1 **Creativity Needs Some Serendipity: Reflections on a Career in Ingestive Behavior**

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16 **Keywords:** Thirst, dietary obesity, sensory-specific satiety, portion size, energy density, food
17 intake

24 **Abstract**

25 I describe my 50 year career in ingestive behavior in the hope of inspiring young scientists to
26 join in the excitement of discovering why animals, especially the human animal, eat and drink.
27 My interest in ingestive behavior started by chance in a freshman biology class at the University
28 of Pennsylvania taught by Alan Epstein. Once I was exposed to the thrill of doing research my
29 plans for medical school were abandoned and I traveled to the University of Cambridge in
30 England where with James Fitzsimons I completed a Ph.D. in physiology on studies of thirst in
31 rats. After I moved on to the University of Oxford, the early training in biologic mechanisms
32 provided a good basis for studies in humans. We characterized the sensations associated with
33 thirst and the mechanisms involved in its initiation and termination. We also continued to work
34 with animal models in a series of studies of dietary obesity. The effect of dietary variety on rat's
35 intake led to studies of sensory-specific satiety in humans. In recent years the primary interest of
36 my lab has been how food properties affect intake, satiety, and body weight. At the Johns
37 Hopkins School of Medicine and now at The Pennsylvania State University, we have conducted
38 systematic studies of the effects of the macronutrients, variety, portion size, and energy density
39 in both adults and children. Currently our research aims to understand how to leverage the robust
40 effects of variety, portion size, and energy density to encourage healthy eating and drinking.
41 Throughout my career I have been lucky to have been in supportive environments surrounded by
42 creative, insightful, and diligent colleagues.

1. Introduction

The recipients of the Bart Hoebel Prize for Creativity awarded by the Society for the Study of Ingestive Behavior (SSIB) are encouraged to share their reflections on the discoveries that led to being honored. With gratitude to SSIB for selecting me for the Hoebel Prize, I share some highlights and insights from my career with a particular emphasis on the early years.

While all scientists strive for creativity, even the most creative need some serendipity. We cannot plan the twists and turns our research paths will take. Over the 50 years that I have been studying drinking and eating behavior there have been many unforeseen developments and opportunities that have driven discovery. How could any of us have imagined where the advances in technology would take us? Nor could we have completely controlled the mentors and colleagues who would impact our ideas and provide opportunities to test them. Let's start at the beginning and journey over my serendipitous fifty years in ingestive behavior.

While growing up I was exposed to extremes of eating behavior. My dad was a six foot tall bean pole who ate mountains of food just to maintain his weight while my mom, who seemed to eat little, at least around us, was obese. With this family background and some struggles with my own "freshman" weight gain, I found myself in an introductory biology class taught by Alan Epstein at the University of Pennsylvania. Harry Kissileff was the lab instructor. Somehow among all the undergrads I caught their attention. Harry claims it was because I took my fetal pig back to my dorm room to continue the dissection. With Alan, I sought him out. I worked on diverse projects in his lab, from the genetics of fruit flies to stereotaxic brain surgery in rats. As an undergraduate I was welcomed into the inner circle of ingestive behavior at Penn that has spawned so many of us in this field: the famous "Feeding Seminar" with luminaries such as Phil Teitelbaum, Paul Rozin, Eliot Stellar, and Alan Epstein. I do not recall if I ever dared speak up in

the intense debates about such topics as the role of the hypothalamus or the definition of a motivated behavior.

Even with this early exposure to the excitement of our science, I planned to go to medical school. While in high school I had been a participant in an immersive summer experience at Georgetown Medical School to encourage kids to become doctors, so the idea of medical school had been implanted early on. I applied to only two medical schools, Penn and Cornell, and was accepted by both—quite a feat as at the time only four percent of the students were women. In the interviews I was consistently asked how I would manage when I had a family and children. I must have given an appropriate response—it is good such questions are now taboo. Even then I knew that I wanted to do research, not be a practitioner. Shortly after I accepted my place at Penn Med, a fellow premed student came to class bragging that Alan Epstein was recommending him for a fellowship to study in England. I stormed off to Alan and demanded to know why I was not the one being sent to England. The reason was that women were not eligible! Let's just say we got that changed and many women have since participated in the program. Off I went with a Thouron Scholarship to promote “Anglo-American affairs” and to study in the Department of Physiology at the University of Cambridge (where there were no female graduate students) with James Fitzsimons as my mentor. It was meant to be just for a year after which I would come back to Penn Med. I stayed 18 years in England starting in 1966.

