

*The highlight for March, 2008 is by Dr. Norman Braveman at the National Institute of Dental and Craniofacial Research in Bethesda, Maryland. Dr. Braveman has a long and active research history in animal learning and behavior, dating back to his early work with Pat Capretta in which he assessed the role of stimulus relevance in the conditioning of taste preferences. Subsequent to this work, he examined behavioral and learning differences between rats and guinea pigs, a comparative approach that eventually led him to explore aversion learning in the guinea pig when he arrived at Memorial University in Newfoundland. One of Dr. Braveman's first endeavors into aversion learning was assessing the ability of visual cues to be associated with toxicosis, an ability that appeared to be consistent with the use of such cues in normal feeding behavior of the guinea pig. Dr. Braveman's interest in and work with aversion learning did not end with these comparative assessments. In the early 1970's, he became one of the major investigators examining the effects of drug history on the acquisition of drug-induced taste aversions. He and his colleagues demonstrated clearly that not only could a drug impact its own ability to induce aversions, but such attenuation could be produced when the preexposure and conditioning drugs were different and even from different classes with distinct mechanisms of action. He not only demonstrated such cross-over effects, but he spent considerable time attempting to determine the nature of the attenuation, an issue that interestingly enough remains unresolved today. His work with US preexposure led Dr. Braveman to explore the mechanism underlying aversion learning in general, an examination that ushered in a possible role of stress and ACTH. Concurrent with, and partially driven by, this work on US preexposure and stress-mediated aversion learning, Dr. Braveman and his students began examining neophobia and its relation to taste aversion learning. In this analysis, he demonstrated when neophobia occurred and how it could be modulated, effects that led him back to the role of stress in the regulation of feeding behavior both in terms of its nonassociative control via neophobia and its associative control via food aversion learning. Although Dr. Braveman stepped away from research on aversion learning in the late 1970's, he made a major contribution in 1985 when he and Paul Bronstein (another of Pat Capretta's students) organized the New York Academy of Sciences' gathering of researchers in aversion learning, a gathering that resulted in the book *Experimental Assessments and Clinical Applications of Conditioned Food Aversions*. This edited collection allowed Dr. Braveman and Dr. Bronstein to bring together a growing field that had gone beyond the demonstration of the phenomenon of aversion learning to evaluating the conditions under which it occurred, assessing its biological base and projecting its applications and implications. Dr. Braveman closes his highlights talking about the need for integrative and comprehensive analyses in behavioral work. His pioneering research in taste aversions and his role in documenting its integration set that stage for this field some 20 years ago.*

## A CTA Retrospective: Research Conducted By Norm Braveman and Colleagues

Norman S. Braveman, Ph.D.  
National Institute of Dental and Craniofacial Research

### **Introduction: A little of this and a little of that...reader beware.**

I was somewhat surprised when Tony Riley asked me if I would write about my research for the CTA database. In fact, I emailed him back to make sure that he hadn't made a mistake, reminding him that I haven't done research in nearly 30 years. He assured me that he had not been coerced by my relatives and that he was not under the influence of any of the toxicants that he's been using in his research for the last several decades.

Obviously, I decided to take him up on his offer. However, early in the process of thinking it over I came to the realization that a paper like this can be a very dangerous undertaking...particularly in my case. And so, in addition to a disclaimer that I will make shortly, I must also provide the following consumer warning. Not only have I not conducted CTA research (or any research for that matter) in nearly three decades, I am also an avid fly fisherman and everyone knows that people like me who spend time stalking leery trout in remote rivers have very 'creative' imaginations and play pretty loose and fast with factual events. The short of it is that each time a story is told, the fish gets larger. It's what my friend Paul, another psychologist, calls the 'rounding up' phenomenon. In the case of science that would probably translate into larger average group differences (or disappearing ones depending on the needs of the situation) and/or the outcome of even the most preliminary and unpublished pilot study becoming the essential test of a crucial point. Add to all of that the normal human tendency to blow things out of reasonable proportion as the time between the actual events and their recall lengthens, and you have a perfect storm. In short, readers beware...I'm old, I'm a fly fisherman and it's been years since I did this research.

### **The 'who' and 'what' of it all...**

Before getting into the CTA story I'd like to take the opportunity to recognize the individuals who participated directly and indirectly in the research that I'll talk about: Joan Crane, Emir Andrews, Paul Jarvis, Calvin Peddle, Louis Katz, Dan Stewart, Hymie Anisman and Dick Noseworthy. Also, I'll share with you, **very briefly**, what's happened to me in the last 30 years...and at the same time include the disclaimer that what I'm saying in this document in no way represents the position, official or otherwise, of the Federal government, which is where I've been working since 1980.

In 1977, I left Memorial University of Newfoundland and went to work with Bob Ader at the University of Rochester School of Medicine and Dentistry. Bob and I had known each other for many years, and he was in the early stages of his work in psychoneuroimmunology and Pavlovian conditioning of the immune system in mice and rats using a CTA paradigm. I spent three years working with Bob and then moved on to a training program in extramural biomedical science development and administration for mid-career scientists at the National Institutes of Health where I'm still gainfully employed, hence the disclaimer. That was also the end of my active research career.

The training introduced us to the whys and wherefores of federal funding of biomedical and behavioral research. During the ensuing years, I've worked in the National Institute on Aging as the Director of the extramural Immunology and Endocrinology Program, at the National Heart, Lung and Blood Institute as the administrator of the extramural Clinical Trials Review Committee, in the Office of the Director of NIH as Director of Planning and Evaluation for NIH, and for the past 14 or so years at the National Institute of Dental and Craniofacial Research where I've served in a variety of capacities and am currently the Assistant to the Director. While I haven't conducted research in all these years, I've been involved in various ways in biomedical and behavioral research at least from the administrative 50,000-foot level.

