*, who routinely made accidental good fortune findings. Nevertheless, serendipity, regardless of its origin, has affected my career many, many times.

I will introduce serendipity to this autobiography by talking about a memorable teaching experience as a new faculty member at University of California, San Francisco (UCSF), an experience that allows me to explain why I am distributing poems throughout this piece. The teaching experience was indeed memorable, but not in a particularly positive way. My first lecture assignment for the UCSF medical students was on spinal cord reflexes, a lecture previously given by Howard Fields, with whom I had completed a postdoc after returning to the United States from London (see "Science with Howard Fields"). I looked at Howard's existing syllabus and considered it remarkably thin. So I completely rewrote it, filling in many details, not limiting the lecture to Ia afferents, and to alpha and gamma motoneurons. I added information about gamma trails and gamma plates, and so on. When I showed it to Howard, he immediately said, "Much too much," but I ignored him. Howard was right; the lecture did not go well. Halfway through the lecture several students interrupted me and asked whether this level of detail was necessary; whether gamma trails and plates are really clinically relevant; and, of course, whether the details would be on the exam. Not surprisingly perhaps, my first teaching evaluations were not encouraging. Particularly painful was the following comment: "Dr. Basbaum seems to be pretty smart, but maybe he should be doing something different."

Well, serendipity stepped in the following year. First, I revised the syllabus, returning it closer to Howard's. But for reasons that I cannot recall, the night before the lecture, I wrote a short poem summarizing key features of the lecture, and read it at the end of the lecture. The poem clearly improved

my reviews, but hopefully, how I adjusted the lecture also helped. Being an entertaining lecturer should never be sufficient. A second short poem on polysynaptic reflexes followed, after which the students expected poems for all of my lectures. So, in this autobiography, I take the opportunity to put them together, sadly for lectures that are no longer assigned to me. Now I only give the pain lecture, and it has been reduced from 4 to 1.5 hours. Perhaps pain is not particularly important in a medical school curriculum.

> **Ode to Spinal Cord Reflexes, with Apologies to Supraspinal Control**
> Of motoneuron activation I have often inquired,
> While preparing the spinal reflex lecture at home by the fire.
> Can feedback alone maintain muscle tone,
> Or is the system controlled from up higher?
>
> I listed with burning desire,
> As the muscles responded with ire.
> You must be insane, if you think the brain
> Is in every stretch reflex required.
>
> Gamma motoneurons, you see, are inspired,
> To maintain the tone that's desired.
> When the spindle pole muscles contract, So the Ia's react,
> And the alpha motoneurons continue to fire.
>
> Thus, contraction's sustained,
> Without help from the brain.
> And one has the tone that's desired.

The second hour of the lecture turned to polysynaptic reflexes, emphasizing the evolutionary significance of a simple polysynaptic circuit:

> **On the Crossed Extensor Reflex**
> If you contract your ipsilateral extensors when you step on a pin,
> Without the crossed extensor reflex,
> Imagine how deep that the pin would go in!

And to summarize the second half of the lecture, which covered polysynaptic reflexes:

> **Beyond the Monosynaptic Reflex: Timing Is Everything**
> This lecture on spinal cord reflexes, I agree, was far too didactic.
> So to read you a poem would be anticlimactic.
> I need some more time to dream up a new tactic.
> Of course, it always takes longer when it's polysynaptic.

Growing Up in Montreal

I was born in Montreal, suffice it to say, years ago. My grandparents, Sophie and David on my mother's side, and Anna and Nija (a nickname) on my father's side, were born in Europe and came to Canada at the turn of the 20th century. Both my mother (Freda) and my father (Ben) were born in Montreal. Of the four children in our family, two of my siblings, an older brother, Mel, and a younger sister, Eleanor (Chava), sadly died several years ago. The youngest of my siblings is Nissa. Her very interesting life story is recounted later in this piece. Neither of my parents attended college (my mother couldn't even complete high school because of diphtheria), but they were very strong proponents of a strong education. The high school system in Montreal was divided on religious grounds, with both Catholic and Protestant schools, as well as some that taught in French and others in English. I attended an English Protestant school, but French lessons began in the third grade, and I took to the language quickly.

I thoroughly enjoyed learning and speaking French, which undoubtedly contributed to the decision to send my kids to a French bilingual school in San Francisco. Although we moved around a lot in Montreal while I was growing up, we finally settled down in the Western part of the city, and I attended a large high school, with more than 2,000 students. But, West Hill High School, with well over 35 students in every class, did provide a great preparation for college. Compared with costs in the United States, university in Canada is inexpensive, and it was traditional for students in Montreal to attend McGill. Of course, this is also very different from the more common tradition in the United States, where students can't wait to leave home for college. I lived at home during my first three years at McGill, and only lived near the campus in my senior year.

We were raised in what could be called an Orthodox Jewish family, with a kosher home, but religion was not a particularly strong influence on my life. In contrast, religion definitely influenced Nissa's life. After attending journalism school at Carlton University in Ottawa, she moved to Newfoundland, where she ran a newspaper. Nissa prefers that I not constantly retell my story about how I learned that she had converted to the Anglican church, but for posterity here goes. I received a call from Nissa, perhaps 40 years ago, while she was in Newfoundland. She said that she had some very important and certainly unexpected news to tell me, that she found Christ. "In Newfoundland!?" I asked. "Who would have guessed?" It's not funny, she quickly replied.

Indeed, it was not. After studying in London and Northern Ireland, but wanting to be ordained, something that at that time, for a woman, was not possible in the UK, she returned to Canada. She attended the University of Toronto, where she met Robin, also an Anglican priest, and they have two children, Rebecca and Ben. After serving as the parish priest in Oakville and then Niagara on the Lake (both in Ontario), she was appointed dean

of the Cathedral in Kelowna, British Columbia. One of my favorite stories occurred when Nissa and Robin visited us in San Francisco, when the 1989 earthquake hit. They were driving downtown and the car started shaking; they initially thought there was a problem with the car. But when they saw bricks falling from some buildings, they realized what had happened. Robin's memorable line was that "there will be a great sermon coming from this experience." I am certain that there was. Very sadly, as I am writing this piece, Nissa and Robin had to abandon their home in Kelowna, because of uncontrolled wildfires.

McGill and Expo 1967

The earliest example of serendipity influencing my career path occurred when I was an undergraduate at McGill University. It was the summer of 1967 and I applied for a position at Expo '67, the World's Fair. I was on the waiting list to be a guide at the Australian Pavilion, a dream summer job. Unfortunately, time was running out, so instead I answered an ad for a summer research technician position in the laboratory of the renowned pain researcher, Ronald Melzack, a professor in the Psychology Department at McGill, an amazing place that included D. O. Hebb of Hebbian synapse fame. I had taken Melzack's undergraduate course on motivation, but I knew little to nothing of the pain research ongoing in his lab. I accepted the position, and one week later heard that the Expo '67 position was mine. I seriously considered switching, but my father convinced me that having accepted the Melzack offer, I should stay the course. I listened to my father, a decision that profoundly influenced my career in research. Timing of the Melzack position relative to the Expo '67 offer was truly serendipitous.

Interestingly, although my experience with Melzack continued through my senior year at McGill, it never led to a joint publication. However, that interaction definitely introduced me to the complexity of the pain experience. More important, perhaps, the study in which I was involved probably triggered my longstanding interest in the descending control systems through which the brain regulates the transmission of "pain" messages at the level of the spinal cord. Two years before, in 1965, Melzack and Wall published their now-famous Gate Control Theory of Pain (Melzack and Wall, 1965). Most of the model focused on circuits in the dorsal horn through which large- and small-diameter afferent fibers regulate the flow of information in the dorsal horn, information that underlies a pain experience provoked by an injury. Largely ignored, however, is that the model also included a Central Control Trigger (CCT), namely a pathway from the spinal cord to the brain that engages supraspinal circuits that, in turn, descend to and control spinal cord processing.

What was unusual was that the ascending pathway in the CCT was hypothesized to be via dorsal column axons, which traditionally carry

non-nociceptive (non-pain-provoking) information. My task in the Melzack lab, during that first summer and for a subsequent honors thesis, was to test the model by training food-deprived cats in a classic Pavlovian-type model. A noxious stimulus that normally would provoke paw withdrawal is applied to the paw. If, however, the stimulus is paired with a food reward, then the noxious stimulus becomes a conditioned stimulus. Continual pairing of the food and the noxious stimulus very quickly led to inhibition of the paw withdrawal to the noxious stimulus. Instead, the cat immediately dropped its head to the food delivery device.

My task was to train the cats and then perform dorsal column lesions, which were intended to disrupt the CCT that Gate Control Theory hypothesized underlay the altered behavior of the cat. Sadly, the results did not support the hypothesis, which perhaps explains why I have never published a paper with Melzack. However, I did write an obituary that was published in *Pain* (Basbaum, 2020), an obituary that describes what a remarkable scientist he was, someone who constantly reminded me that nociception and pain are not the same thing. Melzack also wrote Eskimo (not a great word these days) children's stories. As noted in the following sections, it took many years before I actually turned my attention from nociceptive processing to the neurobiology of pain, which, of course, is a cortical percept and thus very different from the circuits, which according to Ron, "merely" carry the information to the brain.

The Move to the University of Pennsylvania

The big question was what to do after graduating from McGill. Medical school was definitely on my mind. But my research experience in the Melzack lab convinced me to apply to the doctoral program in the Psychology Department at Penn. This was a tumultuous time: 1968, which has to be one of the most memorable years in the past century: first flight to the moon; both Martin Luther King Jr. and Robert Kennedy were assassinated; Lyndon Johnson decided not to run for a second term, but his landmark Civil Rights legislation was passed; and a taste of freedom came with the Prague Spring in Czechoslovakia. Vietnam was raging, which unquestionably contributed to the now infamous Democratic Convention at which Hubert Humphrey was nominated to run against Richard Nixon. This was also the year of the Tet Offensive in Vietnam, and to find new soldiers, the lottery was introduction (a form of conscription based on your birthday). As a Canadian, I was not subject to the draft, but pretty much every other Penn graduate student my age was. I remember the day that the newspaper published the list of birthdays, in the order in which individuals would be required to enlist. I looked through the long lists in the middle of the paper, but couldn't find my birthday. So I checked the front page: I was fourth on the list, and were I American in 1968, this autobiography might have been much, much shorter.

Few of my colleagues know that my degree is actually in psychology, perhaps because I did all of my research in the Anatomy Department at Penn. Other than taking many psychology courses in my first year, I really didn't spend much time with the psychology faculty. I did meet Carol Garten, who came to the Psychology Department from Bryn Mawr. By Christmas of the first year at Penn, we were a couple, and at the end of the year, one week after the first moon landing, we were married in Peekskill, NY, where her parents lived and where she grew up.

There is a famous story about our relationship that has been repeated many times, including at Carol's memorial, by her sister Toby. Carol and I were visiting Carol's parents a couple of months before we married. Carol's mother was not someone you could tell an off-color story to, and she was definitely traditional.

We were having lunch, when Carol's mother asked, "Basbaum; isn't that German for some kind of tree?"

"It is," I said.

"What kind of tree?" she asked.

I said that I wasn't certain, but that I thought that Bas meant lilac. "Well, that's interesting," she said. "You know that Carol's last name (Garten) means garden. When you are married, the lilac tree will be in the garden!" Without missing a beat, although regretting my speedy response, I replied, "The lilac tree has already been in the garden!" Carol's mom turned around, walked out, and didn't talk to me for two weeks.

My knee-jerk response to my future mother-in-law about the significance of my last name, as well as my admittedly inappropriate response upon hearing that Nissa had discovered and turned to Christ, is unfortunately, something that I rarely can prevent. I am an inveterate joke teller and punster, and many of the jokes would be considered off-color. I do enjoy provoking laughter and I do have an ability to tell jokes with accents from countries around the world, French (Quebecois and France), Italian, Scottish, German, Yiddish, and so on. Years ago, when I was first appointed chair of the Anatomy Department at UCSF (see "The Move to San Francisco"), a very close faculty member and friend, Gail Martin, pulled me aside and offered the following advice: "You know, Allan. Now that you are chair, you can't tell those jokes anymore; I have my lawyer on speed dial."

Doctoral Research at Penn

I began my doctoral research under the mentorship of Mel Levitt, whose lab was in the Anatomy Department at Penn. Mel studied primate behavior, with a focus on cortical mechanisms that process somatosensory, including pain, information. Unfortunately, Mel did not receive tenure, so he had to leave Penn, at which point I was left without a thesis advisor. That

serendipitously led to the appointment of Eliot Stellar as my doctoral adviser. Eliot, famous for his studies on the neurobiology of feeding behavior, had no research experience in the pain area, but I continued my studies under his mentorship. What is significant is that Eliot started the Institute of Neurological Sciences, which I believe was the first neuroscience program in the country. I was definitely one of the first doctoral students in this program, around the same time that the Society for Neuroscience was formed (1969). Peter Strick, now head of the Neuroscience Program at the University of Pittsburgh, was another graduate student at the birth of that program. Peter and I actually lived in the same small apartment building and shared a wall. Rent was only $96 a month, but the graduate stipend was only $2,400 a year.