2. University of Cambridge: Studies of thirst

Although I did not know it, Alan had a hidden agenda. He had met James at a meeting in Japan and they were eager to collaborate. I was the facilitator—a very lucky go-between. I arrived in the Fitzsimons lab (it consisted of just him, he had never had a graduate student or

post-doc) when he was in the midst of seminal studies showing that the kidney is a homeostatic organ that plays a critical role not just in excretion, but also in the control of fluid intake (1). In a series of meticulous experiments he had shown that restriction of blood flow to the kidney caused rats in normal fluid balance to increase their water intake, and he suggested there was a thirst stimulus in the kidney, probably renin. James went on to show that intravenous renin was indeed a potent stimulus to drinking. I had joined the lab by this time, and in the next study we infused angiotensin intravenously since the effects of renin are usually mediated by angiotensin. Like renin, intravenous angiotensin caused drinking in rats which were in fluid balance (2). This series of studies supported the view that the renin-angiotensin system plays a role in thirst caused by depletion of blood volume, that is, the extracellular fluid compartment.

When I think back on this exciting introduction to experimental science, I cannot help but recall the simplicity of the equipment at our disposal. James had developed a device to record a rat's water intake (3) which consisted of a long glass tube a glassblower had formed into a spout at the rat end ([Figure 1a](#)). The tube was connected by air-filled pressure tubing to the upper end of a mercury manometer (an instrument for measuring the pressure acting on a column of fluid). A float in the open end of the manometer moved a stylus up as the water level went down. This stylus rested on and etched lines in the thick black residue on a sleeve of paper wrapped around a slowly rotating drum (kymograph) ([Figure 1b](#)). We prepared the paper for the drum ourselves down in the basement by hesitantly holding it in a machine that billowed out clouds of thick black smoke. At the end of a recording session, we returned to the basement and dipped the smoky records in varnish to preserve them. We used a ruler to measure the magnitude and time course of the rat's water intake ([Figure 1c](#)). Statistics (which were non-existent or minimal) were done by hand. While I was a graduate student the department got its first computer, which almost

filled a room, but its use was very restricted. Science has always depended upon the available technology, and the changes over the past 50 years really boggle the mind. At least we had electricity!

Figure 1: A: The original drawing of the drinking meter developed by Fitzsimons (reproduced with permission from ref. 3). B: The kymograph drum connected to the drinking tubes can be seen in the background at the top of the photo. C: An original drinking record from 1969 showing intakes by five rats tested simultaneously.

By the end of my first year in Cambridge, I had decided that I would stay in England and do a Ph.D. and not go back to Penn Med. I was loving doing research. Meanwhile, the

relationship between James Fitzsimons and Alan Epstein was further strengthened by James spending a sabbatical year in Philadelphia. I was left unsupervised for most of my second year as a graduate student and during that time had the opportunity to discover the thrill of testing my own ideas. Intrigued by the idea of the hormonal control of thirst, I studied the role of vasopressin in thirst (4) and mechanisms of drinking in diabetes insipidus (5). These studies, while interesting, reinforced the dramatic effects of the renin/angiotensin system on thirst in comparison to those of antidiuretic hormone.

After months of working on my own, I joined James for a summer in Alan's lab at Penn. The plan was to test the hypothesis that angiotensin stimulates drinking by direct action on the brain. After preparing rats with a cannula in the lateral hypothalamus, or the preoptic or septal regions, we were ready to inject angiotensin in doses that ranged between 1/1250 and 1/5 of the smallest systemic dose found to increase drinking. Despite the importance of this work, especially to James who had spent years working on the role of the kidney in thirst, my mentors wanted me to do the first injection (Figure 2). The result was immediate and convincing, angiotensin caused avid drinking—note that no statistical analyses were performed or apparently needed when we published (6). Here is how I described the discovery in my doctoral dissertation (7):

“All of the animals tested have been found to drink from a few ml of water up to 20 ml with a latency of 10 sec to several min after the angiotensin was injected. Once drinking started it continued vigorously for about 5 to 15 min. The animals continued to respond when injected 6 to 12 times in one day with ½ hour intervals between injections.

The effect of angiotensin is very specific; that is, the only behavioural response which follows its administration is drinking. After intracranial angiotensin a sleeping rat will

wake and go immediately to water. If the animal is awake at the time of injection, it stops whatever it is doing and starts drinking.... A food deprived animal which has just been allowed to start eating but which has only taken a few mouthfuls of food stops eating when injected with angiotensin and then starts to drink after the usual latency.... The drinking which angiotensin elicits appears to be motivated and, although large in quantity, is behaviourally normal.”

Figure 2: A photo taken at Penn in 1968 shortly after we demonstrated that intracranial angiotensin is a potent thirst stimulus (left to right: James Fitzimons, Barbara Rolls, and Alan Epstein).

The culmination of the summer of 1968 was the International Conference on the Physiology of Food and Fluid Intake (ICPFFI) which Alan hosted in Haverford, Pennsylvania. Twenty years before SSIB was born this was the major meeting for ingestive behavior research and James and Alan wanted me to be the one to present our findings there. My talk was placed last in an oral session which included many of the big names such as S.P. Grossman and E.M. Stricker. After they presented and just before I was called to the podium, at least half the audience got up and left—they had never heard of me. My talk (I was so nervous I do not

remember giving it) included a very compelling short movie of a hungry rat tossing a food pellet aside to get to the water spout after the injection of angiotensin.