In preparing for this paper, I went back and reread the articles I wrote...remember it's been 30 years or so since I last thought about these things. While it's easy to say that I haven't done research in all those years, that fact takes on a slightly different meaning when, after all these years and the advent of various internet search engines, I had to go to the 'stacks' in the library to search for my articles in bound copies of journals because they were never digitized and put on-line. That experience itself gives tactile reality to the phrase 'a lifetime ago.' Not only did the studies happen a lifetime ago, but as I read what I wrote I didn't recognize the person behind the words and concepts. And, I really wondered why I ever did that research...what could have possibly been so important to occupy all of those people, resources and time? But there it was in black and white, forever emblazoned on the pages of the 'scientific literature' for all to see. And our friend and colleague, Tony Riley, has made it easier for folks to be reminded of their past with his CTA database and these highlights. Despite all of that I still like Tony, and here I am trying to distil a message from the work.

So, how did I get involved in CTA research and what was I trying to accomplish? I don't recall that I had a grand overall research plan. One thing seemed to lead to another, and I followed my curiosity. However, in reviewing what I published, and with the space of 30 years between me and the actual research, it looks like there were three main themes that captured my interest. One had to do with species/developmental issues, another with methodological/learning issues in CTA and the third with feeding behavior and specifically neophobia.

## **Species comparisons and developmental trajectories...food preferences and conditioned taste aversions.**

The species related research represented a blending of my masters work on the modification of food preferences with Pat Capretta at Miami University with my dissertation research on problem solving in closely related species with different developmental trajectories carried out at Washington State University under the supervision of Gloria Fischer.

Pat was not interested in conditioned taste aversions as much as he was in the modification of food preferences using principles of instrumental learning. His dissertation research was with Maurice Smith at the University of Iowa in the late 1950's (during the era of Spence). It involved modifying chickens' food preferences for artificially colored mash (Capretta, 1961). His approach was to first determine which of two artificially colored foods chickens preferred. Next, he intubated them with either salt water (aversive) or milk (rewarding) each time the chickens consumed the preferred mash or the non-preferred mash, respectively. Later, he allowed them to select from the originally preferred and originally non-preferred test foods. He found that animals receiving the salt water avoided the otherwise preferred food, while those that were intubated with milk or even distilled water continued to ingest large quantities of the preferred food. From this work, Pat coined the phrase 'stimulus relevance.' That is, in order to effectively modify food preferences, the post-ingestional consequences of eating must be related to the act of ingestion.

My master's thesis research followed from Pat's dissertation (Braveman, 1965; Braveman & Capretta, 1965). I presented lab rats with two sweet solutions, one flavored with sugar (sweet) and the other with sugar and saccharin (super sweet). All animals preferred the sweet water. In a series of four experiments, I showed that intubating rats with salt water reduced their preference for sweet water, but painful electric foot shock did not. However, we could not detect a change in preference when drinking the non-preferred flavored water gave hungry rats access to food pellets or when other thirsty rats had access to the non-preferred flavored water. In these last two experiments, we were testing the limits of stimulus relevance. Our thinking was that the reduction in hunger resulting from drinking the non-preferred solution was not as closely related to the act of drinking, and hence was not as 'relevant' as was the reduction in thirst from drinking the non-preferred solution...put slightly differently, in the one instance drinking the non-preferred solution led to immediate reduction of thirst while in the other it led to reduction of hunger which, while related to thirst, seemed to us to be one step away from it. It didn't work.

Pat played a huge role in shaping my thinking about the study of animal behavior, and in particular the developmental influences that could play a role in the establishment and/or modification of food preferences. He introduced me to the writings of Zing-Yang Kuo, a Chinese psychologist trained in the United

States with E. C. Tolman at Berkeley in the early 1900's. Kuo referred to his view of behavior and development as behavior epigenetics and is captured in the following quote from his book:

“...the relationship between the behaving organism and its environment is an extremely complex and variable dynamic process. It goes deeper and beyond the molar level...*the behavior epigeneticist's task is (italics are my words)* to obtain a comprehensive picture of the behavioral repertoire of the individual and its causal factors from stage to stage during development; and to explore the potentials and limitations of new behavior patterns (“behavioral neo-phenotypes”) that are not commonly observed or do not exist in ‘nature’ so as to predict or control the evolution of behavior in the future....” ~ Zing-Yang Kuo (1967, p 25-26).

My doctoral training at Washington State University built on this approach as applied to the study of animal behavior through the influences of two individuals, Gloria Fischer, my dissertation advisor, and F. Dudley (Dud) Klopfer, a comparative psychologist/ethologist. Gloria's influence was in the area of comparative animal learning, while Dud took a very functional approach to studying behavior, something we might call behavioral ecology today. Interestingly, it was Dud who showed me a pre-print of Garcia's initial bright-noisy water experiment (Garcia & Koelling, 1966). He pressed me to explain the functional significance of the selective associations that animals in Garcia's experiments, as well as those in my work with Capretta, seem to form.

He was particularly interested in how taste aversions could have evolutionary significance for an animal since the paradigm as we knew it then required animals to actually ingest potentially poisonous, and hence lethal, substances in order to establish an aversion. He pressed me on this point, and I recall saying something to the effect that if an animal tasted a food that contained a lethal poison it would form the ultimate aversion in one trial and it would be such a powerful association that the animal would never ingest the food again. He wasn't impressed.