Autotomy: A Model of Neuropathic Pain

Although Mel had to leave, one of his observations in primates did influence what proved to be the basis for the second paper that I published. Mel noted that rhesus monkeys would attack their digits after multiple dorsal rhizotomy, which severed all primary afferents in the dorsal roots, completely denervating the limb. The simplest explanation was that the animals were attacking an insensate limb. But I wondered whether a phantom limb–type condition had developed, one associated with an unpleasant, even painful experience that the monkey tried to block. To test this hypothesis, I turned to the rat and performed multiple dorsal rhizotomies, denervating the hindlimb. As in the primate, that surgical procedure led to the rats attacking the denervated hindlimb. The question that I asked was whether unilaterally superimposing different subtotal spinal cord lesions could prevent the biting of the hindpaw that occurred. In other words, could severing a pathway that carries "pain" information to the brain, but does not produce a motor defect, interfere with a phantom limb–like chronic pain condition?

My ability to make lesions of the spinal cord, which was questioned subsequently (see "My First International Association for the Study of Pain Meeting"), is owed to the expertise of two of my amazing Penn mentors, John Liu and William "Bill" Chambers. In fact, a subtotal lesion did prevent the biting of the denervated limb, without producing paralysis. When I presented these results to Fred Kerr, a well-regarded neurosurgeon at a national anatomy meeting, and suggested that this was a "neuropathic pain" condition, I was strongly advised to come up with some other term for the condition. "The clinicians will never buy it," he said. So, the manuscript describing the results only referred to "Disorders produced by multiple dorsal rhizotomy" (Basbaum, 1974). Five years later Pat Wall (see volume 3) and colleagues revisited the phenomenon and gave it the name that persists today: autotomy (Wall et al., 1979).

Multisynaptic Ascending Spinal Cord "Pain" Pathways

With the ability to make spinal cord lesions, my doctoral thesis project turned to a very different question. Traditional textbooks teach that "pain" is transmitted by a straight-through pathway from the spinal cord to the brain, namely through the crossed spinothalamic tract. But I noted that several of the rats in which I performed spinal cord hemisections were still responsive to noxious stimuli applied to the contralateral limb. I wondered through what other routes "pain information" could get to the brain. To address the question, I performed two spaced hemisections, one on each side of the cord, thus cutting all long pathways. Before the surgery the animals were trained to move their head into a light beam to turn off a noxious stimulus to the hindlimb. Using this approach, I found that despite the spaced hemisections, the rats could still respond to a noxious stimulus and concluded that it a multisynaptic system must carry the information in the absence (or perhaps even in the presence) of the long ascending pathways (spinothalamic and spinoreticular).

Only during my postdoc years in London, with Pat Wall, did I meet William (Bill) Noordenbos, the head of neurosurgery in Amsterdam. Most important, after meeting Bill, I learned about his book *Pain*, which was his thesis (Noordenbos, 1959). In this book, Bill wrote about "pain" pathways, and he hypothesized that short, multisynaptic pathways could explain the return of pain after cordotomy, the surgical procedure that supposedly cuts the long ascending spinothalamic and spinoreticular "pain" pathways. Clearly, my thesis studies confirmed, at least in the rat, the Noordenbos hypothesis. But what I also learned subsequently and wrote of recently in an article entitled the "History of Spinal Cord 'Pain' Pathways" (Basbaum, 2022), this conclusion was, in fact, made many, many years before by Austrian scientists, Karplus and Kreidl (1914) who performed the same experiment in cats. That discovery convinced me that I needed to be a better reader of prior literature (difficult as I can't read German literature), but I took some solace in the fact that my findings had been "preconfirmed."

Another study that I performed during graduate school is also worth highlighting, as it not only introduced me to neuroanatomical research but also taught me another important lesson about publishing. With Peter Hand, a superb neuroanatomist in the Veterinary School at Penn, I took advantage of the introduction of the Fink-Heimer method to study anterograde axon terminal degeneration. Previous tracing studies relied on the Marchi method, which only identified areas of demyelinated axons. The Fink-Heimer silver method was an improved Nauta method that could also identify the degenerating terminals of unmyelinated axons. In these studies in rats, I uncovered an unusual projection pattern of primary sensory neurons in the dorsal column nuclei, one that we called "bricks" because of the rectangular pattern of degeneration that we observed (Basbaum and Hand, 1973). Not long after publishing these results in the *Journal of Comparative Neurology*,

I attended an American Association of Anatomy meeting in Dallas and met Aldo Rustioni, a wonderful neuroanatomist and friend from the University of North Carolina. We went to lunch and were discussing spinal cord organization studies, and then Aldo asked if I had seen the very recent publication from Peter Hand. "Yes," I replied, "I was the first author!" That was my introduction to the significance of senior authorship. I try now to be much more attentive to other contributors to a paper's publication.

Of course, the spinal cord has been the major focus of my research, and not surprisingly, I was assigned the lectures on basic spinal cord anatomy and physiology. And following the "success" of my first poem reading to the medical students, they expected a new poem for every subsequent lecture. A poem on the organization of the spinal cord followed. And my graduate student research with Peter Hand, which introduced me to somatosensory neuroanatomy, led years later to a second poem about the homunculus.

Praise the Lord for the Spinal Cord
Funiculi are the columns and fasciculi are the tracts
Which just about covers all the white matter facts.
Via spinal cord pathways, information accesses the brain
So that we all may experience touch, joint position sense, and pain.

In this lecture you learned that if your arm you vibrate
You'd be activating myelinated axons that ascend cuneate.
But, if your penchant is directed at those areas that do thrill us,
You'd be stimulating large fibers that course in gracilis.

Dorsal columns course ipsilateral; spinothalamic tract is crossed.
And after anterolateral cordotomy, pain, and temperature are lost.
From cerebral cortex, the corticospinal tract crosses, creating a complex boulevard.
Which is how a spinal hemisection provokes Le Syndrome Brown-Sequard.

These many ascending and descending pathways are why we cannot afford
To relinquish the functions performed by the cord.
Sure, the brain is important, but the spinal cord's central.
So Come Blow Your Horns, be they dorsal or ventral.
And let us end by rephrasing the words of the Lord
Honor Thy Mother … Don't Cut the Cord!

You Are Only as Sensitive as Your Postcentral Gyrus
Buried in the cortex, in the postcentral gyrus
Is a somatotopic map, of which we can inquire as

To form and to function and overall size
Of the parts of the body from which sensations arise.

The map reflects density of peripheral innervation.
Thus, a distorted homunculus is no aberration.
The map is essential for tactile sensation;
Indeed, there is no perception after S1 ablation.

If you amputate a limb, a phantom persists.
This is no illusion; it really exists.
The eyes say, "Absurd!" but the mind says, "I feel!"
Because it's the map in the brain that makes things seem real.

It has oversized fingers and large luscious lips,
An exaggerated tongue, but no Valkyrian hips.
Unless you're a pig, the nose is quite small;
Some parts of the body are hardly represented at all.
There is only minimal cortex for tendons and bones,
But there's a whole lot of space for erogenous zones.

You see, it may be a body designed from above …
But, it's a body that only your mother could love.

Postdoctoral Fellowship with Pat Wall

After Carol and I received our doctorates at Penn, the question was where to do postdoctoral research. I very much wanted to work in Patrick Wall's lab at University College London, so we made an agreement that Carol would find a postdoc mentor in London (she ended up working with George Gray of Gray's Type I and II synapses), but that she would get to choose the second postdoc. The serendipitous consequence of that arrangement explains how I ended up in San Francisco (see "The Move to San Francisco").

I have often emphasized that my time in Pat Wall's lab at University College London had an enormous impact on my career, not only because of the technical skills that I picked up, but more important, because I also had the opportunity to work with someone who was truly a visionary and creative scientist. Pat and I could be recording from spinal cord neurons in the cat, when we might encounter a neuron with odd response properties. Rather than ignoring the odd neuron and moving on, Pat could completely change direction and aim to figure out what's going on. Getting excited about an unexpected finding, and pursuing its significance, rather than concentrating purely on hypothesis-driven research, I believe, does have an important place in research. Serendipity not only can lead to a change in a research

direction, but also certainly can lead to unexpected breakthroughs. As Ulrike Heberlein told me, despite the preference of most National Institutes of Health (NIH) study sections, she likes to do hypothesis-seeking research.

Following the pioneering collateral sprouting studies of Liu and Chambers (1958), Pat and I asked a question about the extent to which, in the presence of considerable injury, primary afferents can reorganize their connections with spinal cord neurons. Chambers and Liu isolated a single dorsal root (by dorsal rhizotomy of several rostral and caudal roots) and reported extensive sprouting into denervated areas of the dorsal horn, a result that was contentious, and by many, ignored.

Before I arrived in London, in 1972, however, Pat and Gene Merrill published a paper reporting that there are dorsal horn neurons that can be electrically activated from distant dorsal roots, but not by natural stimulation (Merrill and Wall, 1972). They proposed that these neurons normally are innervated by silent synapses. With this background, Pat and I revisited the sprouting question, recording from the spinal cord in a cat in which a single dorsal root had been isolated by rhizotomy, basically the same preparation that revealed collateral sprouting. As predicted, we found that the functional reach of the isolated root had significantly extended. In fact, some dorsal horn neurons now had split receptive fields, receiving input from more rostral, intact afferents, as well as from the sprouting, isolated afferents (Basbaum and Wall, 1976). In many ways, our finding provided a foundation for the remarkable activity and injury-dependent reorganization that Michael Merzenich (see volume 7) and colleagues reported in the somatosensory cortex (Kaas et al., 1983). Of course, Mike has argued that the reorganization involves circuit changes in the cortex itself, rather than influences from changes at spinal cord, brainstem, or thalamic levels.

Beginning to Study Descending Controls

While in the Wall lab, I also initiated a series of studies that in many ways was the introduction to my long-standing research into pain control mechanisms. Three years before I arrived in London, Reynolds (1969) described the analgesic effect of electrical stimulation in the periaqueductal gray (PAG). Particularly striking about his finding was that the analgesia could be produced without motor side effects or effects on food intake. As the analgesia was associated with a decrease of noxious stimulus-evoked reflexes, I decided to study the pathways through which I hypothesized were the PAG-derived descending circuits that generated the pain control. Of course, I had considerable experience making spinal cord lesions, so the study was pretty straightforward: implant stimulating electrodes in the PAG, demonstrate analgesia, and then ask whether subtotal spinal cord lesions could interfere with the pain relief. In a relatively short time, we found that lesions of the dorsolateral funiculus (DLF) of the spinal cord in the rat completely

blocked the pain relief, without introducing motor deficits. Most important, the midthoracic lesions blocked the analgesia when testing hindlimb and tail, but they did not reverse the analgesia of the forelimbs. That important difference ruled out an alternative hypothesis as to the basis of the pain relief. Specifically, as stimulation of the ventrolateral PAG is also rewarding, one proposal was that the reward effectively "masked" the pain that was experienced. Because we could selectively block the pain control of the hindlimbs, preserving that of the forelimbs, it was clear that the analgesia was not secondary to reward (Basbaum et al., 1977).

Morphine and Stimulation-Produced Analgesia

Timing and, of course, more serendipity, I guess, are everything. Around the same time that we were performing these studies and following the discovery of the opioid receptor (Lowney et al., 1974), endorphins were described (Hughes et al., 1975). Subsequently, Huda Akil (see volume 8) and David Mayer in the John Liebeskind lab at University of California, Los Angeles (UCLA) reported that the opioid receptor antagonist, naloxone, not only blocks morphine-induced analgesia but also the analgesia produced by PAG stimulation (Akil et al., 1976). Those observations turned our attention to the circuits through which opiates (notably morphine) exert their analgesic effects. I first asked whether DLF lesions interfered with the analgesia produced by systemic morphine. In fact, bilateral DLF lesions completely reversed the tail-flick blockade produced by systemic doses up to 10 mg/kg. Interestingly, higher doses would reinstate the blockade, almost certainly via a direct action on spinal cord neuronal processing, an observation consistent with the report of Tony Yaksh that spinal administration of opiates can be powerfully analgesic (Yaksh and Rudy, 1976). An interesting sidenote is that our first paper describing these DLF results was coauthored by John O'Keefe, a good friend from my days at McGill and at the time a faculty member with a lab adjacent to Pat Wall's. Years later John won the Nobel Prize for his studies of hippocampal place cells.

Interacting with Patients: Learning from Peter Nathan

Unquestionably, one of the most impactful influences on my career was when Pat Wall introduced me to Peter Nathan, a neurologist at the National Hospital for Neurology and Neurosurgery at Queen's Square in London. Peter was a true Renaissance man. In addition to being a first-rate consulting neurologist who saw a cross section of patients, including among the most difficult chronic pain patients, from throughout the United Kingdom, Peter was also a neuroanatomist who along with the neuropathologist, Marion Smith, studied the anatomy of spinal cord pathways implicated in pain processing. Peter also wrote interesting biographies and was a major

financial supporter of the highly successful play, *Chaucer's Tales*, and he gave all his profits to charity.