Figure 3: No statistics were needed in this first demonstration of the effects of intracranial angiotensin II into the medial septal region of a rat. The isotonic saline control injections elicited small amounts of drinking unreliably. Pure angiotensin elicited 11.3 and 6.7 ml water intake with latencies of 39 and 33 seconds. (Note that drawings such as this were done by hand with draughtsman tools and each could take hours to produce.) Reproduced with permission from ref. 6.

By the time the next ICPFFI meeting came around, most of the studies of thirst were related to angiotensin. Such a compelling demonstration of a hormone eliciting a motivationally specific and robust behavior was novel and an important advance in behavioral physiology ([Figure 3](#)). When the work was published in *The Journal of Physiology* in 1970 (6), there was confusion about who was the senior author. At that time, *The Journal* required authors' names to be listed alphabetically, thus we were Epstein, Fitzsimons, and Rolls (I had changed my name from

Simons to Rolls). Clearly James Fitzsimons was the senior author as this work was the culmination of his years of careful and systematic testing of the role of the kidney in thirst. The collaboration was happy and symbiotic, and according to the obituary for Alan written by Elliot Stellar (8) was considered by Alan to be one of his most important contributions. For me, working with two such creative and generous scientists gave me an inspirational start to a career in ingestive behavior.

3. University of Oxford: Branching out

After three years I had completed the work for my Ph.D. James had hoped that I would stay on at Cambridge and he verbalized what many mentors must think: “Just when you are getting useful, you are leaving.” In 1969 I was off to the University of Oxford as I was engaged to Edmund Rolls, who was working on his doctorate there, and who is now a noted neuroscientist. I needed to find funding, but there were few opportunities. The Oxford colleges provided few post-doctoral fellowships--only a handful of the colleges accepted and funded women. I had my sights set on the Mary Somerville Junior Research Fellowship which had been the first established for women in England and which was open to applicants from any discipline. A scientist had never been awarded this fellowship (never mind an American) as it was thought they could obtain funds elsewhere. Fortunately in the interview for the fellowship it was easy to explain the importance and relevance of studies on ingestive behavior, and our science prevailed.

I was set with a salary, and David McFarland, who is a renowned animal behaviorist, welcomed me to his lab in the Department of Experimental Psychology. David was intrigued by the way that hunger and thirst interact, and the robust and specific nature of intracranial angiotensin on thirst provided a potent tool. In systematic studies, we confirmed our earlier more

anecdotal observation that angiotensin-induced thirst reduces food intake (9). As my career has progressed I have often recalled this finding since it contradicts a favorite piece of diet advice suggesting that you can mistake thirst for hunger and overeat when you are thirsty. This should be tested in humans since in other species thirsty animals eat less, not more.

My move to David McFarland's lab had an unexpected impact on my career. For two years we had been making do in old huts while waiting for construction to finish on the spectacular building that was designed for the departments of experimental psychology and zoology. A suite of rooms was reserved for David in the psychology half of the building, but shortly before we were due to move in, David accepted the position as head of animal behavior in zoology. I did not want to change departments with him so the psychology department needed to find space for me since I had the research fellowship and a grant from the Wellcome Trust. They gave me all of the space set aside for David! Thus at age 26, I was director of my own magnificent lab. It makes me queasy now to think about that. I do not recall any moments of cold feet worrying about funding—not because there was an abundance of money available, but because the possibility of not being able to do research after a Ph.D. was never considered or discussed. My worries were instead about whether I could keep coming up with novel and interesting ideas for studies. My mentors had always been there for me. I did not have a sense of what the current hot topics were. It is hard now to relate to a time when your view of what was going on in your field was limited to waiting for a journal to arrive by mail (in the UK, US journals arrived months after publication), attending meetings (there was limited funding for such), telephoning (expensive), or writing letters to colleagues (the main way of communicating).

What I lacked in global connectivity was more than compensated for by the ability to establish local connections. I was at Oxford so there were plenty of potential collaborators. Luck was with me again when I met David Ramsay, a body fluids physiologist who was intrigued by thirst. He convinced me that you cannot study thirst without an understanding of what is going on with the body fluids—measure all that you can was the lesson. We conducted a series of studies characterizing body fluid changes associated with thirst in several animal models (10, 11).

I had always wanted to work on humans, and if the goal is measurement, they provide not only the opportunity to measure changes in biologic variables, but also to ask about thirst sensations. Even as an undergraduate, I had pored over the 1958 book *Thirst* by A.V. Wolf (12) with its graphic descriptions of aberrant thirst in disease and the thirst experienced by survivors of shipwrecks and long periods in the desert without water. But by the 1970s there had been few systematic studies of thirst in humans. Thus, a team of us set out to characterize thirst following a period of fluid deprivation (13). Following 24 hours without fluids, measurement of plasma variables indicated significant changes in both the cellular and extracellular fluid compartments. Visual analog ratings showed that thirst was experienced as a dry, “tacky” mouth, along with a strong desire to drink some water. Following such dehydration, healthy subjects drank copiously, taking 65% of their total intake within 2.5 minutes. The marked decrease in drinking rate thereafter, and the alleviation of thirst, occurred before plasma dilution had become significant. The attenuation of drinking was attributed to a full stomach. These results indicate that presystemic factors are likely important for the termination of drinking in humans.