The mid-1960's was the era of comparative psychology and research by individuals like Mort Bitterman (1965) and others who were trying to build a phylogeny based on behavior exhibited as animals solved complex discrimination learning problems. The idea of using behavior to sort out evolutionary pathways captivated my imagination, and I became more interested in comparative animal learning than in CTA or the Garcia effect. So, for the next several years I used discrimination tasks like probability learning to study problem solving in first-year college students (Braveman & Fischer, 1968), lab rats and guinea pigs (Braveman, 1971; 1973) or the kinkajou (Braveman & Katz, 1971).

Rats and guinea pigs are phylogenetically closely related species but with very different developmental trajectories...the guinea pig being precocial in its sensory-motor development and showing signs of independent locomotion and pattern vision within minutes after birth. Rats, on the other hand, go through a much slower developmental sequence and hence have a longer caretaker period. What I learned, among other things, was that the 'precocial' guinea pig approached problem solving very differently from the 'altricial' lab rat, even when they were the same developmental age (i.e., taking into account differences in their gestational periods). Equally fascinating to me was that guinea pigs approached the free-feeding situation much differently from lab rats. The potential significance of that for CTA didn't strike me until later when in 1969 I moved to St. John's, Newfoundland in eastern Canada where I did research and taught in the Department of Psychology at Memorial University of Newfoundland. It was about this time that I first met Tony Riley.

During my second year at Memorial, Sam Revusky and Bow Tong Lett joined the faculty. Both are outstanding scholars and good friends and were very much involved in CTA research. They both were very willing to share their thoughts about research with me. Their presence was a stimulus for me to re-look at the CTA paradigm as a way of studying comparative animal behavior and to look at, among other things, the role of species developmental trajectories as a factor in determining whether or not the results of my master's research and Garcia's research, both with lab rats, were also true for the precocial guinea pig who, as I noted in my work with problem solving, seemed to use visual cues in locating and selecting food.

At about this time, I also became aware of CTA research by Hardy Wilcoxin (Wilcoxin, Dragoin & Kral, 1971) with quail. They had shown that quail not only associated the taste of drinking water, but also its appearance, with sickness. Importantly, this study also showed that the appearance was more salient than the taste in the formation of the association. But these were birds, not guinea pigs, and they had evolved in and adapted to different environments and had adopted appropriate feeding strategies for those environments. So it wasn't a surprise to me that they could form CTAs using visual cues. It did spike my interest, however, in determining what the guinea pig might do in a similar situation.

We began our research with guinea pigs using water colored with food dye and a 60-minute interval between ingestion and the injection of lithium chloride (Braveman, 1974). Guinea pigs formed aversions to the appearance of the water. However, we also had to show that the food dye used to change the appearance of the water didn't have a taste...above and beyond a statement to that effect on the product packaging. We did this by mounting the water bottles outside of the test chamber and conducting all tests in the dark. Guinea pigs didn't show signs of an aversion under these conditions, so it appeared that the colored water didn't have a distinctive taste or at least it wasn't distinctive enough for them to

use it as a cue in forming a CTA. Also, we confirmed with an additional experiment that guinea pigs were able to form aversions to the appearance of familiar tap water when the appearance was changed by inserting an acetate sleeve into the water bottle and glass-drinking spout even with a 60-minute delay between ingestion and an injection of lithium chloride.

At the same time, we were using our guinea pig colony to learn more about their 'free-ranging' feeding behavior. This was done inadvertently and, to a large extent, occurred because we had established a large breeding facility in which animals were placed into a single large enclosure. Food and water were available in the same place on an *ad libitum* basis. Every few days, we would clean the litter from the floor of the enclosure and in the process we moved the food and water to a new place. This upset the critters and as anyone who has ever owned a guinea pig knows, when upset these animals make a very high pitched whistle-like sound...we called it the death screech mainly because the sound of 50-75 guinea pigs whistling frantically made all those in ear-shot wish for death. Well, each time we'd move their food and then return it to the original spot, there would be bedlam in the lab for hours and the animals showed a reluctance to eat or drink food and water that they normally consumed in great quantities. It appeared to us that the animals were treating their familiar food and water as something new and that they were, in their vocalization and consummatory behaviors, showing evidence of neophobia even though the ingestibles themselves were the same things that they had been consuming hours before. We even went so far as to put their familiar food and/or water into a novel container with the same result. So it appeared to us that the fact that they formed aversions using visual cues was completely consistent with their natural tendency to use visual cues in feeding. We never published these findings mainly because they were based on casual observations. But as I'll report later, we used it as the basis for a series of studies on lab rats.

Returning to the main story...we had established that guinea pigs, a rodent, could form aversions to the appearance of water and that it was possible even with a relatively long delay. Our subsequent experiments showed that they also formed taste aversions and that taste was the more salient of the cues (Braveman, 1975a; 1977a). We also found that it was possible to get appearance to overshadow taste if the distinctive taste was familiar to animals before the conditioning phase of the experiment. What we didn't do was to test the limits of these findings and so we never determined, for example, whether the delay between ingestion and aversive stimulation was longer for taste than for appearance. Nor did we investigate anything about the limits of latent inhibition of the taste in the multi-cue conditioning experiments (i.e., how few or many preexposures it would take to reduce the salience of the taste cue).

## **Methodological/learning paradigm issues.**

At about the same time that we were doing research with the guinea pigs, we became interested in a totally different aspect of CTA relating to the classical conditioning aspects of the CTA paradigm. My interest in this area was in large part the result of working in the same department with Sam Revusky and Bow Tong Lett and in part from having met Bob Lubow during a sabbatical year that I spent in Israel in 1974.