For more than two years, I sat next to Peter every Wednesday morning and received firsthand experience with patients. I tell my students that for the first three months, I just listened to patients, but the students don't believe me. Most important, I quickly learned that a preclinically studied animal (whether mouse or monkey) is not a human and that the human pain experience is far greater than the magnitude of the injury. And because I often saw the same patients over several months, I also learned what worked and what did not, as well as the heterogeneity of the patients, even those ostensibly with the same injury. Most memorable were the postherpetic neuralgia (PHN) patients, a classic neuropathic pain condition. Opiates were not particularly effective and gabapentin was years away from its discovery. The antidepressant, amitriptyline (a serotonin and norepinephrine reuptake inhibitor, and a cholinergic blocker) had just been introduced for neuropathic pain.

But in my experience, what proved to be remarkably effective, particularly in patients with PHN of the first division of the trigeminal nerve, was local anesthetic (bupivacaine) injection into the supraorbital notch. This injection reliably blocked the ongoing and evoked pain of the forehead. In fact, pain relief occurred in close to 100 percent of patients, But, most interestingly, in some patients, the patient remained pain free for up to three weeks. The pain always returned, but a subsequent injection was also effective. That observation convinced me of the critical significance, indeed necessity, of peripheral afferent input, to sustain neuropathic pain. I have seen comparable results in patients with phantom limb pain; local anesthetic injection of the stump not only can eliminate stump pain, but the phantom would also disappear. Those observations are consistent with a longstanding premise described by Livingston, namely that injury-induced changes in the spinal cord can for a short period independently sustain the pain after peripheral nerve injury, but a peripheral driver is necessary (Livingston, 2012). Of course, we now refer to this phenomenon as central sensitization (Woolf, 1983).

My experience with Peter Nathan convinced me that basic science pain researchers must also learn directly from patients living with chronic pain. Not only will researchers better understand the complexity of the pain experience and appreciate which treatments are effective and which are not, but they also will appreciate how chronic pain influences quality of life and family interactions. And most important, they will also be able to interact with clinicians. I have been fortunate to have brilliant physician-scientists, neurologists, anesthesiologists, and dermatologists complete research fellowships in my lab and have always encouraged students and postdocs in my lab to shadow the pain physicians at the pain clinic. Fortunately, many do. To emphasize the importance of patient interactions, the HEAL Initiative created a video in which I discussed the importance of seeing patients (http://heal.nih.gov/news/stories/p).

My First International Association for the Study of Pain Meeting (Florence, Italy)

Not long after I joined Howard Fields's lab in San Francisco (see "The Move to San Francisco"), Howard encouraged me to present the DLF story, which had just been published in *Pain*, at the first meeting of the International Association for the Study of Pain, in Florence, Italy. That's a meeting that one cannot turn down. So, Carol and I and our London-born daughter, Katherine, who was only one year old, went to Florence. The talk that I gave was all of 15 minutes. After a few simple, supportive questions, a well-known and respected physician scientist, Arthur Taub, who studied pain, stood up and said that he didn't believe our story. He said that making selective lesions of the DLF in the rat is impossible. He argued that there would inevitably be damage to other pathways. He pointed out, correctly, that the published manuscripts only included sketches of the lesions, not the original histology. I was pretty devastated; nobody was going to believe the postdoc who was telling this story.

Fortunately, there is a happy ending to this tale. Near the end of the meeting, Ron Dubner, who I had met while working in Pat Wall's lab, said that he would love to hear more about the DLF story and so he invited me to visit the National Institute of Dental Research, where he oversaw a large pain research group. I eagerly accepted and showed up a couple of months later. I expected to give a one-hour talk, but questions kept coming. After about four hours Ron said, "Oh, Allan, it turns out that Gary Bennett, a fellow in the lab, was about to do some surgeries in rats. Would you be willing to show them how to create the DLF lesions?" Apparently, there was an ulterior motive to Ron's invitation to me to come to the National Institutes of Health (NIH). Not to be proven wrong, I went to the operating room and operated on three rats. What they learned quickly, and what I had previously learned from John Liu at Penn, is not to use scissors to make the lesion as that will produce bleeding and unintended damage to adjacent tissue. Rather, the lesion is created with jeweler's forceps. Target the region of interest and squeeze the tissue for about 15 seconds. This approach effectively crushes, rather than cuts, the targeted pathways and completely avoids bleeding. After an hour or so, the rats awoke from the anesthesia and immediately ran around, with no motor signs obvious. That convinced Ron and his lab that it is indeed possible to make selective DLF lesions, and Ron eventually spread the word. But in my subsequent papers, I did include the histological verification.

The Move to San Francisco

While in London, Carol met John Heuser, who was a postdoc in Bernard Katz's (see volume 1) lab. John was offered a position at UCSF in the Physiology Department, and he invited Carol to do a second postdoc in

his new lab. Carol was an electron microscopist who, from her work in George Gray's lab, was very interested in synaptic architecture. So the offer was superb. Carol also had an offer to work with Tom Reese at the NIH, which was great as I had an offer to work with Steve Gobel at the National Institute of Dental and Craniofacial Research (NIDR), in the pain research unit that was headed by Ron Dubner. But for reasons that I can't remember, Tom encouraged Carol to join John's lab. My problem was that I knew nobody in San Francisco. (To be honest, I had never been to California and thought that the Golden Gate Bridge interconnected San Francisco and Los Angeles). Anyway, serendipity stepped in again. Pat Wall reached out to Howard Fields, who was setting up a lab in the Neurology Department at UCSF. Long story short: I joined Howard's lab and the rest is truly history. My move to San Francisco was the beginning of a very long and productive research collaboration with Howard, and most important, the beginning of what is now a 50-year, very close friendship.

Making the move to San Francisco, however, was not all that straightforward, for several reasons. Most memorable, of course, is that our daughter, Katherine was born in London.

Carol's pregnancy and Katherine's birth were unforgettable. First, Carol was amenorrheic, and we were told that she probably couldn't become pregnant without a lot of medical intervention. In what was to be our last year in London, we decided to take a two-week vacation, skiing in Austria. Carol had a "cold," but our doc said that being in the mountains would be best for her. Unfortunately, Carol broke her leg near the end of our trip and was treated with a nonsteroidal anti-inflammatory drug apparently used in horses, not one that should be prescribed to humans, particularly pregnant ones. When we returned to London, Carol was placed in a cast and then she complained to our physician that she not only had a mild cough but was also nauseous. "Post-influenza colic," the physician concluded. At which point Carol asked whether breast enlargement was also associated with postinfluenza colic. A subsequent pregnancy test confirmed that it was definitely not colic. The problem was that we had no idea how pregnant she was. Early days of ultrasound guessed that she would deliver in mid-August of 1974. Well, a month later, we were still waiting, and my mother was convinced that there were problems with the pregnancy. Katherine, in fact, was born September 28. That was two weeks before we were scheduled to return to the United States, tickets already purchased.

The problem was that as a Canadian citizen, it was not easy for me to get back to the states. So Carol left with Katherine and stayed with her parents in Peekskill, New York. I was busy dealing with immigration. When interviewed at the American Embassy, while applying for a Green Card, I knew that my fingerprints had been sent to every city in which I had lived, including Philadelphia. Apparently, immigration folks were looking for some criminal history that would prevent me from getting the Green Card.

I asked what crimes would be a problem: "Type A crimes: murder, rape and trafficking in drugs," was the reply. "Not a large number of unpaid parking tickets?" I sheepishly asked, all of which I had collected at Penn, remembering what my father-in-law had warned me when he learned that I never paid them. "Not to worry," the agent told me. So, finally, I made it to the states, two months after Carol left and we moved to San Francisco, with a two-month-old daughter in tow.

Within weeks of arriving in San Francisco, the question as to the meaning of my last name again came up. I was walking by the neurology office, when the chief administrative officer, a rather formidable German woman, asked me, "You are Dr. Basbaum, yes?"

"Yes," I said, and then she asked, "What is the meaning of Basbaum?"

I told her that I thought it meant lilac tree, at which point she laughed and stated firmly that: "Bas is not a lilac! Bas is nussing! You are Dr. Nussing Tree," a name that she repeated every time I walked by her office: "Here comes Dr. Nussing Tree!"

It took many years for me to learn the actual meaning of my name. A letter from a distant family member in Brazil, the country to which many of my distant European relatives had emigrated instead of going to Canada. Anna Basbaum explained that the name was originally "Vaisbaum" (i.e., "white tree"). Often V's become B's, which is why I remain Dr. White Tree, with a "B."

Science with Howard Fields

Howard Fields had set up an electrophysiology lab to study spinal cord processing in the cat. He had previously published a series of important studies on the properties of spinoreticular neurons (Fields et al., 1977), a topic that I recently discussed in a review of spinal cord projection neurons that carry "pain" messages to the brain (Wercberger and Basbaum, 2019). Given the recent focus on descending controls and the identification of the DLF pathway, Howard and I turned our attention to the effects of electrical stimulation of neurons in the rostral ventral medulla (RVM), which contains the serotonergic neurons that are the origin of the descending DLF pathway. We demonstrated that RVM neurons project to the spinal cord via the DLF (Basbaum et al., 1978; Basbaum and Fields, 1979) and in an earlier paper, that electrical stimulation profoundly inhibits the firing of dorsal horn neurons that receive pain-provoking input and that DLF lesions blocked the inhibition (Basbaum et al., 1976). Specifically, we observed profound inhibition of the so-called wide dynamic range neurons of lamina V of the dorsal horn and minimal to no effect on the lamina IV neurons, which respond only to innocuous stimulation.

Serendipitously, perhaps, these electrophysiological studies occurred not long after the introduction of a new anterograde tracing method,

autoradiography, using transport of tritiated amino acid, a technique that was significantly improved over silver degeneration methods. You didn't need to make a lesion, and autoradiography was far more sensitive. The protocols not only were incredibly difficult but also required generating emulsion-coated slides of sectioned tissue and weeks of transport and then emulsion development in the darkroom. The problem of great sensitivity had its own issues, namely distinguishing transported signal from background noise; but we persevered.

Our studies, in the cat, were designed to target the reticular formation of the medulla, specifically the nucleus reticularis gigantocellularis. Our objective was to map projections to the thalamus, as part of the spinoreticulothalamic "pain" pathway that Howard's previous spinal cord electrophysiological studies had investigated. We used a beveled needle to inject the tritiated leucine, which would be taken up by neurons, incorporated into protein, and then anterogradely transported, we hoped, to the thalamus. Inadvertently, and yes, serendipitously, instead of aiming the bevel rostrally, we turned it 90 degrees, resulting in injections that targeted the midline, including the nucleus raphe magnus.

We certainly observed significant projections rostrally, but analysis of the caudal medulla, notably the trigeminal nucleus caudalis and the spinal cord dorsal horn, revealed extensive terminations in superficial layers, laminae I and II (Basbaum et al., 1976). As previous tracing studies concluded that there was no descending projection to the superficial laminae, our findings were initially questioned and were considered to be an artifact of the autoradiographic technique. Time proved our findings correct, however, and our observations were followed by our many studies and that of others that examined the controls exerted from the RVM (and midline serotonergic nucleus raphe magnus) on "pain" responsive neurons, not only in lamina V but also in lamina I, which was predicted from the projection to the superficial dorsal horn. Perhaps fortunately, my studies of the brainstem anatomy convinced Henry "Peter" Ralston, who preceded me as chair of the Department of Anatomy at UCSF, to assign the brainstem lecture to me, which prompted the following poem that ended that lecture.

The Brainstem Cranial Nerve Review
Midbrain, medulla, bridged by the pons
Sur le pons d'Avignon, our neuroanatomy course goes on and on.
But to help with your studying, messieurs et mesdames
Here's a review of the brainstem for the final exam.

If you stick out your tongue, it should come out very straight.
But with a lesion of the XIIth nerve, it will almost certainly deviate.
And since intact strong tongue muscles the weak override,
The tongue will stick out on the paralyzed side.

Branchial IX, X, XI exiting nerves are contiguous,
Their cell bodies located in nucleus ambiguus.
Glossopharyngeal's not pure; it's a sensory-motor mixed bag,
Its afferent component might, in fact, make you gag.
VII and IX transmit tongue taste bud information and as the textbooks have taught us,
There's also a Xth nerve taste component for the epiglottis.

The facial nerve, yes that's VII, is particularly hard to get straight,
Because it hooks over VI, before it exits with VIII.
Can you imagine if Hemingway had suffered VIIth nerve woes?
His great novel might have been titled, *For Whom Bell's Palsy Tolls*.
And with no corneal reflex to protect him, he would have so ruined his eyes,
That all he'd have won was the "No Bell Palsy" prize!

Turning to vision, oculomotor is III, Edinger-Westphal constricts,
Trochlear is IV and abducens is VI.
Laterally, medially, in myriad ways,
Through the paramedian pontine reticular formation, the brain controls conjugate gaze.