After this initial study, I was fortunate to have Paddy Phillips doing his doctoral work in my lab. He had obtained his medical degree in Australia, and thus was well-placed to continue

the study of thirst in humans. In one study, we demonstrated that controlled infusions of hypertonic saline reliably stimulated thirst and drinking that was associated with dryness of the mouth and an unpleasant taste in the mouth. It was relief of these symptoms that was associated with drinking termination (14). We also infused angiotensin intravenously, but the results were mixed, with four of the ten men tested reporting thirst that was associated with increased water intake (15).

Although increased thirst and fluid intake followed deprivation and depletion of body fluids, we were interested in why people drink when liquids are freely available. Would they wait for a significant depletion before drinking? To determine whether thirst and drinking during free access to water occur in response to body fluid deficits, blood samples and ratings of thirst were obtained from young men at hourly intervals and also when they were thirsty during a normal working day (16). Although there were significant increases in ratings of thirst, pleasantness of drinking water, mouth dryness, and unpleasantness of the taste in the mouth when subjects were thirsty enough to drink, there were no concomitant changes in body fluid variables. Subjects drank mainly in association with eating. The results indicated that during free access to water humans become thirsty and drink water before significant body fluid deficits develop, perhaps in response to subtle oropharyngeal cues or simply due to habit.

All of our studies on human thirst depended upon our collaboration with John Ledingham, a senior clinician at Oxford. In one of our brainstorming sessions, he shared an observation from his clinical practice that led to what is probably our best known study. He frequently found that older patients with type 2 diabetes were diagnosed later in the disease than younger persons. He proposed to us that this could be because they were not experiencing the thirst that is often an early indicator of diabetes. Thus, we designed a study in which we

271 compared the effects of 24-hour fluid deprivation in healthy men aged 67 to 75 to those in
272 younger men aged 20 to 31 (17). The older men were less thirsty and drank insufficient water to
273 restore fluid losses, placing them at risk for dehydration (Figure 4). The diminished thirst with
274 age is now so well known that the original study is often not cited. For me, the key lesson was
275 that we have a lot to learn from practitioners. We need to pay attention and translate their
276 observations into sound science. In my first book *Thirst*, co-authored with Edmund Rolls in 1982
277 (18), we integrated the science with the clinical implications. We had made quite a lot of
278 progress in understanding thirst since Wolf's 1958 book *Thirst* (12).

279

280 Figure 4: Mean (+SEM) cumulative water intake and changes in thirst and mouth dryness in

281 “old” and young men. Changes in thirst and mouth dryness were measured on visual analog

282 scales. The hatched rectangle represents a sham infusion. From New England Journal of

283 Medicine, Phillips, P.A., Rolls, B.J., Ledingham, J.G.G., Forsling, M.L., Morton, J.J., Crowe,

M.J. and Wollner, L., Reduced thirst following water deprivation in healthy elderly men, Vol. 311, Pg. 377. Copyright © (1984) Massachusetts Medical Society. Reprinted with permission.

4. Dietary induced obesity in rats

Early in my career I became interested in environmental influences on the development of obesity. While I continued with studies of thirst, I began a series of studies in rats on dietary obesity. I was intrigued by the 1976 publication by Sclafani and Springer (19) that described a rat model in which the animals were fed a supermarket diet consisting of rat chow and a variety of high-energy-dense palatable foods. Thus, I and collaborators Edward Rowe, who worked as my research assistant for a number of years, and Robert C. Turner, a noted diabetes researcher, started fattening rats. When we fed rats a cafeteria diet, contrary to previous findings, the obesity that had developed over 90 days persisted when the rats were returned to a chow diet, even after a period of imposed restricted intake (20).

We went on to test how a variety of challenges to energy balance affected the development and persistence of obesity. We demonstrated that running wheel activity helped males resist becoming obese to a greater extent than it did in females (really disheartening as the females were running much more than the males) (21). We also showed that both colder temperatures (22) and lactation (23) helped to prevent or reverse dietary obesity. These descriptive studies led to more biologic investigations of fatty acid synthesis in both brown and white adipose tissue (24), as well as mammary gland lipogenesis (25) and milk composition (26). I find that today few of my younger colleagues realize that I conducted this series of studies on dietary obesity in rats. I attribute this to my move away from studying animal models before I had written a thoughtful and well-cited review article. Review articles should not distract from publications on

the original research, but as my mentors taught, they are the icing on the cake—the consolidation of ideas.