Sam had done much of the seminal early work on CTA within a classical conditioning framework (e.g., Revusky, 1974), showing that with the exception of the long CS-US interval that typified CTA, many of the phenomena occurring within the classical conditioning paradigm also occurred with CTA. And within the context of classical conditioning, Lubow (1973) had shown that conditioning is weaker when an animal is made familiar with the US prior to conditioning than when the US is novel, a phenomenon known as latent inhibition. I thought that it would be interesting to see if this also held for CTAs since I could find nothing in the literature about latent inhibition in CTA.

However, there was one problem here. We used drugs, mostly lithium chloride, to induce CTAs. It was assumed that the drug caused 'sickness' which, in turn, was the US. Pre-exposing an animal to a drug was, operationally, the same as inducing a tolerance to that drug. So the fact that drug preexposure resulted in reduced CTA with that drug could merely be a demonstration of the fact that the physiological impact of a given dose of the drug to which animals had been preexposed was reduced through drug tolerance (i.e., the drug had lost its ability to induce sickness and we were dealing with a reduction in US intensity). In short, it would tell us little or nothing about the associative properties of the novel vs. familiar US in taste aversion learning as the studies of latent inhibition had in the more typical classical conditioning paradigm. Although, now as I write this, I wonder if anyone ever determined whether or not the more 'usual' USs used to study latent inhibition in classical conditioning lost their potency or physiological impact with increasing familiarity?

In any event, we embarked on a series of experiments in which we used one drug during the preexposure or latent inhibition phase and another, very dissimilar drug (but one known to cause CTAs) to induce the CTA. We termed this the 'crossover' experiment, and we used two drugs in order to minimize the possibility that any diminution in the effectiveness of a drug to induce a CTA was the result of drug tolerance. In the first experiments (Braveman, 1975b), we pre-exposed animals with methyl-scopolamine on 0, 3, 5 or 7 occasions and then tried to induce aversions using amphetamine 10 days after the last preexposure. We found that 7 preexposures blocked the formation of aversions while 5 preexposures weakened the formation of aversions; 0 or 3 preexposures had no effect.

Not only were we able to show a preexposure effect, but we had done so with drugs which had been shown by others to induce CTAs via distinctly different physiological mechanisms. Methyl-scopolamine acts peripherally through the area postrema, while d-amphetamine sulfate acts directly on the CNS. In another experiment we pre-exposed animals on 5 occasions with physiological saline or lithium chloride and then tried to induce CTAs with either an injection of lithium chloride or methyl-scopolamine. Results showed that CTAs were formed only by animals that received preexposure to physiological saline and not to lithium chloride. Once again, we obtained a preexposure effect but this time both with the same drug and a different drug.

Judging from these results, it appeared to us that the preexposure effect (and possibly the effective US) in CTA was not specific to the aversion-inducing agent since the drugs used in these experiments were not only different chemically but also in their pharmacological action. Nevertheless, there was always the possibility that they shared a common aversive chemical or drug-related element that mediated the crossover effect. And so we conducted an experiment in which we used a non-pharmacological agent (rotation at 60 rpm for 15 minutes in a cage mounted on a turntable) to induce CTAs following five preexposures to either physiological saline (control), rotation, lithium chloride, d-amphetamine sulfate or methyl-scopolamine. With the exception of the physiological saline, each of these methods had been shown to induce CTAs to sweet water. As before, results showed a crossover effect between each active pharmacological agent and rotation.

So what was a person to make of these findings? One possibility raised by Rudy et al. (1977) was that pre-exposed animals were associating handling cues with the aversive aftereffects of the treatment. Thus animals pre-exposed and trained in the same environment were associating experimenter generated handling cues with the treatment preexposure which, in turn, blocked the formation of subsequent taste-treatment associations. We tested this notion (Braveman, 1978a) by varying the amount of handling animals received prior to the preexposure phase of the experiment, arguing that the more handling prior to the treatment preexposure, the less likely that the handling cues would become associated with the treatment preexposure...a sort of latent inhibition of the handling procedure. We reported weakened aversions following treatment preexposure, independent of the amount of handling animals experienced prior to treatment preexposure, leading us to reject Rudy's speculation.

To us, the crossover findings were suggestive of the nature of the aversive stimulus in the CTA paradigm (Braveman, 1977b). That is to say, in our view the US couldn't be anything specific about the pharmacological aspects of the drugs *per se*. The prevailing lore at the time was that the drugs made the animals sick...and judging from our observations of their post-injection behavior, particularly with lithium chloride, that certainly was possible. On the other hand,

neither methyl-scopolamine nor amphetamine induced sickness. In fact, methyl-scopolamine was used in preparations for preventing nausea. Further, others trying to uncover the nature of the aversion-inducing element in the CTA paradigm had shown that amphetamine would reinforce behavior when an animal self-administered it but would cause an aversion when administered (Wise et al., 1976). And, we had observed the crossover preexposure effect with both methyl-scopolamine and amphetamine. It was speculated that 'stress' from loss of control (Gamzu, 1977) was the culprit, and we hypothesized that the element common to these diverse aversion-inducing agents had something to do with stress and changes in hypothalamic-pituitary-adrenal (HPA) axis. We even did an experiment that showed that inescapable electric foot shock, a very stressful treatment, could produce CTAs in lab rats to the distinctive taste of sweetened condensed milk, a finding that further bolstered our belief in the stress/HPA hypothesis (Braveman, 1977b).