And MLF, III, IV, VI, and vestibular connect,
To maintain eye position when you reposition your neck.
But if the world starts to spin and you can't navigate,
It's likely there's damage to vestibular VIII.

Last but not least, is the Vth cranial nucleus;
Its anatomical organization does nothing but confuse us.
Don't ask me why descending tract axons carry trigeminal "pain."
I only teach … I had no hand in the design of the brain.

Could We Stay in San Francisco?

After a couple of postdoc years in San Francisco, we turned our attention to faculty positions. We considered positions at Columbia in New York, but our visit was not at the most ideal time. New York was a pretty rough place in the mid-1970s, and since we had a two-year-old with us, crime was a concern. There was a wonderful opportunity in the Anatomy Department, which was headed by Michael Gershon, of enteric nervous system fame. However, what clinched our decision not to move to New York came, I guess serendipitously, when I raised our concerns to a Columbia faculty member, whose name will go unmentioned. This individual said that there was no reason to be concerned about crime. She carried a $20 with her at all times

and perhaps had lost $100 a year to muggers. That part of the startup package convinced us to stay on the West Coast.

After a visit to Irvine and another interesting offer of faculty positions for both Carol and me, UCSF asked if we would like to stay. The chair, Peter Ralston, offered me a faculty position. Not much of a startup: $25,000 and a 360-square-foot lab, renovated from half of a former men's restroom. We joked that this lab offered a novel way to do "uranyl" acetate staining of grids for electron microscopy. The lab was on the 13th floor; no superstitious concerns here, although San Francisco did skip 13th Avenue when it named its streets. The lab did have a small, 60-square-foot office, with a great view of the Pacific Ocean. But the lack of a window in the lab proved annoying to my first graduate student, Michelle Moss, who felt that we should restructure the lab and office so that everyone could enjoy the view. Knowing that that was impossible, I went to Sears and purchased an inexpensive painting of a window and hung it in the lab. But Michelle got the last laugh. She said that I should hang the window in my office so that I could get cross-ventilation!

A story that Michelle recounted about her first attendance at Society for Neuroscience is also memorable. Michelle was listening to a small crowd of neuroscientists discussing pain mechanisms, and she tried to engage but was completely ignored. Apparently, she overheard someone mention my name, at which point she spoke up and said that she was a graduate student in my lab. That was followed by someone exclaiming: "Wow, Allan Basbaum. He's semifamous!" I still do not know whether "semifamous" is something of which I should be proud. More likely, it indicated that I had a lot of work to do.

During this time, our studies with Howard continued, and in my own lab, we introduced electron microscopy and immunocytochemistry, a technique largely pioneered for the nervous system by a very close friend and colleague, Tomas Hökfelt. But, after several years at UCSF, some opportunities to move on appeared, in particular, a position at the University of Washington (UW), where John Bonica had established the first Multidisciplinary Pain Clinic and where he founded the International Association for the Study of Pain. Long story short is that Carol, who had a soft-money, in-residence position at UCSF, which was also in the Anatomy Department, was not offered a hard-money position at UW. That was our bottom line, so we stayed in San Francisco. The dean, however, recognized that my scientific kindred spirits were not the cancer and cell biologists next door to me on the 13th floor, but the neuroscientists in the newly established Keck Center for Neuroscience. So, I moved down to the newly renovated eighth floor, where I was surrounded by an amazing group of outstanding neuroscientists, including Steve Lisberger (see volume 12), Alisson Doupe, Michael Merzenich, Christoph Schreiner, and Ken Miller. The energy in the Keck Center was fantastic and unquestionably contributed to my continuing efforts to take a multidisciplinary approach, involving neuroanatomy, electrophysiology, and pharmacology, to dissect the spinal cord circuits that process pain messages.

More Serendipity After the Winter Conference on Brain Research

My communications with John Liebeskind, while in London, definitely led to one of the most serendipitous and particularly significant events in my career. Soon after joining Howard Fields's lab, I received a call (I almost wrote "email," but email didn't exist yet), from John Liebeskind, asking me if I could fill in for him at the Winter Conference on Brain Research (WCBR) meeting, a ski meeting in Keystone, Colorado. I knew nothing about the meeting, but agreed to attend. Having grown up in Montreal, I was very familiar with snow, but I was a hockey player. I did not ski at all. At the Keystone meeting, I gave a 30-minute evening talk about our findings on brain stimulation produced–analgesia and the neuroanatomical connections from the medulla to the spinal cord. A few questions were asked but nothing unexpected.

But the next morning was incredibly memorable. While standing in the ski lift line, another WCBR attendee, recognizable by the WCBR armband that everyone else thought was a radio station, approached me and introduced himself. It was Fred Plum, the editor-in-chief of the *Annals of Neurology*, not a journal that I regularly, or I must admit, ever read. He said that he was interested in the research that I presented the night before and asked if I would be willing to write a review for the journal. I thanked him and said, "Sure." Only after returning to the lab and telling Howard about the invitation did I realize how significant that invitation was. As a neurologist, Howard was much more excited about the opportunity. Together we put together the review "Endogenous Pain Control System," which not only reviewed our neuroanatomical and functional studies of descending controls but also included our hypothesis that morphine analgesia resulted from activation of the same descending control system that could be triggered by electrical stimulation of the PAG (Basbaum and Fields, 1978).

Thanks to the artistic talent of another postdoc in Howard's lab, Stewart Anderson, the review included a diagram that illustrated our view of the circuits through which activity of PAG neurons engaged the raphe neurons of the RVM and the projections of the latter neurons to the dorsal horn. This was still the very early days of endorphins, but we did include a hypothetical circuit in which enkephalin release from inhibitory interneurons in the PAG somehow engages the descending control network. As opioids were inhibitory and activation of the PAG neurons that project to the raphe was required, we hypothesized that a disinhibitory circuit functioned in the PAG. Specifically, we proposed that the disinhibition involved enkephalin-mediated inhibition of GABAergic interneurons that act directly on the PAG-nucleus raphe magnus neurons. That figure was updated years later in an *Annual Review of Neuroscience* paper that Howard and I wrote, and it continues to be cited (Basbaum and Fields, 1984). Not surprisingly, details of the intrinsic circuitry in the raphe have greatly increased, and of course, there is now

evidence for descending inhibitory as well as facilitatory actions that derive from the RVM. Howard, Mary Heinricher and Peggy Mason's studies of RVM derived "on" and "off" cells are a beautiful illustration of the complexity of the circuit that we had considerably underestimated (Fields et al., 1991).

Substance P and Pain Processing

Following the demonstration that opiates exert their antinociceptive effects, in part, by regulating sensory-neuron-derived release of the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) (Jessel and Iversen, 1977), our laboratory studied peptide actions in a variety of acute and chronic pain models. Our earliest foray into transgenic mouse technology involved creation of a mouse in which the preprotachykinin gene that codes for substance P and other tachykinins was knocked out (Cao et al., 1998). The study was led by an outstanding graduate student, Yu-Qing Cao, who is now an associate professor at Washington University, and among the world's experts in migraine pathophysiology. The initial analysis of the substance P knockout mouse was somewhat disappointing. Based on the literature demonstrating a profound substance P-mediated increase of activity in dorsal horn nociresponsive (i.e., presumptive pain-generating) neurons, we expected to observe a significant decrease in the behavioral response to a noxious stimulus, but that was not what we found.

Instead, it appeared that substance P only comes into play under suprathreshold pain conditions. However, the knockout condition did result in opiate sparing, in which the dose of morphine required to reduce pain was reduced. We published the results of this study in *Nature* and interestingly, the minimal baseline effect of deleting substance P turned out to be consistent with later clinical studies that found no utility in treating chronic pain with antagonists of the neurokinin1 receptor, which is targeted by substance P. Subsequently, Pat Mantyh and I published several papers on the functional relevance of the target of substance P, namely the NK1 receptor (Abbadie et al., 1997; Mantyh et al., 1995). Nevertheless, the limited effects of deleting substance P on pain behavior remain a mystery. Perhaps the most memorable result of our knockout study was that it led to a minireview of our study by a close colleague, Clifford Woolf. Well, at least the title of the minireview in *Neuron* was memorable and admittedly creative: "Null Mutations Lacking Substance: Elucidating Pain Mechanisms by Genetic Pharmacology" (Woolf et al., 1998). Fortunately, however, one of the authors of that minireview, Simona Neumann, decided to do a postdoc in my lab!

My lab's very definite move into transgenic mice, including global and Cre-mediated knockout mice, was the motivation for the following poem that I wrote for a plenary lecture that I presented at the Vienna conference of the International Association for the Study of Pain (IASP). The topic was transgenic technology and its application to pain research.

Of Knockout Mice … and Humans
As a graduate student I worked in primates, and with Pat Wall I studied cats
And since moving to San Francisco, I turned to pain research in rats.
But now the peptide circuits that I study are in a 20 micron slice
Figuring out what happens when substance P is lost in preprotachykinin knockout mice.

Of course, some clinicians in the audience may question my advice,
That pain in humans can be helped by studying behavior in a slew of knockout mice.
I remind them that morphine's efficacy in patients we can remarkably predict
By monitoring an opioid's ability in mice to inhibit a heat-evoked tail flick.

Yes, Marilyn Monroe was a knockout, we all can agree.
And without question the greatest knockouts were at the hands of Mohammed Ali.
But to relieve pain, studying pain mechanisms in a knockout mouse still seems to me
A better approach to future therapy than continuing anterolateral cordotomy.

After the knockout mouse story was published, we continued to examine conditions in which substance P derived from nociceptors would come into play. Of particular interest was our *Nature* report of an N-methyl-D-aspartic acid (NMDA)-receptor-mediated regulation of substance P from primary sensory neurons (Liu et al., 1997). Of course, the NMDA receptor was not only implicated in memory formation in the hippocampus but also contributes to what I refer to as "maladaptive memory" in the dorsal horn of the spinal cord. Specifically, injury-induced persistent hypersensitivity has at its basis an NMDA-receptor-mediated sensitization of dorsal horn "pain" processing circuits. When we first investigated the receptor, it was assumed to exist only on postsynaptic neurons, In a series of neuroanatomical studies, however, we demonstrated that the receptor is, in fact, expressed at high levels in primary sensory neurons (Liu et al., 1994).The result was quite surprising as the implication was that glutamate release from sensory neurons could exert a facilitatory perhaps autoreceptor-mediated action on transmitter release from the same afferents. Another very close colleague and friend, Roger Nicoll (see volume 10), not surprisingly, didn't buy into the possibility of presynaptic NMDA receptors. In fact, Roger considered that believing in presynaptic facilitation was heretical. However, when we demonstrated that substance P release from nociceptors is, in fact, regulated

by presynaptic NMDA receptors, Roger relented slightly. Of course, presynaptic NMDA receptors have since been demonstrated in other areas of the central nervous system (CNS).

Peripheral Pain Processing Mechanisms: Science with Jon Levine

My interest in the contribution of substance P was unquestionably an important contributor to a very productive collaboration that I had with Jon Levine, a remarkable scientist. Jon, a rheumatologist who is a physician and holds a doctorate, is interested in inflammatory disease. Jon not only treats patients but also runs a large preclinical lab and has even published many important studies on the pathophysiology of postoperative dental pain. Our early studies addressed the peripheral mechanisms that contribute to the neurogenic inflammatory process, through which the release of chemicals from the peripheral terminals of primary sensory and sympathetic efferent neurons generates a profound inflammatory response. We first used the experimental arthritis model in rats. In a *Science* paper on the pathophysiology of the disease, we demonstrated that the level of substance P was particularly high in joints that developed the most severe arthritis and, more important, perhaps, that injection of substance P into a joint that normally develops less severe arthritis, namely the knee, would increase disease severity (Levine et al., 1984).

Subsequent studies reported that substance P levels are also high in arthritic joints of patients (Pritchett, 1997). In related studies, we demonstrated that the sympathetic nervous system also exerts a pathophysiological contribution to inflammation and pain (Levine, Dardick et al., 1986). The rat studies also led to an important clinical study in patients with pain associated with rheumatoid arthritis. Here, we demonstrated that guanethidine-induced sympathectomy, localized to the painful limb, could significantly reduce the ongoing pain (Levine, Fye et al., 1986). Just as Peter Nathan and Howard introduced me to the neurologist's perspective on clinical pain, which definitely focuses on CNS processes, so Jon taught me about the important peripheral contribution of primary afferents and sympathetic efferents to clinical pain. Of course, those studies predated our recent focus on neuroimmune contribution to pain and itch (see "The Neuroimmune Contribution to Pain Processing").

The Complete Opposite of Serendipity

Unfortunately, good things eventually come to an end. In 2000, Carol developed ovarian cancer. Although her oncologist said that she might survive six months, in fact, she lived for another six years, during which time, although cycling through every chemotherapy possible, her lab flourished.