5. Sensory-specific satiety

One of our studies in rats indicated that dietary variety facilitates the development of obesity (27). Jacques LeMagnen had suggested in a review article that in rats satiety is not a general phenomenon, but rather is specific to a food or foods that have just been eaten. He called this “sensory-specific satiety” (28). These animal studies led us to ask whether we could demonstrate a similar phenomenon in humans. The problem was that we had neither funding nor a facility to conduct such studies. I was teaching an undergraduate course in physiological psychology with Edmund Rolls and we developed a practical class in which the students could experiment on one another using a simple test for the specificity of satiety. The result was the paradigm that is still used and that led to the operational definition of sensory-specific satiety as “the difference in the change in the pleasantness of the taste of an eaten food compared to the change in uneaten foods”. The test is simple: subjects successively sample six to eight foods varying in sensory properties and in turn rate the pleasantness of their taste, appearance, texture, odor, and desire to eat the food. They then eat as much as they like of one of these foods. Two minutes (or longer if the time course of the effect is of interest) after eating has terminated, they rate all the foods again.

The results of our first papers clearly showed that the pleasantness of the eaten food declined more than for the uneaten foods (Figure 5) (29), that these changes were correlated with intake in subsequent courses (30), and that intake in a varied meal was greater than one with a single well-liked food (30,31). Before we conducted these studies, Cabanac had shown that the pleasantness

of foods could vary and he attributed this to a change in the body's need for a particular nutrient (32). He called this "alliesthesia" and proposed that the decrease in pleasantness would be seen only if the substance tasted was similar to that ingested, such that sugar would affect sweet tastes but not salty. We also found that eating sweet foods affected the pleasantness of other sweet foods more than those that were salty, and eating salty foods affected the pleasantness of the salty taste more than sweet (30); however, these hedonic changes did not depend upon the energy (33,34) or the macronutrient content of the ingested food (35). Consuming a food with a non-nutritive sweetener had a similar effect on sensory-specific satiety as did the same type of food containing sugar.

Figure 5: Mean (+SEM) changes in ratings of liking of the taste and quantity subjects wanted to eat from before eating sausages (upper figure) or cheese on cracker (lower figure) to two minutes after eating terminated. This was the first demonstration of sensory-specific satiety in humans. Reproduced with permission from ref. 29.

344

345 It is clear that sensory-specific satiety and alliesthesia are different, though this distinction is
346 not universally accepted. Another issue is whether sensory-specific satiety should be called
347 “sensory-specific satiation” or “food-specific satiety”. Both suggestions have merit, but for the
348 sake of consistency and to honor the legacy of LeMagnen, I propose that we stick to sensory-
349 specific satiety (28).

350

351 **6. Returning to the United States**

352 In the early 1980s, I thought I would be living in England forever. After all, I had spent most
353 of my adult life there since my arrival in 1966. I had married, had two daughters, and terrific
354 students and colleagues. But I had divorced and was ready to move, and once you think of
355 moving you might as well cover all possibilities. I did not need to stay in England and most of
356 what was happening in ingestive behavior was in the U.S. Networking at meetings can have huge
357 benefits in the job search. I had met Paul McHugh at the Benjamin Franklin Symposium in
358 LaNapoule, France and learned that he was building a team to work on ingestive behavior in the
359 psychiatry department at the Johns Hopkins Medical School where he was the chair. In 1984, I
360 was hired to be part of that team which included Marian Fischman, Tim Moran, Richard Foltin,
361 Paul McHugh, and myself. I was fortunate to bring along Marion Hetherington as a Fulbright
362 Scholar. She had been a doctoral student with me at Oxford working on sensory-specific satiety.
363 While she was at Hopkins and during her later training at the National Institutes of Health she
364 developed into one of the leaders in the study of human eating behavior. We have continued to
365 collaborate over the years.

Starting over in a new university in a different country was challenging. On top of that I was in a medical school with a great reputation, but with few women in senior positions, especially those with a Ph.D. Eventually I became the 29th woman to become a full professor with tenure there, and of those the 13th with a Ph.D. Before that was accomplished, I had much to do. In England, I had continuous funding from the Medical Research Council and now I was trying to break into the National Institutes of Health funding system—new players and a very different grant format--and getting used to new computer technology. Just before the deadline on my first grant submission, my computer destroyed my only version of the application. I rewrote lots of it and got the grant in, it got funded, and since I have been continuously funded by the National Institute of Diabetes and Digestive and Kidney Diseases. This funding has given me the freedom to pursue new ideas and to experiment creatively.

The work I was doing on human thirst and eating behavior caught the attention of the food and beverage industry, and I was interested in how our studies could be applied to improving food and beverage choices. Despite the negative press and perception that working with industry receives, my experience is that it can be and should be a mutually beneficial relationship. We can provide industry with the best scientific evidence, and they expose us to the real-world challenges they face in the dynamic interplay between supplying nutritious options and maintaining profitability. In a required course for nutrition graduate students at Penn State, I enjoy discussing the basics of establishing productive collaborative relationships with industry (36). I am proud to say that several of my outstanding doctoral students (Debra Miller, Christine Pelkman, Elizabeth Bell, and Alexandria Hast) have gone on to work with food companies.