Even though we were able to cite evidence that implicated ACTH, it is not at all surprising that 30 years later this proposal seems incredibly naïve and totally inadequate. The changes in physiology and brain chemistry underlying avoidance learning has been shown to be quite complex. For example, using a totally different avoidance paradigm, Anisman and colleagues (e.g., Merali et al., 2004) documented the complexity of the neurochemical pathways involved in escape avoidance tasks and showed that preexposure to stressors other than the one used in escape avoidance (mostly electric foot shock) can have a major impact on brain neurochemistry which in turn can have profound effects on performance. Without knowing where the research has gone over these years, it wouldn't surprise me one bit to find that a similar level of complexity exists for CTAs. Back then, however, the possibility that the effective US in CTA was stress and/or somehow related to the HPA seemed compelling.

But I'm getting ahead of myself here. We were trying to understand the basis for the treatment preexposure effect and the fact that it didn't seem to be 'stimulus' or treatment specific. Was it simply the result of a reduction in the intensity of the US as in latent inhibition or could it have resulted from some other more active associative process such as blocking? There were many 'ifs' in our thinking, and our initial attempt to show that associations between handling cues and treatment during preexposure could block subsequent taste-treatment associations had failed. Some of the 'ifs' had to do with the nature of the effective aversive stimulus (i.e., was it stress or activation of the HPA). Other 'ifs' had to do with whether there were other more potent signaling stimuli during the treatment preexposure phase of the experiment that would become associated with the treatment and subsequently block the formation of new associations between the taste of the target test solution and the treatment.

We really didn't want to discard a possible explanation of the treatment preexposure effect based on the formation of competing associations formed during preexposure. It was attractive in its simplicity. Besides, we had already

started on a group of experiments when Rudy et al. suggested that handling cues might account for the treatment preexposure effect. And, we already had preliminary data which showed that there were cues other than experimenter generated handling cues that could become associated with the US during preexposure which could subsequently block the acquisition of a taste-treatment association. In this series of experiments (Braveman, 1979), we preexposed animals to the treatment in a distinctive environment (i.e., one that was bright, quiet and in a clear plastic solid floored cage with bedding material) and then tested them for the treatment preexposure effect either in the same distinctive environment or in their very familiar home cage (dimly lit, constant background music, and stainless steel case with mesh floor) environment. Not only did we confirm the fact that animals pre-exposed and trained in the presence of the same novel environmental cues exhibited the treatment preexposure effect with the same aversion- inducing drug used during both preexposure and training, but we also showed that the crossover effect (i.e., interference with the formation of CTAs when the aversion inducing modalities were different between preexposure and training) also occurred when preexposure and training took place in the presence of the same novel environmental cues.

These findings were pretty convincing for a blocking explanation of the treatment preexposure effect, although I must say that we were taken a bit by surprise when the experiment involving handling cues didn't work out. Nevertheless, we went one step further by arguing that if the blocking explanation of the treatment preexposure effect was correct then the environmental cues with which the aversive treatment effects were becoming associated ought to themselves become secondarily aversive. As a consequence, animals preexposed in a distinctive environment should drink less in that environment than similarly preexposed animals would in a different environment simply because the distinctive environmental cues had become associated with negative or aversive consequences and would suppress drinking behavior. In fact, we found the exact opposite to be true. Animals preexposed to either lithium chloride or d-amphetamine sulfate in one environment and then given an opportunity to drink novel saccharin flavored solution in that environment drank *more* than animals preexposed to the same drugs and allowed to drink the novel saccharin solution in a different environment.

These findings seemed to be totally inconsistent with an associative blocking explanation of the preexposure effect. They were, however, consistent with other findings in the literature (Domjan & Gillian, 1977) and with other experiments that we carried out in our lab. So, our first thought was that they were an anomalous artifact of the fact that we recorded consumption on the test trial in 15-minute blocks. What if animals that had received preexposure trials in the presence of those distinctive environmental cues really were initially reluctant to drink? But, because they were water deprived and were used to drinking all of their daily water in a 15-minute session, after an initial hesitation they consumed large quantities, over-compensating for their thirst and actually consuming more during

the later part of the drinking test? So, in a subsequent experiment we analyzed drinking behavior in 3-minute intervals in order to determine whether the results of our initial experiment could have been an artifact. Once again we were wrong. Animals preexposed to lithium chloride and administered the drinking test in the same environment did not show any hesitancy to drink the novel saccharin solution from the first 3-minute interval throughout the entire drinking test. They drank more than any other group at every 3-minute interval. So it appeared to us that something else was going on. We concluded that a blocking explanation of the preexposure effect wasn't totally satisfactory in that it couldn't deal well with the increased drinking that appears to occur after preexposure. It was pretty clear that the environmental cues seemed to be acting in a way that enhanced drinking behavior...just the opposite of what we had expected. Old favored hypotheses die hard.

A second possibility is that increased drinking and decreased conditioning are each independently influenced by a single underlying physiological process which is activated when animals are preexposed to an aversive stimulus like a drug injection over which they have no control. And for this, we returned to the possibility that the HPA axis plays an influential role in CTA and drinking. Recall that it was already being discussed as the effective aversive stimulus that caused CTAs. In addition, there were data available at the time to show that injections of lithium chloride increased ACTH levels (Riley, cited in Braveman, 1977b) and that corticosterone levels can be conditioned to a taste CS (Ader, 1976). It was also known that dexamethasone, a synthetic glucocorticoid, suppresses activation of the HPA system *and* interferes with the formation of CTAs (Hennessy, et al, 1976) and that there's a parallel reduction in the HPA system during extinction of a CTA (Righter & Popping, 1976). Further, we and others had shown that the HPA was very much involved in reduced consumption of new flavored solutions (i.e., neophobia) (e.g., Braveman, 1978b; Ader, 1976; Smotherman & Levine, 1978).