Her studies of mucin gene regulation and bacterial influences on epithelial cells (Lemjabbar and Basbaum, 2002) and on the effects of tobacco smoke on mucin genes (Gensch et al., 2004) are particularly notable. In fact, Carol cloned several mucin genes (Muc2, Muc5) for which the Cystic Fibrosis Foundation named a postdoctoral fellowship in her honor. To say that Carol was dedicated to her research is an understatement. To study the gene for CFTR, the cystic fibrosis transmembrane conductance regulator, she often went down to meet arriving boats at Fisherman's Wharf at 5:00 a.m., where she picked up shark rectal glands, which are rich in CFTR. Try to explain to friends that your wife was picking up shark rectal glands at 5 a.m. at the wharf.

Another amusing story relating to Carol's research is worth telling. Very soon after the Monica Lewinsky saga occurred, I suggested that perhaps the world was wrong in their conclusion as to what was on the famous dress. Rather, I suggested that perhaps Bill C. had sneezed on her, and that it was mucus! As Carol had the probes to determine if I was correct, I said that she could be famous. Interested in passing the proposal along, Carol quickly emailed Ken Adler, a major mucin research colleague in North Carolina, and relayed my proposal to probe the dress for Muc2, Muc5, and so on. Within 30 seconds, Ken emailed back that my suggestion was reasonable, but that a greater likelihood of success would arise if the dress were probed for Suc2, Suc5, and such.

The little story about Mucus genes truly illustrated the joy that Carol had in her research and with her colleagues. But when she died, I was lost. For almost 25 years, she and I came to the lab together; we didn't work together and carefully avoided having lunch together. But getting home and seeing our two children, and discussing the science that happened during the day, had ended. At this time, I wondered what direction to go and seriously entertained the idea of moving to industry. I have served on several advisory boards, but it was at Rinat Neurosciences, headed by Arnon Rosenthal, where I consulted regularly. In fact, for one morning every week for almost two years, I attended regular roundtable discussions with Rinat scientists. This was an unusual arrangement, but one that the dean endorsed as he recognized that I needed a change. It was a wonderful experience, very different from the usual advisory board sessions. In fact, the meetings were more like a group meeting, where science was presented, argued, and discussed. Within a few months, I was offered a position as vice president at Rinat, but I decided that industry was not my cup of tea. I didn't want someone else's money and objectives to limit what I could do, no matter how important the indication was (obviously pain) and how cutting edge was the science.

Once again serendipity stepped in, however, thanks to the dean. Recognizing how important a change of environment would be for me, he suggested that I move my lab to the new Mission Bay campus. Here were entirely different surroundings, new buildings, and most important,

a completely new daily driving routine and even better weather. The move was extraordinarily helpful. The lab was moved in less than two days and was up and running soon after. And my research studies with David Julius, who had already moved his lab from Parnassus to Mission Bay, began what has proven to be a continuing collaboration and friendship. And as noted below, remaining at UCSF was key, years later, to eventually meeting and marrying Marcia (see "A New Life With Marcia").

David Julius, TRPV1, and the Nobel Prize

Of course, we all know that David Julius received the Nobel Prize for his discovery of the gene that codes for and the structure of TRPV1, the receptor targeted by capsaicin, the pungent ingredient in chili peppers. The history of the rationale for the search for the capsaicin receptor is particularly interesting. Many years ago, Hungarian scientists demonstrated that injection of capsaicin into neonatal rats would kill small-diameter, presumed nociceptive primary sensory neurons (Jancsó et al., 1977). These animals had dramatically reduced pain behavior to noxious heat stimulation. Recognizing the potential significance of this from a translational point of view, several pharmaceutical companies, notably Sandoz in the United Kingdom, worked hard to identify the receptor. But they failed. After his arrival in San Francisco, David attacked the problem. As a postdoc in Richard Axel's lab, David used expression cloning and identified the 5HT1c receptor gene (Julius et al., 1998). At UCSF, David used the same approach and succeeded in cloning the capsaicin receptor (Caterina et al., 1997). Originally called VR1, the name changed to TRPV1, when it was appreciated that TRPV1 was a member of a very large family of TRP channels.

After David's initial publication, our laboratories began a long and continuing collaboration on the functional relevance of the channel to acute and persistent pain. What David recognized is that many members of the TRP family are characterized not only by their expression in primary sensory neurons, and their responsiveness to temperatures, but also that many respond to natural products, with capsaicin epitomizing this phenotype. To date, we have published 15 papers together, not only on TRPV1 but also on other TRP channels (TPRA1), an irritant receptor (Bautista et al., 2006), and TRPM8, a cold and menthol receptor (Bautista et al., 2007), on the pain-provoking properties of a host of toxins (Osteen et al., 2016) and most recently on the location of the TRPV1 channel that regulates core body temperature (Yue et al., 2022). In several studies, we have taken advantage of the remarkable neuron killing properties of resiniferatoxin, which is about 1,000 times more potent than capsaicin and can kill TRPV1 afferents in the adult (Cavanaugh et al., 2009).

David and I have also published four reviews, one of which was published in *Cell* and is my most highly cited paper (Basbaum et al., 2009).

These collaborations were not serendipitous, but illustrative of the incredible collaborative culture at UCSF, where the scientific strengths of different laboratories readily come together. Let me end this section with some practical advice. As David found, birds express the TRPV1 channel, but it is nonfunctional, presumably allowing the birds to investigate many plants. Of course, birds also like to eat from bird feeders, but so do squirrels. Well, as squirrels have a functioning TRPV1 channel, all that you need to do is add some cayenne to the bird food in your feeder and the squirrels will quickly stay away.

Ongoing Science at UCSF: The Neurochemistry of Pain Processing

Following our studies of the contribution of TRPV1 to pain processing, our laboratory continued to address the incredible molecular complexity of the sensory and spinal cord circuits that transmit injury messages that are interpreted by the brain as painful, as well as circuits that underlie the neurochemical control of nociceptive circuits in the dorsal horn. Of particular interest is our study of the very dense population of PKCγ-expressing interneurons located in inner lamina II of the dorsal horn. In a *Science* paper, we reported that knockout of PKCγ dramatically reduced the pain hypersensitivity produced in a neuropathic pain model, namely partial sciatic nerve section (Malmberg et al., 1997), in part via an influence on a subset of NMDA-receptor regulated dorsal horn circuits (Martin et al., 2011). Other studies examined the contribution of different glutamate transporters (VGlut2; Scherrer et al. 2010, and VGlut3; Seal et al., 2009), dorsal horn glycine receptors (Basbaum, 1998), as well as several very understudied molecules, for example, hippocalcin-like 4 (Alvaro et al., 2020), aquaporin 1 (Shields et al., 2010) and TR4, a testicular orphan nuclear receptor (Wang et al., 2013).

We also reported that dorsal horn calcitonin-gene-related peptide (CGRP), long considered to derive exclusively from primary sensory neurons, is also expressed in a population of lamina III interneurons and contributes to mechanical sensitivity (Löken et al., 2021). Most recently, we demonstrated that sensory neuron derived ACVR1, a receptor that to date is associated with a profound clinical phenotype, namely fibrodysplasia ossificans progressiva, is an important contributor to the pathophysiology of nerve injury-induced pain (Yu et al., 2022). Particularly productive and enjoyable has been a longstanding collaboration with Patty Phelps at UCSF. I know little to nothing about embryonic development of spinal cord circuitry, but together we have been studying the migration and function of lamina I neurons and the interesting contribution of reelin and DAB1 (Akopian et al., 2008).

Of course, as I have worked for years on opiate-induced mechanisms of pain control, it is not surprising that our laboratory also investigated the

differential contribution of the multiple opioid receptor subtypes. Particularly rewarding was a series of studies with Greg Scherrer, a postdoc who trained with Brigitte Keiffer in Strasbourg, and who is now on the faculty at the University of North Carolina. Greg and I were intrigued by the many reports that the mu (MOR) and delta (DOR) opioid receptors dimerize and that this dimerization could underlie the regulation of pain processing at the level of primary sensory neurons (Gomes et al., 2004). Our anatomical studies, however, suggested that dimerization of the receptors in sensory neurons was highly unlikely (Scherrer et al., 2009). In fact, in double-label studies using an antibody against the mu receptor, in a delta receptor reporter (GFP) mouse, we found coexpression in fewer than 5 percent of sensory neurons. Rather, the mu receptor predominated in unmyelinated peptidergic afferents and the delta receptor predominated in the nonpeptidergic MrgprD subpopulation of unmyelinated afferents, as well as in larger, myelinated afferents. And, most important, our pharmacological studies found that an action at the mu receptor regulated heat-provoked pain behaviors and an action at the DOR regulated mechanical pain. Our paper did provoke a rather heated discussion as it also provided evidence that the reported pain-relevant regulation of substance P trafficking from primary sensory neurons to the dorsal horn via the DOR (Guan et al., 2005) is unlikely to occur as substance P and DOR are not found in the same neurons.

Functional Neuroanatomical Tracing: What's All the Fos About?

Without question, one of the most significant influences in the approaches that our laboratory has taken to understand pain processing, particularly at the level of the spinal cord, was the *Nature* report of Stephen Hunt, on the use of *c-fos* expression to monitor the activity of CNS neurons (Hunt et al., 1987). For the record, I was one of the reviewers of that wonderful paper. Once it was published, we incorporated Fos expression into many of our studies, from changes in the spinal cord after injury (Chi et al., 1993) to the regulation of neuronal activity by a variety of analgesics, including morphine (Presley et al., 1990). I did have fun writing a short review of Fos studies in a paper titled: "What's All the 'Fos' About?" (Basbaum, 1994). At the same time, in addition to introducing autoradiography to study descending projection systems, we constantly incorporated new tracing methods into our toolbox. Particularly productive were several earlier studies that used pseudorabies virus (either directly or in a Cre-dependent fashion) to map circuits that engage specific pain transmission neurons, for example, in the spino-parabrachial-amygdalo pathway (Jasmin et al., 1997).

But our laboratory has also developed our own protocols. In a collaboration with Daniel Menétrey, while on sabbatical in Paris, we generated an unusual modification of the traditional wheat germ agglutinin (WGA)-HRP

tracer. Here we replaced the HRP with an apoprotein of the HRP, which was enzymatically inactive (Basbaum and Menétrey, 1987). As a result, it was possible to combine this new tracer with other HRP-linked tracers. More recently, with Joao Braz, a brilliant scientist who joined my lab as a post-doc from Paris and who continues to serve as my right hand in the lab for more than 20 years and 50 joint manuscripts, we generated a remarkable transgenic mouse that permits transneuronal tracing of complex, multisynaptic circuits in the CNS. In this mouse, we are able to trigger anterograde transneuronal expression of WGA in a Cre-dependent manner (Braz et al., 2005). Finally, we continue to use a slew of AAV and HSV viruses to dissect CNS circuits. Most recently, we used retrograde labeling to ribosomal profile spinal cord projection neurons (Wercberger et al., 2021). In these studies, we identified several novel genes that define the spinoparabrachial population, which led to our conclusion that projection neurons are not organized as labeled lines that transmit distinct modalities (i.e., heat, mechanical, cold), but that the neurons are polymodal. Our recent *in vivo* calcium imaging of projection neurons in awake mice supports that conclusion (see "Long-Term Spinal Cord Imaging in the Awake, Behaving Animal").

Gabergic Transplant Treatment of the "Disease" of Neuropathic Pain

I have often spoken of the difficulty of raising funds for fundamental pain research, emphasizing that the problem is that people "die in pain, not of pain." In other words, because the general public considers chronic pain to be a symptom of some other disease, somewhat understandably, their donations for research reach laboratories that study the disease that permanently injured or killed their loved ones (e.g., cancer, multiple sclerosis, heart attack, spinal cord injury). The family rarely donates to laboratories that study pain. Of course, the patients who experience these conditions often have ongoing, difficult to treat chronic pain. In my opinion, the conclusion that pain is a symptom of many diseases (e.g., osteoarthritis) is correct. But that conclusion is not correct for the neuropathic pain conditions that can follow damage to the nervous system.

Rather, neuropathic pain, in my opinion, is a disease of the nervous system, one generally of hyperexcitability secondary to loss of inhibitory controls, in the spinal cord and at higher levels of the nervous system. This designation would include post-stroke pain, pain after spinal cord injury, chemotherapy-induced neuropathic pain, and certainly phantom limb pain. The latter condition is particularly striking, as the pain is experienced in a limb that no longer exists. In many respects, chronic neuropathic pain is comparable to epilepsy, where there is hyperexcitability of cortical circuits, secondary to loss of inhibitory controls, and its manifestation is seizures. Not surprisingly, the first-line therapy for many neuropathic pains, although far

from adequate, is anticonvulsants, which of course, are the first-line pharmacotherapy for seizures.