7. Johns Hopkins: Eating Disorders, Aging, Macronutrients

Since the move back to the U.S. all of my work has focused on the human animal. Hopkins provided a number of new opportunities. I was able to design a purpose-built lab for studying human ingestive behavior in a psychiatry department with an outstanding treatment center for eating disorders. Arnold Andersen (who ran the center and is an expert on eating disorders), Marion Hetherington, Tim Moran, myself, and others were able to conduct a variety of studies in patients with eating disorders. We brought patients into the lab and characterized food preferences (37) and responses to preloads varying in energy (38) or macronutrient content (39). One of the more interesting findings was that patients with anorexia nervosa demonstrated sensory-specific satiety only after a high-energy salad preload, while patients with bulimia nervosa showed sensory-specific satiety only after a low-energy salad preload (40). This suggests that sensory-specific satiety depends upon cognitive factors, and in patients with eating disorders is related to their dietary restrictions.

After the success of our studies of impaired thirst in elderly individuals, I was curious to know if the anorexia associated with aging could be attributed to changes in food intake regulation. To do this we applied some of the basic paradigms that had been used previously to understand eating behavior. We found that compensation for the energy in preloads was less precise in older than younger men, and interpreted this as impaired energy regulation (41). On reflection, I am not sure that we demonstrated an impairment. The older men consumed significantly less energy in the baseline no-preload condition than the younger men, but despite this difference we had both groups consume the same size preload. In a subsequent analysis of pooled data from preloading studies, we have found that the compensatory response depends upon the energy content of the preload in relation to baseline energy intake (42). It would be good to see the study redone with the preloads adjusted for baseline energy intake. Nevertheless,

there are other indications that the response to food changes with age. In another study, we tested individuals ranging from age 12 to 82 to determine if they demonstrated sensory-specific satiety (43). The results clearly showed that sensory-specific satiety was pronounced in the adolescents and declined with age such that it was absent in the oldest group of 62-82 year-olds. We need more studies on changes in ingestive behavior across the lifespan as such studies have the potential to shed new light on mechanisms and strategies for improved nutrition.

Another unique opportunity at Hopkins was provided by a residential facility built by NASA to test the psychological effects of keeping people cooped up together for days at a time. The facility was no longer being used for that and was available for controlled studies of food intake. It had three private rooms similar to an efficiency apartment as well as common rooms with exercise facilities. Food could be passed in and waste passed out, and there were cameras to monitor behavior. Led by Richard Foltin, we conducted two studies aimed at determining the ability of normal weight males to compensate for systematic variations in energy and macronutrients across 2 to 3 days. The results of both studies indicated that while there was compensation for differences in energy content of the foods, there was no indication that the proportion of fat or carbohydrate in the foods affected daily energy intake (44,45).

At the same time as these residential studies were in progress, we were doing studies comparing the effects of fat and carbohydrate on satiety and energy intake. The differential effects of the macronutrients were a source of debate in the 1990s and despite all that has been learned, much of the research on satiety and weight management remains focused there. We characterized the time course of the effects of preloads on test meal intake (46), and we did dose-response preload studies (47). Led by David Shide and Benjamin Caballero, we even compared

responses to intravenous and intragastric infusions of fat and carbohydrate (48). Overall we found few differences between the effects of fat and carbohydrate on satiety.

As I look back on these studies, conducted before power analyses were regularly applied to behavioral studies, it is striking how few people we tested in each study. This was true for the majority of the “historical” studies. Well-conducted studies in humans are expensive and laborious, and likely will get harder to do if funding remains tight. But if we are to resolve the debates that continue, we have to “power up” and carefully design our studies. Often investigators think that studies of human ingestive behavior are easy, but from my experience, the complexity of the drivers of these behaviors makes studies in humans very difficult to conduct rigorously.

While we did not find large differences in the effects of preloads varying in fat and carbohydrate on satiety, we only tested a few kinds of carbohydrate (often sucrose) or fat, and the biological effects can vary significantly across types. The main impact of these studies was that it led us to test in a series of experiments (49) whether the effects of the macronutrients on satiety or satiation depend upon their energy density. Could differences relate to the 9 kcal/gram in fats compared to the 4 kcal/gram in carbohydrates?

8. Moving on to Penn State: Energy density

Why would I move from the collegiality and prestige of Hopkins to Penn State? Hopkins, even for a full professor, was “soft” insecure money and our clinical department did not have a program for training Ph.D. students. I wanted more security (to sleep at night) and opportunities to train our future generations. I started at Penn State in 1992 and established the Laboratory for the Study of Human Ingestive Behavior (The Eating Lab). I was initially in the Department of

Biobehavioral Health, but after three years, I was recruited to the Department of Nutritional Sciences with an appointment to the Helen A. Guthrie Chair. Ingestive behavior is multidisciplinary. My career path reflects this as I progressed through the following departments: biology, physiology, psychology, psychiatry, biobehavioral health, and finally nutrition.