So, activation of the HPA looked like a good bet given what appeared to be anomalous findings in the preexposure-drinking experiments. We thought it might be possible that the enhanced drinking observed only in the environment in which animals had been preexposed to the aversion-inducing agent was mediated by a reduction in HPA activity which had been caused by preexposure to the aversion-inducing agent in that environment. Our reasoning went like this: each preexposure injection caused activation of the HPA which, with repeated injections, became reduced in strength; the preexposure-induced reduction in HPA became associated with the distinctive environmental cues; when animals experienced those cues again, the pre-existing associations resulted in reduced HPA activity; the reduced HPA activity in response to the conditional environmental cues interfered with any initial hesitancy to drink a novel solution in the distinctive environment because that neophobia was driven by increasing HPA activity; as a result there was an increase in intake of the novel solution. Note too that this line of reasoning also accounts for the effect of preexposure on

the formation of a CTA since, if the effective aversive stimulus is activation of the HPA, the necessary aversive element is missing from or at least reduced during the conditioning trial.

So our next experiment involved directly suppressing HPA activity in the presence of the distinctive environmental cues during the preexposure phase of the experiment. During preexposure, animals received either dexamethasone, an HPA suppressor, or physiological saline in their home cage or in a distinctive environment for eight days just before they received their daily access to water. On the ninth day, they were all given a distinctively flavored sodium saccharin solution instead of normal tap water while in the distinctive environment. Once again, we showed increased drinking only in the group that received dexamethasone and the novel saccharin water in the distinctive environment. Animals receiving the novel solution in an environment different from the one in which the distinctive cues had become signals for HPA suppression, showed full-fledged neophobia. This indicated to us that the environmental cues associated with the dexamethasone-induced suppression of HPA interfered with the ability of the novel saccharin solution to induce activation of the HPA. As a consequence, at least a sufficient if not necessary condition for neophobia (i.e., HPA activation in the presence of a novel flavored solution) had been eliminated by associations formed between the distinctive environmental cues and the physiological effects of dexamethasone during preexposure.

Interestingly, at about this time Shep Siegel (1975, 1976) postulated that environment-specific tolerance to the analgesic effects of morphine was the result of classical conditioning of environmental cues with a physiological compensatory mechanism that allows the animal to cope with the direct or systemic effects of the morphine. As conditioning becomes strengthened, the environmental stimuli elicit the compensatory response prior to or during the onset of the action of morphine resulting in what looks to us like a tolerance to morphine. Evidence of morphine-induced analgesia is observed only if the animal is tested in the environment in which tolerance is induced. However, move the animal to a new and distinctive environment and it appears as though it never had been pre-exposed to morphine. We extended this line of reasoning to speculate a similar process could have been occurring in the treatment preexposure experiments. Following preexposure in a distinctive environment, the environmental stimuli elicited a physiological response antagonistic to one responsible for the aversion-inducing properties of drugs such as lithium chloride or amphetamine. As a result, we observed the treatment preexposure effect, i.e., a failure to induce CTA. We went on further to speculate that, in the case of CTAs, the physiological pathway involved in the aversion-inducing characteristics of these drugs, or what Shep referred to as the compensatory mechanism, was activation of the HPA axis. And that's when I left research.

## **One more thing and then I'm done: Preexposure, neophobia and CTAs...a sidebar.**

As we progressed in research on preexposure to the aversion-inducing agent, we developed a parallel interest in neophobia and then with the connection between neophobia and the establishment of CTAs. All of this stemmed from studies that seemed to show that we could interfere with neophobia by preexposing animals to the aversion-inducing agent. In particular, we were struck by the observation that both preexposure to a target novel flavor as well as to the aversion-inducing treatment resulted in increased drinking of the target test solution (i.e., interference with neophobia) and both of these maneuvers also interfered with CTAs. So, we wondered whether or not there was a connection between neophobia and the formation of CTAs. In fact, we weren't the first or the only ones to talk about this possibility. There were ongoing discussions among many of us conducting CTA research at the time around the question whether or not CTAs (i.e., reduced consumption of a novel flavored solution following pairing of that solution with 'sickness') was, in reality, simply a prolongation of neophobia (i.e., based on something other than an associative process) as opposed to true classical conditioning or even instrumental conditioning.

While operationally the establishment of CTAs looked like associative learning, there were unique aspects of the CTA paradigm. Relatively strong CTAs (associations?) could be formed even with long delays between intake of the target ingestible and the onset of sickness. For example, Emir Andrews (Andrews & Braveman, 1975) showed that it was possible to establish CTAs in lab rats with a 13.5 hour delay between ingestion of a sodium saccharin solution and injection of a 12.15% (w/v) lithium chloride solution. So, our observations that preexposure to the aversion-inducing agent interfered with both the formation of CTAs and neophobia added to the possibility that CTAs were an enhancement of neophobia. We turned our attention to looking at the possible connection between CTA and neophobia and then to neophobia itself.

Neophobia for a given substance is characterized by the fact that animals consume the substance in small amounts, if at all, and that they are very hesitant when they do so, exhibiting approach-avoidance behavior. On the other side of the coin, animals consume larger amounts of a substance with which they are familiar and not phobic, particularly if it's a preferred substance like sweet tasting saccharin flavored water. And, as anyone who has done research on CTA knows, animals form stronger CTAs to novel flavored substances than to familiar ones. In fact, Sam Revusky and colleagues carried out painstaking experiments on latent inhibition of the CS that showed this to be the case. Presumably, animals were phobic to these novel substances but not so to the familiar ones. Putting this in terms of the relationship between neophobia and CTAs, one might predict that the more of a target test solution consumed on the training trial the weaker the CTA.