Given this perspective, we asked whether we could introduce a different approach to neuropathic management, namely one that is directed at treating the disease. To this end, Joao and I initiated a program that followed studies of John Rubenstein, Arnold Kriegstein, and Arturo Alvarez-Bullya and colleagues, who transplanted GABAergic inhibitory neuronal precursors from the medial ganglionic eminence of the embryonic mouse into the brain of seizure prone mice (Baraban et al., 2009). The transplants significantly reduced the seizure incidence, presumably by reestablishing inhibitory controls. In our studies, we transplanted the cells into the dorsal horn of mice that exhibited profound mechanical and thermal hypersensitivity after peripheral nerve damage, either partial transection of the sciatic nerve, or following paclitaxel chemotherapy. Electron microscopic studies brilliantly performed by my Australian colleague, Ida Llewellyn-Smith, who worked with us for two months for many years, demonstrated that the transplant integrated remarkably into the host spinal cord, extended axons, and made synapses with host neurons. The host formed synaptic contacts with the transplant (Llewellyn-Smith et al., 2018). Most important, the transplants restored inhibitory controls in the spinal cord and completely reversed the mechanical hypersensitivity and even ameliorated the persistent scratching that occurs in a chronic model of neuropathic itch (Braz et al., 2014).

In related studies we reported that transplanting the cells into the anterior cingulate cortex (ACC), which codes for the affective component of the pain experience, also ameliorated behavior indicative of the experience of pain, not just reflex endpoints (Juarez-Salinas et al., 2019). This approach is now in the clinic; five patients with focal epilepsy have been transplanted, and it is my hope that the company, Neurona Therapeutics, will eventually use the approach to treat different neuropathic pain conditions. Soon after Neurona's formation, I served on its Scientific Advisory Board and remain enthusiastic about the technology.

The Neuroimmune Contribution to Pain Processing

The complexity of pain processing mechanisms grows with every new publication. Of particular interest is the increased emphasis on neuroimmune mechanisms, a subject that we enthusiastically are now addressing. Our studies focus on neuroimmune mechanisms in the generation of chronic pain, notably the neuropathic pain that can follow nerve damage. There is now considerable evidence for an important contribution of spinal cord microglia, which many studies have shown are "activated" following peripheral injury (Milligan et al., 2005). What was not known are the factors that initiate the microglial response. Using an RNASeq analysis of dorsal root ganglion neurons after peripheral nerve injury, we found that nerve-injury induced

de novo synthesis of macrophage colony stimulating factor 1 (CSF1) in sensory neurons is both necessary and sufficient for the activation and proliferation of spinal cord microglia and for their contribution to the development of nerve injury-induced mechanical hypersensitivity (Guan et al., 2016).

And in a follow-up study, we demonstrated that this neuroimmune phenotype is sexually dimorphic, findings consistent with earlier reports of Jeff Mogil and colleagues at McGill (Sorge et al., 2015). Specifically, we found that male microglia are far more responsive to CSF1. In fact, although more than 1,200 genes are altered after intrathecal CSF1 injection in male mice, only 90 are altered in female mice (Kuhn et al., 2021). Furthermore, we found that the CSF1 significantly increased regulatory T (Treg) cell number in spinal cord meninges. Most interesting, in Treg-deficient mice, we found that intrathecal CSF1 in female mice not only activated microglial cells but also provoked hypersensitivity following peripheral nerve injury. That finding also paralleled the report that in the absence of T cells, microglia are contributors to nerve injury–induced hypersensitivity in female mice. Where we do not agree, however, is that we cannot find evidence that activated T cells actually penetrate the spinal cord to influence dorsal horn "pain" processing. Rather, our recent studies suggest that activation of meningeal Treg cells is critical to nerve injury–induced pain processing.

Ongoing Research and New Directions

As noted above, Ron Melzack once chided me at a meeting, saying that our work was great, but the studies are all about nociceptive processing, not pain. Admittedly our studies of spinal cord processing and descending control mechanisms that regulate spinal cord nociceptive processing did not get at the pain experience. So, I agreed with Melzack and indeed always teach medical students that "The Bane of Pain Is Plainly in the Brain." Indeed, to underscore the complexity of pain processing and the importance of the brain, I wrote a short piece on the topic (Basbaum, 2018), as well as the following poem

The Bane of Pain Is Plainly in the Brain
Pain is an intricate potion,
Of sensations, cognitions, emotions,
Acute pain may be terrible
But it's persistent pain that's unbearable;
And rarely responds to mere lotions.

Though pain may not be easy to bear,
There's often a reason for pain being there.
It's critical to know,
Lest a cancer unbeknownst grow.
Pain signals a need for repair.

You learned of children with Congenital Insensitivity to Pain.
They're unaware when they have fractures or sprains.
These children are rare,
But they need constant care.
Or their injuries will not be contained.

You see, A deltas and C's are essential,
To establish the painful potential.
But shake your hand or vibrate,
And you may close Melzack and Wall's Spinal Gate
So that the pain is no longer sequential.

In fact, there are myriad ways to control pain,
Which is perhaps why cordotomy's on the wane.
Find out what the morphine dose is,
Even consider hypnosis.
Remember pain's not a stimulus; it's a perception of the brain.

In this regard, find a pregnant woman and ask her,
Is LaMaze merely a ploy to distract her?
Or when labor pain
Is not "perceived" by the brain,
Are the endorphins a relevant factor?

Speaking of endogenous opioids—there are numerous classes.
Some reportedly are as potent as grass is.
So, if you're in pain
Just depend on your brain
Because the endorphins are the true opiates of the masses.

From the Spinal Cord to the Brain

Despite Melzack's entreaties, it was actually years before our research turned to pain processing in the brain. My transition to the brain began with a very interesting collaboration with Vikaas Sohal, a neuroscientist and psychiatrist at UCSF. Our studies focused on the contribution of the ACC, a region of the brain implicated in the affective, or emotional component of the pain experience. The project was led by Karuna Meda, a joint neuroscience graduate student in Sohal's lab and my lab (Meda et al., 2019). That study integrated behavior, optogenetics, and slice physiology and demonstrated that chronic pain–related aversion did not correlate directly with overall ACC hyperactivity, but rather to changes in the activity of specific pathways that engage ACC circuits, include those arising in the basolateral amygdala and

dorsomedial thalamus. That study emphasized that to understand the basis of pain affect, one needs to examine the circuit changes within the ACC, not merely its overall level of activity. Our recent, calcium imaging and Fos studies of the effects of general anesthetics on ACC activity and pain processing provided results consistent with those conclusions (Weinrich et al., 2023; see "Calcium Imaging and General Anesthesia Mechanisms").

Despite my rather late interest in brain mechanisms and pain affect, as a new faculty member, I was nevertheless assigned to give the limbic lectures, where emotions, of course, are processed. I did write a poem that illustrates the complexity of cognitive and emotional experiences and highlights rather dramatic approaches to treatment.

Neuroanatomy Can Be Stimulating, Especially in the Limbic System

Let me tell you a story about a Med Student named Fred
Who became so depressed that he wished he were dead.
When medication failed the doctors instead
Implanted electrodes in Fred's mixed-up head.

Poor Fred …

The original plan was to make an electrolytic lesion
In the temporal lobe, near the amygdala region.
That idea was abandoned since there's really no reason,
Stimulation techniques can be infinitely more pleasing.

Through a hole in Fred's head the surgeons dropped electrodes towards
The mesolimbic pathway that signals reward.
Nucleus accumbens releases gobs of dopamine, and thus stimulation affords
A feeling so marvelous that Fred's "joie de vivre" was restored.

Interestingly, the electrodes also evoked memories of indescribable smells.
Just where they came from Fred could not tell.
But Fred was so taken with the sensations olfactory
That his depression was almost completely refractory.

As Fred continued to improve and his psyche restored
He was suddenly inspired and shouted, "Good Lord!"
If I could only recall where my memories are stored
I might possibly pass the Part I Medical Boards.

Indeed, Fred passed the Boards and is doing just well.
Did a residency in psychiatry and neurosurgery, Do Tell!
No longer depressed, no more visions of Hell.
He just has to put up with an occasional odd smell.

So, if you're depressed, try this new operation.
Turn yourself on with some self-stimulation.
It may not be as natural as Zen meditation,
But its morbidity is much less than frontal cortex ablation!

Calcium Imaging and General Anesthesia Mechanisms

Unquestionably, Karuna's findings and a plethora of studies on the ACC were the impetus for a major technical change in the lab's approach, highlighted by our introduction of calcium imaging. A postdoc in the lab, Jarret Weinrich, led our foray into the brain. Our initial plan was straightforward: use calcium imaging with miniscopes to monitor activity of neurons in the ACC, so as to better understand the ACC circuits that underlie pain affect. As noted earlier, the prevailing view, based on both clinical (ablation) and imaging (fMRI) studies was that reducing activity of the ACC can reduce the affective component. We introduced GRIN lens-based calcium imaging of neural activity in the ACC, but our first studies were disappointing. We were recording under isoflurane anesthesia and found that the ACC was quiet, in fact, silent, which provided absolutely zero insight into relevant circuits. But these initial recordings once again proved serendipitous. Jarret reminded me of the unusual properties of ether, compared with contemporary general anesthetics. Specifically, stages of anesthesia can be recognized during ether application, beginning with analgesia and amnesia, well before the patient is unconscious (Snow, 1847).

We actually received approval to study ether by the IACUC, but the office of Environment, Health, and Safety strongly discouraged its introduction into the lab, for pretty obvious reasons. So Jarret proposed that we study the dose-dependent action of more contemporary general anesthetics. Most interestingly, when we studied nitrous oxide, which has analgesic properties and has been used in dental and labor procedures, we unexpectedly found profound activation of excitatory neurons in the ACC (Weinrich et al., 2023). Clearly this paradoxical finding of an analgesic *activating* ACC neurons necessitated a reevaluation of the circuits in the ACC through which pain affect is generated. The clue to what might underlie the paradox was revealed when we studied the effect of a noxious stimulus (laser-evoked heat to the paw) in the presence or absence of nitrous oxide. Not surprisingly, the laser increased activity, however, in the presence of nitrous oxide, the increase was much reduced compared with the increase over baseline.

This finding suggested that the extent to which ACC activity underlies pain affect is more a function of the difference between the noxious stimulus–evoked activity relative to baseline activity. We hypothesized that the activity provoked by the laser stimulus relative to spontaneous activity may, in fact, represent a biomarker of the affective component of the pain experience. And interestingly, we suggested that that activity may underlie the phenomenon of connected consciousness, in which there can be perceived pain in an anesthetized, immobile patient presumed to be unconscious (Sanders et al., 2017).

Long-Term Spinal Cord Imaging in the Awake, Behaving Animal

Having introduced calcium imaging, we turned our attention back to the spinal cord. Although trained as a spinal cord physiologist with Pat Wall, I have always appreciated the major limitation of the approach. Specifically, with only rare exceptions, all studies are performed in anesthetized animals, and they are performed acutely, making it impossible to follow the activity of neurons over time, so as to study the transition from acute to chronic pain. Very recently, with brilliant postdocs, Biafra Ahanonu and Andrew Crowther and a fabulous neuroscience graduate student, Mariela Rosa-Casillas, we have solved the post-laminectomy fibrosis problem, which makes long-term imaging possible (Ahanonu et al., 2023). The problem of excessive movement of the spinal cord has also been addressed, so that now we not only can record long-term images from the same population of spinal cord neurons, but also the recordings can be performed in the awake, behaving mouse. Immediately obvious, and admittedly not unexpected, was the increased excitability of dorsal horn neurons, including the presence of spontaneous activity and more pronounced firing in the awake versus the anesthetized state.

With this new ability, we are also now able to study the organization of dorsal horn circuits that process injury messages, before and after tissue or nerve injury, while correlating behavior. We are also addressing the long-standing question of the polymodality of dorsal horn projection neurons in superficial dorsal horn, not only in response to pain-producing algogens but also itch-provoking pruritogens, including histamine and chloroquine. Particularly exciting, although challenging, is our plan to concurrently record from spinal cord and brain regions (e.g., amygdala or ACC) so that we can interrogate mechanisms by which the brain makes decisions based on activity in populations of spinal cord projection neurons. Specifically, if there are no labeled lines for pain and itch, then the brain must decode activity across the projection neurons. Concurrent recordings from brain and spinal cord in the awake, behaving animal will hopefully provide insight into how those decisions are encoded.

Development of Novel Analgesics: Collaborating with the Chemists

This collaborative culture at UCSF is incredibly well-illustrated in our very recent work with UCSF chemists, in a DARPA-funded collaboration in which we seek to identify novel pain pharmacotherapeutics. The major objective is polypharmacology, specifically to develop nonopioid analgesics that concurrently interact with multiple targets in an additive or ideally in a synergistic fashion. Our laboratory has been working with UCSF chemists and biochemists, headed by Brian Shoichet, who use *in silico* screening to identify novel receptor ligands. Brian and colleagues screen against a cryostructure of a known analgesia target or by homology screening of an existing analgesic. Remarkably, they typically screen more than 300 million and, more recently, more than 2 billion structures and then narrow down the search, based on binding, PK, and other factors. The top candidates are synthesized, and to identify the most potent analgesics, our lab studies their effects in wild-type and a variety of knockout mice.