At Penn State the training of graduate students and post-doctoral fellows has been a highlight of my career and without these trainees I would not have received the Hoebel Award. They keep me smart and they do the work. I wish I could name them all, but I send thanks to them and my dedicated staff, who all love working with food. Well, not all of them. Liane Roe, who has been the lab's data manager for the past 17 years, prefers working with numbers and this has brought rigor and a lot of statistics to the analysis of our data.

Before the move, I had noticed both in the animal and human studies a tendency for intake to be more consistent by weight than by energy (50). If intake is guided by the weight consumed, then energy density becomes a critical influence on energy intake. And importantly, the focus turns to water. Water is the main component of the most commonly consumed foods. The combination of water with the macronutrients in foods determines the energy density, and variations in water can be used to separate the effects of energy density from those of the macronutrients.

We embarked on a series of studies seeking to dissociate the effects of variations in the macronutrients from those of energy density. The food formulation required was tricky and had not previously been done systematically. Luckily, Elizabeth Bell was a doctoral student with me and she spent almost a year figuring out how to modify foods to vary the energy density without changing the macronutrient proportions or palatability. The design of her first study was ambitious; she set out to determine the effects of variations in energy density on ad libitum

consumption (satiation) by modifying the main dish at all meals across two days (51). In a within-subjects design, participants were served all of their meals for two days on three separate occasions. The results showed that subjects ate a similar amount of food by weight across three levels of energy density, which varied across conditions by up to 30% (Figure 6). Therefore, the cumulative energy intake over the two days was around 30% less in the lowest energy density condition compared to the highest, while rated hunger did not vary across conditions (51). We have confirmed the effects of energy density on intake in a number of studies (49,52), and also have shown that variations in the fat content of the diet do not influence intake if the energy density is held constant (53).

Figure 6: When provided with meals varying in energy density over two days on three separate occasions, participants ate similar amounts of food by weight over each two-day session (A). Thus, the higher the energy density, the greater the cumulative energy intake (B). Means ($\pm$

SEM) with different letters are significantly different at each time point ($p < 0.05$). B, breakfast; L, lunch; D, dinner; S, evening snack. Reproduced with permission from ref. 51.

At the same time as the studies of the effects of energy density on satiation were moving along, we conducted studies on satiety that were aimed at understanding some of the mechanisms underlying the effects of energy density. We worked with Arun Kilara in Food Sciences at Penn State to match the palatability of preloads that varied in energy density without affecting the energy or macronutrient content. We found that decreasing the energy density of a preload by adding water, and thus increasing the volume, led to a significant reduction in subsequent test meal intake (54). This study led me to wonder whether the additional water had to be incorporated into a food to reduce its energy density or if it could simply be consumed as a beverage along with food. In a crossover study, we had subjects consume a casserole, the casserole served with a glass of water, or the casserole and the water cooked together to make a soup. We found that the soup reduced test meal intake by 26% more than the other preloads, indicating that water has a greater impact on satiety when incorporated into a food than consumed as a beverage (55).

While the reasons that energy density affects satiety are complex and still not well-understood, we have conducted several more studies that shed some light. We have shown that sensory-specific satiety is affected more by the volume consumed than the energy content (56). However, energy density can affect satiety when sensory cues are bypassed, as demonstrated in a study in which the volume and energy content of preloads infused intragastrically were varied independently. Increasing the volume of the infused preload, but not its energy content, enhanced satiety (57).

516

517 It also is likely that food volume affects intake through its influence on the perception of the
518 amount of food available. Foods can be made to look bigger simply by adding air or by changing
519 how they pack down in a container. We found that aerating a milk-based preload to increase the
520 volume affected satiety and decreased test meal intake (58). Satiation was also affected by
521 aeration in that consumers consumed more calories when offered a less aerated cheese snack
522 (59). Even crushing the flakes in a cereal so that more was required to fill a bowl increased the
523 energy consumed for breakfast (60). These studies show that there is a strong perceptual or
524 cognitive component that affects the amount consumed.

525

526 **9. Effects of portion size on intake**

527 It seems obvious that if changing the perceived amount of food affects intake, that changing
528 the actual amount or portion served would also be important. Surprisingly, until we started our
529 studies of portion size in the late 1990s, there were few positive indications that portion size
530 influences intake (61). Years earlier while still in Oxford, I had run a pilot study with two
531 different portions of sandwich wedges and found no effect on intake. I still have a photo of the
532 plates of sandwiches—both portions were huge! This lack of effect is probably explained by our
533 later studies showing that while portion size affects intake, the effect is not linear (62,63). As the
534 portions get bigger, participants leave more uneaten and a plateau is reached (64). When
535 studying the portion size effect, the portions being compared are a critical determinant of the
536 response.

537

Figure 7: Mean ($\pm$ SEM) cumulative energy intake for 10 women and 13 men served baseline and large portions of all foods over 11 days. Serving large portions led to a significant and persistent increase in cumulative energy intake in both sexes ($p < 0.0001$). Reproduced with permission from ref. 67.