We (Braveman & Crane, 1977) tested this relationship by providing animals with measured amounts of saccharin flavored water prior to an injection of lithium chloride. The measured amounts of the target test solution consumed were determined by independent assessments of the average amount of the saccharin flavored water consumed by thirsty rats on the successive 10-minute presentation of the test solution. The amount consumed on the conditioning trial seemed to be important within the limits of our experimental design. However, the relationship wasn't simple or as expected. Aversions got stronger as the amount consumed increased from 0.5 to 1.5 to 5.5 ml; just the opposite of what one might expect from the Revusky experiments. Beyond that level, however, aversions got weaker when animals drank 6.5 or 10.5 ml on the training trial. While we were tempted to declare victory because, in our lab, animals that were neophobic to a target test solution consumed as much as 5.5 ml in 10 minutes, we were unsettled by the fact that the trend in the 0.5, 1.5 and 5.5 ml groups was in the wrong direction. We could only speculate as to the reason for this finding, concluding that nothing is ever simple and deciding to take another approach in delineating the relationship between neophobia and CTAs.

The new approach attempted to manipulate the neophobic response in a way that was closer to procedures used by Revusky in his latent inhibition experiments. In a series of experiments (Braveman & Jarvis, 1978), we showed that preexposure to the target test solution interfered with both neophobia and CTAs, thus replicating the latent inhibition effect for the CS. However, when preexposure was to a series of changing tastes that differed from the target test solution, neophobia to the target test solution was reduced but CTAs were unaffected. This finding would suggest that neophobia and CTAs are not necessarily connected. Our next experiment further reinforced this suspicion. In this experiment, we found that, once formed, the association between taste and US disappeared when animals were given extinction trials with the target test solution but was unaffected when the extinction trials involved the series of tastes. This suggested to us that there were two processes operating. On the one hand, it appeared that there was a specific associative process being influenced by preexposure to the target test taste while something else was being influenced by experience with the varied set of tastes. However, the reason(s) for the difference wasn't clear. We looked at two possibilities.

On the one hand, Siegel (1974) had explained similar kinds of findings by postulating that during preexposure animals learned that a specific flavor was 'safe.' During subsequent experience with that flavored substance, animals would consume it in larger quantities because of its perceived safety and hence would not exhibit neophobia. As an added feature of this explanation, Siegel went on to argue that establishment of an association between the 'safe' familiar taste and aversion-inducing drug would be blocked because of the pre-existing and conflicting association. The fact that this same pattern didn't occur when preexposure was to a series of tastes could be explained simply because it's easier for animals to characterize a single taste than a series of tastes as safe.

In contrast, Capretta et al. (1975) held that the reduced neophobia in animals that received the variable taste preexposure could be explained by the fact that they had become accustomed to dietary diversity and one more new flavor was perceived as part of a normally diverse diet and hence was acceptable.

We tested the two possibilities by pre-exposing animals to familiar tap water, the target test solution or a variable series of flavored waters, none of which included the target test solution. We found that neophobia was reduced rather quickly and that the rate of reduction was about the same for animals pre-exposed to the target test solution as it was for animals pre-exposed to variable solutions. Following three preexposures to either a novel solution or two different flavored solutions, animals were consuming as much of the target test solution (flavored water) as animals given familiar tap water throughout the experiment. Clearly, diversity played an important role in reducing neophobia...but, as we showed in other experiments, it did not have an effect on the formation of an association. Our conclusion, based on the fact that neophobia seemed to be reduced rather quickly following experience with the diverse flavored solutions and on research by Domjan (1976), was that animals seemed to find novelty *per se* aversive. By not ingesting novel flavored solutions, that is, by exhibiting neophobia, animals are minimizing the aversive effects of novelty. The formation of CTAs is interfered with because of a specific and separate associative process, known as latent inhibition, which in the CTA paradigm is dependent on preexposure to a specific taste.

This research whetted our curiosity about neophobia in the feeding situation in general. We wondered how general the taste preexposure effect might be and whether there were other behavioral correlates of taste preexposure. Earlier, I described observations we made with guinea pigs and indicated that whenever we changed the location of their food and water we observed what we assumed was emotional behavior. This led us to a series of experiments in lab rats (Braveman, 1978b) aimed at measuring the effect of taste preexposure on the acceptance of variability in the feeding situation and on emotionality (i.e., the possible aversiveness of novelty). We found that taste preexposure could reduce 'emotionality' in lab rats, as measured in an open field and by bouts of grooming and face-washing, but it did so only in animals that received variable target flavored solutions during preexposure. Exposure to a single target test solution did not impact either open field or grooming and face washing.

Also, because the effect of variable taste preexposure seemed to have an impact on a totally different class of behaviors (i.e., open field exploration) we went on to look at the effects of taste preexposure on other types of feeding situations. In additional experiments, we found that animals receiving variable taste preexposure drank more of a *familiar* solution from a *novel* container than animals that had received either a single flavored target solution or familiar tap water. The reverse also appeared to be true as well...taste neophobia can be disrupted by providing lab rats with feeding experiences in other environments.