Of course, we are particularly interested in analgesics with the best therapeutic window. Especially notable is our recent discovery of several molecules that target the alpha2 adrenergic receptor. These novel ligands are analgesic in a variety of acute and chronic pain models and, most important, they do not show sedative effects at doses that are profoundly analgesic (Fink et al., 2022). By combining neuroanatomical and pharmacological approaches, we also focus on the loci where the novel drugs act. In other studies, we have identified novel ligands that are effective analgesics, including novel cannabinoid 1 receptor agonists (Tummino et al., 2023) as well as novel agonists that engage the EP4 receptor (Gahbauer et al., 2023), which is the target of pain-sensitizing prostaglandins.

The Lure of Industry

Not surprisingly, perhaps, my search for novel analgesics introduced me to small and large pharma. The need is obvious: 100 million people in the United States experience pain in a given year. And for about a third, the pain seriously interferes with quality of life. Of course, the drive to develop something as good as (and hopefully that can replace) opioids has provided a particularly strong incentive for venture capitalists to look for opportunities to translate laboratory findings into a successful company. Unfortunately, my success in the pain world has been less than outstanding. An earlier company in which Clifford Woolf and I engaged with several other colleagues failed when a microglial targeting effort proved ineffective for postherpetic neuralgia. Sadly, that was definitely an example of reverse serendipity. In fact, most of the scientists involved were not in favor of beginning the clinical trial, but the venture capitalists were insistent.

Very recently, I was a cofounder of Coda Biotherapeutics, which was developing chimeric receptors that could be targeted selectively to, for example, primary sensory neurons and activated by an oral drug that had no target other than the chimeric receptor. The logic of Coda's approach is one that I have advocated for years. Specifically, there are many drugs that are effective against pain, but when administered systemically, they are severely limited by inevitable adverse side effects, particularly when the drug enters the CNS. Opioids offer the best example. Morphine is very effective for pain, but misuse liability, constipation, and, of course, respiratory depression are difficult to avoid. Ideally, the Coda chimeric drug would exert an effect only on the receptor, blocking pain, but not inducing adverse side effects. Disappointingly, despite impressive results, the recent difficulty in raising additional funds led Coda's demise.

I continue to emphasize the principle upon which Coda was developed, and it is a principle that I teach medical students. As I have said very often, oral and other systemically administered drugs "don't know where to go." Thus, side effects are inevitable. As part of a TikTok for Science effort organized by graduate students in the Quantitative Biology program at UCSF, I agreed to create a 50-second video that emphasizes this principle. Specifically, I agreed to answer the question "How does the ibuprofen know where to go?" As I knew and still know almost nothing about TikTok, my first effort was not too successful. Marcia, to whom I am now married and who is a complete nonscientist, deemed the video of my answer to the question, "Boring!" Knowing my penchant for writing poems, she suggested that I write a poem, which I did and videotaped myself reading it. "Better, but not good enough," Marcia said. "You need to Rap it!" I also know little about Rap, but I am game. So, for those interested, please check this video out: https://www.tiktok.com/@qbi_ucsf/video/6977811026590878982 As to the words of the poem:

How Does the Ibuprofen Know Where to Go?
You injure your knee, the knee's inflamed, and boy it hurts like hell,
So, you take a pain reliever that you hope will make you well.
Into your mouth go ibuprofen pills, but they're not looking for your knee.
The pills will travel everywhere, of that I guarantee.

You see the ibuprofen has no idea where to go, and so I must advise.
Ibuprofen will work everywhere, so stomach and other side effects could definitely arise.
You see, it's the side effects from oral ibuprofen that limit what dose is needed for your knee.
And taking more pills won't solve the problem; of this your stomach will certainly agree.

Alternatively, treat the injury directly, for example, a medicated patch placed on the knee;
Side-effects less likely, and with luck, you're now pain free.

Memorable Events: The Berlin Dahlem Conference and Nagorno-Karabakh

I have often noted that one of the wonderful benefits of science is the opportunity to attend national and international meetings, where science is not only presented and discussed, but where lasting friendships are made. I believe that I have a close colleague in most of the major cities in the world, and even in some of the less-well-known cities. And often the meetings at which we interact take place in fabulous settings.

Serendipity unquestionably led to perhaps my most memorable international meeting, which Jean-Marie Besson and I organized. For many years, Jean-Marie led the most significant pain research group in France, and it was in his lab that I spent a wonderful sabbatical year. In 1988, we met in Berlin to plan a Dahlem conference, to be held in Berlin the following year. Dahlem conferences were unusual—only 40 attendees, many of whom are not in the field to be discussed. The hope was that bringing scientists from different disciplines, who meet for a week of largely informal discussions, could move the field in ways that do not occur with traditional get-togethers. Well, it turned out that one year later was exactly the date that the Berlin Wall came down, or at least opened up. Attendees arrived in Berlin in November 1989, expecting that the meeting would be canceled. In fact, the meeting went on as planned and was very successful, resulting in a book that included papers submitted ahead of time, as well as several rapporteur reviews of the discussions that took place.

But the evenings after the discussions ended proved most memorable. We went to the wall, hammer in hand, carved out pieces, listened to music, saw East German guards walking on top of the wall, but without guns, and watched as throngs of East Germans crossed the border. I remember seeing two East German and two West German soldiers literally pick up and carry a small Skoda (a two-stroke, single cylinder Czechoslovakian car) that got stuck at the border, into West Berlin. The crowd went nuts. I still have pieces of the wall in my office. Disappointingly perhaps, the initial title of the book (*Towards a New Pharmacotherapy of Pain: Beyond Morphine*) was overly optimistic. Morphine, sadly, is still the most powerful pain reliever available, and we continue to seek something better. So we dropped "Beyond Morphine" from the title of the book (Basbaum and Besson, 1991).

On a more somber note is a meeting that I attended more than 20 years ago, in Nagorno-Karabakh, a small enclave in the middle of Azerbaijan, populated by Armenians, but largely isolated. My dear friend, Vania Apkarian, with whom I recently cowrote an amicus brief concerning the Dobbs decision at the Supreme Court, wanted to make more people aware of the concerns surrounding Nagorno-Karabkh, which in 1994, had won a

battle for independence from Azerbaijan. Vania organized a small meeting, in Stepanakert, the capital. We were housed in a hotel that survived the war, but it was rather run down and had little running water, and electricity often resulted in lights and slides disappearing in the middle of talks. But we met the people who lived in Nagorno-Karabakh, especially the children who loved the candy and even the flashlights that we were told to bring as gifts. I also remember the rather old Russian plane that took us from Yerevan, Armenia, where a post-election-attempted coup initially kept us in our hotel, to Nagorno-Karabakh. The return bus trip was even more eventful. We had to stop for hours at the border with Azerbaijan, so Ze'ev Seltzer organized the building of a large sculpture on the border, made from whatever attendees could collect (rocks, branches, leaves). Unfortunately, these positive memories are very sadly smothered by the recent war in Nagorno-Karabakh, in which Azerbaijan has retaken control. I know that Vania is devastated and is organizing a philanthropic effort to raise funds for the citizens who need support. My thoughts will always be with them.

A Memorable, but Embarrassing Event, and Forgettable Recognition

There is an oft-repeated illustration of the fact that my ability to communicate in French is not perfect. Although I am reasonably fluent in French, and in fact, have presented lectures in French, including a memorial to Jean-Marie Besson at a French Pain Society meeting in Nantes, what I clearly miss is an appreciation of French slang, and especially the evolution of the meaning of specific words. Years ago, I was at a meeting in Italy, with my late wife, Carol, and we were saying goodbye to Jean-Marie. I shook hands with Jean-Marie and said "Au revoir, a la prochaine." Then Jean-Marie shook hands with Carol, at which point I said, "Jean-Marie, tu peux baiser ma femme," which literally means you can kiss my wife (presumably on the cheeks). What I did not know is that a slang adoption had significantly changed the meaning of *baiser*. Translated to its contemporary meaning, what I said was, "Jean-Marie, you can f@&! my wife." Jean-Marie's glasses fell from his head. He laughed out loud, and then corrected me. I soon learned that I could not attribute my mistake to Quebecois French "un baiser" still means "a kiss," but the slang version of the verb is what is now common both in France and in Quebec.

Carol and I did achieve some interesting royal recognition, but not necessarily recognition to put in your CV. My friends jokingly referred to Carol as the Queen of Mucus and me as the King of Pain! There are certainly many colleagues in the field who are better deserving of the title of King of Pain, but it did lead to a wonderful family event. As a gift for my 70th birthday, Marge and Thom Limbert, the brother and sister-in-law of Marcia's son-in-law, Jake Limbert, wrote and sang a song "The King of Pain." This song is an obvious take off on Police's "King of Pain," but their

song instilled considerable humor by including phrases captured from some of my YouTube lectures on pain, including Placebos work! Where's the pain? In my mind, of course.

The song is available at https://on.soundcloud.com/D2HNh. (I am not sure where they found the 1980s picture of me with an afro.)

Allan Basbaum Turns 70, and He's the King of Pain
Lyrics by Marge Limbert; music by Tohm Limbert (and the Police).

There was a little post doc in a lab that day;
He's the same old thing as yesterday.
There's a last-minute present from an airport shop;
There's a mouse he's got and its pain will stop.

Chorus
I have stood by his bar, he's pouring Tanqueray.
With the pain and itch neurons running round his brain, I guess.
We're always hoping that he'll end his reign,
But, it's his destiny to be the King of Pain

Chorus
There's a little postdoc at the lab that day (he's Canadian).
He's the same old thing as yesterday (he's Canadian).
There's an interview with Charlie Rose (he's Canadian.)
There's a dreadful joke turning friends to foes (he's Canadian).

Chorus
There's a golfer who's trapped in the sand his ball (he's Canadian).
There's a researcher altering his protocol (he's Canadian).
There's a jazz standard played by a dorky dad (he's Canadian).
There's a transgenic mammalian in his science lab (not Canadian).

Chorus
There's a condo in Soma with modern;
There's a short man braggin' 'bout his peer review clout.
There's a smart man eating lunch at Panda Express;
There's a PhD made into a bobble head.

Chorus
There's a boss having parties to reward his lab (he's Canadian).
There's a Sharks fan now who cheered on the Habs (he's Canadian).

There was a little post doc in a lab that day.
He's the same old thing as yesterday.

> King of pain, king of pain, he will always be king of pain, he will always be king of pain.

Of course, it has been a while since I was a postdoc, but the birthday song was great fun. Unfortunately, after reading *Empire of Pain: The Secret History of the Sackler Dynasty*, by Patrick Radden Keefe, which is a remarkable book that tells the story about the Sacklers, Purdue Pharma, and the opioid epidemic, I learned that the book includes a pejorative reference to Russell Portenoy as the King of Pain. In my opinion, Russ has made many significant contributions to the clinical effort to treat chronic pain. If he is the King, then it is for those positive contributions.

The UCSF Environment: Amazing Faculty, Students, Postdocs, and Administrative Colleagues

I have often told my students and postdocs that being a scientist and pain researcher is my hobby. One student, Racheli Wercberger, thought that was great, and asked "When will it be my hobby?" I really do consider the science that I do every day to be equivalent in many ways to a delightful hobby, something that I look forward to doing, but definitely one that I take seriously. Of course, the hobby is significantly enhanced by my good fortune at being on the faculty at UCSF. Collegiality among the faculty, outstanding trainees, and an incredibly open and interactive research environment are the hallmarks of this place. Doors (and minds) are always open and establishing a collaboration is incredibly easy.

A few years ago, I looked back at my CV and realized that I had published with close to 40 UCSF faculty, highlighted, unquestionably by my collaborations with Howard, Jon, and David. In contemporary publications, technology is often significant, and it explains why papers now have many authors and a slew of approaches. The ability to engage others who are experts with different technologies is critical. At UCSF that is easy. The contrast with the way science was published in the past century is obvious; many fewer authors on papers, and as one of my graduate students commented after her lab meeting report on a paper published in the 1980s: "Not only did the manuscript from the last century have many fewer authors, but Figure 1 only had 1 figure!" "That's why it's called "Figure 1," I said. Now, of course, every paper has 20 authors and Figure 1 has 20 tiny postage-stamp-size images.

Needless to say, the success of the laboratory owes much to the faculty at UCSF. Without an amazing administrative staff in the Anatomy Department, headed by Stephanie Louie, and without my executive assistant, Linda Toschi-Chambers, my responsibilities as chair for the past 25 years would have made the success of the laboratory impossible. And as department chair, I have received wonderful support from several deans, most recently Talmadge King, and the chancellor, Sam Hawgood. The greatest credit,

however, must go to the incredible students, postdocs, and research technicians with whom I have had the good fortune to work. Many of the trainees have gone on to successful academic positions, including at Loyola University (Dan Cavanaugh), University of Pittsburgh (Brad Taylor), University of North Carolina (Greg Scherrer), Washington University (Yu-Qing Cao), and McGill University (Reza Sharif-Naieni). Additionally, Dana Rohde and Igor Mitrovic are both on the teaching faculty at UCSF. Many others chose industry (a common decision in the Bay Area), including many in leadership positions (Andrew Ahn, head of migraine research, Teva; Annika Malmberg, vice president, research, Sarepta Therapeutics; William (Bill) Martin, global therapeutic area head, neuroscience, Johnson & Johnson; and, last but certainly not least, Susan Hockfield, who was president of MIT. Many continue to hold positions in venture capital, science communication, and other posts in the educational field. Particularly striking is the remarkable breadth of countries from which the scientists in the lab originated: Great Britain, Ireland, Hungary, France, Iran, Israel, Canada, Sweden, Turkey, Norway, Spain, South Korea, Brazil, Venezuela, Germany, Japan, China, Australia, Russia, India, Serbia, Croatia, and, of course, the United States. Many languages are spoken, but the common one is the language of science. Lab meetings are engaging and always useful, during which we present ongoing research, exciting new discoveries, and creative technology, and most important, are never afraid to discuss problems, even experiments that failed. We alternate research meetings with a journal club, where everyone quickly realizes that if you have about 15 "reviewers," no manuscript would ever get published.