Portion size has become one of the villains in the obesity epidemic. It is easy to see, especially when eating out, that we are often served too much food. Despite our failed pilot study, we went on and conducted a number of studies describing the portion size effect. We have shown that the effect is seen with various types of foods and beverages (61-66), is persistent (Figure 7) (67), and affects most people in a variety of settings (61,68).

My interest then became “How can we leverage the robust effect of portion size to encourage people to eat better?” To do this we needed to understand how the effect of portion size combines with the effect of energy density to influence intake. Tanja Kral who was doing her Ph.D. with me, jumped on the idea and developed and conducted one of her careful well-designed studies (69). She demonstrated that the effects of portion size and energy density independently affect intake and that when the goal is to moderate intake, both of these properties of food should be considered. We have since gone on to confirm that the combined effects of portion size and energy density have substantial effects on both satiation (70) and satiety (71). Despite the focus on the impact of portion size, these studies continue to show that the effect of energy density on intake is even greater and is less likely to be noticed by consumers than offering less food (70). My hope now is that the food industry will utilize these findings to help consumers eat less while still feeling satisfied. Several year-long randomized clinical trials indicate that eating a diet lower in energy density can aid weight management, improve diet quality, and control hunger (72-74).

10. Obesity prevention

While we were progressing with our studies of eating behavior, alarm bells sounding an epidemic of obesity had caught the attention of the public and policy makers. What grabbed the most attention was that obesity prevalence was rising in children and they were developing associated diseases such as type 2 diabetes. It became clear that we need to understand children’s eating behavior in order to prevent obesity, and at Penn State we were well positioned to do such research. Leann Birch had arrived there at the same time as I had and although we are good friends and taught together we had not combined our expertise. The studies that my lab had

conducted in adults needed to be extended to children to determine whether they would respond the same way. Young children are thought to be able to self-regulate their energy intake, so they could possibly be resistant to the influences of portion size and energy density. With Leann's consultation, my staff and students (Katie Leahy Lacey, Maureen Spill, and Samantha Kling) have conducted a series of studies showing that preschool children respond to portion size (75) and energy density similarly to adults (76-80). When energy density was manipulated at most meals over two days there was no compensatory response; when dietary energy density was reduced, the children ate significantly less (78).

We also entered the lab's "vegetable phase" during which we have tested various strategies to get kids (and adults) to eat more vegetables in order to reduce the energy density of their diet. Serving bigger portions when children are hungry (79,80), or increasing the variety available increased vegetable intake (81). Probably the most effective strategy was the stealth approach in which we substituted pureed vegetables for other more energy dense ingredients in recipes (82). We are continuing to explore whether preschool children show self-regulatory eating behaviors when either the portion size or energy-density of the available food is varied over multiple days.

The outstanding faculty (Rebecca Corwin, Kathleen Keller, Jennifer Savage Williams, John Hayes, Lori Francis to name but a few) have helped to make Penn State one of the top places in ingestive behavior research. Over the past five years we have had the privilege of training 13 graduate students through funding provided by a USDA Childhood Obesity Prevention Training grant. They have shown commitment as they continue their research and pursue careers related to obesity and ingestive behavior despite the difficulties with funding. We have to find ways to maintain adequate funding for our science—we need to understand the influences on what and how much people eat and drink.

595

596 **11. Reaching out**

597 I suppose that some in ingestive behavior know of my work because of the *Volumetrics*
598 books I have written for a broad audience (83-85). Writing such books has always felt risky for
599 my scientific credibility. When translating our science for the public, we have to gloss over
600 outstanding scientific issues if we are to make the messages persuasive and actionable. This is
601 not what we are trained to do, but on the other hand we are continually urged to disseminate our
602 findings. For me there was never any question about whether I would try to write a popular book.
603 I started making outlines when I was a graduate student. I still have them, and see that it would
604 have been a very different story back then. This urge was not because I am a driven, natural
605 writer. It is like pulling teeth to get me to sit at my computer all day to get the story down. My
606 need to communicate our science is more deeply rooted in the experience of growing up with a
607 mother whose eating behavior so adversely affected her health, and my wanting to do something
608 to help. Our science is compelling, but so often is misrepresented, based more on wishful
609 thinking than data. We must communicate our findings so that people know how to eat and drink
610 strategically for optimal health.

611 After a long career, it is exhilarating to have so many stories to tell. I am grateful to the
612 universities and funding agencies that have provided the opportunity to pursue new ideas. I have
613 been lucky to have worked with stimulating, intelligent, diligent, and fun mentors, colleagues,
614 trainees, and staff. You know who you are and that you were who made it happen. Thanks to you
615 all, and may serendipity (and funding) facilitate your creativity.

616

617 **Acknowledgements**

618 I thank the students, post-doctoral fellows, colleagues, and staff who contributed to the
619 studies. The work is currently supported by National Institute of Diabetes and Digestive and
620 Kidney Diseases grants R01 DK082580 and R01 DK059853, and USDA National Institute for
621 Food and Agriculture grant 2011-67001-30117.

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