When we gave tap water to animals in a distinctive mouse cage, in a distinctive wooden cage or in variable cages (home cage, mouse cage and wooden cages), neophobia was disrupted, while animals who received the tap water in their home cages exhibited neophobia. Our conclusion: novelty in the feeding situation is aversive to lab rats (and guinea pigs judging from their vocalizations) and disrupts their ingestive behavior, something that we call neophobia; variability in feeding-related experiences can have far reaching and profound effects in reducing the aversiveness of novelty, even novelty in other feeding-related situations, possibly by reducing emotionality (maybe by blunting the response of the HPA); and the interference with the formation of CTAs by preexposure to a single target test solution, while perhaps mediated by the HPA, is based on an associative process and, hence, independent of neophobia. And that really is the end.

### **What does it all mean?**

As I said at the beginning, I haven't conducted research on CTA or anything else for that matter in about 30 years. One of the realities of this is that I've lost contact with what has gone on in the field. So it's difficult (and probably not appropriate) for me to assess the importance and/or meaning of my own work. Also, as I warned at the outset, the last person who should do something like this is an old fly fisherman...and I'm both. So I will leave the 'lessons learned' to others.

Having said that, and with the good luck of having been immersed in biomedical and behavioral research for 25+ years during which unprecedented advances in biomedical science have been made, there are a couple of points that I would like to make about my research specifically and perhaps the area in general. Keep in mind, however, that the danger of looking at anything from afar is that the details can get lost and more often than not it is details that define the landscape.

In writing this piece, I keep coming back to the thought, 'how naïve I was.' Focusing on the early research...we used only two species, the lab rat and domestic chickens, in a very limited number of studies, yet we felt confident that we could arrive at a general law of association for all species and situations. Garcia's, Capretta's and my early work tried to understand the formation of taste aversions and/or the modification of food preferences in terms of a principle involving the relationship between ingestional behaviors and their consequences. And, while this principle seemed to make intuitive sense and was certainly supported by data, it also seems to be an oversimplification of what, in retrospect, looks like very complex behavior.

And this resonates with me, particularly in light of recent developments in biomedical research. Having been through the era of molecular biology,

developmental biology, genomics, proteomics and other '-omics', we are now in an era of what is termed systems biology or, more generally, a systems approach to understanding complex diseases. This approach recognizes that everything is connected to everything else and that you can't study or perturb one part of a system without examining or impacting other parts of the system. It derives from one of the principles of chaos theory which states that small changes in complex systems can have very large downstream effects (Gleick, 1988)...the example given in that case being one of butterflies in one part of the world fluttering their wings and in so doing causing changes in air currents which become magnified over time and distance to the point of becoming a tornado in another part of the world.

Feeding behavior and taste preferences are complex in and of themselves, to say nothing about the role they play in even more complex behavioral systems. In CTA research, all we needed to do was to change the conditions slightly in our experiments and our thinking about the selective associations changed. That's not to say that Capretta, Garcia or I was inaccurate. It's to say that we weren't looking at the broader aspects of what we were studying and therefore, in retrospect, probably weren't in a position to generate a general law of anything. To return to the question that Dud Klopfer asked me about Garcia's bright-noisy water experiment and my master's work on stimulus relevance...we didn't look fully at the evolutionary or adaptive significance of our findings or of these principles.

A systems approach in the study of biological, and I suspect behavioral, functioning relies on huge amounts of data and on the field of bioinformatics to deal with that data. I recently organized a conference on the use of systems biology in studying complex diseases. Among the speakers were individuals using a systems approach to study type II diabetes, cancer, epilepsy, peripheral pain and hypertension. Basically, what we heard is that these folks are trying to understand the etiology and pathogenesis of the respective diseases of interest by correlating everything with everything else in order to uncover promising lines of research and even to identify genes and families of genes responsible for the disease under examination. The more data and variables they can include in their studies, the better. They never seem to have enough data sources to include in the mix, including behavioral data. As I listened to these biologists and bioinformaticists talk about their research and their approaches, I recalled that in a very real sense we in psychology have already been there...in the 1950's... but we seem to have dismissed it. Our analytic approach wasn't bioinformatics. We called it factor analysis. Like the systems biologists, we looked for rules that connected the various components of the system and we called them 'nomological networks' (e.g., Cronbach & Meehl, 1955). But we abandoned that approach for a more reductionist one, having dismissed it simply as hypothesis generating rather than hypothesis testing...and often with the statement that behavior, after all, is more variable than biological traits and, therefore, more difficult to study within this model.

Einstein has been credited with the statement that “everything should be made as simple as possible, but not simpler.” While I suspect that in some instances this can help us understand complex phenomena, it may also contain an inherent danger in simplifying inherently complex systems. As a clinical researcher/orthodontist, Shelly Baumrind (1993) puts it

“If the experimental model one studies underestimates or misrepresents the complexity of the system(s) in which one is really interested, the answer(s) one arrives at are likely to be simplistic rather than simple.”

And so, if there’s one lesson that I can distill from revisiting my research it is that we should cast the broadest net possible, collect as much data as we can and let the bioinformaticists or factor analysts help us discover the likely networks underlying the behavior that we’re studying. As stated by Sauer et al. (2007),

“...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration....”

I would add that this may be even truer of behavioral networks.

Finally, before ending I have one more thing to say. Quoting from an email I sent Tony Riley following his invitation to me to write this highlight...

“Tony....I’ve been re-reading the stuff I’ve published...I’m wondering why it was ever accepted for publication...(and) I'm thinking that the highlight (that I write for your database) will simply be an apology to those who have read it and a warning to those who haven't...and my deepest regrets to all for having killed all those trees.”

So I end this article by making a blanket apology, giving a warning and making a commitment to replace some of the trees.

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