Life and Work Outside the Lab

In addition to overseeing a research lab at UCSF, as well as being chair of the Anatomy Department since 1998, I have thoroughly enjoyed engaging in professional work outside the university. I served as treasurer of the IASP, and several years later, lost an election (fortunately) for president. I have been a member of the Board of Scientific Counselors at the National Institute for Dental Research (now the NIDCR), which for years was the home of one of the strongest pain research groups, led by Ron Dubner, who sadly died very recently.

As of this writing I am completing a four year stint on NINDS Council and continue as a member of the MDWG (the Multidisciplinary Working Group) that advises the executive committee of HEAL (Help End Addiction Long-Term). The latter committee was created by Congress and has dispensed significant funds to basic and clinical pain and addiction research efforts to address the ongoing opioid epidemic. Because there is no NIH Pain Research Institute, undoubtedly related to the fact that chronic pain cuts across the interests of almost all existing NIH Institutes, the effort of HEAL is particularly significant. At this time, I also serve as cochair of the Scientific Advisory Board of the Facial Pain Research Foundation, which is

dedicated to finding a treatment for trigeminal neuralgia, and as chair of the IASP Publications Committee, which advises on policy for IASP Pain publications, including *Pain*, *Pain Reports*, and *PRF* (*Pain Research Forum*). I have also served on the advisory boards for small and large pharma, advising on novel pain therapeutics. Importantly, my outside activities are not limited to scientific enterprises. I was appointed to the board of the French American International School, which my daughter and son attended, and I served as president of the board for 10 years. No doubt that service is what led to my receiving the Chevalier French Order of Merit from the French government (not quite the Legion D'Honneur).

As noted earlier, many of my trainees followed my love of science and are in successful careers in academia and industry, and even as teachers in high school science. But it did take a while for the hobby to be firmly established. When I was setting up my first lab, I was probably impatient with the folks in the lab. I often walked through my 360-square-foot lab urging everyone to finish up their experiments, finish the injection, mount the sections, evaluate the slides, and take pictures. Apparently, I said that "I could do that in 10 minutes" once too often, and one day I came into the lab to see that everyone was wearing a t-shirt that said, "Allan does it in 10 minutes." So that was the last time I used that phrase, and over the years, I have calmed down.

On the one hand, I still get excited when new ideas and results are presented at lab meetings, and I thoroughly enjoy putting research findings into print. I appreciate the challenge faced by students and postdocs and enjoy seeing their success. On the other hand, I have to say that I was taken aback at the 2022 SfN meeting, when I was approached by a young student at the Pain and Itch Social. This student introduced herself as my scientific great-granddaughter! Indeed, she was a graduate student in Greg Corder's lab at Penn. Greg not only did his graduate work in a former postdoc's lab, namely Brad Taylor, but Greg was also a postdoc in the lab of another postdoc, Greg Scherrer. Clearly, I have been doing science for a long time, but I still enjoy it. But I can't promise that I'll continue until I meet my great-great-grandchild in pain research.

Katherine and Jesse

My kids unquestionably grew up in an environment very different from many of their friends. From the time we arrived in San Francisco, Carol and I each worked six days per week, splitting the weekends. Vacations were rare, but we did travel together, with Katherine and Jesse, who was born five years later. I thought that Katherine and Jesse might continue our science tradition. Well, not quite. Katherine completed a theater degree at the University of California, San Diego. But even the theater majors had to take a science course, and Katherine not surprisingly took a neuroscience course. I remember her calling me one day saying that she and her dorm mates had a neuroscience exam and they needed help.

"Did I know *anything* about the NMDA receptor?" she asked.

"A little," I said.

After a one-hour telephone tutorial, she did well on the exam, but she did not pursue neuroscience. Interestingly, however, after being convinced that an acting career was not ideal, she went to Tufts, where she received training as a registered dietician. That curriculum, of course, required her to take several basic science courses, physiology, and even molecular biology. Times did change. I remember her calling to tell me about a really interesting paper that she read on epigenetics! She is now a very successful dietician nutritionist at the University of Virginia and has been married for several years to Tony Noble.

My son, Jesse, followed a very different path. In fact, at Oberlin, Jesse did major in molecular biology and comparative English literature and also volunteered several times in my lab. I thought that he might consider medical school. Not at all. After working with immigrant workers in Oberlin and then in Portland, Rhode Island, he moved to New York where he became a private investigator for the Bronx Defenders, a public defender's office. That experience convinced him to get a law degree. He attended Hastings College of Law in San Francisco, now called University of California College of the Law, because of the terrible legacy of its founder.

While in law school, Jesse was editor-in-chief of *Law Review* and then he clerked in Philadelphia for a senior judge, who had clerked for Thurgood Marshall. After a short stint in a major law firm, and another clerkship in Los Angeles, Jesse decided to become a public defender. He is married to an immigration attorney, Kate Mahoney, who he met in law school. They are both committed to using the law to the benefit of those who normally cannot afford it. Recently, after many years as a public defender, Jesse took a position in the state attorney general's office, where he is a deputy attorney general. Needless to say, I was pretty impressed, but according to Jesse, there are many deputy attorney generals.

A New Life with Marcia

About two years after Carol died, dermatology chair, Bruce Wintroub, who at the time I only knew through endless committee meetings, asked me if I was "dating." He said that there was someone who he wanted me to meet. No thanks, I said. Bruce would ask every three months, and finally, I agreed. So, Bruce and his wife, Marya, organized a dinner at their home and invited four friends. I was nervous as all get-out. But Marcia (Fortnoff), who lived a few blocks from Bruce and Marya and whose older daughter Kate was best friends with their daughter Mollie, was incredibly engaging. After dinner, we talked and talked. Marcia's husband Ken had died a year before Carol, so in many ways we had a lot in common. We did start to "date" and three years later decided to get married. Marriage likely would have happened

earlier, but we didn't want to ruin the excitement of the pending marriage of Marcia's oldest daughter, Kate, to Jake Limbert. Interestingly, we were married at City Hall by Gavin Newsom, then the mayor of San Francisco and now California's governor, through a connection that Keith Yamamoto had. The "service" in his office was brief, but Gavin was gracious. Memorable was that when we walked out of his office, Marcia turned to me and said, "Boy, he's handsome." Interestingly, we just saw the movie *Barbie*, which includes Barbie's boyfriend, Ken, and his friend, Allan, which of course, are the names of Marcia's two husbands.

Marcia could not be more different from Carol. First, while Carol was a successful scientist with whom I could discuss the latest findings in my lab, Marcia was a court reporter and then a headhunter in the legal world. Marcia believes in pretty much every alternative therapy that exists, including acupuncture, which I believe is an exotic placebo. But placebo, in my opinion, is a word that needs to be replaced. Specifically, when I suggest to friends that many, if not all, successful alternative or complementary therapies are a placebo, the natural assumption is that I am implying that nothing was wrong in the first place. Far from it, of course. Placebos can be very effective particularly against pain, which is a percept of the brain. In my pain lecture to the medical students, I tell them that at home I can use the "f" word, but not placebo. We need a new word.

Our families have blended incredibly well. Most enjoyably, our sphere of friends, and notably their exceptionally varied backgrounds, have grown. Not surprisingly, many of my closest friends are scientists, but Marcia's friends include many lawyers, artists, hair stylists, and chefs, and we meet regularly. Marcia and I together have four grandchildren, all of whom fortunately, live in the Bay Area. Marcia's older daughter, Kate, is a psychotherapist and is an expert in couples therapy. Kate's husband Jake is interim vice president of Supply Chain and Support Services at UCSF. Marcia's younger daughter, Chase, is a social worker and Veterans treatment specialist. She works with veterans who have pending criminal cases and helps them get diverted to Veterans Treatment Court and connected to VA services. Chase's husband Agustin is also a public defender, and one of the most ardent baseball fans I have ever met, attending both Giants' and A's games, as well as soccer games in San Jose. Kate and Jake have two girls, Willa (11) and Hazel (7), and Jesse and Kate have a son, Aengus (6), who we call Gus, and a daughter, Maeve (3).

Sadly, COVID has limited the times that Katherine and her husband Tony can visit from Charlottesville, but hopefully, passing of the pandemic will allow for more visits in the near future. We have a second home in Napa, which was built when Carol was ill, as a place to get away. However, in 2017, the home was destroyed in one of the too many fires in Napa Valley. Fortunately, the insurance companies were outstanding, and we rebuilt the home. Marcia and I don't get there very often, but our children and

grandchildren thoroughly enjoy it. As a fun aside, after the fire, the insurance agent insisted that everything depreciates. I argued that art, which is one of the areas in which Marcia and I completely agree, never depreciates. I reminded the agent of the Saudi Arabian prince who recently purchased a Da Vinci painting for $450 million; clearly paintings appreciate in price! Probably terrified, the agent asked me: "You didn't have a Da Vinci in Napa, did you?" Fortunately for her, I didn't.

Should I Retire?

Having been involved in pain research for more than 50 years, I do have to look into the mirror and ask whether it is time to pass the torch, not only the scientific one, but also the administrative one. As Marcia, knows I need to be busy. My nonscience hobbies include playing jazz piano, and I still take lessons, and I am a golfer. After our home in Napa burned down, I was invited to join Bruce Wintroub and two other friends and play every weekend in Richmond. I am actually improving and thoroughly enjoy the weekly four hours of camaraderie.

I have, in fact, discussed a transition with the dean (not quite as dramatic as the television series *Succession*), but a discussion that is nevertheless relevant to the Anatomy Department faculty. In fact, about 15 years ago, I seriously considered stepping down. The department was populated by many senior faculty, so there was little that the chair could do; space was occupied and there was no hiring. When a senior faculty member had funding issues, putting out fires predominated. But I stayed on, and after many retirements, the department was truly reborn. We have hired many young, dynamic scientists (interestingly only a couple of neuroscientists). Rather, the department's strength is in cell and development biology, stem cells and cancer. Two years ago, we created an Aging Research Institute, headed by Leanne Jones, whom we recruited from UCLA, and Saul Villeda, whose studies of blood factors that influence aging have truly revolutionized the field. A wonderful gift made possible the creation of the Bakar Aging Research institute (BARI). The Institute is now a vibrant research enterprise, with faculty from many departments focused on the biology of aging. There is hope for me yet.

In Summary: A Gift to Readers—PRM

As it is unlikely that all readers will enjoy reading my autobiography, I am ending with a final poem that I hope will be of interest to most SfN members. Needless to say, we are all overwhelmed by emails. Unfortunately, although the great majority can be immediately deleted, many contain messages that we need to address. But often, for many reasons, we can't answer immediately our email. My concern, however, is that the message will get lost. The oppressive effect of COVID made communication even worse, as in person

interactions led to even greater numbers of emails arriving every day. To reduce the potential negative impact of the increased electronic communication, I created PRM, which stands for Please Remind Me. Specifically, when I want to highlight a message that I must not forget, I forward it immediately to Linda, my administrative assistant, with PRM in the subject line. Every Wednesday and Friday afternoon, I receive a list of the PRMs, so that important messages and relevant dates when an answer is required never get lost or forgotten. That simple solution has greatly improved how I deal with the ridiculous number of emails, only some of which need an immediate response.

PRM (Please Remind Me) Is a Gem

Well, COVID has unquestionably changed how we work; it's all email and Zooming forever.
But prioritizing what to do hasn't changed, our colleagues still hate to hear "Oh, whenever."
Some work still needs to get done, so you should try PRM,
You won't forget a key task, and avoid more mayhem.

Every Wednesday and Friday, you'll receive updates of the PRM lists.
You'll probably recognize some needy individual, who you thought no longer exists.
Some emails seemed unimportant, others portend coming doomsday.
Those can't wait till December, so answer them today.

This reminder method can work miracles; some make my assistant LOL
Especially when I refuse to address them, as they are the emails someone sent from hell.
So give it a try with your colleagues, adopt PRM.
It could alter your life; it's truly a gem.

The last few years have been tough, but working together we did COVID survive.
Everyone's amazing; staff, faculty, students, and postdocs continue to thrive.
We are now really "rounding the corner" and now have reasons to cheer.
So, my PRM for everyone is to have a very successful rest of this year.

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